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Effectiveness of Magnetic Stimulation in the Treatment of Urinary Incontinence:
A Systematic Review and Results of Our Study

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Article

Effectiveness of Magnetic Stimulation in the Treatment of Urinary Incontinence: A Systematic Review and Results of Our Study

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Abstract: Urinary incontinence (UI) is becoming an increasingly common health problem. UI treatment can be conservative or surgical. This paper focuses on the effectiveness of magnetic stimulation (MS) in the treatment of UI. We performed a systematic review in order to combine and compare results with results from our clinical study. A clinical prospective non-randomized study was carried out at the Ljubljana University Medical Center's Gynecology Division. It included 82 randomly selected female patients, irrespective of their UI type. The success rate of using MS in treating UI was based on standardized ICIQ-UI SF questionnaires. Patients completed 10 therapy sessions on MS, and follow-up was performed 3 months after the last therapy session. UI improved after treatment with MS. The ICIQ-UI SF score improved in patients regardless of the type of UI. However, the greatest decrease in post-treatment assessment ICIQ-UI SF scores was seen in patients with stress urinary incontinence (SUI). Based on the findings described above, it can be concluded that MS is a successful non-invasive conservative method for treating UI. Future studies are necessary, all of which should include a large sample size, a control group, an optimal research protocol, pre-treatment analyses, standardization, and longer follow-ups.

Keywords: urinary incontinence; treatment; magnetic stimulation

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1. Introduction

Uncontrolled leakage of urine, or urinary incontinence (UI), is a pelvic floor dysfunction found in all age groups [1]. UI has been used as a term since 2010 for any complaint of involuntary loss of urine, as per the definition by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction [2]. Patients have varied symptoms and signs, and they cite a wide range of problems, from mild to disabling [2–4]. The etiology of UI is multifactorial because risk factors include age, pregnancy, and childbirth (multiparous women), pelvic floor injury during vaginal delivery, pelvic surgery, menopause (due to decreased estrogen secretion), hysterectomy, increased body weight, lack of physical activity, urinary tract infections, chronic cough, prolonged heavy lifting, congenital weakness of connective tissue, and chronic constipation [2,4,5].

According to anatomical criteria, UI is divided into urethral and extra-urethral. Clinically, it is divided into absolute and relative UI [6]. Several types of relative UI are known, and they are divided by the basic pathophysiological mechanisms that cause their onset. They are roughly divided into stress UI (urinary incontinence due to pressure or upon exertion, SUI), urgency UI (urgency urinary incontinence, UUI), mixed UI (with characteristics

of stress and urgency UI, MUI), and overflow UI (involuntary release of urine due to an overfull bladder). In practice, however, the borders between different UI types are often blurred due to mixed etiology [2,4–7].

Magnetic Stimulation and UI

The problem of UI is becoming more common due to the rising elderly population and the trend of rising prevalence of UI with aging. Deciding on a conservative or surgical treatment approach depends predominantly on the type and severity of UI and on comorbidities. Conservative treatment should be exhausted first, and, before surgery is proposed, certain factors must be taken into account: the patient's age, general condition, and health, prior surgeries, and especially the gynecological and lower urinary tract status [4,8,9]. Therefore, new conservative treatment methods are being sought. Magnetic stimulation (MS) is a technology introduced in 1998 that has been used for stimulating the pelvic floor muscles [10]. It is based on Faraday's law of magnetic induction, whereby a time-varying magnetic field induces electrical activity that depolarizes the nerves and causes contraction of the pelvic floor muscles. Repeated activation of the terminal motor nerve fibers and the motor end plates will tend to build muscle strength and endurance [10,11]. MS creates a rapidly pulsating magnetic field whose frequency and pulsation strength can be adjusted on the device [12]. The roots of sacral nerves S2–S4 provide the primary autonomic and somatic innervation of the urinary bladder and urethra, vaginal wall and rectum, and pelvic floor muscles. Stimulation of these roots is an efficient way to modulate the pelvic floor and subsequently control the pelvic organs [13,14]. This method is used for treating all types of urinary incontinence. MS aims to moderate the habit of frequent voiding through practicing resisting the urge to void, postponing micturition, and increasing the voiding interval, which improves the bladder capacity and decreases detrusor instability. It is painless and does not require a probe. Its advantage is that the magnetic field penetrates body tissues without significant alteration and also passes uninterrupted through clothing, and there is no need for the patient to undress [10]. The main stimulation targets in SUI are the pelvic and/or pudendal nerves, and consequently the external sphincters and/or the pelvic floor muscles. In UUI, the afferent branches of the pudendal nerve are stimulated to inhibit the detrusor muscle through central reflexes; at the same time, the efferent nerve branches are also stimulated to facilitate strengthening of the pelvic floor muscles and increase the tonus of the urethral sphincters, thereby inhibiting the detrusor muscle through the guarding reflex [15]. MS has been investigated as an alternative treatment to electrical stimulation in neurology [16,17]. It is offered as a treatment for UI, although weak evidence of the short-term and long-term effects has been found in systematic reviews. Current EUA recommendations advise against treating UI or overactive bladder (OAB) with magnetic stimulation (strength of recommendation = strong) [18].

To demonstrate the prevalence of the issues stated above, we conducted a systematic literature review. The systematic review was carried out to present recently published studies, to comprehensively evaluate the method performance, and to compare it with the results of our clinical study. Moreover, the aim of our clinical study was to determine whether the success rate of using MS to treat UI differs by UI type.

2. Methodology of the Systemic Review

Search Strategy and Selection Criteria

A systematic literature search was conducted using Medline, Cochrane, and ClinicalTrials. All known synonyms were used for the following keywords: "magnetic stimulation" and "urinary incontinence". The analysis included all clinical studies describing the evaluation of MS in the treatment of UI. All research articles in English published between 2010 and 2020 were reviewed. The article examines studies that contain the latest clinical practices for treating urinary incontinence. Potentially relevant research articles were identified by examining the abstracts or the articles as a whole. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to complete

the search and the article selection. Figure 1 demonstrates the PRISMA flowchart and identifies the number of search results, articles meeting criteria, and articles selected for data extraction [19]. It should also be noted that the focus of this article is only research articles. Conference presentations and reports were excluded because the goal was to focus on the most carefully evaluated material. Titles and abstracts of the identified studies were screened independently by two authors (M. Batk., T.K.). The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by another author (D.L.). Any disagreement over the eligibility of particular studies was resolved through discussion with a fourth author (M.M.)

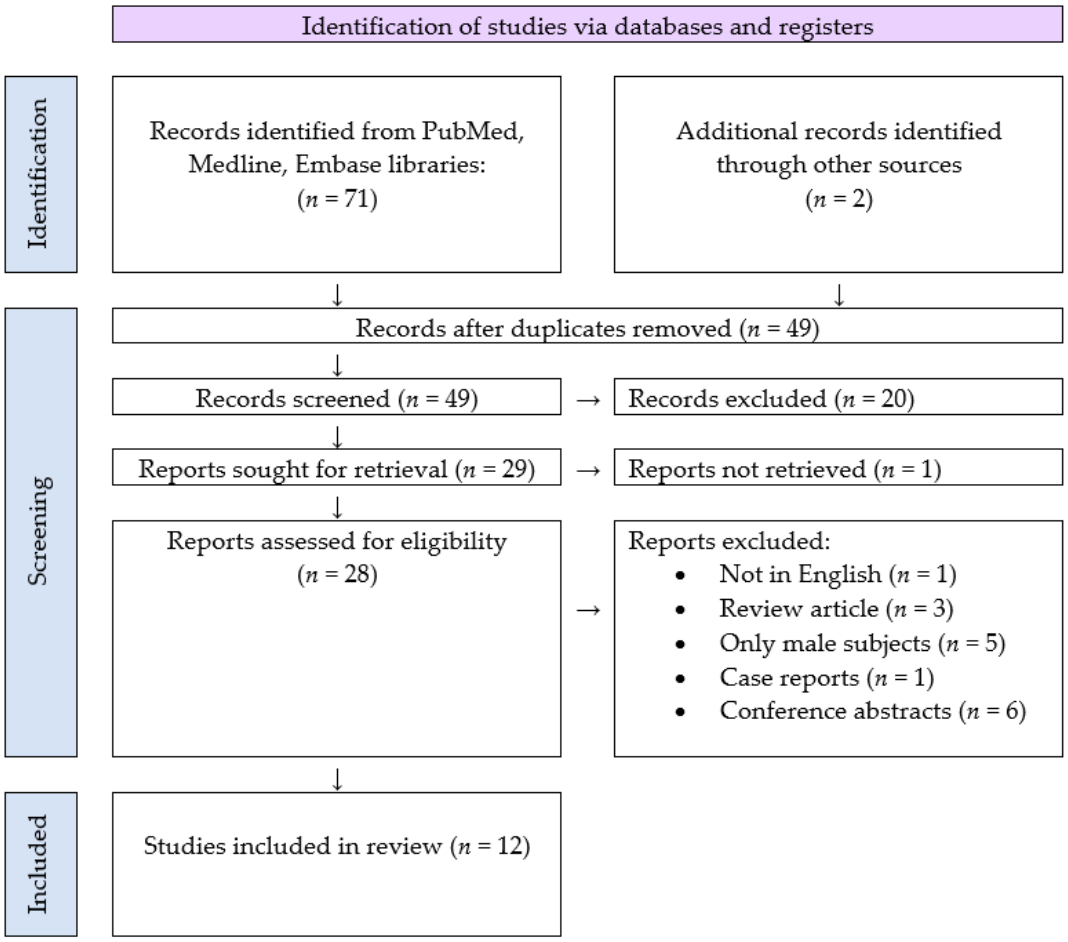

Figure 1. Search strategy and study selection used in this systematic review as per the PRISMA protocol.

3. Results of the Systematic Review

Seventy-three articles were identified and screened at the title and abstract levels. Forty-five articles were excluded for any of the following reasons: they were not in English, they were review articles or meta-analyses, only males were subjects of the research, they were case reports or they were conference abstracts, or there were no possibilities for analyzing the success rate of the treatment. Thus 12 articles [20–32], summarized in Tables 1–5, represented the object of this review.

Table 1. Clinical overview of 12 articles: study type and diagnostic method(s).

Study	Study Type	Diagnostic Method(s)
Lim et al., 2015, 2017 [20,21]	Multicenter, randomized, double-blind, sham-controlled (1:1 ratio)	1. Urinary diary 2. ICIQ-UI SF 3. Perineometer 4. PGI-I 5. ICIQ-LUTSqol 6. 1-h pad test
Yamanishi et al., 2017 [22]	Pilot, randomized, sham-controlled (active: sham = 2:1)	1. 7-day urinary diary 2. 24-h pad test 3. ICIQ-UI SF 4. ICIQ-LUTSqol 5. Urodynamic test
Weber-Rajek et al., 2019 [23]	Randomized, double-blind, controlled pilot study	1. Voiding diary 2. QUID 3. Patient history
Weber-Rajek et al., 2020 [24]	Randomized, double-blind, controlled trial	1. SUI previously diagnosed by urologist 2. Voiding diary 3. Patient history
Özengin et al., 2016 [25]	Open-label, not controlled, data on randomization N/A	1. SUI previously diagnosed by gynecologist 2. EMG-BF measurement of PFM activity at rest and during three maximum voluntary contractions
Sylantieva et al., 2020 [26]		1. 3D transperineal ultrasound 2. Patient history
Samuels et al., 2019 [27]	Prospective, multi-center, open-label, single-arm study; data on randomization N/A	1. Reporting UI symptoms 2. ICIQ-UI SF
Vadalà et al., 2017 [28]	Retrospective observational study	1. Previously diagnosed UI 2. Voiding diary 3. Urodynamic examination 4. Urinalysis
Doğanay 2010 [29]	Prospective, open-label, single-center, not controlled	1. 5-day voiding diary 2. Urodynamic studies 3. I-QOL 4. VAS
Sun et al., 2014 [30]	Open-label, single-center, not controlled	1. Urodynamic studies after RH 2. UDI-6 3. IIQ-7
Bakar et al., 2010 [31]	Open-label, single-center	1. Previously diagnosed SUI 2. 1-h pad test
Tsai et al., 2014 [32]	Sham-controlled, double-blind, parallel study	1. Urodynamic studies 2. U-UDI 3. OAB-q

Table 2. Clinical overview of 12 articles:UI type, sample size, control, length of intervetion period and frequency.

Study	UI Type	Sample Size	Control Group	Length of Intervention Period and Frequency
Lim et al., 2015, 2017 [20,21]	SUI	120	Yes, 1:1 ratio	20 min stimulation twice a week for 8 weeks (16 sessions total)
Yamanishi et al., 2017 [22]	SUI	39	Yes, active stimulation and sham stimulation group, 2:1 ratio	20 min stimulation once a week for 10 weeks (10 sessions total)

Table 2. *Cont.*

Study	UI Type	Sample Size	Control Group	Length of Intervention Period and Frequency
Weber-Rajek et al., 2019 [23]	SUI	52	Yes, active: control = 28:24	15 min stimulation three times a week for 4 weeks (12 sessions total)
Weber-Rajek et al., 2020 [24]	SUI	111	Yes, PFMT (40), MS (37), control (34)	PFMT: 45 min sessions three times a week for 4 weeks (12 sessions total)
Özengin et al., 2016 [25]	SUI	67	No	MS: 20 min sessions three times a week for 8 weeks (24 sessions), EMG-BF: three sessions of 20 min in 8 weeks, PFMT: N/A
Sylantieva et al., 2020 [26]	SUI?	95	Yes	MS: 28 min sessions two to three times a week (10 sessions total)
Samuels et al., 2019 [27]	SUI (49%), UUI (11%), MUI (40%)	75	No	28 min twice a week, for 3 weeks (six sessions total)
Vadalà et al., 2017 [28]	SUI (50%), UUI (20%), MUI (30%)	20	No	20 min stimulation twice a week for 3 weeks (six sessions total)
Doğanay 2010 [29]	SUI, UUI	137; SUI: 68, UUI: 69	No	20 min sessions twice a week for 8 weeks (16 sessions total)
Sun et al., 2014 [30]	SUI, UUI, MUI	32	No	20 min sessions twice a week for 12 weeks (24 sessions total)
Bakar et al., 2010 [31]	SUI	13	No	20 min sessions twice a week for 6 weeks (12 sessions total)
Tsai et al., 2014 [32]	SUI	30	Yes, active group: 18, sham group: 12	20 min every weekday for 12 days (12 sessions total)

Table 3. Clinical overview of 12 articles: device and outcomes (changes).

Study	Device	Outcomes (Changes)
Lim et al., 2015, 2017 [20,21]	QRS-1010 PelviCenter (QRS International, Ruggell, Liechtenstein)	1. ICIQ-UI SF reduction (total and QoL) 2. Cure (objective and subjective) 3. SUI symptoms (IEF, 1-h pad test, PFM examination with perineometer, incontinence severity)
Yamanishi et al., 2017 [22]	Armchair-type magnetic stimulator (Nihon Kohden, Tokyo, Japan)	1. Number of incontinence episodes per week (frequency) 2. Degree of UI (using 24-h pad test) 3. ICIQ-UI SF reduction (total and QoL) 4. ALPP in urodynamic studies
Weber-Rajek et al., 2019 [23]	NeoControl chair (Neotonus Inc., Marietta, GA, USA)	1. Myostatin concentration (before and after treatment) 2. RUIS 3. BDI
Weber-Rajek et al., 2020 [24]	MS: NeoControl chair (Neotonus Inc., Marietta, GA, USA)	1. Better RUIS scores 2. KHQ 3 GSAS (in ExMI group)

Table 3. *Cont.*

Study	Device	Outcomes (Changes)
Özengin et al., 2016 [25]	N/A	1. QoL (in all groups) 2. EMG activity (in all groups)
Sylantieva et al., 2020 [26]	N/A	1. PFM thickness 2. PFDI-20
Samuels et al., 2019 [27]	BTL EMSELLA (BTL Industries Inc., Boston, MA, USA)	1. ICIQ-UI SF 2. Pad usage (urine leakage)
Vadalà et al., 2017 [28]	Magneto STYM (Iskra Medical, Ljubljana, Slovenia)	1. Number of incontinence episodes and nocturia 2. Urodynamic testing results 3. Life stress scores
Doğanay 2010 [29]	Neotonus Inc., (Marietta, GA, USA)	1. 5-day voiding diary 2. 1-h pad test 3. I-QoL 4. VAS (no statistically significant changes in urodynamic parameters)
Sun et al., 2014 [30]	BioCon-2000WTM, Mcube Technology Co. (Korea)	1. UDI-6 2. IIQ-7 3. 1-h pad test (no statistically significant changes in urodynamic parameters)
Bakar et al., 2010 [31]	EMD, E-6000 MAGTHER, TR	1. 1-h pad test, 2. pelvic floor EMG, 3. VAS, 4. UDI-6, 5. I-QoL
Tsai et al., 2014 [32]	Magstim Rapid2 and a 70 mm figure-8 coil/sham coil	1. U-UDI 2. Urodynamic values

Table 4. Clinical overview of 12 articles: follow-up period and benefits.

Study	Follow-Up Period	Benefits (Statistically Significant)
Lim et al., 2015, 2017 [20,21]	1, 2, 5, 8, 14 months	1. Treatment response (regardless of number of MS sessions) and positive outcomes after MS therapy 2. Reduction in ICIQ-UI SF post-treatment score at all follow-ups
Yamanishi et al., 2017 [22]	10 weeks	1. Amelioration of signs and symptoms (subjective and objective evaluation) 2. No device or study-related side effects
Weber-Rajek et al., 2019 [23]	4 weeks	Reduction of: 1. UI severity, 2. Myostatin level, 3. Subjective depression level
Weber-Rajek et al., 2020 [24]	4 weeks	1. Improved general quality of life after both MS and PFMT 2. Reduction of SUI symptoms after ExMI and PFMI 3. Subjective depression level
Özengin et al., 2016 [25]	8 weeks	1. Improved quality of life in all groups, with superior improvement in EMG-BF group 2. Improved PFM EMG activity after three types of treatment (no statistical differences between groups)

Table 4. *Cont.*

Study	Follow-Up Period	Benefits (Statistically Significant)
Sylantieva et al., 2020 [26]	4 weeks	1. Improvement of biometric indices of pelvic floor integrity 2. Profound change in PFDI-20, especially in MS group 3. Substantially greater improvement of subjective intimate health (self-evaluation bimodal questionnaire) in MS compared to ES group
Samuels et al., 2019 [27]	3 weeks, 3 months	1. Improved UI symptoms 2. Improved quality of life 3. Less leakage 4. Use of pads halved
Vadalà et al., 2017 [28]	3 weeks	1. Reduction of micturition frequency and nocturia 2. Improved urodynamic testing results (increased cystometry capacity, MUCP, urethral functional length, PTR) 3. No side effects reported 4. General satisfaction
Doğanay 2010 [29]	2, 4, 6, 8 weeks, 6 months, 1, 2, 3 years	1. Subjective and objective improvement of symptoms in women with SUI and UUI 2. ExMI effect lasted about 1 year, then gradually decreased
Sun et al., 2014 [30]	4 weeks, 12 weeks	1. Objective and subjective symptom amelioration
Bakar et al., 2010 [31]	6 weeks	1. Improvement of subjective symptoms 2. Better EMG results
Tsai et al., 2014 [32]	18 weeks (4.5 months)	1. Significant increase in bladder capacity, urethral functional length, and pressure transmission ratio 2. U-UDI 3. Higher therapeutic frequency within shorter time period can produce greater cumulative effect that most benefits patients with SUI

Table 5. Clinical overview of 12 articles: limitations.

Study	Limitations
Lim et al., 2015, 2017 [20,21]	1. Possible placebo effect in sham group 2. Long follow-up period possible 3. No urodynamic testing performed (reason for SUI: hypermobility and/or intrinsic sphincter deficiency is unknown)
Yamanishi et al., 2017 [22]	1. Small sample size (insufficient statistical power) 2. Low frequency of treatments per week (once a week) 3. Only short-term effects evaluated 4. Possible biased results because of PFMT before MS, although patients were refractory to PFMT
Weber-Rajek et al., 2019 [23]	1. Relatively small study sample 2. No long-term effect evaluation
Weber-Rajek et al., 2020 [24]	1. No objective instruments/measurements included 2. No long-term evaluation
Özengin et al., 2016 [25]	1. No long-term follow-up 2. Relatively small sample size 3. Only one objective instrument used (EMG)

Table 5. *Cont.*

Study	Limitations
Sylantieva et al., 2020 [26]	1. Only young subjects (of reproductive age) included 2. No long-term follow-up 3. Exact treatment protocols not described 4. Detailed diagnostic criteria not enlisted
Samuels et al., 2019 [27]	1. No control group 2. Relatively short follow-up period
Vadalà et al., 2017 [28]	1. Very small sample size (insufficient statistical power) of different types of UI, 2. No follow-up period
Doğanay 2010 [29]	1. Lack of placebo/sham group
Sun et al., 2014 [30]	1. Lack of placebo/sham group 2. Small sample size 3. No pre-surgery evaluation of incontinence 4. No long-term follow-up
Bakar et al., 2010 [31]	1. Very small sample size, 2. No long-term follow-up, 3. Lack of control group, 4. Only older demographic included
Tsai et al., 2014 [32]	1. Small sample size 2. Non-refined study parameters 3. No long-term follow-up

Five studies were randomized, double blinded, and sham controlled [20–24,32], and the rest were prospective studies without a control group [25–31]. Most studies used MS only for treating patients with SUI [20–26,31,32], whereas Samuels et al. [27], Vadala et al. [28], and Sun et al. [30] treated patients with all three types of UI: SUI, UUI, and MUI. On the other hand, Doğanay et al. [29] included patients with SUI and UUI. Our systematic review showed that the studies analyzed used different diagnostic methods to define the type and severity of UI. Initial management of patients with UI should consist of a urogynecological history with analysis of a bladder diary, urine analysis, and clinical examination. The amount and type of fluid consumed during the day should be established. The bladder diary can also be analyzed because it provides valuable information regarding the patient's urination frequency, incontinence episodes, pad use, fluid intake, and degree of urgency and incontinence. Standardized questionnaires are sometimes used, especially to quantify symptoms; one of them is the ICIQ-UI SF. Patient history is followed by a clinical examination. Because of the high prevalence of urinary tract infections in women with lower urinary tract symptoms, urine analysis, urinary culture, and post-void residual evaluation are an indispensable part of the initial assessment of these patients. Urodynamic measurements are an important part of the diagnostic process in patients with complicated UI. The ICS specifies standard and additional urodynamic measurements. Standard measurements include uroflowmetry, post-void residual evaluation, cystometry, and pressure-flow study [1,4,5,18]. However, Table 1 shows that each study used different initial diagnostic methods and Table 3 different tools to measure outcomes. The treatment protocols were also different for each study, from six sessions to a total of 24 sessions. A long follow-up, more than 12 months, was only screened in the studies by Lim et al. [20,21] and Doğanay et al. [29].

Lim et al. [20,21] decided to use ICIQ-UI SF as the primary outcome measure based on the emerging consensus that patient-reported outcomes are the most appropriate when describing treatment success or failure. There were consistently significant improvements in the ICIQ-UI SF scores between 1 and 2 months; however, there was no further reduction of the mean ICIQ-UI SF at the 14-month follow-up in comparison to the baseline mean value of the ICIQ-UI SF. In addition to using the ICIQ-UI SF, Yamanishi et al. [22] also measured outcome with ICIQ-QOL scores and a 24-h pad test, which all decreased significantly after

treatment compared to the baseline in the active treatment group. Moreover, they proved that there was no significant change from the baseline in any of the parameters in the sham treatment group. The ICIQ-UI SF was also used as the primary outcome in the study by Samuels et al. [27]. In addition, changes in the number of absorbent pads used per day were added. At the follow-up, a moderate but highly significant correlation was found between the ICIQ-UI SF score improvement and the reduction in pad usage. Vadalà et al. [28] reported that because of the small subject sample (20 patients in total), it is difficult to draw any conclusions and/or extrapolate the outcome of the study to a wider population that is experiencing UI. However, he measured the effectiveness of MS with patients' impressions, records in urinary diaries, and scores of three life stress questionnaires (the overactive bladder symptom questionnaire [OAB-q], urinary distress inventory questionnaire-short form [UDI-6], and incontinence impact questionnaire-short form [IIQ-7]), which were performed pre- and post-treatment. Using objective methods, urodynamic tests recorded a significant increase in cystometric capacity, maximum urethral closure pressure, urethral functional length, and pressure transmission ratio values compared to the baseline values.

Weber-Rajek et al. [23], in the first study performed by her team, measured blood myostatin levels before and after MS. As outcome measurement tools, different questionnaires were added: the Revised Urinary Incontinence Scale (RUIS), the Beck Depression Inventory (BDI-II), the General Self-Efficacy Scale (GSES), and King's Health Questionnaire (KHQ). In the following year, the same team of Weber-Rajek et al. [24] published an RCT that compared MS with pelvic floor muscle training, and the outcomes were measured with the same questionaries. In both experimental groups, a statistically significant decline in depressive symptoms (BDI-II) and an improvement in urinary incontinence severity (RUIS) and quality of life (KHQ) was seen. However, Weber-Rajek et al. [23,24] did not use the ICIQ-UI SF as a questionnaire to measure the outcome of the treatment. Özengin et al. [25] decided to compare the effectiveness of EMG-biofeedback, MS, and pelvic floor muscle training treatment. They measured the effectiveness of the treatment by evaluating pelvic floor muscles with electromyography. That study used the Incontinence Quality of Life (I-QoL) questionnaire. All three groups (the group using MS, group using EMG-biofeedback, and group performing only PFM) showed a significant improvement in EMG activity values and average QoL scores. However, the greatest improvement was observed in the EMG-biofeedback training group for QoL scores in comparison to MS and pelvic floor muscle training. In the most recent study on this topic, Silantyeva et al. [26] examined the effectiveness of MS versus pelvic floor muscle electrostimulation. In addition to the subjective evaluation with the Pelvic Floor Impact Questionnaire Short Form 7 (PFIQ-7), the researchers also used 3D ultrasound to objectively evaluate and later compare PFM anatomy and integrity. The results showed a statistically significant improvement in both subjective and objective parameters, regardless of the type of treatment; however, the results were superior in the group that underwent MS therapy. Doğanay et al. [29], who together with Lim et al. [20,21] had a longer follow-up, evaluated MS in the treatment of SUI and UUI with a 5-day voiding diary, 1-h pad test, and a validated quality of life survey (I-QOL; visual analog scale, VAS). There was statistically significant improvement in these parameters until the 1st year after the therapy, but it gradually decreased and was close to the baseline at the 3rd year after MS therapy. Bakar's small study investigated the effectiveness of MS in the treatment of SUI before and after the therapy using pelvic floor EMG activity, a 1-h pad test, incontinence conditions utilizing VAS and quality of life using a Turkish version of the UDI-6, and the I-QoL. After MS treatment, urinary symptoms and incontinence conditions decreased, the pad test results indicated a reduction in urine loss, the EMG values also improved, and, moreover, the scores on the I-QoL, UDI-6, and VAS were lower after the treatment.

Tsai et al. [32] decided to treat refractory SUI with a magnetic coil placed directly above sacral roots S2–S4. In his sham-controlled double-blind study, the experimental group showed significant improvements in both UDI-6 and OAB-q scores after the treatment and at follow-up visits compared to the sham group. In addition, significant increases

in bladder capacity, urethral functional length, and the pressure transmission ratio were also noted after the treatment. Sun et al. [30] treated patients with UI for at least 6 months following radical hysterectomy (RH) for uterine cervical cancer. There was a positive outcome after the treatment, with MS resulting in the improvement of the 1-h pad test, UDI-6, and IIQ-7, which showed statistically significant improvement. However, urodynamic parameters between pre-treatment and post-treatment after 24 sessions revealed no statistically significant changes.

A section of Table 5 points out the limitations of each study. Considering the limitations together, it can be concluded that a series of issues exists. First, further large-scale RCTs should be performed to determine consistent intervention protocols. Second, the outcome measurements to generate comparable data should be standardized. In addition, a longer follow-up period will provide more evidence to validate the effects of MS treatment. The main results from the studies analyzed confirmed that MS is effective in the treatment of UI, and similar results are also confirmed in our clinical study.

4. Materials and Methods of the Clinical Study

This article presents a clinical prospective non-randomized study that was carried out at the Ljubljana University Medical Center between 2016 and 2019. Patients were obtained in a urogynecology practice. It should be noted that the type of UI was previously diagnosed by a urogynecology specialist following national guidelines [4]. Before the treatment, we again evaluated the patient history, bladder diary, urine analysis, clinical examination, and the ICIQ-UI SF, and we divided them into 3 main subgroups: SUI, UUI, and MUI. The exclusion criteria included pregnancy, pacemaker patients, patients with a health condition unsuitable for performing the required measurements (hemorrhages, carcinoma, pelvic organ prolapse, inflammatory diseases, and endometriosis), and patients on antimuscarinics or beta-3 adrenergic receptor agonists.

In total, 82 consecutive patients were recruited; however, 7 patients did not provide all data. Finally, 91.4% (75) patients completed all pre- and post-treatment assessments.

The study was carried out in 3 stages. In the first stage, the patients completed a questionnaire adapted to the internationally validated ICIQ-UI SF questionnaire [33], which provides a subjective assessment of UI problems, and signed informed consent. They were informed of the possible risks. In the second stage, MS treatment was carried out, and the third stage included a checkup 3 months after the treatment was completed, during which the patients completed the same questionnaire once again (as before the treatment).

The relevant therapy program on the magnetic chair (Iskra Medical Magneto STYM®, Iskra Medical d.o.o., Ljubljana, Slovenia), based on producer recommendations, was selected and is shown in Table 6. UUI patients received 20-min urgency urinary incontinence therapy, MUI patients were treated with a 20-min mixed urinary incontinence therapy, and SUI patients were treated with 20-min stress urinary incontinence therapy. The magnetic chair's intensity can range from 0 to 100%. The electric impulse intensity was gradually increased to the patient's tolerance level, which allowed the patient to endure a 20-min therapy session. The treatment sessions lasted 4 weeks, with 10 therapy sessions of 20-min each, and it was applied every 2 workdays.

Table 6. Urinary incontinence treatment programs.

Programs	Step	Frequency of Magnetic Stimulation	Time	Active Time	Pause Time	Therapy Time
UUI	1/1	10 Hz	12 s	6 s	6 s	20 min
SUI	1/1	35 Hz	12 s	6 s	6 s	20 min
MUI	1/2	10 Hz	12 s	6 s	6 s	10 min
	2/2	35 Hz	12 s	6 s	6 s	10 min

Categorical variables were used to calculate the incidence and percentage of each factor, and all continuous variables were provided as the median and interquartile range (IQR). The normality of the data distribution was examined with the Jarque-Bera test. To understand whether pre- and post-treatment assessment of the ICIQ-UI SF scores differed based on UI type, a two-way mixed ANOVA with repeated measures was used: namely, a two-way mixed ANOVA with pre- and post-treatment as the repeated measures, and the UI type as the independent measure (pre-treatment assessment of the ICIQ-UI SF scores for MUI and UUI violated the normality assumption, and so these data were subjected to the Tukey ladder of powers transformation. Furthermore, we conducted all analyses with and without a transformation. All substantive results remained unchanged, and thus we reported the untreated solution). We tested for significant interactions: group differences in the change between pre- and post-treatment assessment of the ICIQ-UI SF scores. We performed multiple comparisons correction using Bonferroni correction. Furthermore, to assess the correlation between pre- and post-treatment assessment of theICIQ-UI SF scores, age, duration of problems, body mass index (BMI), number of births, menopause, and diabetes, Spearman's rank correlation was used and the correlation coefficients were then interpreted following the guidelines proposed by Cohen [34], a small correlation being 0.1–0.3, medium 0.3–0.5, and large 0.5–1.0.

Before the analysis was performed, descriptive statistics were used to describe the sample. All data analyses were performed using IBM SPSS Statistics for Windows, Version 22.0, Armonk, New York, with $p < 0.05$ as statistically significant.

5. Results of the Clinical Study

The patients' ages were between 42 and 92 (median 72) years. The demographics of the study sample are presented in Table 7, and descriptive statistics of the pre- and post-treatment ICIQ-UI SF scores according to UI are presented in Table 8. The study included 46.7% (35) patients with MUI, 22.6% (17) patients with SUI, and 30.7% (23) patients with UUI. Furthermore, post-treatment scores were lower than pre-treatment scores in all cases; that is, the median of pre-treatment ICIQ-UI SF scores was 16.0 for MUI (IQR: 14.0–17.0), 10.0 for SUI (IQR: 9.5–15.0), and 16.0 for UUI (IQR: 9.5–15.0), whereas the median of post-treatment ICIQ-UI SF scores was 11.0 for MUI (IQR: 9.0–16.0), 8.0 for SUI (IQR: 6.0–10.5), and 11.0 for UUI (IQR: 8.0–14.0).

Table 7. Participants' demographics.

Variable	UI Type		
	MUI (*n* = 35)	**SUI (*n* = 17)**	**UUI (*n* = 23)**
Age (years) Median IQR (Q1–Q3)	 73.0 15.0 (14.0–17.0)	 63.0 21.0 (14.0–17.0)	 73.0 12.0 (14.0–17.0)
Duration of problems (years) Median IQR (Q1–Q3)	 6.0 7.0 (3.0–10.0)	 6.0 19.5 (3.0–22.5)	 5.0 8.0 (2.0–10.0)
BMI (kg/m^2) Median IQR (Q1–Q3)	 25.7 10.3 (21.6–31.9)	 23.6 4.0 (22.3–26.3)	 26.0 7.4 (24.2–31.6)
Menopause (% yes)	30 (85.7)	13 (76.5)	21 (92.9)
Diabetes (% yes)	1 (2.9)	0 (0.0)	5 (20.0)
Previous gynecological surgeries (% yes)	16 (45.7)	5 (27.8)	11 (48.0)

Table 8. Descriptive statistics for pre- and post-treatment of ICIQ-UI SF scores by UI type.

Variable	UI Type		
	MUI (*n* = 35)	**SUI (*n* = 17)**	**UUI (*n* = 23)**
Pre-treatment (ICIQ-UI SF score)			
Median	16.0	10.0	16.0
IQR (Q1–Q3)	3.0 (14.0–17.0)	5.5 (9.5–15.0)	3.0 (13.0–16.0)
Post-treatment (ICIQ-UI SF score)			
Median	11.0	8.0	11.0
IQR (Q1–Q3)	7.0 (9.0–16.0)	4.5 (6.0–10.5)	6.0 (8.0–14.0)

To evaluate the efficacy of MS, the primary outcome of interest was considered as the change in the total score on the International Consultation on Incontinence Questionnaire (ICIQ-UI SF) score. The ICIQ-UI SF score clearly decreased following treatment of MUI, SUI, and UUI.

5.1. Differences between Pre- and Post-Treatment Assessment of ICIQ-UI SF Scores by UI Type

The results of the two-way mixed ANOVA showed that there was a significant main effect of UI type ($F(1, 75) = 5.593$, $p = 0.005$, $\eta p = 0.13$) on pre- and post-treatment assessment of ICIQ-UI SF scores. This effect indicates that pre- and post-treatment assessment of ICIQ-UI SF scores differed by UI type.

In addition, there was a significant main effect of the pre- and post-treatment assessment of the ICIQ-UI SF scores ($F(1, 75) = 102.14$, $p < 0.005$ $\eta p = 0.577$). This effect indicates that, if ignoring the patient's UI type, the post-treatment assessment of the ICIQ-UI SF score was significantly lower (M = 10.56, SE = 0.46, 95% CI [13.18, 14.85]) compared to pre-treatment scores (M = 14.01 SE = 0.42, 95% CI [9.64, 11.48]).

Moreover, Figure 2 (i.e., the profile plot of the two-way mixed model ANOVA marginal means) shows that the effect of the pre- and post-treatment assessment of the ICIQ-UI SF scores depended on the UI type. Looking at the three lines, there is a decrease in the post-assessment ICIQ-UI SF scores for all UI types. Further, looking between the lines (i.e., comparing UI types for pre- and post-treatment assessment of ICIQ-UI SF scores) shows that, among patients by UI type, compared to the pre-treatment assessment of ICIQ-UI SF scores, SUI had the greatest decrease in the post-treatment assessment of ICIQ-UI SF scores.

The two-way mixed ANOVA test was significant, and another question raised was which UI types differ from one another in the pre- and post-treatment assessment of ICIQ-UI SF scores. Answering this requires testing the differences between all pairs of UI. Therefore, we employed pairwise comparisons for the main effect of UI type corrected using Bonferroni adjustments. The results showed a significant difference ($p < 0.01$) between MUI and SUI and between SUI and UUI, but not between MUI and UUI ($p > 0.05$).

As predicted, patients with the MUI type had lower improvement in their post-test ICIQ-UI SF score compared to SUI ($p = 0.006$), and those with UUI had lower improvement in their post-test ICIQ-UI SF score compared to SUI ($p = 0.024$).

5.2. Correlation between Pre- and Post-Treatment Assessment ICIQ-UI SF Scores by UI Type

The Spearman rank correlation was also calculated between participants' demographics and pre- and post-treatment assessment of ICIQ-UI SF scores by UI type. There was only a moderate statistically significant correlation between BMI and the post-treatment assessment of ICIQ-UI SF scores for the MUI type (rs = 0.416, $p = 0.01$) and a moderate statistically significant correlation between BMI and the post-treatment assessment of ICIQ-UI SF scores for the UUI type (rs = 0.415, $p = 0.04$).

The correlation was also assessed between intensity, improvement (difference between pre- and post-treatment assessment of ICIQ-UI SF scores), and BMI. Only a medium positive

correlation was found between intensity and BMI, which was statistically significant, with rs = 0.277, $p = 0.014$, which means that a higher intensity is associated with a higher BMI.

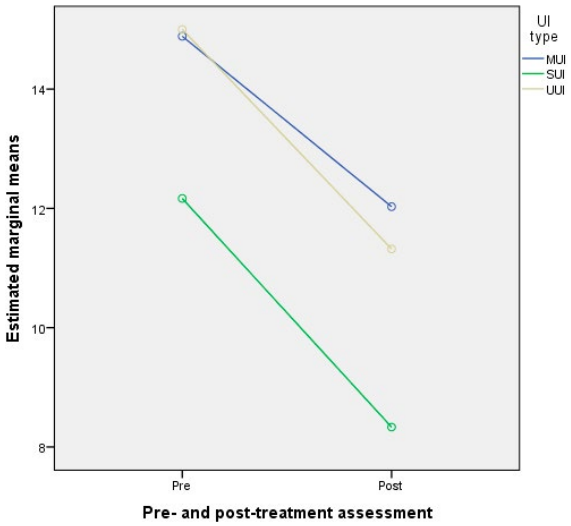

Figure 2. Profile plot of the two-way mixed model ANOVA marginal means of pre- and post-treatment assessment of ICIQ-UI SF scores. Abbreviations: MUI—mixed urinary incontinence, SUI—stress urinary incontinence, UUI—urgency urinary incontinence.

6. Discussion

The aim of this study was to assess and analyze the effectiveness of MS in the treatment of female urinary incontinence. On the basis of the results, it can be observed that UI improved after treatment with MS. The ICIQ-UI SF score improved in patients regardless of the type of UI. However, the greatest decrease in the post-treatment assessment of the ICIQ-UI SF score was among patients with SUI. Moreover, the results also showed that UI type had a statistically significant effect on the post-treatment score of both MUI and SUI but not on UUI.

We treated patients three times a week for 4 weeks, with 10 sessions altogether. Galloway et al. [12] reported that patients were treated twice a week for 6 weeks and MS significantly improved SUI. Yamanishi et al. [35] reported that MS of the pelvic floor twice weekly for 5 weeks significantly improved SUI as well as UUI. In another study, Yokoyama et al. [36] treated female patients twice a week for 8 weeks with the same results. The same ameliorating results were found by Özengin et al. [25], who compared three different treatment methods for SUI: MS, EMG biofeedback, and PFMT. In that study, a statistically significant improvement in PFMT activity was noted in all three treatment groups, with no statistical differences between groups. They concluded that MS is a highly user-friendly modality for the conservative treatment of female UI. In the most recent study on this topic, Silantyeva et al. [26] examined the effectiveness of MS versus electrostimulation after short-term therapy (10 sessions) in postpartum women of childbearing age who had had a vaginal delivery in the previous 6 months. In addition to the subjective evaluation, a 3D ultrasound was used to objectively evaluate and later compare the PFM anatomy and integrity. The results showed a statistically significant improvement in both subjective and objective parameters, regardless of the type of treatment; however, the results were superior in the group that underwent MS therapy. The authors attribute this to the ability of the magnetic field to penetrate deep into pelvic tissues and therefore uniformly activate PFM, whereas electrical stimulators lose a major portion of the energy released on the tissue surface and the PMF are activated with a smaller intensity.

Essentially, each study in the review and the conclusion of the prospective study had a limitation of sorts. For clarifying the impact on the extent of amelioration after therapy with MS, the parameters of stimulation should be unified with regard to timeframe, impulse intensity, and follow-up tracking. Among the limitations, the most common were a relatively small study sample, which significantly decreases the statistical relevance of the study, and the lack of long-term evaluation of the patients. Only five studies [20–24,32] included a control group, and six of them [20,21,23,25,26,30,32] did not have clear treatment protocols, refined study parameters, and/or objective instruments or measurements to evaluate the results. Furthermore, the potential placebo effect of the sham stimulators was not analyzed in any study.

There are also some limitations to the analysis that should be considered when interpreting these results. First, and perhaps most important, our sample was non-randomized. Although this non-probability sampling method is the most applicable and widely- used method in clinical research [37], the sampling method does not guarantee equal chances for each subject in the target, it is less representative of the target population, and it decreases the ability to draw completely impartial conclusions about MS effectiveness. Second, the power of our study was low, as well as the power of most studies in our systematic review (Table 2). An ideal study is one that has high power. This means that the study has a high chance of detecting a difference between groups if it exists, and consequently, if the study demonstrates no difference between groups, the researcher can be reasonably confident in concluding that none exist. According to the literature review, the ideal power for any study is considered to be 80% [38]. For our study to achieve a significance level of 95% and a power of 80%, the sample size should equal 189; in our study, the sample size of 76 accounted for a power of 57% [39]. This means that our study had low power, and studies with lower power increase the likelihood that a statistically significant finding represents a false positive result. Future studies may address all of the above limitations and test the robustness of these results on an extended environment. One limitation could also be that our study included only the ICIQ-UI SF as the tool for measuring the effectiveness of MS in the treatment of UI. However, this questionnaire is the only available validated questionnaire in Slovenian [33]. We are convinced that patient-reported outcomes are the most appropriate when describing treatment success or failure. As we also concluded in the systematic review, we are aware that outcome measurements to generate comparable data should be standardized.

Nevertheless, we assume that this method of treatment has future potential. Last but not least, the population is aging and increasingly more patients are seeking more user-friendly treatment modalities and avoiding surgeries. Behavioral therapy and all the efforts to educate patients and encourage successful management strategies and guarding techniques will serve to promote optimal outcomes and achieve durable benefits [9,12,40–42]. We must be aware that, beyond technical parameters, the improvement of QoL after MS treatment is undoubtedly associated with social predictors (e.g., age, sex, rural living, number of household members, and financial problems) and not only clinical predictors (e.g., disease severity, disability, disease duration, motor impairment, depressive symptoms, complications of therapy, and gait impairment). The success of treatment varies according to the severity of the muscle weakness before treatment. The same statement and conclusions were drawn by Lim et al. [20], who noticed the lack of randomized, sham-controlled trials and the lack of recommendations on the use of MS for the conservative treatment of female UI.

7. Conclusions

Regardless of the limitations of and variations between the studies examined here, some universal conclusions can be drawn. Namely, MS is a non-invasive treatment method that effectively and safely improves quality of life by promoting urinary continence in women that experience refractory UI. These patients, who are perhaps not motivated to perform regular PFM strengthening exercises, can be conservatively treated. The results

after MS treatment show a reduction in the number of daily leakages and pad usage, and therefore a reduced number of incontinence episodes. This is a painless and comfortable method, with good compliance by patients. Additional advantages include no side effects, no need to undress, and automatic contractions.

We conclude that future studies are necessary, all of which should include a large sample size, a control group, an optimal research protocol, pre-treatment analyses, standardization, and longer follow-ups. Relevant conclusions, which could be drawn only from a well-performed study with longer observation periods and cost-benefit analysis, would have a major impact on defining the applicability of MS and standardizing its use in clinical practice as a widespread, non-invasive treatment method for patients with mild to moderate SUI and eventually for other types of UI.

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Institutional Review Board Statement: The study was approved by the Slovenian Medical Ethics Committee (no. 0120-370/2016-2, NMEC 77/07/16; approved on 5 October 2016). The confidentiality of personal data was ensured following the principle of good clinical data protection practice, and in line with the Declaration of Helsinki and the Slovenian Code of Medical Ethics and Deontology.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are openly available with the author.

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Nº 2

Magnetic stimulation in the treatment of female urgency urinary incontinence: a systematic review

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REVIEW ARTICLE

Magnetic stimulation in the treatment of female urgency urinary incontinence: a systematic review

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Abstract

Introduction and hypothesis This systematic review analyzes published studies about magnetic stimulation (MS) treatment for UUI and determines whether this treatment is effective and non-invasive.

Methods A systematic literature search was conducted using PubMed, the Cochrane Library, and Embase. The international standard for reporting results of systematic reviews and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was used to guide the methodology of this systematic review. The key search terms were as follows: "magnetic stimulation" and "urinary incontinence." We limited the time frame to articles published from 1998, when the FDA approved MS as a conservative treatment option for UI. The last search was performed on 5 August 2022.

Results Two authors independently reviewed 234 article titles and abstracts, of which only 5 fitted the inclusion criteria. All 5 studies included women with UUI, but every study had different diagnostic and entry criteria for patients. They also differed in their treatment regimens and methodological approaches to assessing the efficacy of treating UUI with MS, which made it impossible to compare the results. Nonetheless, all five studies established that MS is an effective and non-invasive way of treating UUI.

Conclusions The systematic literature review led to the conclusion that MS is an effective and conservative way of treating UUI. Despite this, literature in this area is lacking. Further randomized controlled trials are needed, with standardized entry criteria, UUI diagnostics, MS programs, and standardized protocols to measure the efficacy of MS in UUI treatment, with a longer follow-up period for post-treatment patients.

Keywords Magnetic stimulation · Urinary incontinence · Urgency urinary incontinence

Introduction

Urinary incontinence (UI) is a common health, hygiene, social, societal, and economic problem [1]. Since 2002, UI has been defined by the International Continence Society (ICS) as any involuntary leakage of urine [2].

Urinary incontinence is differentiated according to the underlying pathophysiological mechanisms and is divided into the most common types: stress (SUI), urgency (UUI), mixed (MUI), and "overflow" UI [2]. This paper focuses on UUI, which is defined by the ICS as the involuntary leakage of urine through the urethra that occurs with the sensation of a sudden strong urge to urinate (i.e., urgency). UUI can be part of a larger syndrome called overactive bladder syndrome (OAB), which consists of urinary urgency, increased frequency of urination, and nocturia, with or without UUI, and without urinary tract infection or other pathological conditions [3]. When OAB is associated with UUI, it is referred to as UUI. According to EUA guidelines, a thorough baseline assessment should be carried out to classify the type and severity of symptoms and elucidate any signs of UI, associated POP, concomitant UTI, current anticholinergic burden, associated neurological dysfunction, or genitourinary symptoms of menopause [4].

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Conservative approaches to UUI treatment include extracorporeal magnetic stimulation (MS), which was approved by the FDA as a treatment option for UUI as early as 1998 [5]. MS is widely offered as a treatment for UI, although weak evidence of the short-term and long-term effects has been found in systematic reviews (SRs). Moreover, current EUA recommendations from 2020 advise not offering magnetic stimulation in the treatment of UI or OAB (strength of recommendation = strong) [6].

The mechanical principle of UI therapy with MS is mostly based on Faraday's law of induction. All the nerves, especially the muscle nerves of weakened and non-active muscles, which are the cause of UI problems, can be represented as a conductor in an alternating magnetic field. This is why the electrical current is induced on all the nerves that are located in the alternating magnetic field created by the MS device. The induced current on the nerves causes the activation of weakened or damaged muscle fibers via the sodium/potassium pump (Na^+/K^+-ATPase) enzyme. In the case of UUI, afferent branches of the pudendal nerve are stimulated by the alternating magnetic field to inhibit the detrusor muscle through central reflexes. Simultaneously, the efferent nerve branches are also stimulated to facilitate strengthening of the pelvic floor muscles and increase the tonus of the urethral sphincters, thereby inhibiting the detrusor muscle through the guarding reflex. Because the nerves that transmit the signal from the brain to the muscle and the nerves that transmit the signal from the muscle to the brain are simultaneously affected by the alternating magnetic field (MS) produced, we achieve a better and stronger signal on a natural biofeedback (nerve) loop, directly affecting all the nerves and muscles inside the magnetic field produced, thereby having a beneficial effect on treating the UUI problems [5, 7–10].

Treatment options for UUI are limited because both UUI and OAB are chronic conditions that vary in frequency and intensity of symptoms and signs over the course of a person's life. Therefore, a multi-stage approach to treatment is needed, because a complete cure is rare, but symptom relief can be expected. This is why MS may have a place in the treatment of UUI.

To demonstrate the prevalence of the issues stated above, a systematic literature review was conducted. The review was carried out to point out the role of magnetic stimulation in the treatment of female UUI and to comprehensively evaluate the studies of the efficacy of magnetic stimulation as a treatment of UUI. We were particularly interested in the methodological approach used by the authors in designing research on the treatment of UUI with MS. Three SRs of the literature on the efficacy of MS have been published in recent years, but all of them focused on UI in general rather than on the efficacy of MS in a specific subtype of UI (SUI, UUI, or MUI), or they devoted only a small part of the review to this topic [11–13].

Materials and methods

The aim of this SR was to analyze published studies on MS treatment for UUI. The following research questions (Q) were addressed through the systematic literature review:

Q1. Do the authors report statistically significant results in improving UUI with MS?
Q2. Which methods are used for monitoring the efficacy of the MS therapy?
Q3. Did the authors follow EUA guidelines for initial diagnostics of UUI?
Q4. What are the limitations of the studies reviewed?
Q5. What is the length of follow-up?

All the research questions are addressed in this article.

The international standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to guide the methodology of this SR [14]. A systematic literature search was conducted using PubMed, the Cochrane Library, and Embase. The key search terms were "magnetic stimulation" and "urinary incontinence." We reviewed all research articles in English published since 1998 (no upper limit). We limited the time frame to articles published since 1998, when the FDA approved MS as a conservative treatment option for UI. The last search was performed on 5 August 2022. It should also be noted that this article focuses only on research articles; to our knowledge, no volume or book chapter relies on empirical work regarding the efficacy of MS in a particular UI subtype.

We identified the potentially relevant research articles by examining the abstracts or articles as a whole. Titles and/or abstracts of the studies retrieved using this search strategy and those from additional sources were screened independently by two review authors to identify studies that potentially met the inclusion criteria of this SR. We only included studies focusing on women diagnosed with UUI, in which an MS stimulator was built into a chair, and with the full text available in English. We emphasize that we wanted to include only studies with patients with UUI and not patients with full-spectrum OAB. Nonetheless, we excluded studies that did not separate the results for women and men, treated other types of UI, or used other types of MS devices (a coin, electrode, etc.), and for which the full text was not available in English. We also excluded SR, meta-analyses, clinical cases, and editors' comments. The full texts of these potentially eligible articles were retrieved and independently assessed for eligibility by two other review team members. The PRISMA flowchart and search strategy are summarized in Fig. 1. Any disagreement between the readers regarding the eligibility of particular articles was resolved through discussion with a third (external) reviewer. Two authors independently

extracted data from articles about study characteristics and outcomes. Any discrepancies were identified and resolved through discussion (with a third external reviewer where necessary). A systematic literature review was peer-reviewed by experts in the field (urogynecology consultants A.L. and M.B.) to ensure that the methods used in the review were appropriate and that the conclusions are supported by the evidence. Nevertheless, based on the literature, we followed several methods to assess the quality of our systematic literature review and the studies included; that is, we used some common methods: in addition to the PRISMA checklist, the methodological quality of the reviews included was assessed using the AMSTAR2 (A Measurement Tool to Assess Systematic Reviews) quality assessment tool, which showed moderate quality of the studies included. Moreover, we used NHLBI Study Quality Assessment Tools in order to assess the quality of the studies included [15–17]. This SR was registered in PROSPERO (no. CRD42022351055).

Results

A total of 234 titles and abstracts were reviewed, and 211 articles did not meet inclusion criteria shown in Table 1. Furthermore, articles in which the authors included patients with UUI (different UI subtypes included, including UUI), but no separate analysis of MS success in patients with UUI was performed, were excluded. In the end, five articles that met the inclusion criteria were identified. They are presented in Table 1.

The study conducted by Yamanishi et al. was a randomized, sham-controlled trial, but the other four were prospective studies without control groups [11, 18–21]. All five studies included women with UUI, but each study used different diagnostic procedures and entry criteria for patients.

Table 1 shows that each study diagnosed UUI in a different way. Chandi et al. simply used patient histories. Yamanishi et al. added urinalysis and bladder diaries, and Lukanović et al. used all of these in addition to the ICIQ-UI SF questionnaire, which is the only one validated in Slovenian [11,

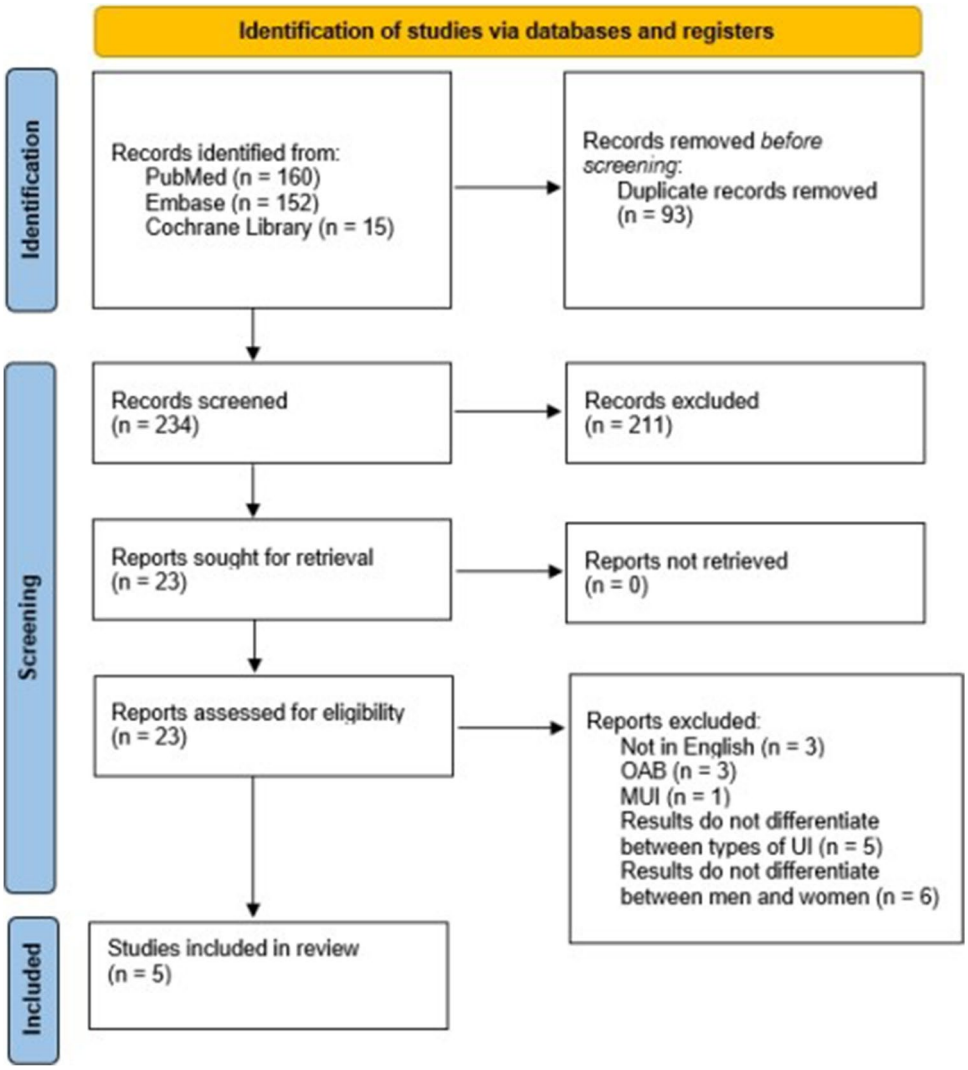

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. *OAB* overactive bladder, *MUI* mixed urinary incontinence, *UI* urinary incontinence)

Table 1 Overview of studies included in this systematic review

Reference	Type of study	Equipment used	UUI patients (*n*)	Control group	Treatment regimen	UUI diagnostic methods	Methods for assessing therapy efficacy	Results (statistically significant)	Length of post-treatment follow-up	Limitations
Ünsal et al. [21]	Prospective	Neotonus Inc., (Marietta, GA, USA)	17	No	20 min MS (10 min at 5 Hz, 10 min at 10 Hz) twice a week, 8 weeks	Gynecological history and status; bladder ultrasound; urinalysis; urodynamic measurements	Three-day bladder diary; pad test; urodynamic measurements; recovery (no UI); improvement (frequency of incontinence episodes reduced by more than 50%)	Increased FDV and MCC; fewer incontinence episodes in 24 h; 3. Reduced number of daily voids	12 months	No control group; small sample size
Chandi et al. [18]	Prospective	NeoControl (Neotonus Inc., Marietta, GA, USA)	12	No	21 min MS (2 × 10 min at 10 Hz, 1-min break in between) twice a week, 8 weeks	History	Bladder diary; urodynamic measurements; pad test (at the end); VAS 5; recovery (<3 g of urine in 24-h pad test); improvement (50% or greater reduction in incontinence episodes or more than 50% fewer daily voids)	Reduced number of daily voids; less urine loss in 24-h pad test; lower VAS score	–	No control group; small sample size; no monitoring of efficacy duration after completion of therapy
Doğanay et al. [19]	Prospective	Neotonus Inc., (Marietta, GA, USA)	69	No	20 min MS (10 min at 5 Hz, 1–5 min rest, 10 min at 50 Hz) twice a week, 8 weeks	N/A	Five-day bladder diary; urodynamic measurements; I-QOL questionnaire; VAS; improvement (reduced frequency of incontinence episodes by more than 50%); recovery (no incontinence episodes)	Increased FDV and MCC; improved I-QOL results	36 months	No control group
Yamanishi et al. [20]	Multicenter, randomized, sham controlled	SMN.X (Nihon Kohden Corp., Tokyo, Japan)	151	Yes	25 min MS at 10 Hz twice a week, 6 weeks	Urinalysis; bladder diary; history	Bladder diary; OABSS questionnaire; IPSS QOL questionnaire	Reduced number of incontinence episodes per week; reduced number of voids per day; increased urine volume per void; lower IPSS QOL values	–	No urodynamic measurements; no monitoring of efficacy duration after completion of therapy

Table 1 (continued)

Reference	Type of study	Equipment used	UUI patients (*n*)	Control group	Treatment regimen	UUI diagnostic methods	Methods for assessing therapy efficacy	Results (statistically significant)	Length of post-treatment follow-up	Limitations
Lukanović et al. [11]	Prospective	Iskra Medical Magneto STYM (Iskra Medical d. o. o., Ljubljana, Slovenia)	23	No	20 min MS at 10 Hz every other working day for 4 weeks up to a total of 10 sessions	History and status; bladder diary; urinalysis; ICIQ-UI SF questionnaire	ICIQ-UI SF questionnaire	Lower ICIQ-UI SF values	–	No control group; no urodynamic measurements; no monitoring of efficacy duration after completion of therapy

UUI urgency urinary incontinence, *MS* magnetic stimulation, *UI* urinary incontinence, *FDV* first desire to void, *MCC* maximum cystometric capacity, *I-QOL* incontinence quality of life, *VAS* visual analog scale, *IPSS QOL* International Prostate Symptom Score-QoL index, *OABSS* Overactive Bladder Symptom Score, *ICIQ-UI SF* International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

18, 20]. Ünsal et al. also used bladder ultrasound and urodynamic measurements [21]. Doğanay et al. did not especially emphasize the diagnosis of UUI [19]. The European Association of Urology (EAU) recommends that the diagnostics of treated patients should include history and status, suitable validated questionnaires, at least 3 days' bladder diary, and urinalysis in order to rule out lower urinary tract infections. Urodynamic measurements are not indicated in uncomplicated forms of UI, because they do not affect the outcome of conservative treatment and often lead to invasive procedures [6].

Treatment regimens also differed between the clinical studies. Lukanović et al. decided on the least therapy; that is, ten sessions. Doğanay et al., Chandi et al., and Ünsal et al. selected the most sessions, that is, 16. Yamanishi et al. settled on 12 sessions [11, 18–21]. Only Lukanović et al. offered therapy every other working day; the other studies carried out therapy twice a week [11, 18–21]. The duration was relatively similar, ranging from 20 to 25 min. The magnetic field pulsation frequency also varied. Yamanishi et al., Chandi et al., and Lukanović et al. used stimulation at 10 Hz for the entire duration of therapy [11, 18, 20]. Ünsal et al. used 10 min of stimulation at 5 Hz and 10 min at 10 Hz, whereas Doğanay et al. used 10 min at 5 Hz and the other 10 min at 50 Hz [19, 21].

The studies used different criteria to determine treatment efficacy. For their main criteria, Ünsal et al. used bladder diaries, pad tests, and urodynamic measurements. All the tests showed statistically significant improvement 1 year after completing therapy. Using their definition of recovery, 6 patients (40%) were UUI symptom-free after 1 year [21]. Chandi et al. also chose to use urodynamic measurements, bladder diaries, and pad tests. They also added the visual analog scale (VAS) to assess patients' satisfaction with therapy. The VAS values were statistically significantly higher, which indicated subjective UUI symptom improvement in participants. Significant reductions were seen in the pad tests and void frequency, whereas the urodynamic measurements did not show improvement. They argued that this could result from using pulsed magnetic fields at frequencies that are not effective for treating UUI [18]. Doğanay et al. used bladder diaries, urodynamic measurements, and the VAS for patients' subjective assessment of therapy efficacy. They also added the Incontinence Quality of Life (I-QOL) questionnaire. Using their definition of recovery (Table 1), 40 (58%) patients recovered and 18 (26%) improved. Their urodynamic parameters increased significantly, as did their quality of life (QoL). After 6 months, symptoms recurred in 53% of patients [19]. Yamanishi et al. monitored treatment efficacy with bladder diaries, the Overactive Bladder Symptom Score questionnaire (OABSS), and the International Prostate Symptom Score QoL (IPSS QOL) index. Patients were randomized into treatment and control (sham

treatment) groups by age, number of incontinence episodes at the start of the bladder diary, previous treatment attempts, and the centers where the treatments were carried out. In the bladder diaries, the number of incontinence episodes per week in the treatment group compared with the control group decreased significantly (p=0.038), as did the number of episodes of voiding urgency in 24 h (p = 0.011). A statistically significant increase in the treatment group compared with the control group was also seen in the average volume of urine excreted per void. The treatment group also had a significant drop in the average number of points on the IPSS QOL index (p=0.035). The average number of points on the OABSS questionnaire in the treatment group compared with the control (sham treatment) group did not significantly decrease (p=0.057) [22]. Lukanović et al. used the ICIQ-UI SF as their main tool for monitoring therapy efficacy. Their study included not only patients with UUI but also patients with SUI and MUI, and so separate analyses were conducted for each type. They established that the symptoms and signs of UUI improved following MS therapy. The ICIQ-UI SF results improved, regardless of patients' UI subtype, but the best improvements in ICIQ-UI SF results were in patients with SUI. Moreover, the results show that the UI subtype had a statistically significant impact on treatment assessment in both MUI and SUI, but not UUI [11].

Table 1 presents the limitations of each study. Only Yamanishi et al. used a control group [20]. Only Doğanay et al. and Yamanishi et al. had trial samples of more than 25 patients [19, 20]. Doğanay et al. monitored therapy efficacy for 36 months, and Ünsal et al. for only 12 months [19, 21]. The others did not carry out long-term follow-up [11, 18, 20].

Discussion

Magnetic stimulation is a method approved by the FDA as a conservative approach to treating UI, which is not believed to cause serious side effects. According to the EAU guidelines, MS is still not recommended as a treatment method owing to the lack of methodologically sound studies that scientifically evaluate findings on the efficacy and long-term effects of the treatment [4].

The systematic literature review from 1998 onward revealed only five published studies that analyzed the efficacy of MS treatment for UUI, ranging from 2003 to 2019. Only Yamanishi et al. conducted a randomized, controlled trial (RCT), but this study did show a statistically significant difference in the efficacy of MS treatment for UUI between the treatment and control (sham treatment) groups. The number of incontinence episodes per week was lower, as was the number of daily voids, and the QoL improved. The other studies had similar conclusions. Their results confirmed that MS is an effective and non-invasive way to treat UUI [11, 18–21].

Answering the research questions posed here leads to further discussion and joint conclusions. Each of the studies reviewed has its limitations, which are presented in Table 1 and are the answer to Q4. These limitations should be considered when interpreting the results published in the studies. First, and perhaps most importantly, most samples, except for the study by Yamanishi et al., were nonrandomized [20]. Although this nonprobability sampling method is the most applicable and widely used method in clinical research, the sampling method does not guarantee equal chances for each subject in the target, it is less representative of the target population, and it decreases the ability to draw completely impartial conclusions about the effectiveness of MS [22]. Second, the power of most studies in our SR was low (Table 1). An ideal study is one that has high power. This means that the study has a high chance of detecting a difference between groups if it exists, and consequently, if the study demonstrates no difference between groups, the researcher can be reasonably confident in concluding that none exists. According to the literature review, the ideal power for any study is considered 80%. For example, for the study by Lukanović et al. [11], to achieve a significance level of 95% and a power of 80%, the sample size should equal 189 [23, 24]. Only the study by Yamanishi et al. included more than 100 patients; precisely 151 [11, 20]. This means that all other studies in our SR had low power, and studies with lower power increase the likelihood that a statistically significant finding represents a false-positive result.

The studies used various means of monitoring the treatment efficacy (Q2). These results cannot be directly compared with one another even though the results, which were statistically analyzed, did indicate successful treatment of UUI with MS (Q1). As early as 1998, the International Consultation on Incontinence (ICI) and EAU recommend five domains of interest that should be reported in research studies, including patient observations, quantification of symptoms, clinician observations (anatomical, functional, compliance), QoL, and socioeconomic outcomes. Unfortunately, none of the studies reviewed reported all five domains. However, according to the last report by the EUA, questionnaires should be validated for the language in which they are being used and demonstrated to be sensitive to change [4, 25]. For example, only ICIQ-SF as a patient questionnaire for UI is available as a validated questionnaire in Slovenian, which makes it impossible for smaller countries to equally and objectively participate in measuring outcomes according to the guidelines mentioned above [26]. Moreover, there is no evidence to indicate whether the use of QoL or condition-specific questionnaires has an impact on the outcome of treatment. Therefore, it would be necessary to standardize monitoring of the efficacy of MS treatment for UUI, which would allow direct comparison between studies

and define the appropriate time frame for monitoring therapy efficacy (Q5).

Single-arm clinical studies by Doğanay et al. have shown that the effects of MS continued for about a year post-treatment, but efficacy progressively diminished and came close to baseline at the 2nd and 3rd year after treatment [19]. The only RCT included in our review has no follow-up, which makes the long-term efficacy of MS for UI questionable [20].

In reviewing the studies, we found considerable variability in patient characteristics and data collected. The SR of these studies shows that it is necessary to standardize the entry criteria (Q3) and the diagnosis of UUI (Q3).

Further adding to our quandary are the poorly standardized MS protocols. To clarify the impact on the extent of amelioration after therapy with MS, the stimulation parameters should be unified with regard to time frame, impulse intensity, and follow-up tracking. A specific therapy program for different types of UI is usually suggested by producers and based on previous experience. To date, the optimal frequency and pulse duration have not yet been established, although a higher dose of 50 Hz has been reported to be the dose required to achieve good pelvic floor contraction for the treatment of SUI, and a lower dose of 10–20 Hz is required for UUI [5, 11, 13]. Moreover, the number of treatment sessions and session frequency have not been established either, which might be potential confounders contributing to the heterogeneity in studies.

In evaluating the safety of MS, most patients generally tolerated treatment well. However, this safety profile should be interpreted with caution owing to the small sample sizes of the studies included and possible under-reporting of adverse events.

This review has several strengths and weaknesses. No meta-analysis was really performed because the studies were clinically diverse, and therefore a meta-analysis may give biased results and genuine differences in effects may be obscured. A particularly important type of diversity is in the comparisons being made by the primary studies. Furthermore, the lack of a control group can limit the validity of the meta-analysis, and, as mentioned above, only one study (by Yamanishi et al.) was an RCT. For this reason, the results are presented as a narrative review with clinical outcomes. With a comprehensive search strategy, using two main repositories, we ensured that no article on our topic was neglected. We have attempted to systematically and clearly display all outcomes analyzed; however, we did not include studies that analyze the entire spectrum of OAB because we wanted to focus exclusively on UUI. Our SR was designed as a single-arm study, and so we could not compare MS therapy with other therapeutic methods.

We are aware that, considering the lack of studies of consistent RCT data for MS in UUI, further trials are warranted, and a longer follow-up period will provide more evidence to validate the effects of MS treatment. However, taking into account the limitations of our SR, the main results from the studies analyzed confirmed that MS is effective in the treatment of UUI. Another potential limitation of our SR could be that only articles published in English were included.

According to the conclusions in the studies reviewed, MS is a simple form of treatment that can help many UUI patients from the medical, social, and also financial perspective. Because it is non-invasive, it could be used as a treatment approach at the primary level of urogynecological treatment and would thus reduce the number of unnecessary invasive treatments. When adherence to "healthy habits for a healthy bladder" (behavioral therapy) proves ineffective, MS could be the next step in UUI treatment. According to the literature, the MS treatment method does not cause the patient stress because this type of treatment is comfortable, safe, and relatively painless [7, 20].

Conclusion

This systematic literature review concludes that MS has been demonstrated to be an effective way of treating UUI that could represent part of a tiered treatment plan for UUI. Given the drawbacks of other conservative treatments, such as the side effects of pharmacotherapy and the invasiveness of electrostimulation, vaginal cones, botulinum toxin A injections, percutaneous stimulation of the posterior tibial nerve, and sacral nerve stimulation, further research on MS is warranted, considering its inherent advantages: non-invasive nature, no need to undress, patient acceptability, automatic contractions, and minimal adverse effects. In addition, the SR process offers advantages such as being comprehensive, objective, evidence-based, and transparent. These findings suggest that MS is a viable and promising treatment option for women with UUI. Taking into account all the limitations of the published studies, which were discussed in the previous section, and the answers to our research questions, it can be established that there are various methodological approaches to determining the efficacy of treating UUI with MS. Further clinical studies are needed, especially randomized control trials with comparable and relevant outcomes, as well as standardized protocols for measuring the efficacy of MS as a conservative form of UUI treatment. It must be emphasized that studies with a longer follow-up after completing MS therapy are needed. These would offer data on the long-term efficacy of MS treatment for UUI. Furthermore, patients and clinicians need more data about possible adverse events and a cost-effectiveness analysis, which will give them the opportunity to make informed choices supported by evidence.

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Declarations

Conflicts of interest None.

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Nº 3

Efficacy of 3 Tesla Functional Magnetic Stimulation for the Treatment of Female Urinary Incontinence

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Article

Efficacy of 3 Tesla Functional Magnetic Stimulation for the Treatment of Female Urinary Incontinence

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Abstract: Functional magnetic stimulation (FMS) is a new technique for the conservative treatment of Urinary incontinence (UI), based on magnetic induction. It induces controlled depolarization of the nerves, resulting in pelvic muscle contraction and sacral S2-S4 roots neuromodulation. The aim of this study was to assess the efficacy of the new 3 Tesla FMS chair, both in patients with pure stress urinary incontinence (SUI) and in women with pure overactive bladder (OAB) symptoms. A prospective observational study was conducted in our urogynaecologic unit. All the patients involved were consecutive women with pure SUI or pure OAB symptoms treated by a 3 Tesla electromagnetic chair. The primary outcome was a subjective outcome evaluation by the PGI-I Scale and a patient-satisfaction scale. The secondary outcome was the change score of the UDI-6, IIQ-7, ICIQ-SF and OAB-q SF questionnaires from baseline to final visit. At 2 months follow-up, 28 out of 60 patients (47%) with SUI symptoms and 20 out of 40 patients (50%) with OAB symptoms declared themselves cured. Considering cured and improved patients, the subjective cure rates were 68.3% (41/60) and 70% (28/40) for patients with SUI and OAB symptoms, respectively. The results of this study showed that the 3 Tesla electromagnetic chair may be an effective option for the treatment of UI.

Keywords: functional magnetic stimulation; extracorporeal magnetic innervation; chair; female urinary incontinence; stress urinary incontinence; overactive bladder

1. Introduction

Urinary incontinence (UI) is a common health problem with a negative impact on female quality of life (QoL). The prevalence of UI in the female population is variable. In the literature, it has been reported to be as high as 55%, and the trend increases with aging [1–3]. The guidelines of the leading urological and urogynaecological societies recommend pelvic floor muscle training (PFMT) as the first-line treatment for different types of UI [4]. In the last years, new technologies and applications, such as electrical stimulation, radiofrequency, laser therapy and pulsed magnetic stimulation, have been introduced in this field as an alternative or in addition to classical rehabilitation.

FMS is a technique based on Faraday's law of magnetic induction, approved by the United States Food and Drug Administration (FDA) in 1998, for stimulating the central and

peripheral nervous system [5,6]. It generates electrical activity, which induces controlled depolarization of the nerves, resulting in pelvic muscle contraction and sacral S2-S4 roots neuromodulation [5]. For this peculiarity, it has been applied for the treatment of all types of UI. In addition, the setting (patient sitting on a chair with clothes) and the lack of direct activation of skin sensory receptors and C-fibres, which can cause pain and discomfort, make this procedure more comfortable than conventional electrical stimulation [5,7]. However, few studies in the literature have assessed the efficacy of this device on female UI treatment, with different protocols and different outcome measures [8]. Furthermore, the devices used developed dissimilar magnetic field power up to a maximum of 2.5 Tesla. Similar to PFM and Electric Functional Stimulation, the FMS chair could be an effective and safe procedure in all types of incontinence, with high patient acceptance. Patients were seated comfortably in the chair and fully clothed. This feature is an advantage, especially for the elderly population.

The aim of this study is to assess the efficacy of the new 3 Tesla electromagnetic chair stimulation in patients with stress urinary incontinence (SUI) and overactive bladder (OAB) symptoms.

2. Materials and Methods

This is a prospective study performed in our urogynaecological unit, namely the EOC—Beata Vergine Hospital, Mendrisio, Switzerland, between January 2020 and September 2021. We enrolled all consecutive women who complained of pure SUI and OAB symptoms according to the International Urogynecological Association (IUGA)/International Continence Society (ICS) terminology for Female Pelvic Floor Dysfunctions [9], for at least 3 months. Exclusion criteria were as follows: pregnancy, implanted pacemaker or cardioverter defibrillator, implants made of ferromagnetic metal at or near the site of stimulation, clinically significant voiding dysfunction, postvoid residual volume >100 mL, previous pelvic surgery for the treatment of pelvic organ prolapse (POP) or of UI, neurological diseases, mixed urinary incontinence (MUI) symptoms, pelvic organ prolapse quantification (POPQ) $\geq$ stage II, documented recurrent urinary tract infections, and previous pharmacological treatment for OAB during the last 3 months.

At the initial visit, patients underwent medical history collection, physical examination, urine laboratory analyses and post-void bladder ultrasound. A stress test was performed in the lithotomy and upright positions with a full bladder (ultrasonographic measurement > 300 mL). All women also completed the following questionnaires before and after treatment: Urogenital Distress Inventory Short Form (UDI-6), Incontinence Impact Questionnaire Short Form (IIQ-7), International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), and OAB-questionnaire Short Form (OAB-q SF).

All patients deemed eligible for the treatment were scheduled for 3 Tesla electromagnetic chair (FMS Tesla Care ®, Iskra Medical d.o.o., Ljubljana, Slovenia).

It is based on Faraday's law of magnetic induction, whereby a time-varying magnetic field induces electrical activity that depolarizes the nerves and causes the pelvic floor muscles to contract or relax. Repeated activation of the terminal motor nerve fibres and the motor end plates tend to build muscle strength and endurance [8,10]. The main stimulation targets are the afferent branches of the pudendal nerve to inhibit the detrusor muscle through central reflexes and the efferent nerve branches to facilitate strengthening of the pelvic floor muscles and increase the tonus of the urethral sphincters, thereby inhibiting the detrusor muscle through the guarding reflex [10].

The FMS treatment was administered for 20 min per session, twice per week for a total of 8 weeks. We used specific therapy program for different types of UI as suggested by producers and based on previous experiences [8] (Table 1). During the treatment session, the electric impulse intensity was adjustable according to the patient's tolerance.

Table 1. FMS Tesla Care® chair program for different type of UI.

Programs	Frequency (Hz)	Time (s)	Pulsed Time (μs)	Active Time (s)	Passive Time (s)	Therapy Time (min)
SUI	35	12	300	6	6	30
OAB	10	12	250	6	6	30

Hz: Hertz; s: seconds; min: minutes.

Before and during treatment, physiotherapists with specialized training in pelvic floor dysfunctions followed these patients. The primary outcome was subjective outcomes evaluation. All women completed the Patients Global Impression of Improvement (PGI-I) Scale [11], and a patient-satisfaction scale (a single, self-answered, Likert-type scale of 0–10 that grades the patient's degree of satisfaction regarding continence: 0 represents "not satisfied", and 10, "satisfied") [12]. Subjective success was indicated both by "very much improved or much improved" (PGI-I $\leq$ 2) and by a patient-satisfaction score $\geq$ 8, while subjective improvement was indicated both by "minimally improved" (PGI-I $\leq$ 3) and by a patient-satisfaction score $\geq$ 7. The secondary outcome was the change score of the UDI-6, IIQ-7, ICIQ-SF and OAB-q SF questionnaires from baseline to final visit. The Declaration of Helsinki was followed, and pretreatment written informed consent for the FMS procedure was obtained from all the patients in this observational prospective evaluation. The study does not require ethical/institutional review board approval because normal clinical practices have been followed [13].

3. Statistical Analysis

Statistical analysis was performed with IBM-SPSS v.17 for Windows (IBM Corp, Armonk, NY, USA). Descriptive statistics were used to describe basic patients' characteristics. Non-parametric paired samples test was used to compare results before and after FMS treatment. Pearson's correlation was used to perform the correlation analysis. A p value < 0.05 was used to define statistical significance. The Cox proportional hazards model was used for univariate analysis to evaluate factors potentially affecting the risk of failure during the study period. Statistical significance was considered achieved when $p < 0.05$.

4. Results

One hundred consecutive women (60 with pure SUI and 40 with OAB symptoms), who fulfilled the inclusion criteria, had undergone FMS treatment, were considered. Baseline patients characteristics are summarized in Table 2. No statistically significant differences were found between the study groups.

At 2 months follow-up (16 treatments), all patients were available for evaluation. No patients were lost to follow-up. No adverse effects have been reported.

Twenty-eight out of sixty patients (47%) with SUI symptoms and 20 out of 40 patients (50%) with OAB symptoms declared themselves cured. Considering cured and improved patients, the subjective cure rates were 68.3% (41/60) and 70% (28/40) for patients with SUI and OAB symptoms, respectively. No statistically significant differences were found between the study groups (Table 3).

Furthermore, statistically significant differences were found between patients' reported outcomes pre- and post-procedure. Post-treatment questionnaires scores were lower than pre-treatment scores for both SUI and OAB symptoms (Table 4).

Table 2. Baseline patients characteristics.

Patients Characteristics	SUI (60)	OAB (40)	*p* Value
Age, yr, median, (IQR)	52 (52–63)	63 (63–72)	0.06
BMI, kg/m^2, median, (IQR)	26 (26–29)	29 (29–30)	0.23
Menopausal, no. (%)	24 (48)	25 (83.3)	0.05
HRT, no. (%)	4 (8)	4 (13.3)	0.71
Previous vaginal deliveries, median, (IQR)	1 (1–3)	2 (1–3)	0.88
Macrosome, ≥4000 g, no. (%)	2 (4)	5 (16.7)	0.11
Operative delivery, vacuum/forceps, no. (%)	3 (6)	5 (16.7)	0.22
Cesarean delivery, no. (%)	4 (8)	2 (6.7)	1.00
Recurrent Urinary Tract Infection, no. (%)	4 (8)	2 (6.7)	1.00

IQR: Interquartile Range; BMI: Body Mass Index; HRT: Hormonal Raplacement Therapy.

Table 3. Cure and Improvement rate at 2 months follow-up.

Patients Symptoms	Cure Rate % (*n*/*n*)	Cure and Improvement Rate % (*n*/*n*)
SUI	47 (28/60)	68.3 (41/60)
OAB	50 (20/40)	70 (28/40)
	p value 0.84	*p* value 1.00

n: number.

Table 4. Changes in patients reported outcomes at 2 months follow-up.

Questionnaire	SUI Pre (m/IQR)	SUI Post (m/IQR)	*p* Value **	OAB Pre (m/IQR)	OAB Post (m/IQR)	*p* Value **
ICI-Q SF	9 (9–14)	5 (5–8)	0.001	11 (10–13)	6 (6–9)	0.001
UDI-6 SF	46 (46–54)	41 (41–46)	0.001	50 (50–54)	38 (38–42)	0.001
IIQ-7 SF	17 (17–24)	6 (5–17)	0.001	17 (17–33)	11 (11–17)	0.001
OAB-q SF	-	-		48 (28–55)	38 (38–53)	0.001

m: median; IQR: interquartile range. ** Pearson's chi-squared test.

Figures 1 and 2 displays pre- and post-treatment changes for SUI and OAB symptoms.

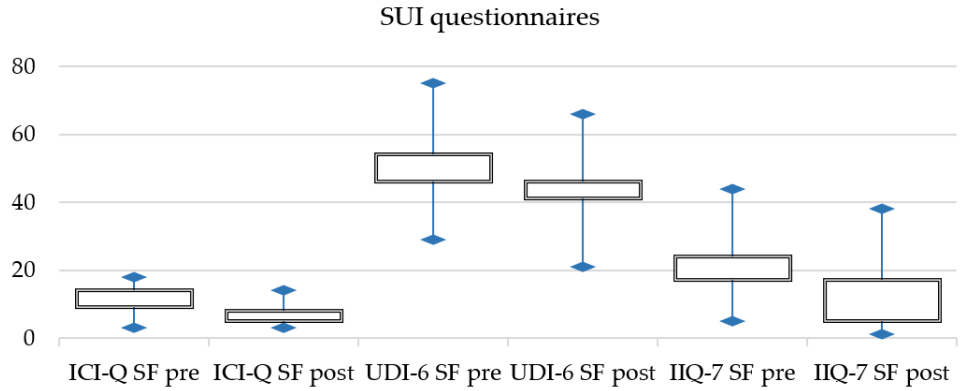

Figure 1. SUI changes in patients reported outcomes.

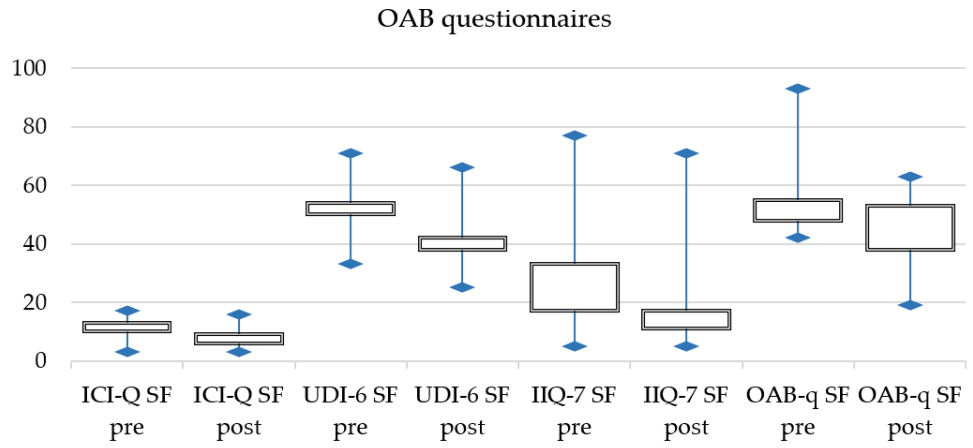

Figure 2. OAB changes in patients reported outcomes.

Tables 5 and 6 reports univariable analysis of factor potentially involved in the risk of FMS failure for SUI and OAB symptoms respectively. We did not find any risk factor statistically associated with the FMS failure.

Table 5. Univariable analyses of variables potentially involved in the risk of FMS failure for SUI.

Characteristics	Cured (n = 28)	Not Cured (n = 32)	p Value **
Age, year, median (IQR)	49 (33–63)	55 (45.5–67)	0.21
Menopause, n (%)	15 (53.5)	14 (43.7)	0.60
BMI, kg/m^2, median (IQR)	24.7 (21.8–30.1)	24.6 (24.28–27.5)	0.72
UDI-6 SF pre, median (IQR)	45.8 (41–56)	47.9 (43.7–54)	0.89
ICIQ-SF pre, median (IQR)	10 (7–14)	12.5 (7–14.5)	0.71
IIQ-7 SF pre, median (IQR)	16.5 (0–30)	22 (11–38.2)	0.25

IQR: interquartile range. ** Univariate Cox proportional hazards model.

Table 6. Univariable analyses of variables potentially involved in the risk of FMS failure for OAB.

Characteristics	Cured (n = 20)	Not Cured (n = 20)	p Value **
Age, year, median (IQR)	56 (53–73)	67.5 (51.5–73)	0.66
Menopause, n (%)	5 (25)	3 (15)	0.69
BMI, kg/m^2, median (IQR)	24.8 (24–29)	29.3 (23.8–31.35)	0.86
UDI-6 SF pre, median (IQR)	50 (44–62)	45.8 (41.6–60)	0.45
ICIQ-SF pre, median (IQR)	10 (8–15.5)	10 (3.5–15)	0.36
IIQ-7 SF pre, median (IQR)	16.5 (5.5–49.5)	16.5 (14–58)	0.79
OAB-q SF pre, median (IQR)	52 (48–67)	46 (37.5–74)	0.78

IQR: interquartile range. ** Univariate Cox proportional hazards model

5. Discussion

The present study, to the best of our knowledge, evaluated for the first time in the literature, the subjective outcomes of the 3 Tesla functional magnetic chair device in women with UI. We found that FMS might be an effective and safe procedure in patients who complain of both SUI and OAB symptoms. Subjective cure rates were found in 47% and 50% of patients with SUI and OAB, respectively. In addition, when we consider the rate of improvement, the effectiveness is higher, 68.3% for patients with SUI and 70% for patients with OAB symptoms.

Although the US FDA has approved extracorporeal FMS for UI treatment since 1998, few studies in the literature have assessed the efficacy of safety for this procedure. Lukanovi'c et al. [8], in a recent systematic review on the effectiveness of magnetic stimulation in the treatment of UI, which included articles published between 2010 and 2020,

showed that only 12 studies were eligible. These studies, which have mainly considered patients with SUI, used different devices with various magnetic field power (up to a maximum of 2.5 Tesla), different diagnostic methods to define the type and severity of UI and different tools to evaluate outcomes (standardized questionnaires are sometimes used).

In addition, the authors reported the results of their clinical prospective non-randomized experience for 82 patients with UI, treated with FMS and assessed by a standardized ICIQ-UI SF questionnaire. They found an improvement in terms of UI and ICIQ-UI SF score after treatment, regardless of UI type, especially in women with SUI.

Changes in UI by ICIQ-SF and changes in the number of pads used per day, were also used by Samuels et al. [14] to evaluate 75 women with all types of UI. The average improvement of 49.93% in ICIQ-SF score was observed after the sixth treatment, which further increased to 64.42% at follow-up. The highest level of improvement was reached in patients suffering from MUI (69.90%). Furthermore, a highly significant medium correlation ($r = 0.53$, $p < 0.001$) was found between the ICIQ-SF score improvement and the reduction in pad usage.

Weber-Rajek et al. [15], in a randomized controlled trial, compared 40 women who underwent 12 sessions of pelvic floor muscle training (PFMT) with 37 women who received 12 sessions of extracorporeal magnetic innervation for SUI symptoms. In both groups, a statistically significant decline in depressive symptoms and an improvement in UI and quality of life were found.

Another comparative study of three different treatment methods for SUI:FMS, Electromyographic (EMG) biofeedback and PFMT by Özengin et al. [16] showed that all methods were effective of increasing pelvic flooor muscle (PFM) strength. This reduced UI symptoms and improved Qol.

Doğanay et al. [17], in a prospective study, evaluated long-term effects of extracorporeal magnetic innervations (ExMI) on 68 women with SUI and 69 women with urge incontinence. At 6 months after 16 sessions of ExMI, 32 (47%) patients with SUI were totally dry in a negative stress test, and 27 (39%) showed improvement in the frequency of daily leak episodes from 3.2 times to 1.2 times. In the urge incontinence group, 40 (58%) patients were dry, and 18 (26%) significantly improved the average number of incontinence episodes decreased from 3.7 times to 1.7 times per day. However, beneficial effects are temporary, and there is high recurrence rate (53% at 6 months).

Our study seems to show that the 3 Tesla FMS chair can be associated with excellent subjective satisfaction not only in SUI patients, but also in those with OAB symptoms. The higher cure and improvement rate found in these patients could be related to higher magnetic power than previous devices analysed in literature. Moreover, our electromagnetic chair has two magnetic field generators placed on the seat and on the back, which are powered and controlled by an external power supply. The second (back) generator makes it easier for sacral S–S4 roots neuromodulation, which could explain the positive effect on OAB symptoms.

Further points of strength include: (1) a highly homogeneous study population with the exclusion of women with mixed incontinence, (2) a clinical evaluation performed in all patients, (3) the subjective outcomes evaluation using four standardized questionnaires, and (4) no patients were lost to follow-up.

We acknowledge that the weaknesses of this study could be (1) the limited sample size, (2) the lack of objective evaluation, and (3) the lack of randomization and/or control group. However, we also emphasize that no studies in the literature have assessed 3 Tesla devices thus far, no larger investigations evaluated both SUI and OAB symptoms, and few studies used standardized questionnaires.

6. Conclusions

The results of this study showed that the 3 Tesla electromagnetic chair (FMS Tesla Care, Iskra Medical®) may be an effective option for the treatment of SUI and OAB symptoms, with great patient acceptance and no side effects.

The treatment is painless, and the patients were seated comfortably on the chair fully clothed. This characteristic represents an advantage, especially for elderly population.

Author Contributions: Conceptualization, A.B.; methodology, A.B.; software, A.B. and M.S.; formal analysis, A.B. and M.S.; data curation, A.B. and F.C.; writing—original draft preparation, A.B. and F.C.; writing—review and editing, A.B. and M.S.; visualization, G.C., L.R. and C.S.; supervision, A.P., M.T., F.G. and S.S.; project administration, A.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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Nº 4

High-power Magnetotherapy: A New Weapon in Urinary Incontinence?

LUTS LOWER URINARY TRACT SYMPTOMS

LUTS (2017)

ORIGINAL ARTICLE

High-power Magnetotherapy: A New Weapon in Urinary Incontinence?

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Objective: Urinary incontinence (UI) is one of the most common urinary system diseases that mostly affects women but also men. We evaluated the therapeutic efficacy of functional magnetic stimulation (FMS) as potential UI treatment with improvements in the pelvic floor musculature, urodynamic tests and quality of life.
Methods: A total of 20 UI patients (10 females and 10 men, mean age 64, 14 years), including 10 with stress UI, four with urgency UI and six with mixed UI, were treated with FMS (20 min/session) twice a week for 3 weeks. The patients' impressions, records in urinary diaries, and scores of three life stress questionnaires (overactive bladder symptom questionnaire [OAB-q], urogenital distress inventory questionnaire-short form [UDI-6], incontinence impact questionnaire-short form [IIQ-7]) were performed pre- and post-treatment.
Results: Significant reductions ($P < 0.01$) of micturition number and nocturia after magnetic treatment were evidenced. The urodynamic tests recorded a significant increase in cystometric capacity ($147 \pm 51.3\%$), in maximum urethral closure pressure ($110 \pm 34\%$), in urethral functional length ($99.8 \pm 51.8\%$), and in pressure transmission ratio ($147 \pm 51.3\%$) values compared with the baseline values.
Conclusions: These preliminary findings suggest that FMS with Magneto STYM (twice weekly for 3 weeks) improves the UI and may be an effective treatment for this urogenital disease.

Key words frequency, magnetic stimulation, pressure, stress, urinary incontinence

1. INTRODUCTION

Urinary incontinence (UI) is a common urogenital disease, defined as the involuntary leakage of urine in the absence of a detrusor contraction, usually due to the weakness of the urethral sphincter and pelvic floor.[1] The main symptoms are: reduced ''warning time'' of the need to void with consequently increased frequency and reduced volume voided per micturition, with the potential to result in nocturia.[2] According to the International Continence Society (ICS), the UI affects more than 200 million people worldwide, and mainly women (55%) rather than men.[3] This number may be an underestimate, because up to half of women may fail to report UI probably due to embarrassment, lack of knowledge about treatment options, or a conviction that UI is a normal inevitable part of aging.[4]

This pathological condition has a negative impact on the quality of life of patients and can also affect men and is primarily caused by urethral sphincteric deficiency after radical prostatectomy.[5]

UI can be categorized in: (i) urethral underactivity (stress UI) that accounted from 29 to 75% of the women;[6,7] (ii) bladder overactivity (urgency UI), that accounted for 7–33% of the total population (22% of women vs 2.6% of men);[8–11] (iii) a combination of the two previous types (mixed UI), that accounted from 14 to 61% of the population.[2,12]

The management of UI includes restoration of continence, reduction of the number of UI episodes, and prevention of complications (e.g. pressure ulcers).

New and emerging therapies aim to improve the overall efficacy compared with existing therapies (behavioral, pharmacological, surgical therapies), while minimizing adverse effects/complications, improving tolerability, and reducing invasiveness (Table 1).

Several clinical studies have focused on developing novel, non-invasive techniques to treat the UI, including magnetic stimulation and there have been reported improvements of the urinary symptoms (e.g. reduction

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TABLE 1. Treatment types of UI

	Behavioral therapy	Pharmacologic therapy	Physical therapy	Surgical therapy
Stress UI	Pelvic floor muscle training (PFMT)	Injectable bulking agents		Mid-urethral slings, autologous pubovaginal slings, retropubic suspensions (for women); sling, artificial urethral sphincter (for men)
Urge UI	Lifestyle modifications, timed voiding, bladder retraining	Antimuscarinics agents; Beta-3 agonists	Posterior tibial nerve stimulation (PTNS); sacral neuromodulation	
Mixed UI	PFMT	Alpha blockers; 5-alpha reductase inhibitors (for men)	Sacral neuromodulation	Bladder outlet procedures (e.g. transurethral resection of prostate)

in frequency of leakage, urodynamic improvement, maximum bladder capacity) with no side-effects.[13–20]

There are several types of magnetic stimulation, including extracorporeal magnetic stimulation (ExMS) mainly used for urgency UI, functional magnetic stimulation (FMS) for stress and mixed UI. The action mechanism is the same for both types: the magnetic therapy stimulates both central and peripheral nerve pathways in the pelvis;[21]and induces a flow of ions, at the tissue level, establishing electrical eddy currents that can lead to membrane depolarization, consequently causing the pelvic floor muscles to contract and reducing UI.[22]

The aim of this study has been to investigate the effectiveness of FMS as potential UI treatment with improvements in the pelvic floor musculature, urodynamic tests and quality of life of patients who consulted our ''Second Opinion Medical Network'' (Modena, Italy) for the evaluation of their urinary symptoms.

The ''Second Opinion Medical Network'' is a consultation referral web and Medical Office System recruiting each time a wide panel of real time available specialists, to whom any patient affected by different diseases not adequately satisfied in terms of diagnosis and treatment can apply for an individual clinical audit.[23] Most of the patients, in fact, often wander around the web jumping into the medical Web-sites, looking for proper answers to their health problems, but this screening becomes often obsessive and compulsive, and frequently misleading, ending into the ''Web Babel Syndrome (a doctor-patient communication gap that especially dealing with multiple synchronous pathologies, copes with heterogeneous and misleading information/advice, with the impending risk of confused, contradictory statements and prescriptions).[24,25] To face this problem, the ''Second Opinion Network'' aims to be a useful problem-solving support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognosis, but also to avoid un-necessary investigational procedures, undue unhelpful and expensive medical and surgical treatments.[26]

2. METHODS

The anecdotic an retrospective observational study enrolled 20 patients (10 males and 10 females, age 38–82 years) who visited the ''Second Opinion Medical Network'' (Modena, Italy) as new patients for their UI: 10 patients (50%) with stress UI, 4 (20%) with urgency UI, 6 (30%) with mixed UI (Table 2).

TABLE 2. Clinical characteristics of patients

Number patients	20
Mean age (years)	64.14
Menopause	6
SUI	10
Urgency UI	4
Mixed UI	6
Mean duration of symptoms (years)	2.9

Fig. 1 Patient (women, 66 aa) with Urge Urinary Incontinence in treatment (first session) with Functional Magnetic Stimulator-Magneto STYM. [Colour figure can be viewed at wileyonlinelibrary.com].

The specific inclusion criteria are: (i) clinical urinary signs reported by participant and confirmed further by its medical record; (ii) UI history of at least 6 months, (iii) no history of surgery or hormone replacement therapy for UI treatment. All the patients provided written informed consent before participation and detailed personal history, age, previous diseases, urinary diary (number of leaks per day, frequency of micturition, nocturia), physical examination, urinalysis and urodynamic evaluation, including cystometric capacity (intravesical volume at which the patient has a normal, strong desire to void), maximum urethral closure pressure -MUCP- (pressure in

the urethra keeping the urethra closed over the baseline bladder pressure), functional urethral length (length of the urethra over which the urethral pressure exceeds baseline bladder pressure), pressure transmission ratio-PTR- (ratio between urethral pressure spikes and bladder pressure spikes); in order to define the UI type. The study excluded the patients wearing a cardiac pacemaker or other implanted metallic pacemaker, or implanted metallic instrument such as urethral stent, and women who were pregnant or suspected of being pregnant.

The device used was a functional magnetic stimulator -Magneto STYM- (Iskra Medical [Stegne 23, 1000 Ljubljana, Slovenia]) including the magnetic coil that was positioned beneath the sitting bottom of the chair. During the treatment, each patient was instructed to sit on the seat so that the perineum was positioned at the centre of the coil and so that the patient would feel the muscle contraction (contraction of the pelvic floor and sphincter muscles) during stimulation (Fig. 1).

The patients underwent 20 min/session, twice a week for 3 weeks (six sessions total).

Stimulation intensity (max 2 Tesla) was gradually increased, by the clinician, up to the limit of tolerability as indicated by the patient (average 15–30% of the maximum). While stimulation frequency was fixed at 10 Hz for 10 min, and at 35 Hz for another 10 min, with a rest period (active time and pause time) of 6 sec, respectively. The control unit displayed the status, the pulse generation and the possibility for external communication via a modem.

The efficacy of the FMS was evaluated by the patients' impressions, records in urinary diaries, urodynamic tests (performed in the same manner before and after treatment) and scores of three life stress questionnaires administered pre and post-treatment: (i) Overactive bladder symptom questionnaire (OAB-q): comprises 33 items divided into coping, concern, sleep, social interaction, and total health-related quality of life subscales, during the past week, and it is scored on a five-point scale (0 for ''not at all'', 1 for ''a little bit'', 2 for ''some what'', 3 for ''quite a bit'', 4 for ''a great deal'', 5 for ''a very great deal'');[27] (ii) Urogenital distress inventory questionnaire-short form (UDI-6): comprises seven questions on urine leakage and urgency symptoms over the last 3 months, with a scale of 0–3 (0 for ''not at all'', 1 for ''slightly'', 2 for ''moderately'', and 3 for ''greatly'');[28]and (iii) Incontinence impact questionnaire-short form (IIQ-7): comprises seven questions to assess the adverse effects of UI in terms of physical activities, household chores, recreation, travelling, social activities, emotional health and the feeling of frustration. The average, which ranges from 0 to 3 (0 for ''not at all'', 1 for ''slightly'', 2 for ''moderately'', and 3 for ''greatly'') is multiplied by $33 \times 1/3$ to put scores on a scale of 0–100.[29]

The statistical analysis was evaluated using Mann–Whitney test (continuous variables not normally distributed) and χ^2 test (categorical variables). A commonly-used measure of linear correlation, the Pearson correlation coefficient, denoted by r, was reported. Statistical significance was set at *P*-value less than 0.05, and all data and graphics were analyzed using the R software, version 3.1.2.[30]

3. RESULTS

The mean age of the patients was 64.14 ± 13.61 years. The changes in UI status were evaluated by comparing urodynamic tests and life stress scores before FMS and at 3 weeks after treatment (Tables 2–4).The patients noticed significant reductions of micturition number and nocturia after FMS ($P < 0.01$).

The urodynamic tests recorded a significant increase in cystometric capacity ($147 \pm 51.3\%$), in MUCP ($110 \pm 34\%$), in urethral functional length ($99.8 \pm 51.8\%$), and in PTR ($147 \pm 51.3\%$) values compared with the baseline values (Fig. 2).

The urodynamic testing values that decreased with bladder filling or when the UI patients assuming an upright posture, were increased after 3 weeks of treatment: maximum urethral closure pressure increased in all the stress UI patients, bladder capacity at first desire to void and maximum cystometric capacity significantly increased in four urgency UI patients after stimulation ($P < 0.01$).

4. DISCUSSION

Several studies have evidenced that FMS affects UI through the large fiber somatic nerve and afferent neural pathway: it induces a magnetic current in the autonomic and somatic nervous systems, innervating the lower urinary tract in a manner similar to that of electrical stimulation, and improves bladder hyperreflexia by desensitizing C-afferent fibers and reducing *c-fos* gene expression.[31] Indeed, Yamanishi and co-workers studied the urodynamic effects of FMS on urethral closure in healthy volunteers and concluded that this technique significantly increased the maximum intraurethral and urethral closure pressure after stimulation: pulsed electromagnetic fields (PEMFs) generated by a coil penetrate deep into the pelvic floor, to reach the relevant conductive tissues, and induce a flow of ions to propagate electromagnetic currents.[16] Voltage gradient ensues, and membrane depolarization occurs in the pelvic floor that leads to pelvic floor nerve stimulation (stimulation of motor end plates) and to pelvic floor muscle contraction.[32] Further, Galloway et al.[13] developed a pulsed magnetic device for pelvic floor muscle strengthening in the UI treatment and confirmed a significant reduction in the frequency of leakage episodes and detrusor instability.

Several reports confirmed also the long-term post-treatment duration of therapeutic effect.[17,33] For instance, Yokoyama and co-workers reported that 17/20 patients with urgency UI reduced their urinary symptoms with FMS, and that 9 of 17 patients (53%) maintained improvements until 24 weeks after the last treatment.[17] In the present study, all of the patients who did not need to undress for the treatment underwent a six-session FMS protocol, showing a significant improvement in symptom scales compared with the baseline values and this effect

TABLE 3. Urodynamic testing results (median values) pre and post-treatment

Urodynamic exams	Pre-treatment	Post-treatment	*P*-value
Cystometric capacity (normal values 300–600 mL)	200 (IQR [145.75–239.25])	419 (IQR [383–429])	<0.01
Maximum urethral closure pressure (MUCP) (normal values ≥30 cm H_2O)	21 (IQR [16.75–22.25])	41 (IQR [38.75–42.25])	<0.01
Urethral functional length (normal values 3.5–5.25 cm)	2.25 (IQR [1.9–2.5])	4.4 (IQR [3.68–4.93])	<0.01
Pressure transmission ratio (PTR) (normal values ≥100%)	48 (IQR [40–56])	118 (IQR [109–125])	<0.01

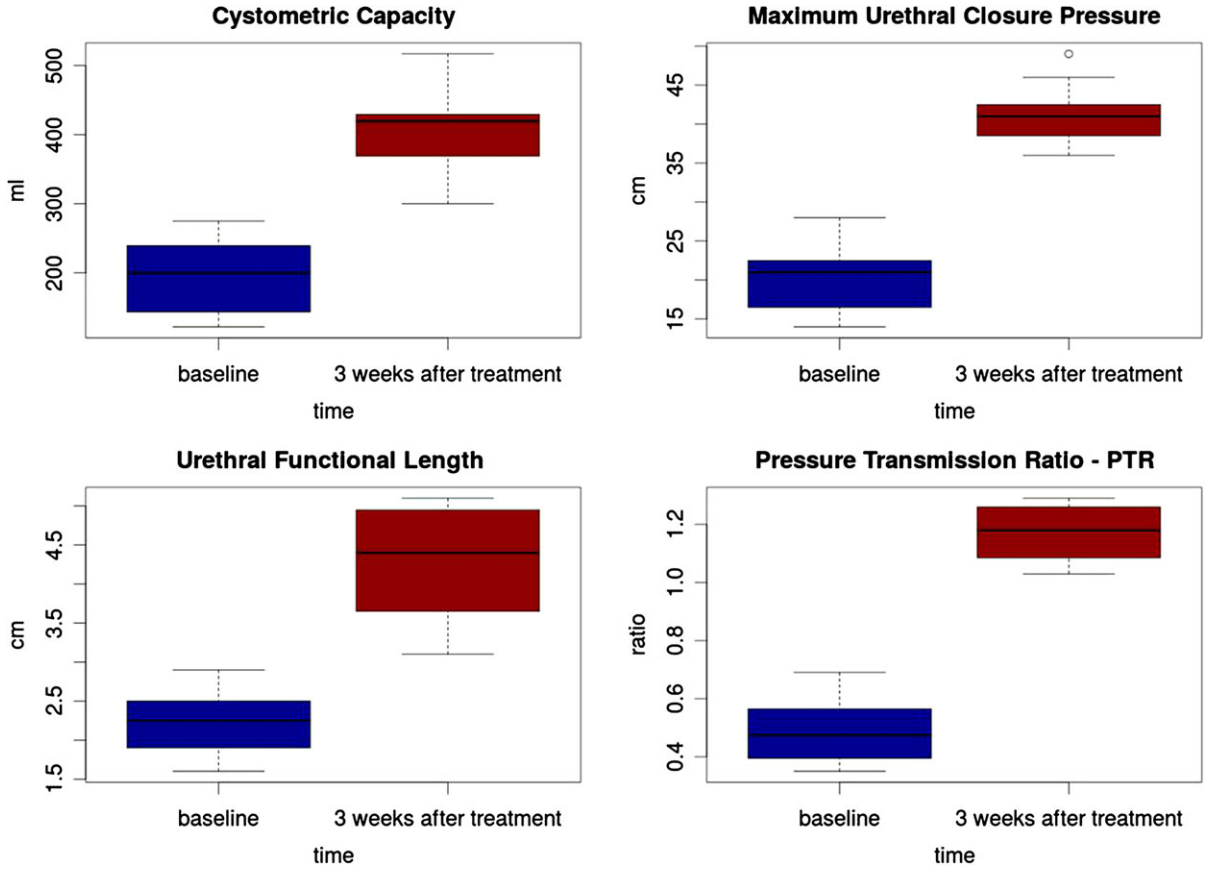

Fig. 2 Graphic illustration of Urodynamic testing results (median values and *P*-value), including cystometric capacity, maximum urethral closure pressure (MUCP), urethral functional length, and pressure transmission rate (PTR), of all the patients pre-and post-functional magnetic treatment. [Colour figure can be viewed at wileyonlinelibrary.com].

TABLE 4. Life stress questionnaires scores (median values) pre and post-treatment

Questionnaire type	Baseline (pre-treatment)	3 weeks (post-treatment)	*P*-value
OAB-q	4 (IQR [3–4.25])	1 (IQR [0.75–2])	<0.01
UDI-6	3 (IQR [2–3])	0 (IQR [0–0.25])	<0.01
IIQ-7	22 (IQR [22–33])	5.5 (IQR [0–11])	<0.01

persisted until the follow-up visit at week 6. However, the therapeutic effect could be maintained for a considerably long time after discontinuation of treatment, as confirmed by the follow-up questionnaire (by post) which revealed that urodynamic improvement and maximum bladder capacity was maintained in all of the patients without any additional pharmacological therapy. This may show a ''re-education effect'' of FMS, as showed by Suzuki et al.,[33] but it could be necessary to perform a longer follow-up study in a greater number of patients in order to verify the therapeutic efficacy of FMS, including the duration of its re-education effect. Regarding the safety of the treatment, no adverse effects due to FMS were noted in this study, as confirmed by Yamanishi and co-workers in the recent multicenter, randomized, sham-controlled study; they did record severe adverse events and observed that the number of leaks/week in bladder diary, as well as the voided volume and in the number of urgency/24 h, were all significantly reduced in 101 women with urgency UI.[34]

However, these data confirm the safety, non-invasiveness and painlessness of FMS compared to electrical stimulation which has side-effects, such as abdominal cramp, diarrhea, pain, and bleeding.[35]

5. CONCLUSION

Our preliminary study suggests that FMS with MagnetoSTYM (twice weekly for 3 weeks) has significant advantages (no reported adverse effects, unnecessary to undress, automatic contractions and no pain), improves the UI and may be an effective treatment for this urogenital disease.

Nevertheless, further investigation of the optimal stimulation parameters, and standardization protocol is required to optimize therapeutic treatment.

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DISCLOSURE

No competing financial interests exist.

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Nº 5

Treatment of Uncontrolled Urine Leakage Problems

TREATMENT OF UNCONTROLLED URINE LEAKAGE PROBLEMS

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1. Introduction

Undesired, uncontrolled leakage of urine, referred to as urinary incontinence, occurs when the sphincter muscles, the muscles of the pelvic floor and bladder muscles do not work properly and consistently [1]. It is a common and embarrassing problem affecting males and females of all ages. Urinary incontinence is more common with women, of which according to the expert estimations 40% are suffering from it. 33% of them are under the age of 40 and 50% are over the age of 60 [2]. During pregnancy, 60% of women have problems with uncontrolled urine leakage; after childbirth 52% of them remain incontinent [3]. 76% of people consider urinary incontinence a normal disorder related to aging. However, people with urine leakage problems often feel ashamed and begin to avoid social life, retreating to solitude. A particular problem is also urine leakage during the sexual relation, which can lead to rejection of the partner and gradual alienation. These people rarely talk about their urine leakage problems, hide it from their close ones and often also from their doctors. This is why only a few people seek professional help on time [4].

However, a timely initiation of treatment before mild and moderate incontinence progresses to severe problem is extremely important. The success of the timely treatment with non-invasive methods is more efficient and sustainable [5]. With non-invasive methods it is possible to treat stress, urge and mixed urinary incontinence. The goal of the treatment is to strengthen the pelvic floor muscles and decrease the detrusor activity, what contribute to urine control. Consequently, the surgical treatment can be avoided or at least postponed for several years.

Stress urinary incontinence occurs during periods of increased intra-abdominal pressure, when the intravesical pressure rises higher than the pressure that the urethral closure mechanism can withstand, and urine loss results. Urine most often leaks during coughing, sneezing, lifting loads, jogging, skipping and other activities. The main causes are weakened pelvic floor muscles and connective tissues, which impede the bladder neck urine control function. Stress urinary incontinence is most common form of urinary incontinence.

Major risk factors for the weakness of the pelvic floor muscles in women are pregnancy and childbirth. Urine leakage can also appear after gynecological and urological operations (after a prostatectomy in men), due to neurological disorders or aging. Tissue and muscular structures of the pelvic floor muscles can be damaged with hard physical

work or chronic cough, chronic closure and excessive straining, which cause excessive pressure in the lower urinary tract and pelvic floor. If these adverse effects are pronounced and prolonged, the position of the bladder can change, causing urinary incontinence, and involuntary passage of feces and winds can occur as well.

Urge urinary incontinence is a consequence of an overactive bladder. The urine leaks after previous urgent need to urinate. The patient must go to the bathroom more than eight times a day and because of the need to urinate they also get up several times per night. Problems often occur on the way to the bathroom, listening to running water or during work with cold water. It is the most common form of urine incontinence in older women.

A large number of women, especially older patients, are faced with a combination of stress and urge incontinence, the so-called mixed urinary incontinence.

Strong pelvic floor muscles can withstand the increased pressure in the abdominal cavity and effectively participate in the retention of urine and feces. They also contribute to the stability of the spine and pelvic girdle. Last but not least they are important for the sexual experience. Pelvic floor muscles can be strengthened with intensive exercises for the pelvic floor muscles (Kegel exercises). With these exercises the urinary incontinence can be treated and even prevented. It is important that the exercises are performed continuously over lifetime (three sessions per day, 15-20 times per session) and correctly, i.e., the right muscles are strained in the right way. Although nearly all gynecologists are familiar with these exercises, they rarely are thought and used properly. Therefore, exercises based on this approach are not only disappointing in their results, but can also train women to become dysfunctional voiders.

There exists a possibility for a faster regeneration of muscles and other tissues of the pelvic floor with functional magnetic stimulation (Functional Magnetic Therapy). This therapy can replace and upgrade electro-stimulation used so far. With the use of magnetic stimulation stronger pelvic floor muscles can be achieved in three to four weeks. The therapy is carried out two or three times per week for twenty to thirty minutes. Because people differ from each other, it is important that the treatment is individualized. For the optimum performance throughout the treatment, the therapy program is adapted according to incontinency improvement reported by the patient. During the therapy patients are dressed and sitting in a comfortable chair. Because there is no direct contact with the skin or unpleasant electrode insertion, the treatment is painless, comfortable and has no known side effects. An advantage of functional magnetic stimulation is also that the patients can learn the proper implementation of Kegel exercises through the therapy. The patients may then continue to carry out these exercises at home.

Magnetic therapy has proven to be an effective treatment for all types of urinary incontinence. In June 1998, the U.S. FDA recognized functional magnetic stimulation as a conservative method for treatment of urinary incontinence.

Treatment of the stress urinary incontinence can be upgraded with laser, which strengthens the tissue binding structures. The binding structure strength can be improved with local application of estrogen. A surgical therapy is also possible. Additional treatments of urge and mixed urinary incontinence include a healthy lifestyle, regular pelvic floor muscles exercise, bladder training, adjusting diet regime, drinking a lot of water, and relaxation techniques (autogenic training and medical hypnosis). With that in mind we can do a lot to maintain the health of our bladder.

2. Materials and methods

In total 78 females with urge, stress and mixed urinary incontinence were included in a study of the effects of electromagnetic chair device (Magneto STYM®, Iskra Medical d.o.o., Slovenia). Patients with a history of epilepsy, severe cardiac arytmias, a pacemaker or metal implants, as well as concurrent pregnancy, malignancy or physiotherapy during the study, were excluded. From 78 women included in the study, 11 suffered from urge urinary incontinence (UUI), 30 from stress urinary incontinence (SUI), 23 from mixed urinary incontinence (MUI), and 14 from incontinence after childbirth. They were treated in three different medical centers in Slovenia: Private health center ZZZ-Štrumbelj, Medical center Podnar and Private health institution for gynecology and obstetrics Zdravka Koman -Mežek.

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During magnetic therapy, a focused, time-varying magnetic field penetrates into the perineum and activates the motor neurons of the pelvic floor muscles. The pelvic muscles contract and relax with each magnetic pulse, thereby strengthening the muscles. The goal of the therapy is the rehabilitation of the pelvic floor musculature to reduce urinary incontinence [11], [12]. During the treatment, patients are seated on the electromagnetic chair. Magnetic stimulation of the muscles is conducted by an electromagnetic coil built into the seat and controlled by an external unit. The coil can produce magnetic fields with strength up to 2 Tesla with frequencies between 1 and 80 Hz. Magnetic coil offers the greatest magnetic field at the center of the coil, so the perineum must be in the middle of the seat, right above the center of the coil.

All patients were treated twice a week for 8 weeks (16 therapies in total). 30 Women suffering for stress urinary incontinence were treated with two different frequencies. The treatment protocol used for the first treatment session consisted of two episodes of 10 min, one at 10 Hz and another at 23 Hz, with 2 min pause in between. For the second treatment session the 23 Hz was changed for 35 Hz frequency, while other parameters stayed the same. 11 women having urge urinary incontinence were treated with three different frequencies, 2, 10 and 15 Hz. Each of those lasted for 9 minutes, with 1 minute of pause in between. The protocol for treatment of the 23 women suffering from mixed urinary incontinence was combined of two different sessions with 3 different frequencies. First session includes therapy of 9 minutes at 2 Hz, 9 minutes at 10 Hz and another 9 minutes at 23 Hz (after each 9 min there was a minute of pause). In the second session frequency of 23 Hz was replaced with 35 Hz. Activation time was the same for all protocols at all frequencies (5 seconds of activation and 5 second pause). The stimulus intensity was gradually increased up to the limit of tolerability as indicated by the patient. Results were obtained using patients' self-evaluation questioner. Results were collected after the last therapy.

The study was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients before the first treatment.

3. Results

7 out of the 11 female patients suffering from urge incontinence were completely dry after the therapy (64,0%), 3 out of 11 patients showed significant improved (27,0%) and 1 out of 11 did not show any improvement after the treatment (9,0%).
23 out of 30 patients suffering from stress incontinence were completely dry after the therapy (76,7%), two patients showed significant improvement (6,7%) and 5 out of 30 did not show any improvement (16,6%).
13 out of 23 patients suffering from mixed urinary incontinence were cured (56,5 %), 9 patients showed significant improvement (39,0%) and 1 out of 23 women did not show any improvement (4,5%).
The best results are representing patients with urine incontinence after the childbirth. All 14 women were completely dry after even less than 16 therapies (100%).

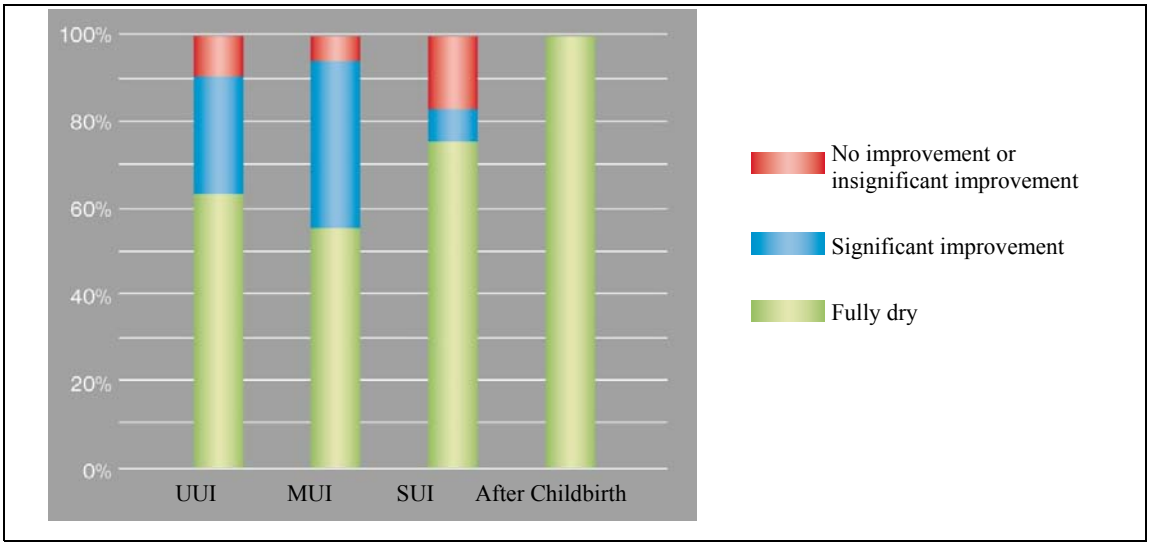

Figure 1: Multi-center results in treating urge urinary incontinence (UUI - 11 women), mixed urinary incontinence (MUI - 23 women), stress urinary incontinence (SUI - 30 women) and incontinence after childbirth (14 women). acquired at Private health center ZZZ-Štrumbelj (Tadeja Štrumbelj, MD), Medical center Podnar (Polona Podnar, MD) and Private health institution for gynecology and obstetrics Zdravka Koman -Mežek (Zdravka Koman Mežek, MD).

4. Discussion

The so far options for conservative treatment of the urinary incontinence were Kegel exercises conducted by the patients themselves or induced with the electrical stimulation. The electrical stimulation treatment was reported to be effective for stress incontinence

and urge incontinence, where 60–90% and 50–80% of patients became completely dry or showed significant improvement [4], [6]. After the magnetic stimulation treatment 84% of women with SUI became completely dry or showed significant improvement, whereas 91% of women suffering from UUI showed the same progress. The best success rate was achieved with MUI, where 95% of patients became completely dry or showed significant improvement. Overall, the success rate of magnetic stimulation therapy is higher compared to the electric stimulation therapy used so far.

For the Kegele exercise conducted by the patients themselves, it was established by researches summarized in Novak's Gynecology, that 32% of patients with SUI became completely dry and other 68% showed observable improvement. However, the Kegel exercises in these cases were conducted under complete supervision and lasted 3 months. Since Novak's also reported shortcomings in learning of Kegel exercises and lack of patients will do conduct them on a regular basis, such results could be considered too optimistic. The magnetic stimulation treatment induces the same muscle contraction as Kegel exercises, but does not require any interaction of the patient. The improvement rate of both treatments is comparable.

Besides the objective improvement of urine retention, one of the aspects of treatment is also patient comfort during treatment. However, the insertion and use of probe during the electrical stimulation therapy can cause discomfort or irritation with some patients [7]. On the other hand, the Kegel exercises are often conducted too seldom, the wrong way and consequently do not produce optimal results. The magnetic stimulation therapy combines the advantages of electric stimulation, where the muscle activity is induced by the probe, and the comfort of Kegel exercises, because the muscle activity is induced by the coil built into the chair, while the patient is sitting in the chair fully dressed.

Because of all the benefits that this method has compared to electrical stimulation, the magnetic stimulation is regarded as a safe, non-invasive alternative treatment for urinary incontinence. The results presented in this paper confirm that. Our study based on patients personal observations, but majority of them were satisfied after the treatment, which is the most important. The success of treatments varies according to the severity of the muscle weakness. Mild weakness can be improved by appropriate pelvic muscle exercises. Moderately weakened muscles can be strengthened either by exercise and biofeedback. With help of electromagnetic chair patients also learned how to perform pelvic floor muscle exercises themselves. This is going to help them to maintain the strength of the muscles after the conclusion of the therapy. The 8 week therapy block presents a good basis for the long term pelvic floor muscles ability for urine flow control. However, muscles need to stay active to maintain their strength and function [13]. This is achieved by regular and right exercise of Kegel exercises by the patients themselves.

One of the limitations of the present study is the lack of a control group. It is difficult to design an effective placebo treatment because the patients are aware of the strong contractions of the pelvic floor muscles during the treatment.

5. Conclusions

According to presented patients' improvement and their positive feedback it can be said that magnetic stimulation is an effective non-invasive therapy for all types of incontinence. It is, however, required to emphasize that the results presented in this paper are based on patients personal observations revealed in a questioner. Since the patients' satisfaction is an important part of every rehabilitation and medical treatment, the goal is reached with magnetic stimulation therapy. Further studies are required to determine other diagnostic parameters and to include a control group. However, based on the presented results, it can be concluded that the magnetic stimulation therapy offers a suitable alternative treatment option for all types of female urinary incontinences.

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Nº 6

The Impact of Extracorporeal Magnetic Stimulation as Addition to Mirabegron in Overactive Bladder Treatment in Women: A Single-Centre Randomized Sham-Controlled Study

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The Impact of Extracorporeal Magnetic Stimulation as Addition to Mirabegron in Overactive Bladder Treatment in Women: A Single-Centre Randomized Sham-Controlled Study

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Abstract: (1) Background: The purpose of our prospective, single-blinded, randomized, sham-controlled study was to investigate the effect of the additional extracorporeal magnetic stimulation (ExMI) to pharmacological treatment in overactive bladder syndrome (OAB) in women. **(2) Methods:** We recruited 56 women with OAB, who were allocated into two study groups: the active group received mirabegron 50 mg daily and a total of 16 sessions of ExMI in 8 weeks, whereas the sham group received mirabegron 50 mg daily and sham stimulation following the same treatment protocol. Treatment success was evaluated after 4 and 8 weeks. **(3) Results:** Both groups experienced significant reduction in daytime urinary frequency, nocturia, and number of weekly incontinence episodes after 8 weeks. There were no statistically significant differences in end-point daytime urinary frequency and nocturia between groups. However, the overall average reduction rate in weekly number of incontinence episodes was 43.7% in treatment group and 24.2% in the control group. The number of urinary incontinence episodes in the treatment and control group was reduced for 3.8 ± 11.8 vs. 2.5 ± 4.3 episodes at week 4 and additional 3.3 ± 6 vs. 0.4 ± 3.2 episodes at week 8, respectively ($p = 0.013$). Moreover, IIQ-7 score showed a significantly greater score reduction and patients' evaluated improvement of symptoms was higher in the active group. **(4) Conclusions:** The addition of ExMI to mirabegron in OAB treatment further improves the weekly incontinence episode reduction rate and also leads to grater improvement in symptoms.

Keywords: magnetic stimulation; mirabegron; overactive bladder; patient satisfaction; urge urinary incontinence; urgency

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1. Introduction

The clinical syndrome of overactive bladder (OAB) is characterized by urinary urgencies with increased urinary frequency and nocturia, with or without urge urinary incontinence in the absence of urinary tract infection or other obvious pathologies [1]. This condition shows a 12.8% prevalence among the female population, with an increasing prevalence with age [2], thus resulting in an important economic impact [3]. Because of the nature of the disease, patients often experience impaired quality of life, accompanied by social isolation, low self-esteem, frustration, anxiety and depression [3]. Due to its high prevalence and the effect on the quality of life, OAB represents an important economic burden for the society. It has been evaluated that OAB-related costs in the United States of America (USA) were as high as USD 1925 per inhabitant or USD 65.9 billion in total. According to projections, these costs would increase to USD 76.2 and USD 82.6 billion until the years 2015 and 2020, respectively [4,5]. Another more recent systematic review from

2018 estimated that the total economic burden of OAB in the USA is over USD 100 billion annually [6]. It has also been evaluated that compared to a similar patient without OAB, the healthcare costs of OAB patients were more than 2.5 times larger [7]. In the future, the ageing of the general population will probably lead to a further increase in the OAB prevalence. It is thus important to increase our understanding of pathophysiology of this syndrome and to develop clinically and economically efficient treatment options.

Contemporary OAB treatment typically starts with less invasive behavioral and educational interventions, which are followed by pharmacological treatment. Typically, pharmacological treatment for OAB starts with antimuscarinics. While antimuscarinic treatment is more effective than a placebo, its ability to reduce symptoms is relatively limited [8]. Antimuscarinics often come with side effects such as dry mouth, constipation, blurred vision, fatigue, and potential cognitive decline. As a result, patient adherence is quite poor, with only 6–12% of patients still continuing the prescribed therapy after two years [9]. Various reasons contribute to this poor adherence, but most commonly, patients discontinue treatment due to inadequate therapeutic effects (41.3%) or side effects (22.4%) [10]. Another pharmacological treatment choice is beta-3 agonists, which achieve bladder relaxation by activating beta-3 receptors in the bladder wall. Mirabegron, a beta-3 receptor agonist, has demonstrated the ability to reduce the frequency of urination and urgency episodes without a significant difference in side effects compared to a placebo [11]. However, despite its fewer side effects, adherence issues with mirabegron are still comparable to those associated with antimuscarinics [12]. Therapy-resilient cases require surgical interventions, such as bladder wall injection of botulinum toxin A, sacral nerve stimulation, and rarely, bladder augmentation or urinary diversion [13].

Because of the relatively poor efficacy of first- and second line treatments, some alternative treatment options have been investigated in the past years. One of them is extracorporeal magnetic innervation/stimulation (ExMI) therapy, which represents an alternative to pharmacological or surgical treatment of urinary incontinence [14]. It is a non-invasive, non-surgical treatment that stimulates pelvic floor muscles through the induction of an electric current with the aid of a magnetic field [15,16]. Most studies focus on its effect on treating stress urinary incontinence [16], but some authors have shown that it is as effective in treating urgency incontinence in female patients with OAB [5,17]. Furthermore, with the adjacent magnetic stimulation of the sacral roots, symptoms of urinary frequency as well as urge incontinence can improve [18].

The aim of our study was to investigate whether the addition of ExMI to pharmacological treatment with mirabegron additionally improves OAB treatment success and patient satisfaction.

2. Materials and Methods

We designed a single-centre, prospective, single-blinded, randomized, sham-controlled study, which was conducted at Department of General Gynaecology and Gynecological Urology, Clinic for Gynecology and Perinatology, University Medical Centre Maribor, Slovenia, between years 2019 and 2023, including a 2-year COVID-19 pandemic gap.

This study followed the principles embodied in the Declaration of Helsinki. Research protocol was developed following the CONSORT guidelines [19]. Prior to patients' enrolment, the trial was registered as an internal research project at our institution (project number IRP-2018/01-16). Study was approved by the National Medical Ethics Committee (approval number 0120-234/2018/4). The trial was also retrospectively registered on clinicaltrials.gov (registration number NCT06123364).

The primary aim of this study was to evaluate whether the addition of ExMI to mirabegron (treatment arm) reduces the OAB symptoms (urgency urinary incontinence episodes, daytime frequency, nocturia), Patient Perception of Intensity of Urgency Scale (PPIUS) score, and urinary flowmetry results in comparison to treatment with mirabegron and sham ExMI (control arm). Secondary aim of the study was to investigate the effect of the addition of ExMI to mirabegron on patients' quality of life, Incontinence Impact

Questionnaire—short form (IIQ-7) score, and Urogenital Distress Inventory—short form (UDI-6) score compared to the control arm. Figure 1 shows a flow chart of the patient enrolment and the follow-up process.

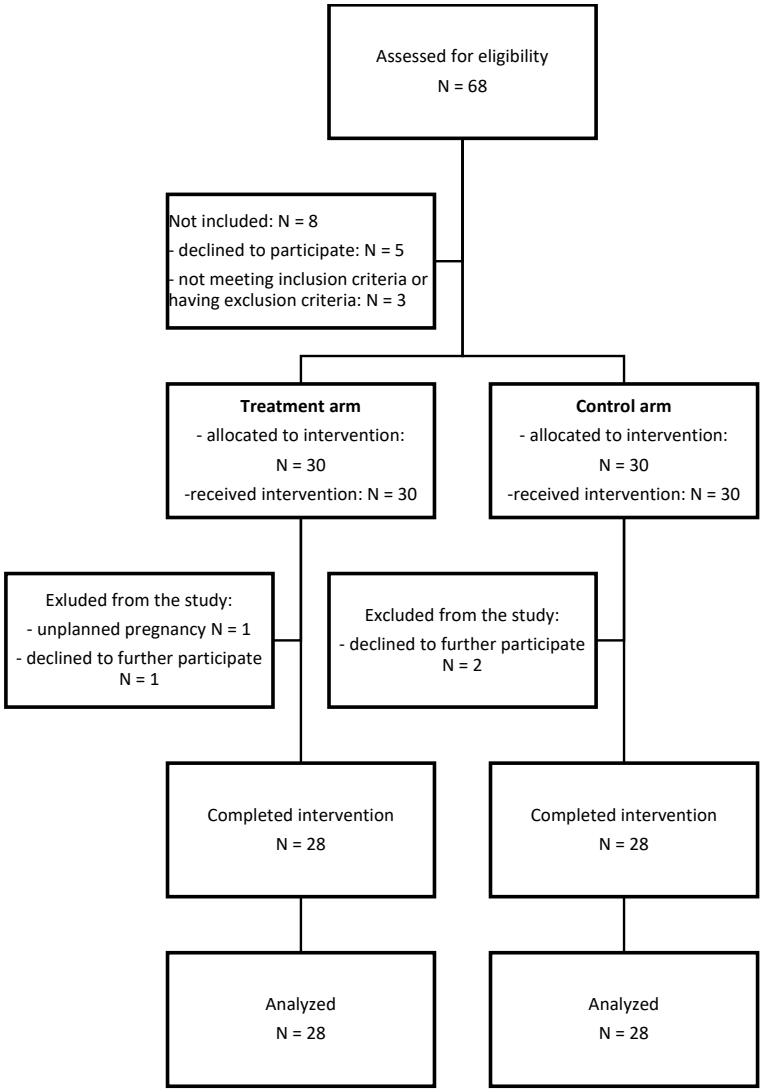

Figure 1. Flow chart of patient enrolment and the follow-up process.

We included women with OAB who fulfilled the following inclusion criteria: (i) aged between 30 and 80 years, (ii) experiencing OAB symptoms, and (iii) agreed to participate in the study. The diagnosis of OAB was made based on the patient's visit at our urogynecology clinic, where initial diagnostics were performed. Exclusion criteria included positive urine culture or urinary tract infection, treatment with anticholinergics or mirabegron in the last 3 months, contraindications for treatment with mirabegron, pelvic floor muscles therapy (e.g., pelvic floor exercises, electrical stimulation, etc.) in the last 3 months, stress urinary incontinence, pelvic malignancies, pregnancy, cardiac pacemaker or implantable cardiac defibrillator, and electronic device or metallic implant applied to areas between the lumbar region and lower extremities. Patients who discontinued the prescribed treatment during the study or initiated other medications for OAB were also excluded from the study. All patients were informed about the study protocol and signed an informed consent form.

An a priori power analysis was carried out using G*Power software v3.1 and using reference values of weekly incontinence episodes after treatment estimated by the study conducted by Yamanishi et al. [17]. With an estimated effect size d of 0.795 and by using Wilcoxon–Mann–Whitney test, the a priori sample size was calculated as 28 individuals per group in order to retain 80% statistical power at alpha set as 0.05. Considering an up to 20% drop out rate, we decided to include a total of 68 patients.

After recruitment, patients were evenly allocated to two study groups in a randomized, single-blinded, consecutive manner using computer-generated numbers. In the active group, participants received a daily dose of mirabegron 50 mg and underwent ExMI using an electromagnetic chair (Iskra Medical Magneto STYM®; Iskra Medical d.o.o., Ljubljana, Slovenia). The magnetic stimulation was administered twice a week for 8 consecutive weeks, following the manufacturer's recommendations: a magnetic stimulation frequency of 10 Hz for a total of 12 s per cycle (active time 6 s, pause time 6 s), with a total therapy time of 20 min per session. In the control group, patients received a daily dose of mirabegron 50 mg and underwent a sham stimulation on the same electromagnetic chair, following the same protocol.

Before treatment, each patient underwent a detailed assessment. Urinary culture was performed to exclude urinary tract infection. They evaluated their daytime frequency, nocturia, and urinary incontinence episodes. They also completed validated questionnaires, including PPIUS, I-QOL, IIQ-7, and UDI-6. Uroflowmetry tests and post-void residual (PVR) volume measurements were performed in a standardized manner, involving the emptying of the bladder using a urinary catheter before measurement and then filling it with 250 mL of room-temperature physiological saline through the urinary catheter. Measurements were performed by a consultant urologist. Prior to these measurements, patients kept a voiding diary for three consecutive days. At weeks 4 and 8, the whole assessment was repeated, and patients also completed a patient satisfaction survey (PSS) related to the intervention.

We performed the statistical analysis using IBM® SPSS® Statistics, version 22. Basic patients' characteristics were calculated using simple statistics. Non-parametric Wilcoxon Signed Ranks test and Mann–Whitney tests were used to compare numerical differences within and between groups, respectively. Chi-square/Fisher's exact test was used to compare categorical data between groups. Statistical significance was set at $p < 0.05$.

3. Results

In the enrollment period, 68 women were assessed for eligibility, and 60 were included in the study (88.2% response rate). Of these, 28 women in each group completed the 8-week treatment course (either ExMI or sham) with simultaneous pharmacological treatment with mirabegron (Figure 1).

The treatment and control group were balanced with respect to most baseline characteristics: age (60.3 ± 11.9 years (range 35–78) vs. 54.9 ± 11.7 years (30–78), respectively, p-value = 0.101), PPIUS score (3.8 ± 0.9 vs. 3.5 ± 0.7, p-value = 0.097), daytime urination frequency (8.7 (range 6–13) vs. 9.0 (range 5–15), p-value = 0.554), nocturia (1.1 (range 0–3) vs. 1.4 (0–4), p-value = 0.408), maximal urinary flow (Q-max) (24.3 ± 12.5 mL/s vs. 27.9 ± 13.7, p-value = 0.372), and PVR (9.3 ± 26.8 mL (range 0–120) vs. 2.5 ± 7.5 (range 0–30), p-value = 0.293). However, patients in the treatment group experienced a statistically significantly longer duration of symptoms (mean value of 9.2 years (range 1–30) vs. 5.6 years (range 1–30), respectively, p-value = 0.005). Of the 28 women in each group, 26/28 (92.3%) had urge urinary incontinence (UUI). In women with UUI, mean number of weekly incontinence episodes in treatment group was 13.3 ± 16.1 and 6.7 ± 9.1 in the control group. This difference was also statistically significant (p-value = 0.044).

During the treatment period, there was a significant improvement in weekly incontinence episodes, daily urinary frequency, nocturia, and PPIUS score in both groups, but without impact on the urinary flowmetry results or PVR (Table 1). There were no statis-

tically significant differences in daytime urinary frequency, nocturia and PPIUS scores between groups at the end of the treatment period.

Table 1. Comparison of study endpoints between both groups at the inclusion (week 0) and at both follow-ups (weeks 4 and 8).

	Week 0		Week 4		Week 8		Comparison within Groups (Week 0–Week 8)	
	Treatment Group *N* = 28	Control Group *N* = 28	Treatment Group *N* = 28	Control Group *N* = 28	Treatment Group *N* = 28	Control Group *N* = 28	Treatment Group *N* =28	Control Group *N* = 28
PPIUS score (mean ± SD)	3.8 ± 0.9	3.5 ± 0.7	3.4 ± 0.6	3.1 ± 0.9	2.9 ± 0.9	2.9 ± 0.8	**<0.001** *	***0.001*** *
Weekly incontinence episodes × (mean ± SD)	13.3 ± 16.1	6.7 ± 9.1	9.5 ± 11.3	4.1 ± 7.7	6.2 ± 8.9	3.8 ± 8.1	**<0.001** *	**0.008** *
Daily urinary frequency (mean, range)	8.7 (6–13)	9.0 (5–15)	8.2 (5–13)	8.2 (5–15)	7.7 (5–13)	7.6 (5–14)	**0.023** *	**0.001** *
Nocturia (mean, range)	1.1 (0–3)	1.4 (0–4)	1 (0–3)	0.9 (0–3)	0.7 (0–3)	0.9 (0–3)	**0.008** *	**0.002** *
Qmax [mL/s] (mean ± SD)	24.3 ± 12.5	27.9 ± 13.7	23.7 ± 12.9	28.6 ± 11.4	22.9 ± 10.5	27.9 ± 10.2	NS	NS
PVR [mL] (mean, range)	9.3 (0–120)	2.5 (0–30)	13.7 (0–170)	0.4 ± 1.9 (0–10)	11.3 (0–110)	0 (0)	NS	NS
I-QOL: total	52.8 ± 27.2	58.6 ± 25.2	58.0 ± 25.8	63.0 ± 26.5	68.4 ± 23.4	71.1 ± 24,3	**<0.01** *	**<0.01** *
- ALB	50.9 ± 6.7	54.5 ± 23.6	56.4 ± 24.4	59.4 ± 24.5	67.7 ± 22.6	68.0 ± 24.0	**<0.01** *	**<0.01** *
- PSI	58.4 ± 29.1	66.1 ± 27.5	62.5 ± 28.5	69.8 ± 27.3	72.9 ± 25.9	76.6 ± 24.2	**<0.01** *	**<0.01** *
- SE	45.5 ± 29.8	52.0 ± 27.8	52.3 ± 27.3	56.6 ± 30.2	61.3 ± 24.4	66.3 ± 28.0	**<0.01** *	**<0.01** *
UDI-6	53.8 ± 21.3	44.6 ± 24.1	47.2 ± 20.3	37.5 ± 26.5	35.5 ± 21.1	33.1 ± 20.2	**<0.01** *	**<0.01** *
IIQ-7	38.9 ± 33.3	26.7 ± 30.3	28.6 ± 29.7	19.9 ± 21.6	22.4 ± 29.9	18.7 ± 26.4	**<0.01** *	**<0.05** *

Legend: PPIUS—patient perception of intensity of urgency scale, SD—Standard Deviation, Qmax—maximum urinary flow (mL/s), PVR—post-void residual urine volume (mL), I-QOL—Incontinence Quality of Life Questionnaire: ALB—avoidance and limiting behavior, PSI—psychosocial impacts, SE—social embarrassment; IIQ-7—Incontinence Impact Questionnaire—short form, SD—Standard Deviation, UDI-6—Urogenital Distress Inventory—short form, *—statistically significant difference, NS—no statistically significant difference, × *N* = 26 for both groups.

However, baseline differences in number of weekly incontinence episodes precluded comparison of this variable at the end of the treatment period, which is why we decided to compare the change in the weekly number of urinary incontinence episodes between the baseline and the corresponding follow-up between both groups. As seen from Figure 2, the number of urinary incontinence episodes in the treatment group was reduced for averagely 3.8 ± 11.8 episodes at week 4 and for an additional 3.3 ± 6 episodes at week 8. In the control group, these values were 2.5 ± 4.3 and 0.4 ± 3.2 episodes, respectively. While there were no statistically significant differences in the reduction in weekly incontinence episode at week 4, this difference was statistically significant at week 8 in favor of the treatment group ($p = 0.013$). The overall average reduction rate in weekly number of incontinence episodes was 43.7% in the treatment group and 24.2% in the control group.

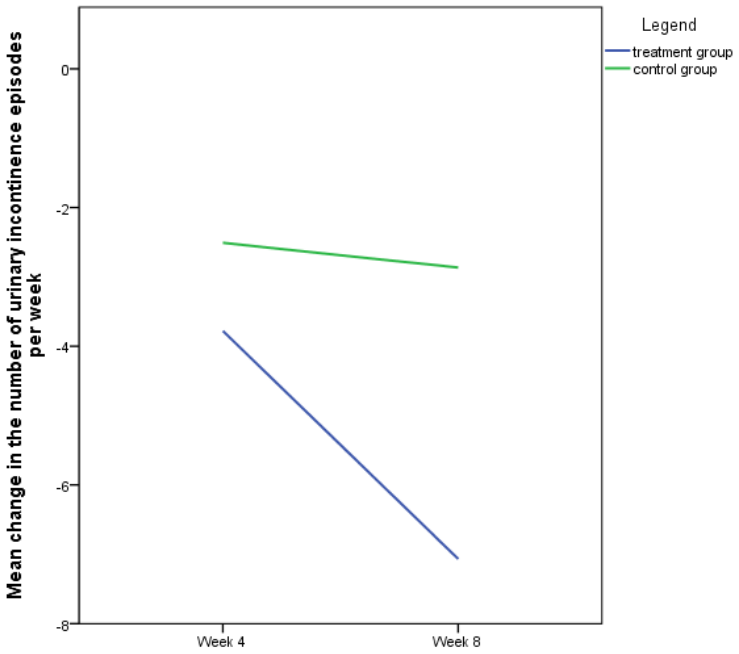

Figure 2. Decrease in number of weekly urinary incontinence episodes between the baseline and the follow-up visits.

Scores for each individual questionnaire at the enrolment and at both follow-up visits were calculated. Table 1 shows significant improvement in all questionnaires' scores in both groups. The mean change in questionnaire scores between week 0 and 8 between groups was statistically significant for IIQ-7 score (-16.5 ± 17.4 for treatment group and -8.0 ± 17.6, p-value < 0.05), whereas other values did not reach statistical significance (Figure 3). Regarding the PSS related to the intervention, 21/28 (75%) patients in the treatment group reported some improvement, and 7/28 (25%) reported substantial improvement after treatment. In the control group, these results were 14/28 (50%) and 2/28 (7.1%). The difference between groups was statistically significant ($p < 0.001$). Patients' satisfaction rate was comparable between groups, and all patients would recommend this treatment to their friend. No serious side effects were reported in the study. However, milder side effects of treatment were reported in three patients, namely one in the treatment group and two in the control group. In the treatment group, one patient reported an unpleasant, hot skin sensation during ExMI therapy. In the control group, one patient reported an episode of cystitis, and another patient reported occasional headaches occurring after initiation of therapy. None of those patients considered the side effects so discomforting that they would want to discontinue their participation in the study.

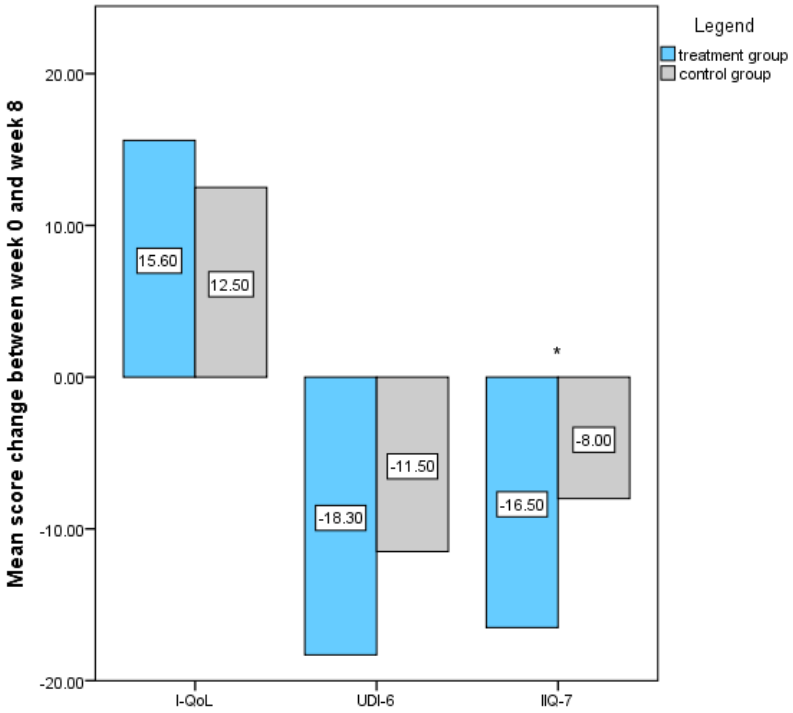

Figure 3. I-QoL, UDI-6, and IIQ-7 score changes between week 0 and week 8 of treatment among both study groups. Legend: *—statistically significant difference.

4. Discussion

Magnetic stimulation has been utilized in utilized in urogynecology and other fields of medicine for quite some time. It has the advantages of being non-invasive, safe, and simple; it can directly treat the site of injury, pain and/or dysfunction; and has the ability of nerve stimulation without eliciting pain, which can be a bothersome side effect of electrical stimulation [20,21]. To the best of our knowledge, our study was the first that aimed to investigate whether the addition of ExMI to pharmacological treatment with mirabegron additionally improves treatment success in women with of OAB.

Several different studies have evaluated the effect of ExMI in OAB treatment. While some studies show that ExMI leads to short- and medium-term improvement of OAB symptoms in women and increases maximal cystometric bladder capacity [17,22–24], others could not confirm its beneficial effect [25,26]. A randomized placebo controlled trial from 2002 has established that ExMI of sacral roots with the aim to address the symptoms of urinary frequency and urge incontinence can result in significant symptomatic improvement following just one treatment session [18]. Similarly, one prospective trial and one retrospective study that evaluated the effects of ExMI on OAB symptoms in women observed substantial symptom improvement after ExMI treatment [27,28]. Up to this date, two systematic reviews have investigated the effect of ExMI therapy for OAB and urinary incontinence in women. A recent systematic review, published in 2023, evaluated ExMI for the treatment of female urge urinary incontinence (UUI). While the authors emphasized that the literature in this area is lacking, they also concluded that ExMI is an effective conservative method of UUI treatment [29]. Another systematic review from 2019 also indicated that ExMI is effective in urinary incontinence treatment. According to their results, ExMI reduces the frequency of urinary incontinence and improves quality of life of women with urinary incontinence [30].

Our study is the first that evaluated the addition of ExMI to pharmacological treatment with mirabegron. Moreover, searching the PubMed database, no similar study has also been

performed using antimuscarinics. While both groups of our patients experienced symptom improvement, patients in the treatment group had a statistically significantly larger reduction in the number of weekly urinary incontinence episodes between weeks 4 and 8. While the reduction in the number of weekly urinary incontinence episodes in the treatment group continued even after week 4, there was a minimal additional reduction in the control group, which could suggest a cumulative effect of mirabegron and ExMI. Considering the fact that at the individual level, urgency incontinence is one of the most bothersome lower urinary tract symptoms for both men and women [31], and given the well-known psychological effects of urinary incontinence [32], our results suggest that by further reducing the number of incontinence episodes, the addition of ExMI to pharmacological treatment could further improve patients' well-being and quality of life. A similar possibility of an additive effect has already been speculated regarding the use of ExMI in addition or after cholinergic treatment by some authors [17]. Moreover, patients' evaluated improvement of symptoms was higher in the treatment group. Our results also show that the addition of ExMI to medical therapy with mirabegron improves some aspects of incontinence's impact on daily activities (IIQ-7). However, based on calculated scores from the validated quality of life questionnaires used in our study, these findings do not necessarily reflect in a better quality of life.

One of the main advantages of ExMI compared to other non-pharmacological and non-surgical treatments are that it is non-invasive, atraumatic to the surrounding tissues, it has minimal side effects, and that is well-accepted by the patients [22]. Moreover, patients do not need to undress, and there is no need for vaginal or anal probes [14]. The results of our study confirm this, as all of our patients would recommend ExMI treatment to a friend with similar symptoms, regardless of whether they were treated with the active or sham ExMI.

The main advantages of our study are that it was a randomized sham-controlled study and that the sample size was calculated based on the number of urinary incontinence episodes, which was one of our primary outcomes. However, due to significant differences in number of urinary incontinence episodes between groups at inclusion despite the randomization process, we decided to compare the reduction in number of urinary incontinence episodes between groups. One of the limitations of our study is the lack of a longer follow up. Studies show that more than half of patients treated with ExMI only show recurrence of symptoms after 6 months [14]. Since our patients were treated with a combinational therapy, we do not know if this could lead to a better adherence to the pharmacological treatment and consequently to better outcomes. Another limitation is the statistically significant difference in the duration of OAB symptoms. Since patients were allocated into two study groups in a randomized, single-blind, consecutive manner, we could not influence or avert this from happening. Controversially, the treatment group, with the longer history of OAB symptoms, showed better symptom improvement in comparison to the control group with shorter duration of symptoms. This could potentially be explained with the fact that they were treated with a dual therapy (mirabegron + ExMI), or alternatively, since they have suffered from OAB symptoms longer, their expectations of treatment results may be lower. As already stated before [17], it is difficult to completely blind the patient while using an active ExMI device and the sham device, since it causes muscle contractions during activation. In our study, most patients did not have any previous experience with ExMI due to its unavailability in our public healthcare system. Patients from different study groups had their sessions on different days, so that they could not meet and exchange information. Furthermore, both devices produced the same noises and showed an identical therapy progress on the display in both study groups.

5. Conclusions

The results of our study show that the addition of ExMI to mirabegron in women with OAB further improves the outcome of treatment by reducing the number of urinary

incontinence episodes. It also leads to greater improvement in IIQ-7 scores and higher patients' evaluated improvement of OAB symptoms.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by The National Medical Ethics Committee of the Republic of Slovenia (approval number 0120-234/2018/4, 10 April 2018). The trial was registered as an internal research project at our institution: University Medical Centre Maribor (project number IRP-2018/01-16). The trial was also retrospectively registered on clinicaltrials.gov (registration number NCT06123364).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Available on request and with regulations.

Conflicts of Interest: The authors declare no conflicts of interest.

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Nº 7

Effects of extracorporeal magnetic stimulation in fecal incontinence

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Research Article

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Effects of extracorporeal magnetic stimulation in fecal incontinence

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Abstract: Background. Fecal incontinence (FI) is a common condition that has devastating consequences for patients' QOL. In some patients, the conventional functional pelvic floor electrical stimulation has been effective but is an invasive and embarrassing treatment. The object of the study was to evaluate the feasibility of functional extracorporeal magnetic stimulation (FMS) in strengthening the pelvic floor muscles without an anal plug and the embarrassment of undressing.

Materials and Methods. Thirty patients (26 female and 4 males) with FI were enrolled. All patients were assessed during a specialized coloproctology evaluation followed by endoanal ultrasonography and anorectal manometry. All patients underwent an FMS treatment once weekly for 8 weeks. Patients' outcome was assessed by the Cleveland Clinic Fecal Incontinence Score (CCFIS) and by the fecal incontinence QOL questionnaire (FIQL).

Results. After 8 weeks, the number of solid and liquid stool leakage per week was significantly reduced ($p<0.05$) with a significant improvement of the CCFIS and of the FIQL ($p<0.05$). Moreover, the authors recorded a missed recruitment of the agonist and antagonists' defecation muscles.

Conclusion. FMS is a safe, non-invasive and painless treatment for FI. It could be recommended for selected patients with non-surgical FI to ensure a rapid clinical improvement.

Keywords: Functional extracorporeal magnetic stimulation; Fecal incontinence; Pelvic floor rehabilitation; Magnetic chair

1 Introduction

Fecal incontinence (FI) is defined as the involuntary loss of solid or liquid feces. It is a prevalent condition with unpleasant consequences for quality of life (QOL) [1]. FI can affect individuals of all ages; its overall prevalence in adults is calculated to be 11% to 15%, increasing with age QOL [2]. However, its real epidemiology appears to be underestimated as patients tend to avoid seeking medical care due to considerable embarrassment, social isolation, and stigma [3]. Different types of incontinence manifestations can range from unintentional elimination of flatus, soiling, to the complete loss of bowel contents, but in all cases it greatly impairs QOL. Mechanisms of continence involve a complex interplay between stool consistency, rectal compliance as reservoir, muscle groups of the pelvic floor, and proper function of the anal sphincter complex. Alterations in any of these elements, starting from stool consistency to muscular proficiency, may impact continence to flatus, liquid and solid stool, and arouse FI-connected symptoms. FI severity depends on the type and frequency of loss episodes, and of course, their role in modifying patients QOL.

In selected patients, functional pelvic floor treatment as electrical stimulation has been reported to be effective for FI as confirmed by several randomized controlled

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trials [4-6]. Its usefulness may be related to its unique role in inducing consciousness of the anal area, a feature that may be as useful as the stimulation itself [7-8]. In this perspective, increasing sensitivity in those body areas might help to improve the specific recruitment of anal sphincters, thereby avoiding the inappropriate recruitment of agonists and antagonist groups of muscles. However, although it is an effective technique, electric stimulation can be considered an invasive and embarrassing treatment because of patients' having to be undressed while undergoing rehabilitation and the necessity of insertion of an anal plug.

The aim of this study was to investigate the effectiveness of functional extracorporeal magnetic stimulation (FMS) as a non-undressed and no-probe-needed alternative technique to other functional therapies in patients affected by idiopathic FI, as an option for functional pelvic floor treatment.

2 Materials and methods

2.1 Patients and methods

Consecutive patients affected by FI and referred to a Teaching Hospital (Division of General, Mini-Invasive and Obesity Surgery - Master of Coloproctology and Pelvic Floor Rehabilitation, University of Campania "Luigi Vanvitelli", Naples, Italy) between October 2018 to March 2019 were enrolled in the study. The local ethical committee approved the study protocol. The study was conducted in accordance with the Helsinki Declaration.

All patients were informed about aims, procedures and follow-up; participants also signed a written informed consent.

Selection criteria for the study were patient's clinical history of FI for stool, liquid or flatus, and a Cleveland Clinic Fecal Incontinence Score (CCFIS) > 10. [9,10] Patients affected by urge incontinence were excluded from the study. The selection of patients with defecatory disorders amenable for rehabilitation treatment was obtained using a diagnostic protocol comprising proctologic examination, clinico-physiatric assessment, muscular synergies and instrumental evaluation [11].

All patients were assessed during a specialized coloproctology evaluation in a teaching hospital. A clinical examination was performed on all patients and information on bowel function, pregnancies, episiotomy, possible presence of pudendal nerve neuropathy, diabetes, and other associated diseases were recorded. Each patient underwent a physical examination to evaluate the resting anal tone and the muscular synergy: by inviting the patient to contract the anal sphincter, it was verified whether adductor (agonist muscles) or abdominal muscles (antagonist muscles) were contracted [11,12]. The CCFIS was then obtained in all patients. This scoring system, through 5 items (solid stool leakage, liquid stool leakage, gas leakage, pads use, lifestyle restriction) each graded from 0 to 4, allows objective evaluation of incontinence severity in patients with FI [9,10]. The Fecal Incontinence QOL Scale (FiQL) was submitted to all patients to evaluate the impact of FI on four aspects of patients' QOL before the rehabilitation program and to rate the patients' QOL improvement after treatment. The score consists of 29 questions ranging over different domains of the patient's life: their lifestyle, their forced behaviour due to incontinence loss episodes, their personal perception of the disease, and finally, rating the subjective embarrassment caused by FI. In detail, a lower mean value of the domains corresponds to a worse clinical condition [13]. A 3D endorectal ultrasonography (3D EAUS) was performed before magnetic chair treatment, and a high-resolution anorectal manometry (HRAM) was performed both pre- and post-treatment.

2.2 3D Endorectal Ultrasonography (3D EAUS)

The device used to practice the 3D EAUS was BK Medical Flex Focus 800 fitted with a rotating 360° probe (model n.2050), covered by a cap filled with water. All the patients were placed in left lateral (Sims) position; the examination identified any lesion of the internal anal sphincter (IAS) and external anal sphincter (EAS) [14,15].

2.3 High Resolution Anorectal Manometry (HRAM)

HRAM was performed using a solid-state probe (ManoScan™ AR catheter, Medtronic, Minneapolis, USA). Pressure sensors were placed 1-cm apart from each other; each one counted 4 radially recording sensors for a total of 28 pressure sensors. Intrarectal and intra-balloon pressures were recorded by two additional pressure sensors placed at the probe's distal end (TactArray; Pressure Profile Systems, Los Angeles, California). A disposable inflatable balloon was located at the catheter tip. The patient was positioned in left lateral (Sims) position during the exam; the probe was then positioned in the anal canal with at

least one recording site in the distal rectum, and then the procedure was delayed a few seconds to guarantee the patient self-awareness of the probe's presence. The anal canal length, anal resting pressures, maximum voluntary contraction, and rectal sensitivity were evaluated using Bioview Analysis software (Sandhill Sci) [16]. Evaluating rectal sensitivity consisted of assessing first conscious rectal sensation, maximum tolerate volume, and evacuation stimulus, having an increasing pressured balloon placed in the rectum. The patients was asked to communicate the volume of the balloon that caused its perception (first conscious rectal sensation), the one that caused the beginning of the evacuation stimulus, and the one that led to the urge need of defecation.

2.4 Design of the study

Every pelvic floor rehabilitation treatment session began with augmenting the patient's awareness of the pelvic floor by showing them pictures of the different structures involved in continence to assist the patient to construct a proper muscles recruitment.

The device used was an armchair type magnetic stimulator FMS Tesla Care® (Max Medical Sassari – Italy) wherein the magnetic coil was placed in the bottom of the chair. [Figure 1] The stimulation was provided by an electromagnetic generator in the seat, controlled by an external unit. The intensity of the stimulation was 50–60 Hz, patients seated for an average time of 15 minutes on the chair, once weekly for 8 weeks. The magnetic field could be properly modified by the clinician by changing the frequency and amplitude on the generator. The perineum needed to be in the center of the seat because the highest power of the magnetic field corresponded to the center of the chair.

The treatment intervals were intermittent (5 seconds on, then 5 seconds off) to avoid muscle fatigue. The pulsed magnetic field generated by the device caused the contraction of the muscles of the pelvic floor without the need for an electrode. In detail, the rapid changes of the intensity of the magnetic field are generated by a phenomenon called electromagnetic induction, which is an electric current in neuronal cells. The depolarization of the latter passes distally to motor end plates and to the muscle fibers. The depolarization will also occur in sensory afferent fibers and autonomic nerves that may regulate local blood flow and other factors.

FMS treatment, while generating intermittent muscular contractions, increases the strength and endurance of the pelvic floor muscles. Additionally, the patient learns how to properly perform exercises that strengthen the muscles.

2.5 Follow up

After the 8 weeks treatment, the patients were clinically scored with CCFIS and instrumentally evaluated with HRAM. Moreover, the FIQL questionnaire was re-submitted to the patients.

2.6 Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS, version 16.0, Chicago, IL). Qualitative data are expressed as percent, and quantitative data are expressed as the means. Statistical significance was defined as $p<0.05$ with a confidence interval (CI) at 95%.

3 Results

Thirty patients met the aforementioned inclusion criteria, 26 females (86%) and 4 males (16%). Nine patients suffered of idiopathic FI (4 males and 5 females), 21 females had previously given birth, and 7 of them had undergone episiotomy reporting a I-II degree according to Sultan classification of perineal obstetric injury [17]. Overall mean age was 65 (range 38–74). Seven patients were affected by type 2 diabetes. Patient demographics are summarized in Table 1. Clinical and instrumental evaluations were

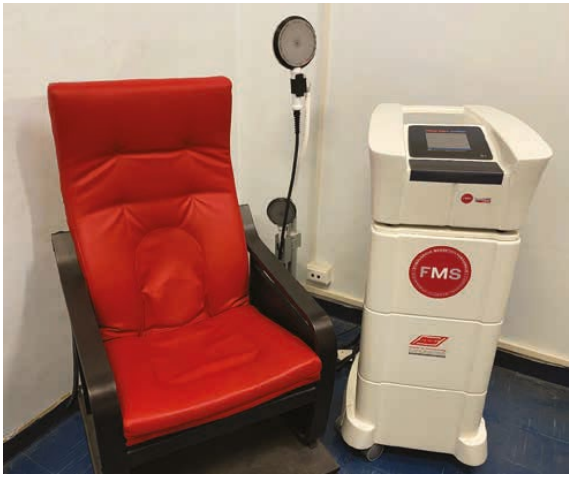

Figure 1: Tesla Care®Armchair for functional extracorporeal magnetic stimulation (FMS)

appointed at the beginning of the treatment session. The mean CCFIS value before treatment was 12.4. The mean subscore values of the four domains of FiQL were, respectively, lifestyle 2.6, coping 2.0, depression 3.1, and embarrassment 1.8. Physical examination showed incorrect synergies in 21/30 of the patients (70%), involving buttocks, adductors, and abdominal muscles antagonist synergies only in 2/21 patients (10%). All features improved by the treatment are summarized in Table 2. Anal manometry showed a mean basal pression value of 46 mmHg (min 35 mmHg−max 65). Moreover, mean maximum voluntary contraction value was 110 mmHg, with an average duration of 14 seconds. Rectal sensibility was valued as 30 (25−35) mL, 60 (55−70) mL, and 120 (110−130) mL. Endoanal ultrasound demonstrated in 7/30 (23%) patients a lesion of the internal anal sphincter (transversal extension 35° mean (30−40), longitudinal extension 1 cm (0.8−1.4). Only 3/30 (10%) patients had lesions of the internal sphincter (transversal extension 40° mean (35−45), longitudinal extension 1.2 cm (1−1.6). None of the patients had concurrent lesions of internal and external sphincters.

After treatment, a significant improvement of the CCIFS was recorded in 24 patients (80%). The mean CCIFS post-treatment value was 4.7, with a mean value reduction of 60% ($p<0.05$), its deducible clinical correlation was given by a statistically significant reduction of liquid and solid stool leakage per week. CCIFS modifications are represented in Figure 2 and Table 2.

Physical examination after treatment showed incorrect synergies in 3/30 of the patients (10%), involving buttocks and adductors, whereas abdominal muscles were stimulated in none of the patients. [Table 2]

FiQL domains scores improved in 27 out of 30 patients (90%). Post-treatment FiQL scores were 3.2, 2.7, 3.6, and 2.4

Table 1: Patients demographics features. Values are expressed as number of cases or mean (*). FI (Fecal Incontinence)

	Patients group (n=30)
Age	65* (51-69)
Gender	26 females (86,7%) 4 males (13,3%)
Idiopathic FI	5 females (16,7%) 4 males (13,3%)
Past deliveries	21 (70%)
Previous episiotomy	7/21 (23,3%)
Comorbidities	7 (type II diabetes) (23,3%)

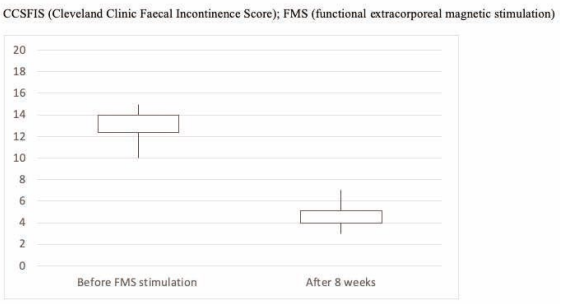

Figure 2: Modifications of the CCSFIS before and after FMS treatment

Table 2: Pre and post treatment clinical and instrumental parameters. Values are expressed as mean or number of cases (*). FMS (functional extracorporeal magnetic stimulation); CCSFIS (Cleveland Clinic Faecal Incontinence Score); FiQL (Fecal Incontinence Quality of Life Scale); HRAM (High Resolution Anorectal Manometry)

Item	**Before FMS**	**After FMS**	**p**
CCSFIS	12.4	4.7	<0.05
FiQL			
		3.2	
-lifestyle	2.6	2.7	<0.05
-coping	2.0	3.6	<0.05
-depression	3.1	2.4	<0.05
embarassment	1.8		<0.05
Buttocks/adductor synergies	21/30*	3/30*	<0.05
Abdominal synergies	2/30*	0/30*	NS
HRAM			
- basal pression	46 mmHg	48 mmHg	NS
- maximum voluntary contraction	110 mmHg	114 mmHG	NS
- contraction duration	14seconds	15 seconds	NS

regarding lifestyle, coping, depression, and embarrassment patterns respectively. FiQL modifications are shown in Figure 3 and Table 3 showed the number of patients improved after FMS according to the clinical items.

No statistically changes were recorded in anal manometry after the eight weeks' treatment time. In fact, the mean basal pression value was 48 mmHg (36–68 mmHg) and the mean maximum voluntary contraction value was 114 mmHg with an average duration of 15 seconds (p=NS) [Table 2] [Fig 4].

4 Discussion

Fecal incontinence is a multifactorial disease. Different mechanisms of continence are involved in the retention of gas and stools. Loss of continence can result from solitary anatomic defects, or more often, from alterations such as lesions or sphincters either caused by deliveries [18,19].

Hence, fecal incontinence is not only a diagnosis but a frequent and debilitating common final pathway symptom resulting from numerous different causes, regarding muscles competence, proper innervation, and the complex functioning of all these structures as a unit. That is, pelvic floor rehabilitation, having a primary target to recreate harmony among all the pelvic floor structures rather than curing symptoms, clearly has its important role in improving FI. The first step is to induce awareness of the pelvic floor muscles areas; the role of these areas in determining rehabilitation usefulness has exhaustively been studied [7].

Among other rehabilitation treatment techniques, anal electrostimulation is presently routinely performed and known as an effective nonoperative treatment for FI. It's also been speculated that aside from the mere electric stimulation, this technique might owe its curative role to its ability to arouse the patient's consciousness of the anal canal based on the fact that the sole knowledge of certain parts of the body better allows their selective recruitment [7]. Besides its usefulness, the extremely low compliance of patients to electrostimulation has also been assessed [20]. As a matter of fact, patients need to be undressed and experience the insertion of an anal plug; both details that strongly determine patients embarrassment and discomfort leading to the avoidance of this treatment. Therefore, the FMS is a relatively new technique that combines electrostimulation's usefulness to a higher compliance. FMS represents a novel application of a classic principle of physics: a flow of electrons within the field will be induced by a changing magnetic field. The pulsing of the magnetic field precisely induces small currents to flow in the tissue that has the role of inducing depolarization of nerve axons, leading in turn to a nerve impulse travelling both in proximal and distal directions. The subsequent relapse of acetylcholine will result in the depolarization and contraction of the corresponding muscle fibers; the key to the efficacy of FMS is the depolarization of nerve fibers as it induces the strengthening of the muscles. FMS clinical effect is changing the activity of muscle groups in the pelvic floor. The repeated activation of a muscle's activity caused by its nerves depolarization builds muscle strength and endurance. FMS is painless, and no electricity passes through the body, only a magnetic flux. Moreover, in functional electrical stimulation, a greater electrical current is needed to modulate the nerves because

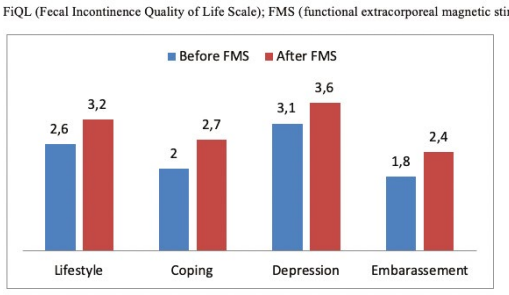

Figure 3: Modifications of the four domains of FiQL after FMS

Table 3: FI clinical items improvements. Values expressed as number of cases and percentage. FI (fecal Incontinence) FMS (functional extracorporeal magnetic stimulation); CCSFIS (Cleveland Clinic Faecal Incontinence Score); FiQL (Fecal Incontinence Quality of Life Scale);

Item	Patients improved after FMS	Percentage
CCSFIS	24/30	80%
FiQL	27/30	90%
Buttocks/adductor synergies	21/30	70%
Abdominal synergies	30/30	100%

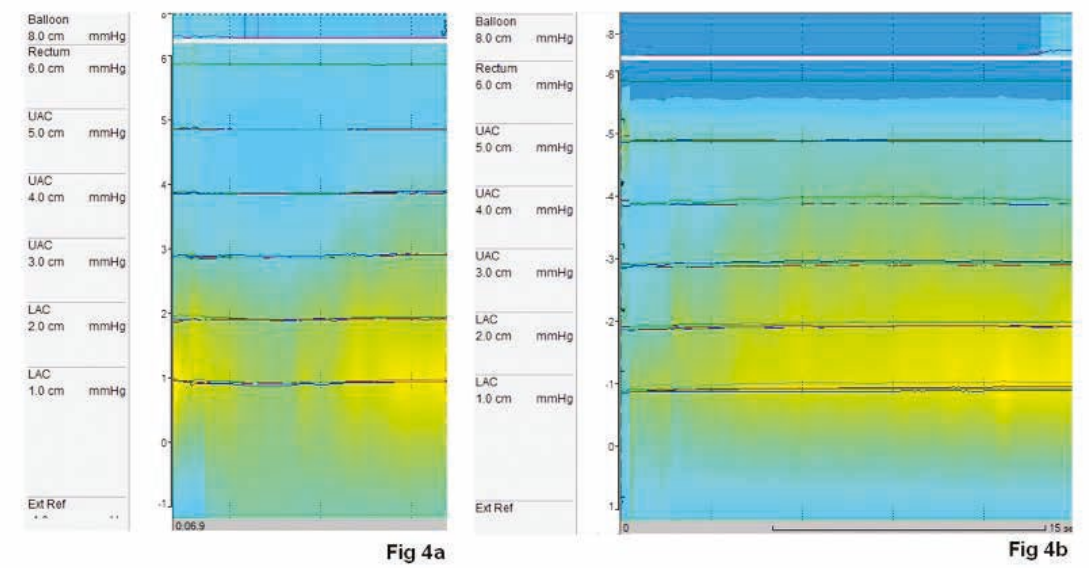

Figure 4: Pre FMS treatment (a) and post FSM treatment (b) HRAM (High Resolution Anal Manometry) showing no significant sphincteral improvement

of the high impedance of the tissues and bones than demanded by FMS [21].

Different studies have assessed FMS effectiveness in urinary incontinence [22]. Yamanishi et al examined the effects of magnetic stimulation as well; they studied how FMS augmented urethral closure in healthy volunteers. During pelvic floor stimulation, they demonstrated and recorded significant increases in maximum urethral closure pressures [23]. These above-mentioned principles studied in urinary incontinence are applicable also to fecal incontinence, although literature examining them is still meager. To the best of our knowledge, the current study is the first reporting the effectiveness and feasibility of FMS in the treatment of FI.

The present study included patients with idiopathic FI. In comparison with the baseline value, a statically significant improvement in CCFIS score was recorded: it was found to be decreased after the treatment period, with a mean value reduction of 60%, and an absolute mean value of 4.7. FMS clearly improved gas, liquid, solid stool leakage, and improved the satisfaction of all patients in our cohort, according to a statistically significant increase of all the four domains of FiQL values ($p>0.05$). This result attests the decrease of psychological distress related to the patients' clinical condition as well as a reduction of the forced everyday life changes imposed by the pathology. In our series we did not observe a significant improve in of basal pressure, maximum voluntary contraction, and duration of contraction at HRAM. This is apparently in contrast with the clinical parameters improvements recorded in our cohort. Most likely, the clinical symptoms relief is associated to a better recruitment of antagonist and agonist muscles, to the increase of strength and endurance of the pelvic floor muscles, and to the awareness of the pelvic floor itself acquired by the patients.

Therefore, compared to anal electrostimulation, FMS increases major patient compliance as it is painless, not invasive, and does not requiring undressing. FMS creates neural stimulation which can penetrate into all kinds of tissue with no attenuation; therefore, intensity of the energy is lower than anal electrostimulation, drastically reducing pain. Given lack of invasiveness, FMS might be particularly suitable for children as well, even if there a lack of results in literature remains. On the other hand, other kinds of conventional electro stimulations have been studied in children affected by pediatric voiding dysfunction, which have proved effective but uncomfortable. Undressing for attaching electrodes at every stimulation session can, in fact, make children nervous and noncompliant, and the required electrical stimuli for actual neural stimulation causes more pain and discomfort in children than in adults [24]. Yokoyama et al reported that frequencies of 20 to 50 Hz were effective for stress urinary incontinence and significantly increased the maximal intraurethral pressure [6]. Presently, no study reports the optimal pulse duration and frequency of FMS in FI. In our series, we adopted a frequency of 50–60 Hz for 15 minutes on the chair, once a week, for 8 weeks. A drawback of the FMS

treatment is certainly the cost. FMS, in fact, is an expensive method with the chair cost that is about 40.000 € [21]. Contrary to most authors [6,21,24], Voorham et al in their study of 74 patients affected by urinary incontinence, reported no differences in pelvic floor muscle activity, pad-test, QoL, voiding diary, and urodynamics in patients treated with FMS. Those authors underlined the importance of patient selection and concluded that 'the chair' is suitable to train awareness of the location of the pelvic floor, but the need for active pelvic floor muscle exercises remains [4].

The present study has some limitations. First is the small sample size, which precluded any analysis of the effect of covariates. In addition, the real question of neuromodulation is the long-term recurrence of symptoms when the neural stimulation treatment stops [25,26]. We do not yet have long-term follow-up data after stimulation, as the present study was prospective and focused on assessing FMS effectiveness and feasibility. Moreover, different programs of stimulation can be used by the physician to increase effectiveness and likely to reduce recurrence of the symptoms; thus studies on the appropriate duration of stimulation, combined treatments, and randomized controlled studies with a sham-stimulation group are needed.

5 Conclusions

FMS of the pelvic floor is an effective treatment for idiopathic fecal incontinence, resulting in patients improved QOL and decrease of incontinence scores, comparable to conventional anal electrostimulation. Extracorporeal magnetic stimulation is a comfortable technique as it avoids patient embarrassment through no need to get undressed; it also eliminates the discomfort and invasiveness related to the anal probe. Further long-term and comparative studies are needed to investigate the efficacy of the treatment in a large population with pelvic floor disorders.

Conflict of Interests: No author has a conflict of interest

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Nº 8

The use of Functional Magnetic Stimulation in the Treatment of Erectile Dysfunction

MJMR, Vol. 31, No. 3, 2020, pages (317-319). Abd El-Rahman et al.,

Research Article

The use of Functional Magnetic Stimulation in the Treatment of Erectile Dysfunction.

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Abstract
A previous study in humans has demonstrated that magnetic stimulation (MS) of the cavernous nerve produced an increase of the intracorporeal pressure and full penile erection. In view of these results, We tested the potential use of this procedure in humans with erectile dysfunction (ED). The study comprised 60 patients with ED (age 39.7±13.555 y). A hand peace was placed over the ventral aspect of the penis followed by FMS chair session. FMS was performed using a stimulation of 40% intensity, 10 Hz frequency, 10s on and 10 s off for 10 minutes duration followed by a stimulation of 40% intensity, 25 Hz frequency, 10s on and 10 s off for 10 minutes duration. In the healthy volunteers, the coil was placed as aforementioned but was not activated. The international index of erectile function showed a significant improvement in erectile function after the procedure.
Keywords: functional magnetic stimulation; erectile dysfunction; impotence; international index of erectile dysfunction; FMS chair; FMS hand peace.

Introduction

The causes of erectile dysfunction (ED) are different and include hormonal, neurogenic, psychological, arterial and venous disorders. Neurogenic disorders are caused by diseases or dysfunctions of the brain and spinal cord, cavernous, pudendal nerves and terminal nerve endings and receptors. The commonest hormonal disorder is diabetes mellitus. Arteriogenic impotence is often a component of systemic arterial disease. Abnormalities in venous flow can be due to a tunica albuginea defect, excessive or enlarged veins, or fibrous replacement of the smooth cavern muscles. Treatment for ED depends on the etiology. Several well-established processes have been developed.

However, the results are dissatisfying in many cases until now (Fishman 1986). Studies on dogs (Shafik 1994) and on patients with ED (Shafik 1996) have demonstrated that extra pelvic cavernous nerve (CN) stimulation effected full penile erection. Also preceding studies in patients with ED have demonstrated that Functional Magnetic Stimulation (FMS) of the CN is believed to be suitable for application in patients with ED and is effective in producing penile rigidity (Shafik et al., 2000). FMS has been used to activate the neuromuscular tissue and magnetic stimulators are applied for neurophysiologic investigations. Motor-evoked potentials were generated from the urinary bladder upon FMS of the cauda equina (Bemelmans et al., 1992).

Neuromodulation of detrusor hyperreflexia could also be achieved by FMS of the sacral roots (Sheriff et al., 1996). FMS produces its effect by creating, according to Faraday's law, an electric field which can stimulate the neuromuscular tissue (Barker et al., 1987).

A study on dogs (Shafik 1998) and another one on human healthy volunteers (Shafik and El-Sibai 2000) have demonstrated that sacral muscle of both the full and the empty rectum effected a significant increase in rectal and vesical pressures and a decrease in the anal pressure. Evacuation of the full rectum using intermittent Magnetic Stimulation (MS) was achieved. FMS was also used for the treatment of patients with constipation due to rectal inertia (Shafik 1998).

The efferent activity of the penis occurs in the 2nd ,3rd and 4th segments of the sacral spinal cord. These sacral nerves, known as erect nerves form three to six district tribes in men. They are united, to form the pelvic nerve that merges into the pelvic plexus. CN, the autonomic nerve of the penis, comes from the pelvic plexus. It moves along the posterolateral side of the prostate to approach the membranous urethra at the 3 and 9 o'clock positions. The nerves on either side proceed forward with medial inclination. They pierce the urogenital diaphragm to enter the corpora cavernosa at the 1 and 11 o'clock positions beneath the symphysis pubis (Shafik et al., 2000).

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Materials and Methods

After obtaining Institutional Ethical Committee approval and written informed consent, this study will be conducted on 60 adult male patients with ED aged from 18 to 70 years. They will be allocated into 3 groups (20 patients on each group): Group I (A group): Diabetic patients with ED, Group II (B group): Patients with venogenic ED and Group III (C group): Patients with psychogenic erectile dysfunction. The procedure will be performed without anesthesia and with the subject lying supine. A commercially available magnetic stimulator (TESLA Stym, Functional Magnetic Simulation (FMS), Iskara Medical, Ljubljana, Slovenia) with a FMS hand piece and FMS chair will be used in the study. Every subject will undergo 20 sessions. FMS was performed using a stimulation of 40% intensity, 10 Hz frequency, 10s on and 10 s off for 10 minutes duration followed by a stimulation of 40% intensity, 25 Hz frequency, 10s on and 10 s off for 10 minutes duration. In the healthy volunteers, the coil was placed as aforementioned but was not activated. The international index of erectile function showed a significant improvement in erectile function after the procedure.

Results

Our subjects were evaluated by IIEF questionnaire which is an internationally applicable questionnaire, a multidimensional scale and an effective and validated tool used to evaluate erectile function. It addresses the most relevant aspects of male sexual function, such as erectile strength, orgasm, desire, satisfaction with intercourse, and overall satisfaction. In the present study, response to this procedure showed that about 95% of the patients were either satisfied with the effect of the FMS sessions on their erections or reported improvement of their erections over the last 8 weeks of treatment. There was no significant between before and after treatment in group B regarding the sexual desire domain score, however there were significant difference between before and after the treatment in sexual function domain score in group A and group C.

There was significant difference between before and after the treatment regarding erectile function domain score, orgasmic function domain score, intercourse satisfaction domain score and overall satisfaction domain score. To our knowledge, there no any other previous study discussed the role of FMS in the treatment of the erectile dysfunction or evaluate the results with IIEF except (Shafik et al., 2000) who discussed the effect of magnetic stimulation in increasing the intracorporeal pressure of the penis.

Discussion

This study demonstrates the effectiveness of FMS in the treatment of erectile dysfunction. It seems that FMS has activated the cavernous nerve. The optimal site of the FMS hand piece was found to lie over the ventral of the penis.

FMS produces its effect by creating a magnetic field which, according to Faraday's law, generates an electric field that seems to activate the CN. When a time varying magnetic field is applied close to neuromuscular tissue, the induced electric field creates a current that can stimulate the neuromuscular tissue. The magnetic fields can pass through structures of high resistance like skin, fat and bone (Barker et al., 1987).FMS applicator, as it overlies the ventral of the penis, could stimulate the cavernous nerve and the deep dorsal nerve of the penis. The latter, arising from the pudendal nerve, proceeds forward through the suspensory ligament to lie over the dorsum of penis.

The branches of the cavernous nerve go along the back of the penis in the vicinity of the dorsal nerve of the penis. The dorsal nerve forms the afferent limb of the erectile reflex of the penis by transmitting sensory impulses to the skin of the penis, the glans and prepuce. In addition, it contains efferent autonomic fibers in some species. The physiological significance of these efferent pathways is uncertain. Researchers have postulated that such efferent contributions to the dorsal nerve of the penis control the blood vessels in the skin of the penis or modulate the sensitivity of afferent receptors. Activation of the cavernous nerve by FMS, as noted above, likely causes the smooth muscles that surround the lacunar spaces of the penis and helical arterioles to relax.

Theoretically, electrostimulation of the cavernous nerve, which is autonomic, induces changes in blood flow. Furthermore, Stimulation of the pudendal nerve, which is somatic,

with one-off 10 seconds causes contraction and relaxation of the ischiocavernosus muscle which leads to strength this muscle and increase its vascularity. Neither Shafik et al., 2000 nor any other previous studies discussed the role of FMS chair in the treatment of ED in humans before and many other studies considered Functional Magnetic Stimulation as a conservative, safe, non- invasive and effective intervention for the treatment of stress urinary incontinence by contraction of the pelvic floor muscles with simultaneous inhibition of the antagonistic reflex mechanism for emptying the bladder.

How neuromodulation works is not yet fully understood. FMS induced magnetic field which acts mainly on the membranes of the motor nerves. As a result, the muscle contraction resulting from FMS is most likely caused by depolarization of the motor nerves. Motor nerves that supplies pelvic muscles floor like levator ani and related sphincters. This act as pelvic motor floor exercise.

Conclusion

We can say that FMS is an effective, conservative, non-invasive and safe method in the treatment of erectile dysfunction. Thus, we recommend further studies should be undertaken to comprehensively analyze this option to the other options like medical and surgical options.

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Nº 9

Evaluation of Possible Side Effects in the Treatment of Urinary Incontinence with Magnetic Stimulation

medicina

MDPI

Systematic Review

Evaluation of Possible Side Effects in the Treatment of Urinary Incontinence with Magnetic Stimulation

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Abstract: *Background and Objectives*: Magnetic stimulation is a type of conservative treatment of urinary incontinence. Our aim was to evaluate the possible side effects of this method. *Materials and Methods*: We conducted a systematic literature review. The key search terms were urinary incontinence, magnetic stimulation, and female. All known synonyms were used. Results: 255 titles and abstracts were retrieved, and 28 articles met our inclusion criteria. Out of 28 studies, 15 reported no side effects, five reported side effects, and eight did not report anything. There was no significant difference in the incidence of side effects between the sham and active treatment groups. *Conclusions*: Side effects of magnetic stimulation in comparison to other active treatments are minimal and transient. Among the conservative UI treatment methods, magnetic stimulation is one of the safest methods for the patient and as such a suitable first step in treating UI.

Keywords: magnetic stimulation; urinary incontinence; female; treatment; side effects

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1. Introduction

Urinary incontinence (UI) is a common health, hygiene, social, societal, and economic problem, defined since 2002 as any involuntary leakage of urine by the International Continence Society (ICS) [1,2]. The etiology of UI is multifactorial because risk factors include age, pregnancy and childbirth (multiparous women), pelvic floor injury during vaginal delivery, pelvic surgery, menopause (due to decreased estrogen secretion), hysterectomy, increased body weight, lack of physical activity, urinary tract infections, chronic cough, prolonged heavy lifting, congenital weakness of connective tissue, and chronic constipation [1,3,4]. Several types of UI are known, and, based on the basic pathophysiological mechanisms that cause their onset, they are roughly divided into stress UI (urinary incontinence due to pressure or upon exertion), urgency UI (urgency urinary incontinence (UUI)), mixed UI (with characteristics of stress and urge UI), and overflow UI (involuntary release of urine due to an overfull bladder). In practice, however, the borders between different UI types are often blurred due to mixed etiology [1,3–5]. Nevertheless, UUI is only part of the syndrome known as overactive bladder (OAB) [1].

Most population studies from various countries have reported that the prevalence of UI ranges from around 25% to 45%. However, this figure is expected to be even higher because many affected women do not even address the problem with their general practitioner or gynecologist [4,6]. Due to the high prevalence of urinary incontinence, a number of treatments have emerged. A detailed diagnostic workup is important to classify the

type of urinary incontinence appropriately, which allows for further guidance in the treatment modality. Treatments vary according to the type of urinary incontinence and can range from conservative management to an invasive operative approach [4,7,8]. Recently, laser treatment, Er-YAG and CO2, and magnetic stimulation have been gaining popularity worldwide. The therapeutic role of laser treatment has been at the forefront of research. Despite studies that have confirmed subjective and objective improvements in the symptoms of patients with SUI, there is still a lack of quality evidence in the form of multicentric, randomized, and placebo-controlled studies [9–15].

On the other hand, magnetic stimulation (MS) is an approach to the conservative treatment of urinary incontinence, which was approved by the FDA in 1998 as a treatment option for UI with pelvic floor muscle stimulation [16]. Given the drawbacks of other conservative treatments for UI, such as the side effects of pharmacotherapy and the invasiveness of electrostimulation, vaginal cones, botulinum toxin A injections, percutaneous stimulation of the posterior tibial nerve (TMS), sacral nerve stimulation, bulking agent injections, and nonabsorbable transvaginal mesh and midurethral slings, research on MS is warranted, considering its inherent advantages: a non-invasive nature and patient acceptability [5].

MS is widely offered as a treatment for UI, although weak evidence of the short-term and long-term effects has been found in systematic reviews (SRs) and meta-analyses. EUA recommendations from 2020 advised not offering magnetic stimulation in the treatment of UI or OAB [17]. However, current EUA recommendations from 2023 no longer contain this statement in the recommendations [18].

2. Methods

To evaluate the possible side effects of MS in the treatment of UI, it is first necessary to present the basic principles and effectiveness of magnetic stimulation, magnetic stimulation vs. electrostimulation, and the possible side effects of MS. Because we were interested in determining whether published studies report and prove the side effects of MS in the treatment of UI, we conducted a systematic review.

The international standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to guide the methodology of this SR [19]. To comprehensively evaluate published studies, we conducted a systematic literature review search using Medline, Pubmed, Embase, Cochrane, and ClinicalTrials. All known synonyms were used for the following key search terms: urinary incontinence, magnetic stimulation, and female. All known synonyms were used for the selected words. We reviewed all research articles, with no lower or upper limit of publication year. The last search was conducted on 28 April, 2023. It should be noted that this article only focuses on research articles. We identified the potentially relevant research articles by examining the abstracts or articles as a whole. Titles and/or abstracts of the studies retrieved using the search strategy were screened independently by two review authors (M.P. and A.A.) to identify studies that potentially met the inclusion criteria of this review. The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by another author (D.L.). Any disagreement over the eligibility of particular studies was resolved through discussion with a fourth author (A.L.). We only focused on studies conducted on female patients, in which an MS stimulator was built into a chair.

3. Magnetic Stimulation

3.1. Basic Principle of Magnetic Stimulation

MS is the latest method used in the conservative treatment of UI, which is based on Faraday's law of induction. It follows the principle of magnetic induction, which triggers depolarization of the nerve fibers, which, in turn, causes passive muscle contraction (Figure 1) [16]. The primary goal of this method is to affect the sacral nerves (S2–S4) that innervate the bladder, urethra, vaginal and rectal walls, and pelvic floor muscles [20]. A time modulation of the magnetic current induces an electrical current, which triggers

depolarization of the nerve fibers and the consequent contraction of muscle tissue. Repeated activation of the nerve fibers and the subsequent muscle contraction increase muscle strength and endurance (Figure 2). The main and primary target in UI treatment is the afferent fibers of the pudendal nerve, which inhibit the bladder detrusor muscle via the central reflex [16,21]. This inhibition is the result of three activities:

1. Activation of the hypogastric nerve (Lat. *nervus hypogastricus*);
2. Direct inhibition of the pelvic plexus (Lat. *plexus hypogastricus inferior*);
3. Supraspinal inhibition of the detrusor reflex [21–23].

A second target important in UI treatment is the efferent nerve fibers, which, when activated, increase pelvic muscle strength and urethral sphincter tone, thus inhibiting the detrusor muscle via the guarding reflex [16]. Ultimately, the repeating muscle contractions work as passive Kegel exercises that stimulate the conversion of fast twitch muscle fibers into slow twitch muscle fibers, making the pelvic floor muscles stronger, more resilient, and more effective (Figure 2) [24].

Because the alternating magnetic field produced affects the afferent and efferent nerve fibers that innervate the bladder, which are located within the produced magnetic field, it can be speculated that, with MS, a better and stronger effect on the entire natural nerve biofeedback loop of the bladder can be achieved.

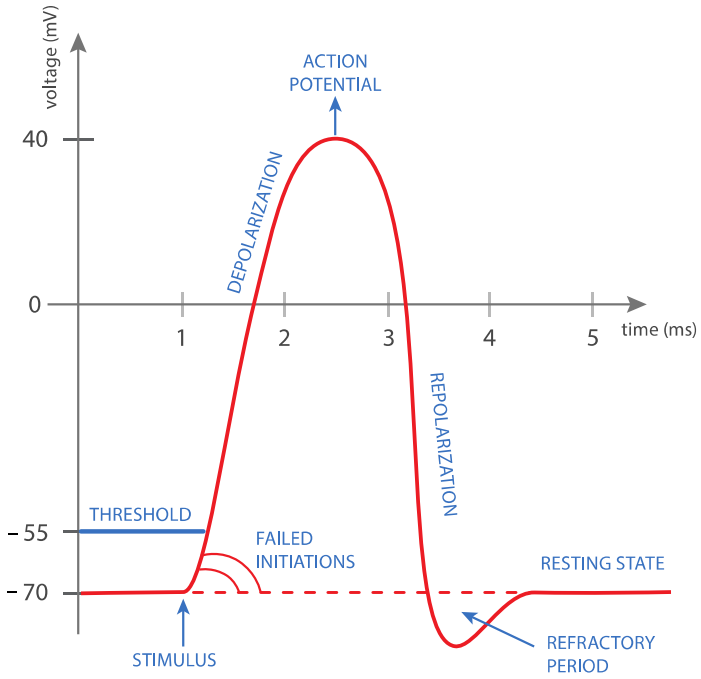

Figure 1. Rapid changes in magnetic field intensity induce an electrical current in the neuron. This phenomenon is called electromagnetic induction. Once the current reaches a certain value, a so-called neuron action potential is achieved. This causes the neuron cell to depolarize, which eventually leads to complete muscle contraction.

The magnetic field penetrates through the fibers without altering them significantly, and the magnetic field magnitude decreases in reverse proportion to the cube of the distance. The magnetic field current also runs uninterruptedly through clothes, and so patients do not have to take their clothes off during therapy. This is one of the advantages of MS compared to other UI treatment methods [25]. At present, UI is treated with MS therapy on a chair, which can contain only one magnetic field generator installed under the seat, and thus the closest to the pelvic floor muscles, or two generators, with the other one installed

in the lower part of the backrest, where it is closer to the sacral plexus (S2–S4) (Figure 3). This affects the UUI symptoms and signs [16,24]. Currently, a 3 T magnetic field is in use; this makes it possible to reach the targeted areas such as the sacral plexus and pelvic floor muscles, and, at the same time, as the measurements and information presented in the literature suggest, prevents tissue overload or overheating.

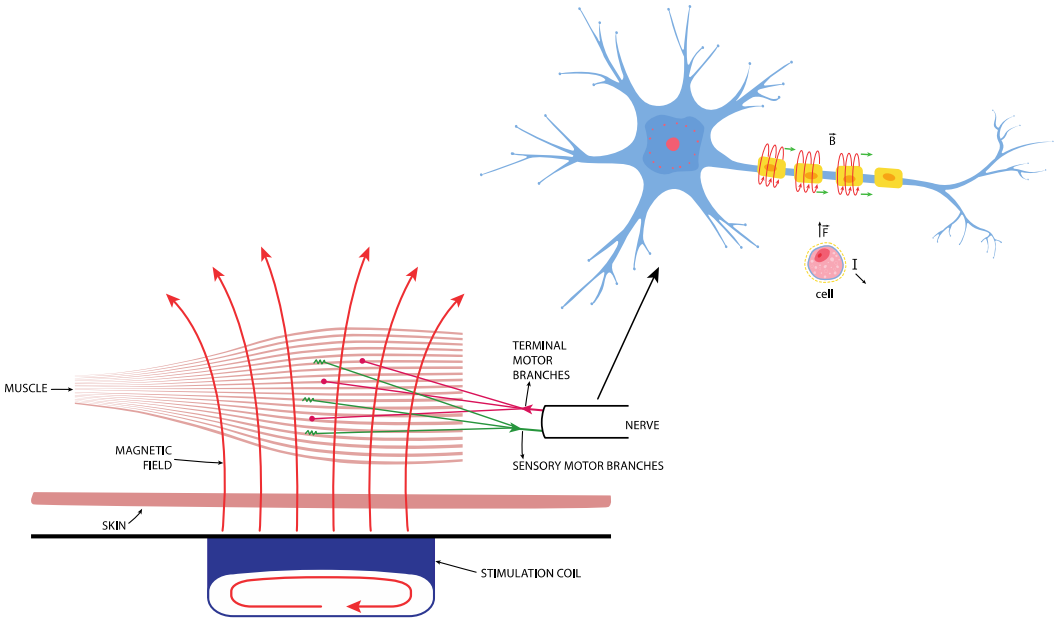

Figure 2. Repetitive effect of magnetic stimulation on the muscle.

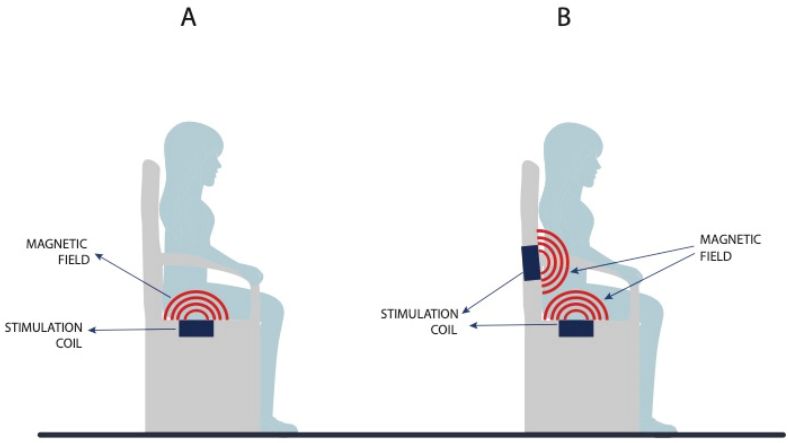

Figure 3. Difference between a magnetic chair with a single magnetic field generator (**A**) and two magnetic field generators (**B**).

The programs used in medical institutions to treat a specific type of UI differ by both the intensity and frequency of MS. What they have in common is lower and restricted frequencies (up to 35 Hz), which allow for the controlled rehabilitation of damaged tissue and hence prevent deterioration in already damaged tissue. SUI therapy uses higher frequencies because the main problem being addressed is the anatomy of the pelvic floor muscles, their endurance, and their strength. In contrast, the frequencies used in UUI treatment are lower. With UUI, the focus is less on the damage to the pelvic floor muscles

itself; rather, the focus is on the functioning of the nervous system and the psychological component, which have a strong impact on the success of MS treatment. The frequencies and intensities during therapies are also lower because we may be dealing with healthy muscles, where only the neural pathway is damaged or the sensitivity of the sensory fibers or the proper regulation of muscle groups is disrupted, which makes it impossible to detect the actual effect of MS on the patient. This can ultimately lead to adverse effects.

The intensity of MS is adjusted individually based on the patient's sensations, which makes the therapy more patient-friendly and tailored to an individual. There are breaks between individual MS applications to benefit both the device and the patient. The breaks and appropriate cooling methods prevent the device from overheating while retaining the optimal operational conditions during therapy. The breaks also allow for the patient's muscle tissues to relax, indirectly resulting in appropriate blood circulation in the areas exposed to MS therapy. The flow of fresh blood to the treated tissue supplies the necessary nutrients and removes the waste products generated by muscle contraction during therapy; this increases the effect of MS and reduces the likelihood of side effects.

However, because the programs used to treat UI with MS vary, additional clinical trials are required to standardize them.

3.2. Effectiveness of Magnetic Stimulation in the Treatment of UI

The success and effectiveness of treating UI with MS have been both subjectively and objectively proven in many studies. They have mainly been proven subjectively through questionnaires, such as the Incontinence Quality of Life (I-QOL) questionnaire, which showed improved quality of life after treatment with MS, and the ICIQ-SF questionnaire, which demonstrated improvement in symptoms of UI and improved quality of life [23,24]. In addition, the efficacy of treatment has been demonstrated objectively through urodynamic testing, which showed increased bladder volume at first sensation to void, along with increased maximum cystometric capacity and bladder compliance at maximum sensitivity [16,24]. The effectiveness of treatment can also be assessed through a bladder diary analysis, which examines the frequency of urination and the level of urgency before and after therapy. The effectiveness of treating UI with MS is estimated to be between 29–53% and 86–94% for SUI and between 20–25% and 50–85% for UUI [20]. The effectiveness of MS is influenced not only by clinical parameters (the severity and duration of illness, depression, etc.), but also various other factors (age, sex, financial status, etc.), which is why it should be assessed individually, together with the patient's medical history and clinical picture [26].

A meta-analysis by He et al., which examined 11 randomized controlled trials with a total of 612 patients, showed that MS is a method that decreases UI symptoms, alleviates UI frequency, increases the likelihood of becoming continent, and improves quality of life. It is especially well-suited to patients without sufficient motivation to perform regular pelvic floor muscle training [27]. Yamanishi et al. established that MS is an effective method of treating all types of UI, with recorded symptom improvements in 86% of SUI patients and 75% of UUI patients. Urodynamic testing showed that, in patients with SUI, the maximum intraurethral pressure increased by 34% during stimulation and maximum urethral closure pressure increased by 20.9%. In patients with UUI, significant increases in bladder capacities at first and maximum desire to void during stimulation were noted [20]. Similar findings were also presented by Lo et al., who reported that the efficacy of treatment with MS was 42.1% for SUI and 61.7% for OAB [28]. Lopopolo et al. proved the effectiveness of MS without adverse side effects in patients with MUI. The score of the ICIQ-UI-SF questionnaire decreased by 91% from the baseline, and the score of the ICIQ-OAB and IIQ-7 questionnaires decreased by 86% and 98%, respectively [29]. Gözlersüzer et al. concluded in their SR that MS treatment leads to an improvement in the symptoms of UI, in addition to associated improved quality of life for patients, without any reported side effects [30]. A meta-analysis by Peng et al., which looked at four randomized controlled trials involving a total 232 patients, showed a statistically significant improvement in symptoms in patients

with SUI after MS therapy, without any detected side effects. They observed statistically significantly fewer leaks/3 days, less urine loss on a 24 h pad test, higher QoL scores, and lower ICIQ scores [31]. In turn, a systematic review by Antić et al. summarized the efficacy of UUI treatment with MS [5].

Among other things, many clinical trials have also studied long-term improvements after therapy with MS. Yamanishi et al. proved the long-term efficacy of treatment [20]. Similarly, Yokoyama et al. showed that MS cured or improved the condition in 17 out of 20 patients with UUI, and that 53% of patients continued to feel the effect of treatment 24 weeks after the last therapy [32]. Ünsal et al. demonstrated that, after 1 year of treatment, the efficacy of MS is comparable to that of surgery in SUI [33]. In contrast, Doğanay et al. concluded that the effects of treating both SUI and UUI with MS were only temporary, with a high (53%) recurrence rate at 6 months [26]. Bradshaw et al. showed that the effects were only acute and not enduring, whereas Voorham-Vander Zalm et al. described post-treatment changes as statistically insignificant [34,35]. Mikuš et al. recently conducted a randomized controlled trial on the efficacy between Kegel exercises and MS in the treatment of female SUI. They concluded that patients treated with MS had a lower number of incontinence episodes, a better quality of life and higher overall satisfaction with treatment than patients who performed Kegel exercises. No side effects were reported in both groups [36].

After analyzing over 300 articles, the systematic reviews by Lukanović et al. and Antić et al. showed a need for further clinical trials to determine the entry criteria and diagnostic procedures for UI, and to standardize the MS treatment protocols. In addition, longer follow-ups are needed. These are issues that should urgently be addressed in further clinical trials [5,23].

3.3. Magnetic Stimulation vs. Electrostimulation

Electrostimulation and MS have been more recent conservative approaches to treating UI. In clinical application, the question often arises regarding which method is more suitable for the patient. Based on the findings in the literature to date, it can be concluded that MS is a good and effective method of treating UI, which causes fewer adverse side effects than electrostimulation [16,22,24,37,38]. Unlike electrostimulation, MS generally does not cause pain. In electrostimulation, the pulse amplitude falls off due to reflections at the boundaries between tissues with different impedance. Thus, to achieve the desired effect, higher electric currents must be delivered to the tissue, thereby activating pain receptors. The density of the magnetic field is the same inside and outside the tissue, which makes it possible to use magnetic fields that do not activate the C pain fibers in the skin [16,22,37]. A comparative study by Yamanishi et al. showed that MS resulted in a greater improvement in symptoms compared to electrostimulation. In addition, overactive detrusor contractions were inhibited in a certain percentage of patients treated with MS; however, the same was not achieved with electrostimulation [38]. The advantages of MS over electrostimulation were also shown by Silantyeva et al., who highlighted the fact that the generated magnetic fields can be used to cause muscle contractions deeper in the tissue [39]. In contrast, Fujishiro et al. established that MS has a stronger effect on the pudendal nerve than ES, which leads to a greater improvement in UI symptoms and signs [40]. A clear advantage of MS over electrostimulation is also evident in the method of application. In MS, the patient sits in the chair without the need to undress, whereas in ES, electrodes are inserted into the vagina or anus, which of course can cause discomfort for the patient. Most importantly, the patient must learn how to use the electrostimulation device properly, whereas with MS she can simply sit in the chair under the operator's supervision, without the need to learn and know anything in advance. Ultimately, there is also a great difference in terms of side effects: pain, bleeding, urinary tract infections, and mucosal irritation have been observed in electrostimulation, but not MS [20,25,38]. No adverse effects due to continuous MS were noted, which demonstrates its superiority compared to electrical stimulation with regard to pain or noninvasiveness [20].

3.4. Possible Side Effects of MS

Possibly the strongest evidence confirming the safe use of MS is the absence of side effects during and after the application of peripheral TMS on patients and after MRI (magnetic resonance imaging), which applies a strong and continuous electromagnetic field through the entire body [25,41]. Even though the research published to date has been dominated by studies that do not record any adverse effects (described below), the interest, in this study, was the possible adverse effects of MS treatment, based on the known facts about the effects of magnetic fields on the human body. Taking into account the theory behind MS, possible side effects could include the following:

1. Muscle overload: During therapies, the muscles that are located in the magnetic field of the MS device are constantly being activated by the device. If the magnetic field or the response of the patient's muscles is intense, there is a possibility of muscle overload, leading to a longer recovery rate and temporarily weakened muscles.
2. Tissue damage: Although MS is mostly used for tissue repair and faster healing, intense treatment with MS that does not leave adequate time for recovery between pulses/treatments can damage already weakened tissues [42–44]. There is a theoretical possibility of electrical overload of the nerve fiber with the induced current. This could only happen if the magnetic field was high enough and directly focused on an already damaged nerve, resulting in an unacceptable level of activity for physiological structures [45]. The actual probability of such a scenario is only theoretical and has never been mentioned or occurred during treatments. It is presumed that such high-voltage exposure would result in visible tissue damage such as burns, and invisible tissue damage such as permanent numbness and/or pain in the skin in the treated area. On the other hand, it is presumed that, if such an electrical overload of the nerve fiber occurred during MS therapy, this resulted in improvements in the final outcome for the patient—presumably by forcing the body to repair the nerve fiber by promoting nerve regeneration with increased blood flow, increasing serum ceruloplasmin expression, improving angiogenesis, and facilitating nerve fiber growth indirectly from vascular tropism. There is also some evidence that this would have positive effects on remyelination [46].
3. Reduction in or loss of sensation on the fibers: If the patient's nerves and tissue are exposed to an unsuitable duration and/or intensity of magnetic field during MS treatment, the result for the patient could be a tingling sensation, warm skin sensation, poor temperature perception, and so on. The recovery time in such scenarios is brief because it only affects the superficial nerves in the skin.
4. Ineffectiveness of MS therapy: The magnetic field density decreases by the cube root of length, which means that if we increase the distance from the magnetic-field-generating device to a specific point on the patient by a factor of two, we decrease the magnetic field density at the same spot by a factor of eight. We can conclude that the tissue closer to the device generating the magnetic field will always be exposed to a denser magnetic field. Knowledge of the effects and responsiveness of the patient's body to the magnetic field are crucial when treating deeper areas with MS.
5. Heating or overheating of affected tissues: By exposing the patient's body to the magnetic field, some energy is transferred to the patient's body in the form of heat. Very high and intense MS therapies could lead to heating and/or overheating in some parts of the tissue located in the magnetic field. Patients with cardiovascular problems are more affected by this issue because the blood flow is restricted, and thus the tissue-cooling is compromised. More attention should be paid to the patient when there is a risk of seminal fluid being affected by the accumulating heat and when the accumulating heat could lead to an increased risk of vaginal or bladder infection because of the faster development of bacteria in the body. These problems have never been mentioned in the literature and are, therefore, only theoretical. We can conclude that they have a very low probability of occurrence. This kind of side effect is normally avoided by the manufacturers of MS devices with longer pause

times in therapy programs that allow for heat to dissipate through the body faster that it can accumulate.

6. The effect of frequencies and magnetic fields on intestinal function and metabolism: During MS therapies, part of the intestine is located in the magnetic field. At present, no accurate measurement can be made determine the overall effect of MS on patients' intestinal function, organs, and metabolism. The majority of the empirical evidence shows that MS therapy affects patients' intestinal function in a beneficial way by increasing the metabolic rate, probably mostly through contractions in the surrounding muscles and tissue. Most patients feel a normal need to defecate or urinate after treatments with MS. However, this could lead to an altered metabolic rate, resulting in diarrhea or constipation.

Taking into account the theoretical background of MS, the absolute contraindications for using MS as a method of treatment include pregnancy, certain neurological conditions, active urinary tract infections, and connective tissue diseases.

Despite the theoretical predictions regarding the possible side effects of MS, the main interest was in their occurrence in clinical practice or, specifically, their frequency and type, and their impact on the individual's treatment satisfaction. In addition, the study also examined the safety of this conservative treatment method, which also greatly depends on the occurrence of side effects.

4. Results of Our Literature Review

A total of 255 titles and abstracts were reviewed, resulting in 141 unique full-text articles in English. In the end, 28 articles that met our inclusion criteria were identified (Figure 4). Fifteen of the included studies, involving a total of 774 patients, reported no side effects, seven of the studies did not mention the monitoring of possible side effects, and one study mentioned monitoring for possible side effects but failed to report whether they were present [16,20,21,23,25,26,28,29,32,33,38,47–58]. However, only five studies reported side effects [22,35,59–61]. In these five studies, involving 426 patients, side effects were only observed in 56 patients, of whom only 8 were part of the sham group. The results of studies reporting side effects are presented in Table 1.

The prospective, uncontrolled clinical trial focusing on treating SUI with MS conducted by Ismail et al. showed adverse effects in 25 patients (52.1%). Nine patients (18.8%) reported pain in the lower extremities, seven reported abdominal pain, six patients developed cystitis, and six suffered from indigestion. Other reported problems included back and neck pain, palpitations, and paresthesia. The dropout rate was 35.4%. Only in a third of cases was the occurrence of side effects reported as the reason for discontinuing UI treatment with MS [59]. Despite the occurrence of diarrhea and constipation in 16 (15.8%) patients in the active group and three (6.0%) patients in the sham group, Yamanishi et al. concluded that MS is a safe and effective method of treating UI. In addition, they established no statistically significant difference in the occurrence of side effects between the active and sham groups [22].

Lim et al. investigated the efficacy of MS in 120 patients with stress incontinence, establishing side effects in three (5.7%) patients in the active group and five (8.6%) patients in the sham group. They determined no statistically significant differences in the occurrence of side effects between the active and sham groups. The observed side effects included gluteal and pelvic pain, a yellow vaginal discharge, constipation, diarrhea, late periods, and dysuria [60]. A prospective randomized trial by Tezer et al., involving OAB patients with incontinence symptoms, showed no serious side effects. Three (8.5%) patients reported a temporary unpleasant sensation in the pelvic floor, and one patient (3%) reported that she was not feeling well. No patients dropped out of the trial [61].

Voorham et al. reported no side effects expressed by patients, but the EMG measurements of the pelvic floor muscle basal tone showed an increased basal tone in some patients, which they attributed to the effect of MS on the pudendal nerve [35].

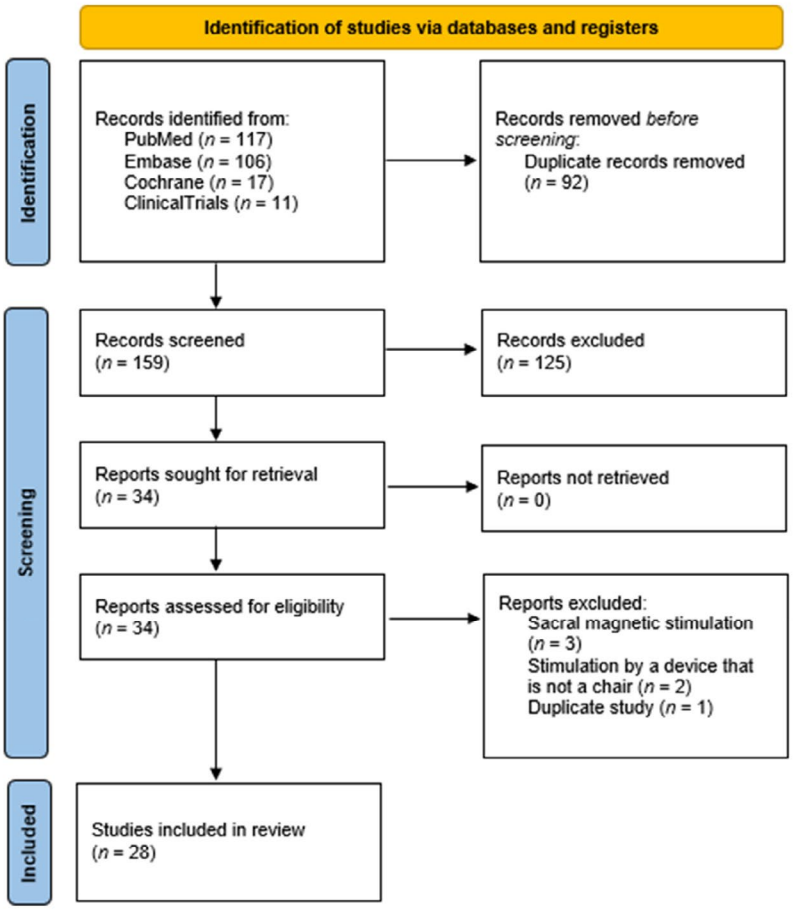

Figure 4. PRISMA flowchart.

The above suggests that the side effects of MS are not serious. It is also interesting that the trials comparing the active and sham groups established no differences in the occurrence of side effects between the two groups [22,60]. Is MS the real reason for this, or does this also involve some other component? It is already widely recognized that the severity of symptoms in SUI depends on previous physical fitness, lifestyle, and the anatomic relations in the pelvis, whereas the psychological component is very important in UUI. The latter can also explain the occurrence of side effects in the sham group. The study by Ismail et al. stands out in this regard because it reported more side effects than any of the other 27 reviewed studies. In addition, only a third of the dropouts were due to side effects [59].

What proves problematic is the fact that eight (28.5%) studies published on this subject did not monitor side effects. Because this therapy has not yet been fully established and included in the guidelines, more high-quality trials and an accurate recording of side effects are needed to objectively assess its safety and efficacy. Because the trials use various therapy programs to treat UI (with various densities and strengths of the magnetic field and various frequencies), it is unknown whether these side effects can be compared. This indicates a need to standardize therapy programs and consistently record side effects. Based on this, therapy programs could be compared and ultimately eliminated; this will provide evidence that MS is a safe and conservative method for treating UI.

Table 1. Results of studies reporting side effects. n—number, UI—urinary incontinence, SUI—stress urinary incontinence, UUI—urgency urinary incontinence, MUI—mixed urinary incontinence, MS—magnetic stimulation.

	Patients (n)	Type of UI	Treatment Regimen	Side Effects (n, %)	Examples of Side Effects (n)
Yamanishi et al. [22]	151	UUI	Active vs. sham in 2:1 order. Active: 25 min MS, 10 Hz continuously. Sham: 25 min MS, 1 Hz, alternating 5 s on, 5 s off. Twice a week, 6 weeks.	Active: 16 (15.8%) Sham: 3 (6.0%)	Diarrhea (6), constipation (3), myalgia (3), somnolence (3), flatulence (1), muscular weakness (1), pain in extremity (1), limb discomfort (1), back pain (1), . . .
Voorham et al. [35]	65	SUI, UUI, MUI	21 min MS SUI: 2 × 10 min at 50 Hz, 1-min break in between UUI: 2 × 10 min at 10 Hz, 1-min break in between MUI: 10 min at 10 Hz, 10 min at 50 Hz, 1-min break in between. Twice a week, 8 weeks.	0 patient reported	EMG registered rest tone of the pelvic floor muscles was higher after treatment.
Ismail et al. [59]	48	SUI	5 s on, 5 s off starting at 5 Hz, gradually increasing until 50 Hz. 2 × 10 min at 50 Hz, 2-min break in between. Twice a week, 8 weeks.	25 (52.1%)	Lower limb pain (9), abdominal pain (7), cystitis (6), bowel symptoms (6), backache (5), chair powerful (3), difficult positioning (2), tingling (2), perineal pain (2), neck pain (1), etc.
Lim et al. [60]	120	SUI	Active vs. sham in 1:1 order. 20 min MS Active: 8 s on, 4 s off at 50 Hz. Sham: 8 s on, 4 s off with tilted magnetic coil. Twice a week, 8 weeks.	Active: 3 (5.3%) Sham: 5 (8.6%)	Pain at gluteal muscles and hipbone, yellow vaginal discharge, constipation, diarrhea, mouth ulcer, delayer menstruation, burning sensation or difficulty in passing urine.
Tezer et al. [61]	76	UUI	Bladder training vs. bladder training + MS in 1:1 order. 20 min MS, 10 Hz continuously Twice a week, 6 weeks.	MS: 4 (11.5%)	Temporary discomfort due to pelvic floor pain (3), malaise (1).

Fifteen trials involving a total of 774 patients did not monitor side effects. They concluded that, compared to pharmacological therapy and electrostimulation, MS is a more pleasant method, with fewer side effects, that is non-invasive and safe [16,20,21,26,28,29,32,33,38,49,50,52–54,57]. However, the trials that also monitored the side effects showed that these were experienced by 56 patients (in absolute terms). This means that they were reported by only around 13% of all patients involved in trials that also monitored the side effects. Even though the side effects were recorded, they were described as minimal, temporary, and having no effect on the trial's success rate.

The systematic literature review by Lim et al. showed that, in the trials involving SUI and MS, adverse effects of the therapy were either not present or not monitored, whereas in trials in which UUI was treated with MS, the most frequently reported adverse effects included diarrhea, myalgia, and somnolence. Lim et al. concluded that, among conservative UI treatment methods, MS has rare and mild adverse effects [62]. In a later article, Lim et al. also reported that, despite the occurrence of adverse side effects, patients did not drop out of the trials because they did not experience them as a major burden. This suggests that these side effects are minimal and that MS is tolerable, nonpainful and causes no anxiety in the majority of patients [63].

Due to the vast variability in treatment programs between studies, it is difficult to comprehensively compare and analyze the data. Therefore, no meta-analysis was performed because the studies were clinically diverse, a meta-analysis may lead to biased results and genuine differences in effects may be obscured. Furthermore, many of the

included studies lacked a control group, which can limit the validity of the meta-analysis. We only focused on the treatment efficacy and side effects of magnetic stimulation, and we compared it to electrostimulation, which is the most similar treatment modality. To thoroughly assess the pros and cons of each type of conservative treatment, larger reviews should be carried out. Another limitation of our SR could be that only articles published in English were included.

5. Conclusions

The increasing awareness among patients that there are other, more conservative methods that can be used, in addition to surgical treatment, facilitates a more preventive approach. In this way, patients will not wait to seek medical assistance when they are already experiencing severe UI symptoms but will opt for preventive approaches and earlier treatment. MS is an effective, safe, and painless treatment method, which allows for the treatment of UI to begin before the symptoms seriously affect an individual's quality of life [25]. Nonetheless, further clinical trials are needed to more accurately define the optimal duration of MS therapy, suitable stimulation parameters, and a standardized protocol to ensure optimal efficacy. Standardizing the duration of the MS therapy program will make it possible to compare the results of various future trials. Despite the occurrence of side effects, these were not a reason for dropping out of the treatment. Noncompliance with treatment was primarily the result of long-term treatment, which is time-consuming, and a lack of portability. A technical limitation of MS as a method of treatment is also that it is not targeted but, due to the way in which the magnetic field penetrates the tissue, also affects the surrounding tissue. Nonetheless, this method is safe and effective.

Hence, MS could become the first-choice method for treating UI, especially in patients not responding to medication or those for whom medication causes adverse side effects. It could also be the best choice for patients that are not suitable for surgery, do not know how to or refuse to use electrostimulation electrodes, or fail to perform regular pelvic floor exercises [24]. Even though some studies also mention adverse effects of MS treatment, these are minimal and only temporary compared to other conservative treatment methods [62], do not require acute treatment, and do not put the patient's life in danger. Among the conservative UI treatment methods, MS is one of the safest methods for the patient and, as such, a suitable first step in treating UI.

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Nº 10

Treatment of Female Urinary Incontinence with Magnetic Stimulation: Is it Effective or Not?

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TREATMENT OF FEMALE URINARY INCONTINENCE WITH MAGNETIC STIMULATION: IS IT EFFECTIVE OR NOT?

Hypothesis/aims of the study

Urinary incontinence (UI) is becoming an increasingly common health problem around the globe, especially due to the growing share of the elderly population. In terms of etiology, several types of UI can be distinguished. UI treatment can be conservative or surgical, depending on several factors. Extracorporeal magnetic innervation (ExMI) is a conservative method that uses a magnetic field to stimulate the pelvic floor muscles by depolarizing the sacral nerve roots and causing contraction of the pelvic floor muscles.

This study assessed the success rate of ExMI in treating various types of UI. The following hypotheses were tested: 1) The success rate of using ExMI to treat UI differs by UI type; 2) UI improvement after ExMI therapy depends on patient age; and 3) ExMI intensity affects the success rate of UI treatment.

Study design, materials, and methods

A clinical prospective non-randomized study was carried out at the University Medical Center. It included 84 randomly selected female patients, irrespective of their UI type. During the first session, each patient completed an ICIQ-SF and Gaudenz questionnaire. This was followed by 10 therapies on an ExMI chair. Three months after the therapy was completed, each patient came for a check-up and completed the third part of the questionnaire. The results were statistically analyzed using the Wilcoxon matched pairs test and the McNemar test for dichotomous variables.

Results

The patients were 65.6 years old on average and 44% had a body mass index between 18.5 and 24.9. The majority of them (74.7%) reported moderate physical activity and 86.6% were postmenopausal. Nearly half (44.6%) had previously had gynecological surgery. Almost all of them (97.6%) had been treated for UI before entering this study, and just under half (47%) had already been receiving pharmacology therapy. Nearly half (48.8%) had experienced UI problems for less than five years.

As part of the study, results were obtained on the frequency of micturition, the amount of the urine leaked, the daytime frequency of urine leakage, the frequency of daytime and nighttime micturition, the circumstances of urine leakage, the number of pads used, and the assessed impact of UI problems on quality of life.

The results showed a statistically significant reduction in the frequency of urine leakage ($p = 0.012$) and the amount of the urine leaked ($p = 0.014$) in stress urinary incontinence (SUI) patients after therapy. Urge urinary incontinence (UUI) patients showed a statistically significant reduction in the frequency of urine leakage ($p = 0.001$), the amount of the urine leaked ($p = 0.001$), the daytime frequency of urine leakage ($p = 0.004$), the frequency of daytime micturition ($p = 0.003$), nighttime micturition ($p = 0.008$), and the frequency of nighttime micturition ($p < 0.001$) after therapy. In turn, mixed urinary incontinence (MUI) patients showed a reduction in the frequency of urine leakage ($p < 0.001$), the amount of urine leaked ($p = 0.003$), the daytime frequency of urine leakage ($p < 0.001$), and the frequency of nighttime micturition ($p = 0.001$) after therapy.

After therapy, a statistically significant reduction was evident in the impact of urine leakage on the everyday lives of SUI patients ($p = 0.002$). UUI patients showed a reduced impact of urine leakage on their everyday lives ($p = 0.001$). In addition, the number of pads used was also reduced ($p = 0.008$). MUI patients showed improvement in the following circumstances of urine leakage: before they managed to reach the bathroom ($p = 0.016$), when coughing or sneezing ($p = 0.039$), or when experiencing urine leakage for no special reason ($p = 0.008$). The impact of urine leakage on everyday life was reduced ($p < 0.001$) and so was the daily number of pads used ($p = 0.008$).

Interpretation of results

A statistically significant reduction in the frequency of urine leakage and a reduced amount of urine leaked was determined for all three UI types. A statistically significant reduction in the daytime frequency of urine leakage was determined only for UUI and MUI, and a reduction in the frequency of daytime and nighttime micturition was established for UUI. The use of pads was reduced for all UI types. Improvement was largely established in younger, premenopausal subjects that do not have a neurological disease and/or diabetes. No statistical correlation was established between the intensity of magnetic stimulation and the success rate of UI treatment.

Concluding message

Our results indicate that magnetic stimulation therapy for treating UI has a positive effect. The impact of urine leakage on everyday life was reduced in all UI types, and the stimulation intensity had no effect on the therapy success rate. UI improvement after ExMI therapy depends on the patient's age. Furthermore, the therapy demands good organization on the part of patients, which requires good personal motivation and more accessible ExMi devices.

Disclosures
Funding: NONE **Clinical Trial:** Yes **Public Registry:** No **RCT:** No **Subjects:** HUMAN **Ethics Committee:** Komisija za medicinsko etiko Ministrstva za Zdravje Republike Slovenije (Commission of Medical Ethics, Ministry of Health of Republic of Slovenia) Number: 0120-370/2016-2, KME 77/07/16 **Helsinki:** Yes **Informed Consent:** Yes

N° 11

The Short-Term Effect of Functional Magnetic Stimulation on Symptoms of Refractory Neuropathic Overactive Bladder Syndrome in Women

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THE SHORT-TERM EFFECT OF FUNCTIONAL MAGNETIC STIMULATION ON SYMPTOMS OF REFRACTORY NEUROPATHIC OVERACTIVE BLADDER SYNDROME IN WOMEN

Hypothesis / aims of study

Functional magnetic stimulation (FMS) has been approved as a conservative treatment method for overactive bladder syndrome (OAB) by the United States Food and Drug Administration in 1998 [1]. Since then, several studies have tried to evaluate the effect of this kind of treatment. Results of some of these studies and meta-analyses suggest that FMS improves OAB symptoms in the short- and medium-term, while others could not confirm its efficacy [1-3]. The aim of our study was to evaluate the short-term effect of FMS on bothersome lower urinary tract symptoms in women, who suffer from refractory neuropathic OAB. Neuropathic OAB is usually a consequence of nerve entrapment by disc protrusion, spinal stenosis or neural foramina narrowing. In our experience, these patients are especially difficult to treat, as the first- and second-line conservative therapy often does not result in improvement of their condition.

Study design, materials and methods

Women with OAB and coexisting chronic degenerative lumbar spine disease in whom first- and second-line conservative therapy did not relieve the symptoms were included in this prospective study. Contraindication for participation in the study were pregnancy, active urinary tract infection (UTI) and implanted pacemaker or cardioverter defibrillator. Women who were taking an anticholinergic or beta-agonist were able to continue with the therapy during stimulation.

Before FMS, a thorough urogynaecological history was taken in each patient. Then, an urogynaecological examination with transvaginal ultrasound, the Q-tip test, stress test and urinary flowmetry with post-voiding residual volume measurement were performed. Patients also filled out the following questionnaires: *Incontinence Impact Questionnaire 7* (IIQ-7), *Urogenital Distress Inventory 6* (UDI-6), *Patient Perception of Intensity of Urgency Scale* (PPIUS), and *Urinary Incontinence Quality of Life Scale* (I-QOL) along with a three-day bladder diary.

FMS was performed using “magnetic chair”, which stimulates lumbar and pelvic area simultaneously. Each patient received 16 FMS courses in 2 months, meaning on average 2-3 courses per week. Approximately 1 month after the therapy, a brief urogynaecological history was taken and the patients filled out the questionnaires and the bladder diary once again.

Descriptive statistics were used to describe basic patients’ characteristics. Non-parametric paired samples test was used to compare results before and after FMS. Statistical significance was set at $p<0.05$.

Results

Thirteen women were included in the study; one was excluded because she developed an UTI right after the beginning of the FMS. Overall, 12 patients were included in the analysis. Their average age was 63±15 years (range 23-75 years), ten patients (83.3%) were menopausal, and 10 (83.3%) were taking an anticholinergic or beta-agonist before and during FMS.

When comparing number of daytime and night-time voids, number of pads used per day, PPIUS score, and urgency symptoms bother score, there was a statistical significant decrease in all variables except number of pads used per day (table 1).

Table 1: Comparison of number of daytime and night-time voids, number of pads used per day, PPIUS score, and urgency bother score before and after FMS.

Variable	Before FMS	After FMS	p-value
Number of daytime voids [No±SD, range]	8.2±3.4 (3.5-13)	5.9±3.1 (1.5-11)	0.007
Number of night-time voids [No±SD, range]	5.2±5.5 (2-20)	2.7±2.7 (0-9)	0.005
Number of pads used per day [No±SD, range]	2.5±2.8 (0-8)	2.1±2.2 (0-6)	0.197
PPIUS [value±SD, range]	3.2±0.7 (2-4)	2.5±0.9 (1-3,5)	0.016
Urgency bother score [values±SD, range]	68.7±15.6 (44-90)	52.7±26.4 (5-80)	0.008

When comparing questionnaires’ scores before and after FMS, there was a statistically significant decrease in UDI-6 and IIQ-7 scores. Although all of the I-QOL components and the total score improved after the FMS, the difference was not statistically significant.

Table 2: Comparison of UDI-6, IIQ-7, I-QOL Avoidance, Psychosocial Impact, Embarrassment, and Total scores before and after FMS.

Variable	Before FMS	After FMS	p-value
UDI-6 [value±SD, range]	75.4±24.7 (25-100)	34±19.5 (0-62.5)	0.004
IIQ-7 [value±SD, range]	65.5±33.5 (0-95.1)	15.8±16.9 (0-52.4)	0.004
I-QOL Avoidance [value±SD, range]	18.3±9.2 (9-35)	22.8±8.6 (12-38)	0.059
I-QOL Psychosocial Impact [value±SD, range]	20.9±9.7 (9-39)	26±11.1 (14-44)	0.075
I-QOL Embarrassment [value±SD, range]	12.8±5.4 (7-24)	14.5±5.7 (9-25)	0.245
I-QOL Total [value±SD, range]	51.9±23.6 (28-98)	63.3±24.3 (38-106)	0.054

Eleven (91.7%) patients would recommend FMS to their friends. Only two (16.7%) stated their condition did not improve after the stimulation, one of them was found to develop an UTI immediately after the FMS and was treated appropriately. Five (41.7%) women were extremely satisfied, one (8.3%) very satisfied, and four (33.3%) satisfied with the results of FMS.

Interpretation of results

According to our results, FMS significantly decreases the number of daytime and night-time voids in women with refractory neuropathic OAB. It does not seem to decrease the number of pads used per day, but in our experience, some women keep on using pads because of the feeling of safety rather than the incontinence episodes. Moreover, FMS significantly improves PPIUS, urgency bother, UDI-6, and IIQ-7 scores, but the difference in I-QOL scores was not statistically significant. It seems that FMS has some positive short-term effect on lower urinary symptoms of the group of patients, which we often find most difficult to treat. The therapy was well accepted by the patients. Some of them experienced lower back or back thigh pain during stimulation, but the pain was only transient and subsided after the stimulation. In the future, it would be necessary to determine the duration of these positive effects and evaluate whether these patients would benefit from repetitive FMS courses.

Concluding message

FMS significantly improves bothersome lower urinary tract symptoms in women, who suffer from refractory neuropathic OAB, and decreases the number of daytime and night-time voids in the short term.

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Disclosures

Funding: The magnetic chair prototype was donated to us by Iskra Medical company for the time of the study. **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Institutional Review Board of University Medical Centre Maribor **Helsinki:** Yes **Informed Consent:** Yes

Nº 12

The Duration of Effect and Satistfaction Rate of Functional Magnetic Stimulation in Women with Refractory Neuropathic Overactive Bladder Syndrome

14 - THE DURATION OF EFFECT AND SATISFACTION RATE OF FUNCTIONAL MAGNETIC STIMULATION IN WOMEN WITH REFRACTORY NEUROPATHIC OVERACTIVE BLADDER SYNDROME

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INTRODUCTION AND AIM OF THE STUDY

In 1998, the United States Food and Drug Administration approved functional magnetic stimulation (FMS) as a conservative treatment method for overactive bladder (OAB) syndrome. Different studies and meta-analyses have suggested that FMS improves OAB symptoms in the short- and medium-term, while others could not confirm its efficacy [1-3]. The aim of our study was to focus on the effect of the FMS on OAB symptoms in women with refractory neuropathic OAB. Neuropathic OAB is usually a consequence of nerve entrapment by disc protrusion, spinal stenosis or neural foramina narrowing. In our experience, these patients often do not respond to the first- and second-line conservative therapy and are especially difficult to treat.

MATERIALS AND METHODS

This was a small prospective cohort study. Women with OAB and coexisting chronic degenerative lumbar spine disease in whom first- and second-line conservative therapy did not relieve the symptoms were included. Contraindication for participation in the study were pregnancy, active urinary tract infection (UTI), and implanted pacemaker or cardioverter defibrillator. During FMS, women were able to continue with their regular pharmacological therapy for OAB. Institutional review board ethical approval was obtained.
Before FMS, we performed a complete urogynaecological work-up in each patient. Patients evaluated the bothersomeness of their OAB symptoms on a scale from zero (not bothersome at all) to 100 (very bothersome) and filled out the following questionnaires: Incontinence Impact Questionnaire 7 (IIQ-7), Urogenital Distress Inventory 6 (UDI-6), and Patient Perception of Intensity of Urgency Scale (PPIUS). Urine analysis and urinary culture were also performed to exclude an underlying UTI.
FMS was performed using a “magnetic chair”, which stimulates both lumbar and pelvic area simultaneously. Each patient received 16 FMS courses in 2 months (2-3 courses per week). We performed a follow-up of these patients up to three months (FU-3) and twelve months (FU-12) after the treatment. At the follow-up, patients evaluated their satisfaction with FMS, the bothersomeness of their symptoms and again completed the questionnaires. Moreover, they evaluated the duration of effect of FMS on their OAB symptoms. Results were analysed using SPSS Statistics programme. Descriptive statistics were used to describe basic patients’ characteristics. Non-parametric paired samples test was used to compare results before and after FMS. Statistical significance was set at $p<0.05$.

RESULTS

Thirteen women were included in the study; one was excluded because she developed an UTI right after the beginning of the FMS. Overall, 12 patients were included in the analysis. Their average age at the beginning of FMS was 63±15 years (range 23-75 years). Ten patients (83.3%) were taking an anticholinergic or beta-agonist before and during FMS. All patients attended FU-3 and eleven patients were available for the FU-12.
When comparing results before FMS and FU-3, there was a significant improvement in daytime frequency ($p=0.007$), nocturia ($p=0.005$), bothersomeness of OAB symptoms, and UDI-6 ($p=0.004$), IIQ-7 ($p=0.004$) and PPIUS scores ($p=0.016$). At FU-12, 10 out of 11 patients (90.9%) stated that their OAB symptoms have recurred. However, the difference in patients’ outcomes between FU-3 and FU-12 was significant for daytime frequency only ($p=0.034$) (table 1). The average duration of FMS effect was 5 months (range 2-6 months).

Table I: Comparison of patients' outcomes before FMS and at the three-month and twelve-month follow-up

Parameter	Before FMS	FU-3	FU-12
Frequency [No±SD, range]	8.2±3.4 (3.5-15)	5.9±3.1 (1.5-11)	7.2±4.2 (2.5-16)
Nocturia [No±SD, range]	5.2±5.5 (2-20)	2.7±2.7 (0-9)	3±2.2 (1-8)
Bothersomeness of OAB symptoms [value±SD, range]	68.7±15.6 (44-90)	52.7±26.4 (5-80)	57.8±27.4 (8-100)
PPIUS [value±SD, range]	3.2±0.7 (2-4)	2.5±0.9 (1-3.5)	2.9±0.8 (2-4)
UDI-6 [value±SD, range]	75.4±24.7 (25-100)	34±19.5 (0-62.5)	50±19.4 (16.6-79.1)
IIQ-7 [value±SD, range]	65.5±33.5 (0-95.1)	15.9±16.9 (0-52.4)	37.6±34.9 (0-95.1)

At FU-3, only two women (16.7%) stated their condition did not improve after the stimulation; one of them was found to develop an UTI immediately after the FMS and was treated appropriately. Five (41.7%) women were extremely satisfied, one (8.3%) very satisfied, and four (33.3%) satisfied with the results of FMS. At FU-12, again only two patients (18.2%) stated their condition did not improve after FMS, two (18.2%) were extremely satisfied, one (9.1%) very satisfied, six (54.5%) satisfied, and two (18.2%) only partially satisfied with the results. All patients would recommend FMS to their friends. Out of ten symptomatic patients, nine would decide for another course of FMS treatment.

INTERPRETATION OF RESULTS

According to results of our small prospective study, FMS improves OAB symptoms in women with refractory neuropathic OAB. FMS significantly decreased daytime frequency, nocturia, bothersomeness of OAB symptoms, PPIUS, UDI-6, and IIQ-7 scores. However, the symptoms tended to recur after approximately 5 months post FMS, although there were no statistically significant differences in patients' outcomes between the three-month and the twelve-month follow-up. The therapy was well accepted by the patients, although some of them experienced some transient lower back or back thigh pain during stimulation. All patients would recommend FMS to their friends and almost all would decide for another course of FMS treatment. In the future, it would be reasonable to assess the effect of repetitive FMS on OAB symptoms in a larger number of patients and to determine whether FMS could serve as an adjunct to pharmacological therapy in patients with refractory OAB before referring them to more invasive treatments such as intra-vesical injection of botulinum toxin or sacral nerve stimulation.

CONCLUSIONS

In patients with refractory neuropathic OAB, FMS offers significant short-term improvement that lasts approximately 2-6 months.

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Nº 13

Magnetic Stimulation in the Treatment of Female Urinary Incontinence in Women

64 - FUNCTIONAL MAGNETIC STIMULATION IN THE TREATMENT OF URINARY INCONTINENCE IN WOMEN

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INTRODUCTION AND AIM OF THE STUDY

Undesired, uncontrolled leakage of urine occurs when the sphincter muscles, the muscles of the pelvic floor and bladder muscles do not work properly and consistently. Pelvic floor muscles training (PFMT) is a first-line conservative treatment for all types of incontinence in women. Functional magnetic stimulation (FMS) allows automated and standardized pelvic floor muscles training.
During magnetic therapy, a focused, time-varying magnetic field penetrates into the perineum and activates the motor neurons of the pelvic floor muscles. The pelvic muscles contract and relax with each magnetic pulse, thereby strengthening the muscles. The goal of the therapy is the rehabilitation of the pelvic floor musculature to reduce urinary incontinence.

MATERIALS AND METHODS

From 57 women included in the study of effects of an FMS, 15 suffered from urge urinary incontinence (UUI), 25 from stress urinary incontinence (SUI), 17 from mixed urinary incontinence (MUI). All patients were treated with FMS twice a week for 8 weeks (16 therapies in total) using the treatment protocol adequate for the type of urinary incontinence. The results were obtained using a patient self-evaluation questionnaire and collected before starting the treatment and after finishing the last therapy.
The patient seated dressed on an electromagnetic chair. It was used Magneto Stym device, Iskra Medical, with magnetic field power of 2 Tesla and frequency range of 1-80 Hz. Magnetic stimulation of the muscles is conducted by an electromagnetic coil built into the seat and controlled by an external unit. The stimulus intensity is gradually increased up to the limit of tolerability as indicated by the patient.
FMS is not appropriate for patients with a history of epilepsy, severe cardiac arrhythmias, a pacemaker or metal implants, as well as concurrent pregnancy, malignancy, or acute pelvic infections.

RESULTS

58% of patients suffering from UUI were completely dry, 31% of patients showed significant improvement and 11% did not show any improvement after the treatment. 80% of patients suffering from SUI were completely dry after the therapy, 15% of patients showed significant improvement and 5% did not show any improvement. 69% of patients suffering from MUI were dry, 29% of patients showed significant improvement and 2% of women did not show any improvement (Fig.1, 2).

INTERPRETATION OF RESULTS

FMS treatment showed immediate and effective outcome in properly chosen patients, especially in the frequency of micturition, episodes of incontinence and nocturia. FMS has presented as reliable and repeatable, non-invasive treatment for urinary incontinence in women with favourable initial efficacy and perspective future. Also, frequency and urgency symptoms of patients were decreased with this method.

CONCLUSIONS

The presented patient's improvement and their positive feedback confirm previous literature reports that magnetic stimulation is an effective non-invasive therapy for all types of incontinence. It is, however, necessary to emphasize that the presented results are based on the patient's personal observations revealed in a questionnaire. Since patient satisfaction is an important part of every rehabilitation and medical treatment, the goal is achieved with magnetic stimulation therapy.
With the aid of the electromagnetic chair, patients also learned how to perform pelvic floor muscle exercises themselves. This is going to help them maintain muscle strength after the conclusion of the therapy. The 8-week therapy block offers a good basis for the long-term pelvic floor muscles ability for urine flow control. However, the muscles need to stay active in order to maintain their strength and function (Doğanay et al., 2010). This is achieved by performing regular Kegel exercises correctly by the patients themselves.
One of the limitations of the present study is the lack of a control group. It is difficult to design an effective placebo treatment because the patients are aware of the strong contractions of the pelvic floor muscles during the treatment.
Further studies are required to determine other diagnostic parameters and the need to include a control group. However, based on the presented results, it can be concluded that magnetic stimulation therapy offers a suitable alternative treatment option for all types of female urinary incontinences.

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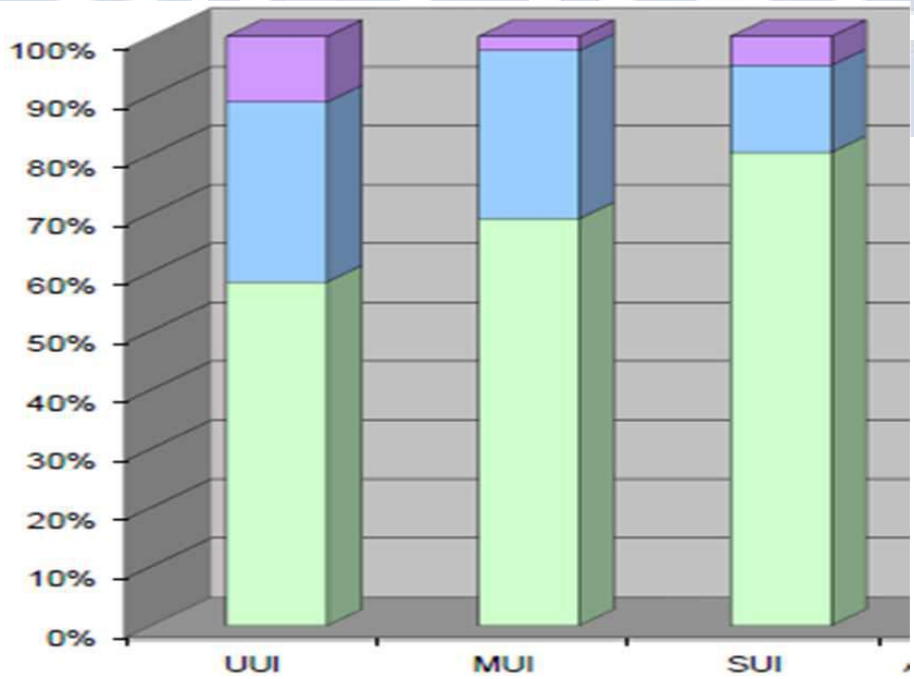
Figure 1.

	UUI		MUI		SUI	
	N	%	N	%	N	%
Completely dry	9	58	11	69	19	80
Significant improvement	4	31	5	29	4	15
No improvement or insignificant improvement	2	11	1	2	2	5
All	15	100	17	100	25	100

Figure 2.



Nº 14

Effects of the functional magnetic stimulation on the urinal incontinence in persons with multiple sclerosis (MS): The introduction and the results.

Effects of the functional magnetic stimulation on the urinal incontinence in persons with multiple sclerosis (MS): The introduction and the results.

Purpose

Functional magnetic stimulation (FMS) with a magnetic probe installed in the centre of a special chair is used for treating different types of incontinence. The used magnetic field reaches strengths up to 2 T. This field causes the muscles of the pelvic floor to contract. Each interval of contraction lasting 6 seconds is followed with 6 second interval of rest. The therapy lasts for 20 minutes. The appropriate program of stimulation is chosen from the device's programs based on the type of the incontinence (urgent, mixed or stressed) diagnosed by the doctor. Therapy is performed at most every second day. Important aspect of this kind of therapy is its non-invasiveness and the fact that the patient can stay dressed. The purpose of this study was to determine if the FMS therapy with 6 treatments in 14 days can significantly improve the incontinence problems in persons with multiple sclerosis (MS).

Sample

The sample included 58 persons with MS who visited natural spa Terme Topolscica (Topolscica, Slovenia) for a restorative rehabilitation, consented to treatment of miction problems with FMS and had no contraindications. We calculated statistics for 56 persons form the sample that had problems of urgent incontinence and patients with problems with urgent incontinence combined with the stress incontinence (mixed incontinence). The remaining 2 persons were excluded because their stress incontinence was not a consequence of MS. The study was started on 26.1.2015 and concluded on 18.4.2015

In the sample there were 43 females and 13 males (56 persons all together). The youngest person was 22 years old and the oldest 73 years old. The mean age was 52.89 years.

They were diagnosed with MS from 1 to 40 years before the start of the study. The mean time since the diagnosis to the beginning of the study was 13.88 years.

37 person had urgent incontinence and 19 persons had mixed incontinence.

Method

At the beginning of the restorative rehabilitation every person from the sample was thoroughly interviewed about their problems with urination. Based on the interview diagnosis was made. If there were no contraindications and the person agreed to the treatment with the FMS the most appropriate program was selected

At the beginning of the therapy every person was interviewed with a validated questionnaire for miction problems (IPSS – the international questionnaire about symptoms related to prostate problems). We choose this questionnaire despite it being made for detection of symptoms of prostate problems because it includes all the important questions for diagnosis of urination problems

Questions in the questionnaire regard problems with incomplete emptying of the bladder, frequency of urination, interruptions to urination, urgency of the urination, the strength of the flow, the

exertion needed to urinate, urination during the night and how urination affects the quality of the living. The participant is asked to rate the question with numbers from 0 to 5. The smaller the number the less severe the problem is judged to be. The quality of living is measured on the scale from 0 to 6, smaller number means better quality of living.

After 6 FMS therapies we repeated the interview with the IPSS and again after one month after the last FMS. The first two interviews were done in person and the last one over the phone.

All the data were entered in to the SPSS (program for statistics) and a simple t test was performed.

Results

1. Incomplete emptying of the bladder. How many times in the last month did you have a feeling of incomplete emptying of the bladder? The possible answers:
   0- never
   1- less than 1 time per 5 urinations
   2- with less than half of the urinations
   3- with half of the urinations
   4- with more than half of the urinations
   5- almost always

Before the therapy the average of result was 2.482, after conclusion of the therapy the average of result was 1.768, after one month after the therapy the average of results was 1.250. The improvement in the feeling of incomplete urination after one month was 1.232.

The difference was statistically significant with $p < 0.001$.

2. Frequency of urination. How many times in the last month did you had to urinate less than 2 hours after the last urination? The possible answers:

0- never
1- less than 1 time per 5 urinations
2- with less than half of the urinations
3- with half of the urinations
4- with more than half of the urinations
5- almost always

Before the therapy the average of result was 3.036, after conclusion of the therapy the average of result was 2.375, after one month after the therapy the average of results was 2.018. The improvement in the frequency of urination after one month was 1.018.

The difference was statistically significant with $p < 0.001$.

3. Interruptions to the urination. How many times in the last month did you experience interruption to the flow of the urine and had to start the urination several times? Possible answers:
   0- never
   1- less than 1 time per 5 urinations
   2- with less than half of the urinations
   3- with half of the urinations
   4- with more than half of the urinations
   5- almost always

Before the therapy the average of result was 2.143, after conclusion of the therapy the average of result was 1.625, after one month after the therapy the average of results was 1.411. The improvement in interruptions to the urination after one month was 0.732.

The difference was statistically significant with $p < 0.001$.

4. Urgency of urination: How often did you have problems delaying urination in the last month? The possible answers:
   0- never
   1- less than 1 time per 5 urinations
   2- with less than half of the urinations
   3- with half of the urinations
   4- with more than half of the urinations
   5- almost always

Before the therapy the average of result was 3.232, after conclusion of the therapy the average of result was 2.464, after one month after the therapy the average of results was 2.054. The improvement in the feeling of urgency of urination after one month was 1.178.

With $p < 0.01$.

5. Weak urine flow: How many time in the last month did you have a weak flow of urine? Possible answers:
   0- never
   1- less than 1 time per 5 urinations
   2- with less than half of the urinations
   3- with half of the urinations
   4- with more than half of the urinations
   5- almost always

Before the therapy the average of result was 1.929, after conclusion of the therapy the average of result was 1.214, after one month after the therapy the average of results was 1.000. The improvement in the weak urine flow after one month was 0.929.

The difference was statistically significant with $p < 0.001$.

6. Exertion needed to urinate: How many times in the last month did you have to exert yourself to achieve urination? Possible answers:
   0- never
   1- less than 1 time per 5 urinations
   2- with less than half of the urinations
   3- with half of the urinations
   4- with more than half of the urinations
   5- almost always

Before the therapy the average of result was 0.982, after conclusion of the therapy the average of result was 0.464, after one month after the therapy the average of results was 0.393. The improvement in the exertion needed to urinate after one month was 0.589.

The difference was statistically significant with $p < 0.001$.

7. Urination during the night: How many times per night do you on average have to get up to urinate? Possible answers:
   0- never
   1- 1x
   2- 2x
   3- 3x
   4- 4x
   5- 5x or more

Before the therapy the average of result was 2.196, after conclusion of the therapy the average of result was 1.518, after one month after the therapy the average of results was 1.036. The improvement in the urination during the night after one month was 1.160.

The difference was statistically significant with $p < 0.001$.

8. Quality of life: How would you feel if you had to live for the rest of your life with your current state of urination: Possible answers:
   0- happy
   1- content
   2- mildly content
   3- mixed feelings
   4- mostly discontent
   5- unhappy
   6- miserable

Before the therapy the average of result was 2.536, after conclusion of the therapy the average of result was 1.929, after one month after the therapy the average of results was 1.554. The improvement in the urination during the night after one month was 0.982.

The difference was statistically significant with $p < 0.001$.

Discussion

On the basis of this study we can conclude that the most common problems of persons with MS are the frequency of urination, feeling of incomplete emptying of the bladder, urgency of urination and urination during the night.

The FMS therapy showed to be most effective in treating the feeling of incomplete emptying go the bladder, urgency of urination, night urination and the frequency of urination. In all cases improvement was more than one point.

In addition the persons in the sample noticed improvements in bowel movement, lessening of lower back pains and hips. One of the males reported return of night erections. Several reported reduced need to go to the toilet during swimming sessions in thermal water. Women reported that they were noticeably more relaxed during strolls as they no longer had to plan for possible needs to go to the toilet. To evaluate these effects we would need to complete another study as they were not the object of this one.

At the conclusion here are some things people told to the nurse Mirijam after the conclusion of the interview:

During the sessions on the chair I learned how to do kegel exercises in the correct manner.

My bowel movements were improved after the chair sessions.

The chair rocks!

The chair is just the thing!

I am really happy because I no longer have so many problems with urination.

Acknowledgment: Special thanks goes to the nurse Mirijam Salobir for performing interviews and for work with the patients during the therapy.

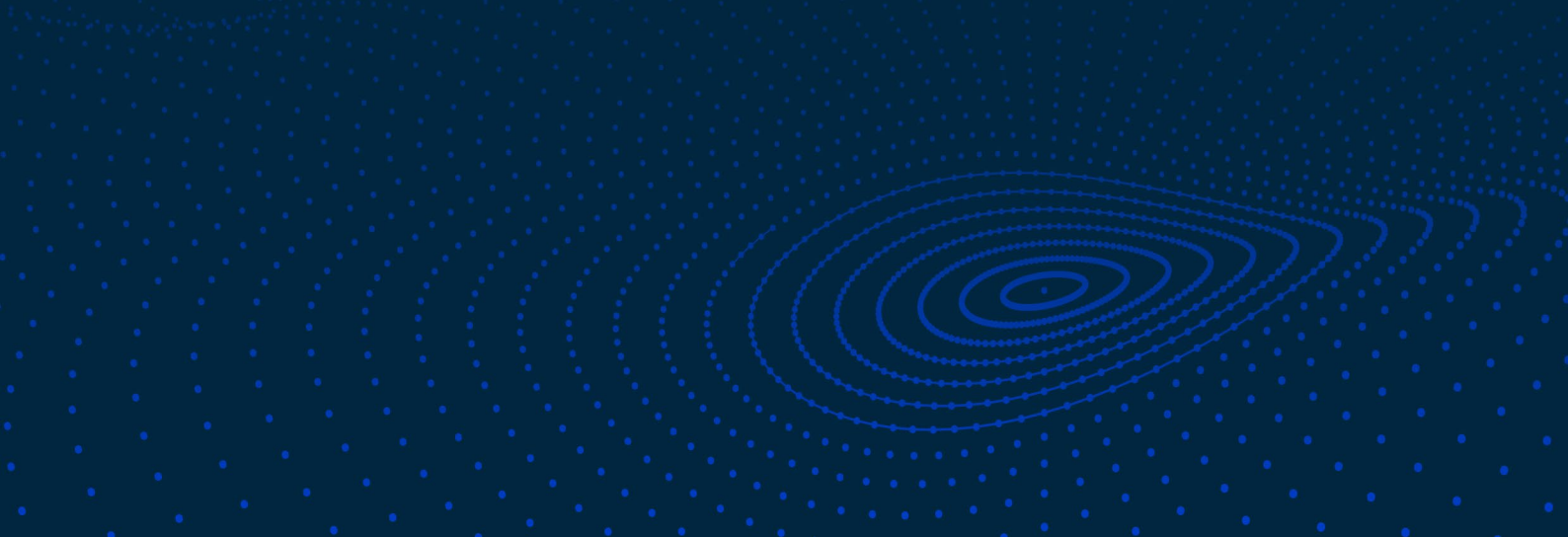
Written by:

Katarina Lahovnik, M.D.

FMS

FUNCTIONAL MAGNETIC STIMULATION

Musculoskeletal & Rehabilitation



Nº 1

Electromagnetic Field Therapy: A Rehabilitative Perspective in the Management of Musculoskeletal Pain - A Systematic Review

Journal of Pain Research

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REVIEW

Electromagnetic Field Therapy: A Rehabilitative Perspective in the Management of Musculoskeletal Pain – A Systematic Review

This article was published in the following Dove Press journal:
Journal of Pain Research

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Abstract: Electromagnetic fields (EMFs) provide a non-invasive, safe, and easy method to treat pain with respect to musculoskeletal diseases. The purpose of this systematic review was to describe the use of electromagnetic therapy in the rehabilitation field by investigating the efficacy in acute and chronic pain in the musculoskeletal disorders. A database search was conducted using the following resources: PubMed, Cochrane, PEDro, SCOPUS, and WoS. The following MESH terms were used: [Electromagnetic field AND/OR Rehabilitation], [Electromagnetic field AND/OR Pain], [Pulsed Magnetic field AND/OR Rehabilitation] and [Pulsed Magnetic field AND/OR Pain], [Pulsed Electromagnetic field AND/OR Rehabilitation] and [Pulsed Electromagnetic field AND/OR Pain], per the guidelines of the PRISMA statement. Articles published between January 1, 2009 and December 31, 2018 were included as assessment of musculoskeletal pain conditions, randomized clinical trial including crossover and prospective design studies, full English text available, population age > 18 years; instead were excluded neurological randomized clinical trials, transcranial magnetic stimulation application, neuropathic pain, animal/in vitro studies, and articles without English abstract or English full text. Three independent investigators (AMC, NG, and LP) retrieved all the information. Twenty-one RTC (N=21) were considered for the inclusion and exclusion criteria. The results showed as pulsed magnetic fields at low intensity and frequency (from 1 Hz up to 100 Hz) are commonly used with efficacy in resolving musculoskeletal pain. EMFs therapy is a well tolerated, effective with no negative side effects, which can be integrated with rehabilitation for the treatment of chronic and acute pain in musculoskeletal diseases, but further studies are needed to examine the use of more standardized protocols.

Keywords: pulsed electromagnetic fields, rehabilitation, physical medicine, magnetic therapy, pain

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1]

Musculoskeletal diseases comprise several conditions that are characterized by pain and limitations in mobility, dexterity and functional ability, reducing people's ability to work and participate in social roles with associated impacts on mental wellbeing. The most common and disabling musculoskeletal diseases are osteoarthritis, back and neck pain, tendinopathy, fibromyalgia and myofascial pain. Among the clinically relevant pain conditions treated in rehabilitation, pain with respect to

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the musculoskeletal system is most frequent and has a major impact on people's quality of life.[2] Chronic low back pain (CLBP) has a significant impact on musculoskeletal pain with a prevalence increases linearly from the third decade of life on, until the 60 years of age, being more prevalent in women.[3–5]

The use of electromagnetic fields (EMFs) and in particular of the magneto-therapy has had a notable increase in the last decade in rehabilitation treatment and provides a non-invasive, safe, and easy method to directly treat the site of injury, the source of pain and inflammation, and other types of disease.[6–8] Magnetic field therapy was applied to promote bone healing, treat osteoarthritis and inflammatory diseases of the musculoskeletal system, alleviate pain, enhance healing of ulcers and reduce spasticity[9] and, also, extremely low frequency (ELF) magnetic fields in the pico tesla and milli tesla ranges are aimed at improving neurotransmission and correcting local immune pathology, respectively.[10] An analgesic and anti-nociceptive efficacy, similar to the opioid analgesic effect respect of pulsed electromagnetic field (PEMF) is reported by scientist literature but the clear biological and biochemical mechanism of the effect of magnetic therapy on pain remains unknown.[11] Also, some studies have shown that short-term exposure to electromagnetic fields influences several inflammatory cellular and neurological processes, such as patterns of cortical activation and inhibition and the activity of various neurotransmitters.[12]

Above all, the magneto-therapy recognizes an important use in the field of both chronic and acute pain in musculoskeletal disorders using protocols with specific intensities and frequencies: magnetic fields applied in magneto-therapy for pain, in line with the criteria generally accepted in physical medicine, have the frequency below 100 Hz and magnetic flux density in the range between 0.1 mT and 30 mT.[13] When used alone, the PEMF seems to have a good effect in reducing the pain intensity in low back patients, independently of the low-back pain condition. However, when added to other standard therapies (such as standard physiotherapy or analgesic therapy) seems to do not add any additional effect.[14–16]

Furthermore, the efficacy of magnetotherapy compared to some forms of chronic pain such as fibromyalgia (FM) still remains debated.[17,18] Moreover, also in neurological pathology, ELF magnetic field was revealed to induce a significant improvement in functional and mental status in brain stroke patients and clinical parameters had positive correlation with the level of enzymatic antioxidant protection.[7]

Thus, surely, the efficacy of magneto-therapy is related to the type of electromagnetic fields used and in the rehabilitation field there are today very different treatment protocols: certainly, in the last decade, the use of ELF magnetic fields has been on its increase. Innovative and still experimental approaches concern, for example, the use of cyclotronic resonance (CR), a kind of specific ultra-weak pulsed electromagnetic fields, in low back pain:[19] the theory of the CR considered that the endogenous electromagnetic forces generated by the activity of the cells of the human body are of infinitely low intensity. Then, the effect of ELF fields, however, does not depend directly on their very low frequency and intensity, but more on the fact that if they are structured with a correct form, intensity, frequency and sequence, they synchronize with the frequencies of the biological system that disturb, triggering an effect. CR involves electrically charged ions and molecules that oscillate at specific harmonic frequencies, within a continuous feedback system with the cells themselves. This mechanism of interaction between ELF magnetic fields, the earth's magnetic field, and living organisms has been called Cyclotron Resonance (CR) by Liboff.[20]

Despite the widespread use of magneto-therapy in rehabilitation field it is difficult to find standardized treatment protocols especially when aimed at treating musculoskeletal pain, be it chronic or acute.

Musculoskeletal pain often develops over time resulting in more hyperalgesia and larger pain areas. Peripheral and spreading sensitizations are probably important mechanisms for the translation of acute local pain to chronic musculoskeletal pain conditions. The transition from acute to chronic musculoskeletal pain is not well understood.[21] Acute pain is a direct outcome of the noxious event and is reasonably classified as a symptom of underlying tissue damage or disease. Chronic pain may not be directly related to their initial injury or disease condition, but rather to secondary changes including some that occur in the pain detection system itself. Thus, the mechanisms underlying chronic or persistent pain may be quite different from acute pain.[22] The distinction between acute and chronic pain is sometimes determined by an arbitrary interval of time since onset; the two most commonly used markers being 3 months and 6 months since onset, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months.

Thus, the aim of this systematic review was to investigate the scientific evidence over the last decade with

respect to the use of electromagnetic therapy in the rehabilitation field by investigating the efficacy in acute and chronic pain in the musculoskeletal disorders.

Materials and Methods

Search Strategy

A systematic review of the literature was performed using the following search engines: PubMed, Cochrane, PEDro, SCOPUS and Web of Science (WoS), per the guidelines of the PRISMA statement.[23] In order to perform the search, the following algorithm was developed, based on the PICO acronym,[24] to evaluate the effects of electromagnetic fields respect the reduction of pain (acute and chronic) as the primary outcome in musculoskeletal diseases.

These keywords were used (MESH terms): [Electromagnetic field AND/OR Rehabilitation], [Electromagnetic field AND/OR Pain], [Pulsed Magnetic field AND/OR Rehabilitation] and [Pulsed Magnetic field AND/OR Pain], [Pulsed Electromagnetic field AND/OR Rehabilitation] and [Pulsed Electromagnetic field AND/OR Pain].

Reference lists of most relevant studies were scanned for additional citations; country, author, affiliated institutions, and enrollment periods were extracted and reviewed to identify and exclude duplicate publications from the same cohort.

Study Criteria and Selection

Inclusion criteria were: (1) articles published between January 1, 2009, and December 31, 2018, (2) assessment of musculoskeletal pain conditions, (3) randomized clinical trial including crossover and prospective design studies, (4) full English text available, (5) population age > 18 years.

Exclusion criteria were (i) neurological randomized clinical trials, (ii) transcranial magnetic stimulation application, (iii) neuropathic pain (iv) animal/in vitro studies, and (v) articles without English abstract or English full text.

Data Extraction

Three independent investigators (AMC, NG, and LP) retrieved all the information. The main outcome of interest was the quantification of intensity of pain in musculoskeletal diseases. The secondary outcomes were the recovery of function and quality of life with respect to the disability in musculoskeletal diseases. Thus, after the application of the eligibility criteria and the included studies were determined, the studies were analyzed based on sample demographics, study's aim, statement of conflict of interest, study duration and follow-up (period of time and percentage), EMF devices used, evaluation time, intervention protocol, and outcome parameters assessed (clinical and functional).

Methodology Quality and Risk of Bias Assessment

Establish a quality assessment of each study using the PEDro scale (Physiotherapy Evidence Database, 1999): this scale has shown good reliability for scoring RCTs.[25] The PEDro scale consists of 11 items related to scientific rigor. The scale's items 2 to 11 contribute to internal validity, and the study is given 1 point for each of these items that are met. The first item relates to external validity and is not included in the final score. The quality assessment was performed independently by the three reviewers, and any disagreement was discussed until consensus was reached. We considered trials with scores of ≥6 as having high quality and trials with scores of ≤5 as having low quality.

The assessment of the risk of bias was done independently by the same three authors (AMC, NG, and LP), and was assessed according to the Cochrane Collaboration's domain-based evaluation framework.[26] Main domains were assessed in the following sequence: 1) selection bias (randomized sequence generation and allocation concealment); 2) performance bias (blinding of participants and personnel); 3) detection bias (blinding of outcome assessment); 4) attrition bias (incomplete outcome data, eg, due to dropouts); 5) reporting bias (selective reporting); 6) other sources of bias. The scores for each bias domain and the final score of risk of systematic bias were graded as low, high, or unclear risk.

Results

The PRISMA flow-diagram showing the selection of studies is given in Figure 1.

Twenty-one articles (N=21) satisfied the inclusion criteria and were considered in the review: 8 articles treated pain of the knee for osteoarthritis (OA),[27–34] 2 articles treated Shoulder Impingement Syndrome (SIS),[35,36] 5 articles treated spine pain, of which 1 study about chronic mechanical neck pain (CNP),[37] and 4 studies were about low back pain (LBP),[14,16,38,39] 3 articles treated Fibromyalgia Syndrome

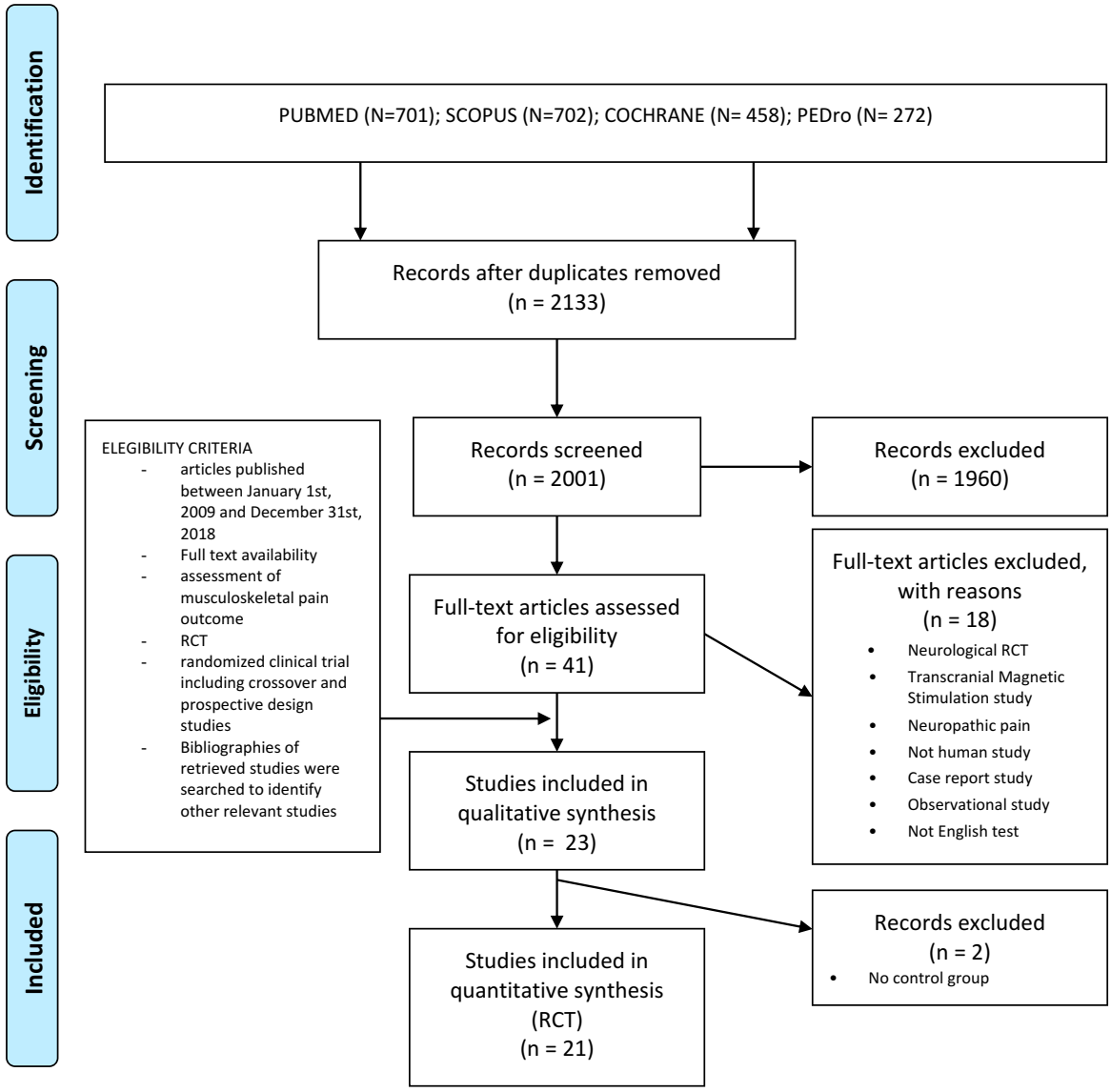

Figure 1 Flowchart of the included studies in the review according to the PRISMA 2009 guidelines.

(FM),[17,18,40] then 1 article showed the effect of EMF respect of patellofemoral pain (PFP),[41] 1 article treated Plantar fasciitis (PF),[42] and 1 article treated Hand osteoarthritis (HO).[43] The PEDro score values and other characteristics of the included studies were shown in Table 1: the methodological quality of the twenty-one included articles, according to the PEDro scale, with averaged between 4/10 and 10/10, averaged 7.57/10 and only 4 studies have a PEDro score ≤5 indicating low quality. Furthermore, in Table 2 were specified type of magnetic field and parameters used in the individual studies included in our review. In detail, 15 studies have used Pulsed Electromagnetic Field (PEMF),[14,16,17,27-29,31,33-35,37,38,40,41,43] one study has used Extremely low-frequency magnetic field (ELF-MF),[18] 2 studies have used Pulsed Radiofrequency Electromagnetic Field (PRFE),[30,42] one study has used Electromagnetic transduction therapy (EMTT),[36] and another one has used Pulsed electromagnetic energy (PEME),[39] and Gökşen et al[32] have used Magnetic resonance treatment. Lastly, the risk of bias was considered High for 4 studies,[31,33,34,38] Unclear for 2 studies[14,43] and Low for fifteen studies (see Table 3). The most frequent source of potential bias was the performance

Table 1 PEDro Score Values and Other Characteristics of the Included Studies

Author (Year Published) [Ref.]	Diagnosis	N (M/F) Mean± SD Age (Years)	Study	N TG (Mean± SD Age) CG (Mean± SD Age)	Intervention	Outcome Parameters	Evaluation Time	Conclusions	PEDro Score
Ay et al (2009)[31]	OA	N=55 (15/40)	RCT	TG=30 (58,9±8,8) CG=25 (57,7±6,5)	TG: PEMF, hot pack, TENS and exercise program; CG: sham-PEMF, hot pack, TENS and exercise program	VAS: pain; Likert pain scale: pain; LI: function	T0: baseline T1: 3 weeks	VAS: TG=CG LI: TG=CG	6/10
Bagnato et al (2016)[30]	OA	N=60 (43/17) y=67,7 ±10,9	RCT	TG=30 (68,6±11,9) CG=30 (66,9±10)	TG: PRFE CG: placebo	VAS: pain; WOMAC: function, pain, disability SF-36: QoL	T0: baseline T1: 1 month	VAS, WOMAC: TG>CG SF-36:TG=CG	9/10
Brook et al (2012)[42]	PF	N=70 (18/52)	RCT	TG=42 (53,2±14,7) CG=28 (49,7±15,2)	TG: PRFE CG: sham-PRFE	VAS: pain	T0: baseline T1: 1 day T2: 2 days T3: 3 days T4: after 4 days T5: 5 days T6: 6 days T7: 7 days	VAS: TG>CG	8/10
Dündar et al (2016)[34]	OA	N=40 (11/29)	RCT	TG= 20 (56.8 ±14.5) CG= 20 (57.6 ±13.8)	TG: hot pack, ultrasound, TENS, isometric knee exercise and PEMF CG: hot pack, ultrasound, TENS, isometric knee exercise and sham-PEMF	VAS: pain WOMAC: function, pain Ultrasonographic effusion of the knee Serum YKL-40 a novel biomarker of osteoarthritis	T0: before treatment T1: 1 month	WOMAC: TG=CG VAS: TG=CG	5/10
Galace de Freitas et al (2014)[35]	SIS	N=56 (20/36) y=50,5 ±8,9	RCT	TG=26 (50,1±8,2) CG=30 (50,8±9,6)	TG: PEMF and exercises; CG: placebo and exercises	VAS: pain; CMS: function; UCLA: function; Handheld dynamometry: strength	T0: baseline T1: 3 weeks T2: 9 weeks T3: 3 months	VAS, UCLA, CMS, Dynamometry: TG>CG	9/10

(*Continued*)

Table 1 (Continued).

Author (Year Published) [Ref.]	Diagnosis	N (M/F) Mean± SD Age (Years)	Study	N TG (Mean± SD Age) CG (Mean± SD Age)	Intervention	Outcome Parameters	Evaluation Time	Conclusions	PEDro Score
Giombini et al (2013)[37]	CNP	N=45 (14/31)	Prospective RCT	TG=15 (44.0±9.6) CG1=15 (40.5±7.4) CG2=15 (43.0±9.4)	TG: PEMF CG1: neck balance system CG2: neck balance system with negligible balancing	VAS: pain NDI: disability NPDS: QoL	T0: baseline; T1: end of 8 week T2: after follow-up 12 weeks	VAS: CG1>TG>CG2 NDI: CG1>TG>CG2 NPDS: CG1> CG2 > TG	8/10
Gökşen et al (2016)[32]	OA	N=97	RCT	TG=49 (54.02 ±6.79) CG= 48 (54.92 ±7.5)	TG: magnetic treatment CG: sham-magnetic treatment	VAS: pain WOMAC: function, pain, disability SF-36: QoL	T0: baseline; T1: end of 2 week T2: follow-up after 12 weeks	VAS, WOMAC, SF-36: TG=CG	9/10
Kanat et al (2013)[43]	HO	N= 50	RCT	TG= 25 (64±2.6) CG= 25 (62±2.4)	TG: PEMF + exercise CG: sham PEMF + exercise	Likert scale: pain at rest, pain at motion, joint stiffness SF-36: QoL Duruöz: function AUSCAN: pain, stiffness and disability HG and PG: strength	T0: baseline T1: after treatment T3: follow-up one month after treatment	SF-36: TG>CG Duruöz: TG>CG AUSCAN: TG>CG HG: TG=CG, PG: TG=CG	7/10
Klüter et al (2018)[36]	SIS	N=86 (41/45)	RCT	TG=44 (50,21±8,5) CG=42 (49,21±7,3)	TG: EMTT/ESWT; CG: sham-EMTT /ESWT	VAS: pain; CMS: function	T0: baseline T1: 6 weeks T2: 12 weeks T3: 24 weeks	VAS: TG>CG CMS: TG>CG	9/10
Krammer et al (2015)[39]	LBP	N=40 (20/20)	RCT	TG=20 (35,7) CG=20 (30,2)	TG: PEMF and physiotherapy treatment; CG: sham -PEMF and physiotherapy treatment	NRS: pain ODI: disability PSFS: function	T0: baseline T1: 1 week T2: 4 weeks	NRS, ODI, PSFS: TG=CG	8/10
Külcü et al (2009)[33]	OA	N=45	RCT	TG =15 (65.8 ±10.3) TG1 = 15 (63.1±13.6) CG =15 (62.0±6.0)	TG: PEMF TG1: US CG: control	VAS: pain WOMAC: function, pain, stiffness	T0: baseline T1: end of three weeks	VAS, WOMAC: TG, TG1>CG	5/10

Multanen et al (2018)[17]	FM	N=108 y=47±10	RCT (cross-over)	TG=57 CG=51	TC: PEMF CG: sham-PEMF	VAS: pain, stiffness FIQ: QoL and disability	T0: baseline T1: end of 12 week T2: after washout 16 week T3: end of 28 week	VAS: TG= CG FIQ: TG= CG	10/10
Nelson et al (2013)[27]	OA	N=34	RCT	TG=15 (55.5±2.5) CG= 19 (58.4±2.5)	TG: PEMF CG: Sham-PEMF	VAS: pain	T0: baseline T1: end of day 3 T2: end of day 14 T3: end of day 29 T4: end of day 42	VAS: TG>CG	10/10
Oke et al (2013)[38]	BP	N=16 (9/7) y= 26.00 ± 8.62	RCT	TG=8 CG=8	TG: PEMF + FANS CG: FANS	NRS: pain Functional Activity Scale	T0: baseline T1: end of treatment (after 5–9 days)	NRS, Functional Activity Scale: TG>CG	4/10
Omar et al (2012)[14]	LBP (Unilateral Radicular Pain)	N=40	RCT	TG=20 (37.5±8.5) CG= 20 (40.0±8.3)	TG: PEMF CG: sham-PEMF	VAS: pain OSW: disability SSEPs: nerve conduction	T0: baseline T1: end of 8 week T2: after follow-up 12 weeks	VAS, OSW, SSEPs: TG>CG	5/10
Özgüçlü et al (2010)[28]	OA	N=40	RCT	TG=20 (60.55±7.7) CG= 20 (62.15 ±8.1)	TG: isometric knee+ hot pack+ therapeutic ultrasound+ PEMF exercise CG: isometric knee+ hot pack+ therapeutic ultrasound+ sham PEMF	VAS: pain WOMAC: function, pain, disability	T0: baseline T1: end of 2 week	VAS, WOMAC: TG=CG	6/10
Paolucci et al (2016)[18]	FM	N=37 (F) y=50.33 ±10.94	RCT (cross-over)	TG1=16 (49.5 ±9.38) TG2 =17 (51.12±12.47)	TG1: ELF/sham-ELF TG2: sham-ELF/ELF	VAS: pain FAS: pain, fatigue and quality of sleep FIQ: QoL and disability HAQ: QoL and daily activities	T0: baseline; T1: end of 1 treatment cycle T2: beginning of 2 treatment cycle (after a 1-month washout) T3: end of 2 treatment cycle T4: follow-up after 1 month	VAS, FAS: T1:TG1<TG2 T3:TG2<TG1 FIQ, HAQ: T1: TG1<TG2 T3: TG2<TG1	8/10

(*Continued*)

Table 1 (Continued).

Author (Year Published) [Ref.]	Diagnosis	N (M/F) Mean± SD Age (Years)	Study	N TG (Mean± SD Age) CG (Mean± SD Age)	Intervention	Outcome Parameters	Evaluation Time	Conclusions	PEDro Score
Park et al (2014)[16]	LM (Lumbar Myalgia)	N= 38 (11/27) y=31.95 ±12.30	RCT	TG=19 (33.00 ±11.06) CG=19 (30.89 ±13.66)	TG: PEMF CG: placebo	VAS: pain ODI: function SF-36, EQ-5D: QoL BDI: depression RMDQ: disability	T0: baseline T1: after the 6th treatment T2: follow-up after 1 week	VAS, RMDQ: TG>CG ODI, SF-36, EQ-5D, BDI: TG=CG	9/10
Servodio Iammarrone et al (2016)[41]	PFP	N= 31 y=22.5	RCT	TG: 13 (21±7) CG: 17 (24±8)	TG: PEMF, Home exercise program CG: Home exercise program	VAS: pain VISA: pain, functional mobility, QoL	T0: baseline T1: 2 months T2: 6 months T3: 12 months	VISA T1: TG=CG VISA T2-T3: TG>CG VAS: TG<CG	6/10
Sutbeyaz et al (2009)[40]	FM	N=56	RCT	TG=28 (42.96 ±9.57) CG=28 (40.89 ±6.88)	TG: PEMF CG: sham-PEMF	VAS: pain FIQ: QoL and disability BDI: depression SF-36: QoL PGART: patient's global assessment	T0: baseline; T1: end of 3week T2: follow-up after 12 weeks	VAS: TG>CG FIQ, SF-36: TG >CG BDI: CG>TG PGART: debated	8/10
Wuschech et al (2015)[29]	OA	N=57	RCT	TG=44 (63.4±12.1) CG=13 (55.5±10.8)	TG: PEMF CG: placebo	VAS: pain WOMAC: function, pain, disability	T0: baseline; T1: end of 18 days	VAS, WOMAC: TG>CG	9/10

Abbreviations: OA, knee osteoarthritis; PF, plantar fasciitis; SIS, shoulder impingement syndrome; CNP, chronic mechanical neck pain; HO, hand osteoarthritis; LBP, low back pain; FM, fibromyalgia; BP, back pain; LM, lumbar myalgia; PFP, patellofemoral pain; PPS, parallel prospective study; RCT, randomized controlled trial; TG, treatment group; CG, control group; PEMF, pulsed electromagnetic fields; PRFE, pulsed radiofrequency electromagnetic field therapy; US, therapeutic ultrasound; EMTT/ESWT, electromagnetic transduction therapy/extracorporeal shockwave therapy; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; RMS, Roles–Maudsley score; CMS, Constant–Murley scale; UCLA, University of California/Los Angeles; SF-36, Short-Form 36 version-2; NDI, Neck Disability Index; NRS, numerical rating scale; LI, Lequesne algofunctional index; FIQ, Fibromyalgia Impact Questionnaire; FAS, Fibromyalgia Assessment Scale; HAQ, Health Assessment Questionnaire; BDI, Beck Depression Inventory; PGART, patient's global assessment rating scale; NPDS, neck pain disability scale; OSW, Modified Oswestry Low Back Pain Disability Questionnaire; SSEPs, somatosensory evoked potentials; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; ROM, range of motion; VISA, Victorian Institute of Sport Assessment score; AUSCAN, Australian Canadian Osteoarthritis Hand Index; Duruöz, Duruöz Hand Index; HG, hand grip; PG, pinch grip; ODI, Oswestry Disability Index; EQ-5D, EuroQol-5 Dimension; RMDQ, Roland-Morris Disability Questionnaire; PSFS, Patient Specific Functional Scale.

Table 2 Type of Magnetic Field and Parameters Used in the Included Studies

Author (Year Published) [Ref.]	Diagnosis	Magnetic Fields	Frequency	Intensity	Duty Cycle	Wave's Type	Duration of Singles Session/Number of Sessions of Treatment Group
Ay et al (2009)[31]	OA	PEMF	50 Hz	105 μT	NA	NA	30 min/5 per week/3 weeks
Bagnato et al (2016)[30]	OA	PRFE	27,12 MHz (pulse rate of 1000 Hz and a 100 μs burst width)	NA	NA	NA	Nightly/11,3± 0, 8 h/day/4 weeks
Brook et al (2012)[42]	PF	PRFE	27,12 MHz (pulse rate of 1000 Hz and a 100 μs burst width)	NA	NA	NA	Nightly for 7 days
Dündar et al (2016)[34]	OA	PEMF	50 Hz	100 μT	NA	NA	20min/5 per week/4 weeks
Galace de Freitas et al (2014)[35]	SIS	PEMF	50 Hz	20 mT	NA	NA	30 min/3 per week/3 weeks
Giombini et al (2013)[37]	CNP	PEMF whole body	5–25 Hz	5–70 μT	NA	Sinusoidal wave	2 hours/twice a day/8weeks
Gökşen et al (2016)[32]	OA	Magnetic Treatment	17–85 kHz	NA	NA	NA	1 hour/5 per week/2weeks
Kanat et al (2013)[43]	HO	PEMF	NA	3.5–25 mT	NA	NA	20 min/once a day for 10 days
Klüter et al (2018)[36]	SIS	EMTT	3 Hz	80 μT	NA	NA	20 min/2 per week/4 weeks
Krammer et al (2015)[39]	LBP	PEME	27.12 MHz (1000 pulses/s)	0.03 mT	NA	NA	For 7 days
Külcü et al (2009)[33]	OA	PEMF	2–100–25 Hz consecutively	2–10 mT	NA	NA	35 min/5 per week/3 weeks
Multanen et al (2018)[17]	FM	PEMF whole body	33,3Hz	0–150μT	NA	Sinusoidal half-wave	8 min twice a day/12weeks
Nelson et al (2013)[27]	OA	PEMF	6.8 MHz	NA	NA	Sinusoidal wave	15 min/twice a day/2 weeks
Oke et al (2013)[38]	BP	PEMF	NA	NA	NA	NA	2 hours per session; 4 per day for 5–9 days
Omar et al (2012)[14]	LBP (Unilateral Radicular Pain)	PEMF	7–4000 Hz	5–15 G	NA	NA	20min/once a day/3 weeks
Özgüçlü et al (2010)[28]	OA	PEMF	50 Hz	30 G	90-s interval	NA	30min/5 per week/2 weeks
Paolucci et al (2016)[18]	FM	ELF-MF whole body	1–80Hz	100 μT	NA	NA	30 min/3 per week/4 weeks
Park et al (2014)[16]	LM (Lumbar Myalgia)	PEMF	8.56 kHz	820 mT	NA	NA	10 min/3 per week/2 weeks
Servodio Iammarrone et al (2016)[41]	PFP	PEMF	75 Hz	1.5 mT	10%	Square waveform	4 h per day/6 weeks
Sutbeyaz et al (2009)[40]	FM	PEMF whole body	0.1–64Hz	40 μT	NA	NA	30 min/twice a day/3 weeks
Wuschech et al (2015)[29]	OA	PEMF	4–12 Hz	105 mT	NA	NA	5 min/twice a day/18 days

Abbreviations: OA, knee osteoarthritis; PF, plantar fasciitis; SIS, shoulder impingement syndrome; CNP, chronic mechanical neck pain; HO, hand osteoarthritis; LBP, low back pain; FM, fibromyalgia; BP, back pain; LM, lumbar myalgia; PFP, patellofemoral pain; PEMF, pulsed electromagnetic field; PRFE, pulsed radiofrequency electromagnetic field; ELF-MF, extremely low-frequency magnetic field; EMTT, electromagnetic transduction therapy; PEME, pulsed electromagnetic energy.

Table 3 Risk of Bias Summary of 21 Included Studies

		Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Ay et al (2009)[31]	High	–	?	–	+	+	–	–
Bagnato et al (2016)[30]	Low	+	+	+	+	+	–	?
Brook et al (2012)[42]	Low	+	+	+	+	+	+	?
Dündar et al (2016)[34]	High	?	–	–	+	–	+	?
Galace de Freitas et al (2014)[35]	Low	+	+	+	+	+	+	?
Giombini et al (2013)[37]	Low	+	+	–	–	+	+	?
Gökşen et al (2016)[32]	Low	+	+	+	+	+	+	?
Kanat et al (2013)[43]	Unclear	?	?	+	–	+	–	?
Klüter et al (2018)[36]	Low	+	+	–	+	+	+	?
Krammer et al (2015)[39]	Low	+	+	+	+	–	–	?
Külcü et al (2009)[33]	High	+	–	–	–	–	+	?
Multanen et al (2018)[17]	Low	+	+	+	+	+	+	–
Nelson et al (2013)[27]	Low	+	?	+	+	+	–	?
Oke et al (2013)[38]	High	?	–	–	–	–	+	?
Omar et al (2012)[14]	Unclear	?	–	?	?	–	+	?
Özgüçlü et al (2010)[28]	Low	+	–	+	?	–	+	?
Paolucci et al (2016)[18]	Low	+	+	+	+	–	+	–
Park et al (2014)[16]	Low	+	+	+	+	+	+	?
Servodio Iammarrone et al (2016)[41]	Low	+	+	+	–	–	?	?
Sutbeyaz et al (2009)[40]	Low	+	+	+	+	+	+	?
Wuschech et al (2015)[29]	Low	?	+	+	+	–	?	?

Notes: The "+" means low risk of bias; the "–" means high risk of bias; the "?" means unknown risk of bias. Trials involving three or more high risks of bias were considered as poor methodological quality.

bias related to incomplete outcome data, due to not mentioning adverse events, and the inadequate blinding participant and personnel. Furthermore, the articles analyzed share the same contraindications to the use of magnetotherapy as patients with pacemakers (or other electrical devices) and/or with cancer or in pregnant women.

Outcomes of Interest

Regarding the primary outcome, acute and chronic pain, in the included studies, the Visual Analogue Scale (VAS)[44] was the main evaluation tool, except for Kanat et al,[43] which presented 10-point Likert Scale to quantify pain at rest and at motion of the hand. Also, Oke et al[38] used the numeric rating scale for pain (NRS).[45]

Regarding the evaluation of the recovery of function, the authors use specific scales depending on the musculoskeletal diseases. In fact, to evaluate the patients with OA was administrated the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[46] or Lequesne Algofunctional index of knee (LI).[47]

Instead, to measure pain in SIS[35,36] was used the Constant–Murley Scale (CMS)[48] and University of California/Los Angeles scale (UCLA);[49] in addition, to evaluate the hand's function was used Duruöz and Auscan Hand Osteoarthritis Indexes (AUSCAN).[50,51] The evaluation of function in neck and low-back pain was assessed with the Neck Disability Index (NDI),[52] the Modified Oswestry Low Back Pain Disability Questionnaire (OSW),[53] the Korean version of Oswestry Disability Index (ODI)[54] and Modified Version Functional Activity Scale.[38] The Fibromyalgia Assessment Status scale (FAS)[55] and the Fibromyalgia Impact Questionnaire (FIQ)[56] have been administered specifically in FM to quantify pain and the secondary outcomes like recovery of function, disability and quality of life. Last, the Victorian Institute of Sport Assessment score (VISA)[57] was used to quantify mobility and function in patellofemoral pain.

Finally, in order to evaluate the increase in quality of life (QoL) perceived by patients, five studies[16,30,32,40,43] used the 36-item Medical Outcomes Study Short-Form 36

(SF-36);[58] then the Health Assessment Questionnaire (HAQ)[59] or the EuroQol-5 Dimension (EQ-5D).[60]

Discussion

The purpose of this systematic review was to investigate the scientific evidence of the last decade regarding the use of EMF in rehabilitation about its efficacy of acute and chronic pain in musculoskeletal disorders. The results suggest as EMF therapy is an optional treatment in the management of musculoskeletal pain disease that can reduce pain intensity and improves function.

Our review shows that PEMF are the most widely used magnetic fields, particularly in knee OA.[27–34] Among non-pharmacological treatments, PEMF have beneficial therapeutic effects on knee joint tissue.[61] PEMF signals modulate calmodulin (CaM)-dependent nitric oxide (NO) signaling cascades in articular chondrocytes and other cells, as demonstrated by a previous study that used CaM antagonists and NO downstream inhibitors.[62,63] This mechanism could promote the resolution of pain by accelerating the removal of inflammatory substances. PEMF stimulates chondrocyte proliferation, differentiation, and extracellular matrix synthesis through the release of anabolic morphogens, such as bone morphogenetic proteins and anti-inflammatory cytokines, by adenosine receptors $A2_A$ and A3: in clinical translational study, a beneficial effect was observed in improving function in knee OA.[64] In 4 studies dealing with knee OA,[27,29,30,33] there were good results in the reduction of pain and improvement of function compared to the control group. In detail, Nelson et al[27] proposed a short protocol of 2 weeks (15 mins per session, twice daily) with 6.8 MHz and an intensity of 30 Gauss in OA: patients in the PEMF group had a mean self-reported maximum daily VAS pain score at baseline of 6.85 ±0.33 and 4.19±0.71 at the end of treatment, compared with 7.18±0.31 and 6.11±0.54 for the sham group. Thus, PEMF effects significant and rapid reductions in pain in early knee OA (p=0.036). Also, in Wuschech's et al[29] study, a PEMF portable device was used and a total of 57 patients were enrolled, 44 patients randomly assigned to the treatment group but only 13 patients to placebo group. At the end, the PEMF group showed a great improvement in pain, disability and function. Another study[33] compared PEMF respect of therapeutic ultrasound (US) and authors suggested as PEMF and US were more effective than no treatment and PEMF may be a good alternative to other physical therapies in the management of knee pain in the osteoarthritis. A further study to the efficacy of the PEMF in knee OA was a double-blind, placebo-controlled, randomized clinical trial by Bagnato et al[30] randomly allocated 60 patients with OA of the knee into 2 groups (treatment PEMF and control placebo-PEMF), reporting a decrease in pain but not in the quality of life (SF-36 in the PEMF group) after 12 hrs/daily for 1 month of treatment. The results showed a decrease in pain in the PEMF group but quality of life (SF-36) did not change in a statistically significant way in the two groups.

In the RCT study of Ay et al[31] 55 patients have been recruited and randomly assigned to PEMF group and placebo-PEMF group. Both groups have carried out hot pack, transcutaneous electric nerve stimulation (TENS) for 20 mins and isometric quadriceps exercise program. PEMF was applied for 30 mins, treatment consists of 15 sessions, 5 times/week for 3 weeks. After the treatment period both groups improve their symptoms (pain and functional capacity) but without statistically significant difference in two groups. Only morning stiffness and daily living activity have shown a statistical difference in the two groups in favor of the treatment group. Also, in Özgüçlü's study[28] forty patients with OA were randomized into two groups: both groups received 20-min hot pack, 5-min therapeutic ultrasound instead treatment group underwent also PEMF therapy for 30 mins. A bias was that patients could take the acetaminophen as needed. Their results conclude that PEMF did not show additional effect on reducing knee pain. This study showed that were no statistically significant differences between groups in WOMAC pain, stiffness, and physical function scores after treatment (p = 0.906, p = 0.855, p = 0.809, respectively).

Only one study of Dundar et al[34] provide a measure of a YKL-40, a serum marker made in OA by chondrocytes and neutrophils in inflamed joints. Forty patients were included and randomized into two groups: group 1 (PEMF) and group 2 (sham-PEMF). Both groups receive a physical therapy consist of therapeutic US, TENS, hot pack and isometric exercise five-session/week for 4 weeks. Each patient underwent to knee ultrasound to assess the knee effusion and has compiled a VAS score and WOMAC questionnaire at baseline and at the end of the treatment (1 month). A venous blood sample was collected for each patient before and after the protocol period to measure YKL-40 serum marker. Results showed no effect or additional result from PEMF therapy with conventional therapy. Also, there was a significant improvement in both groups for VAS and WOMAC. The only significant

correlation among these parameters was between delta-VAS and delta-WOMAC (r = 0.512, p = 0.001). Moreover, YKL-40 level was not correlated with the change in VAS, WOMAC questionnaire scores, as well as knee effusion. In conclusion, PEMF therapy had no additional effect on knee OA when associated with other physical therapy, but this study still has a low risk of bias but a Pedro score of 5. In fact, Vavken et al[65] in their review suggested that PEMF has clinical relevance as a successful adjuvant option in the management of OA rather than a stand-alone therapy.

While being a magnetic field therapy method, Gökşen et al[32] used the effects of magnetic resonance therapy (MRT) in OA versus placebo-MRT with a high frequency of 17–85 kHz. They enrolled 100 patients and randomized them equally into 2 groups (MRT and placebo-MRT). The treatment consisted of magnetic fields, 1 hr per day 2 two weeks. Their results did not show positive effects in favour of the treatment group, because both groups improved significantly regarding pain after 2 and 12 weeks: thus, MRT was safe but not superior to placebo.

Conversely, Brook et al[42] analysed a pulsed radiofrequency electromagnetic field device in treating plantar fasciitis, noting positive results with respect to morning pain; however, this study had several limitations, such as the lack of long-term follow-up and the lack of interceptor analysis.

Kanat et al[43] evaluated the efficacy of magnetotherapy in hand osteoarthritis. In this study, the treatment group received magnetotherapy with flux intensity from 3.5 to 25 mT, 450 pulse/s, and 5–80 G, for 10 days, 20 min/day, combined with exercises for the hand. The control group received sham-magnetotherapy for 20 min/day for the same duration, combined with the same exercises. Pain and quality of life for SF-36 scale improved in favour of the treatment group.

Servodio-Iamarrone et al[41] assessed whether the combination of a home exercise program with PEMFs was more effective than the program alone in patellofemoral pain syndrome, concluding that PEMFs improve the reduction of pain favouring the earlier start of the exercise the therapeutic exercises, accelerating the recovery and reducing pain in this condition.

Other groups have reported the use of PEMFs at frequencies of 50 Hz,[35] reporting good results in SIS, as with standard physical therapy, with no negative effects. Patients in the treatment PEMF group showed a higher level of function and less pain at all follow-up time frames compared with baseline. On the contrary, the placebo-PEMF group had increased function and reduced pain only at the 9-week and 3-month follow-ups that is, after performing the associated exercises. Instead, in Klüter et al[36] 86 patients with SIS were randomized to undergo 3 sessions of extracorporeal shock wave therapy in combination with 8 sessions of electromagnetic transduction therapy or sham-electromagnetic transduction therapy. Therefore, the two treatment modalities seem to have a synergetic effect and electromagnetic transduction therapy can be useful to improve the results after extracorporeal shock wave therapy. For example, a study compared PEMF and therapeutic ultrasound (US),[33] suggesting these modalities are more effective than no treatment and that PEMF is a good alternative to other.

Other groups have proposed very-high-frequency treatment protocols of 27.12 MHz,[30,39,42] because in 1947, the Federal Communications Commission assigned 3 frequencies at the short end of the radiofrequency band for medical use. McGaughey et al[66] underline that pulsed electromagnetic energy encloses the terms pulsed shortwave diathermy, pulsed electromagnetic field (PEMF) and diapulse, but if we move on frequencies of 27.12 MHz, then we considered diathermy effect related to therapy. Energy is emitted in a sequence of impulses with the "off" period much longer than the "on" period which entails a lower dose that is given to the patient and any heat produced is dissipated by the circulation.[67] For this reason, Goats et al suggest that "pulsed electromagnetic energy therapy cannot correctly be called diathermy because little or no heating of the tissue occurs".[67] An electric field is influenced by a magnetic field and vice versa, for this reason, an exogenous electromagnetic field influences many biologic processes which are important for therapeutic interventions.[68] Markov et al[68] in their work they showed that the magnetic and electromagnetic fields that are used today can be classified as follows: permanent magnetic fields (created by several permanent magnets or by passing a direct current through a coil); electromagnetic fields from low-frequency sine waves; pulsed electromagnetic fields usually low-frequency and forms of looking specific signal; pulsed radiofrequency fields with selected frequencies in the radiofrequency range and short but intensive magnetic pulses for transcranial magnetic stimulation.[68] In literature, other studies report the efficacy of other forms of energy that are based on magnetic fields in rehabilitation for shoulder pain that exploit other clinical effects of magnetic fields

but equally effective. For example, short-wave diathermy utilizes electromagnetic waves to convert energy to deep heat, and diathermy is thought to exert its therapeutic effects by both thermal and nonthermal mechanisms. The primary nonthermal mechanism associated with the use of therapeutic short-wave diathermy occurs via vibration induction of tissue molecules when exposed to radio waves. By changing the characteristics of the shortwave applicator, the therapist can target the specific type of tissue he or she wants to heat.[69,70]

Concerning LBP, four studies analysed the efficacy of electromagnetic fields.[14,16,38,39] Krammer et al[39] investigated PEMFs with the frequency 27.12 MHz for the treatment of LBP, generating uncertain results on the effectiveness of magnetic fields in combination with typical physiotherapy. To avoid the thermal effect, the analysed studies proposed a pulse rate of 1000 Hz and a 100-microsecond burst width. Also, Oke et al[38] assessed the efficacy of PEMF in the treatment of LBP without specifying the frequency, and their results were positive, as in Krammer et al.[39] Moreover, Park et al[16] performed a randomized-controlled trial to determine the efficacy of PEMFs in alleviating lumbar myalgia in acute LBP in 38 patients. All patients were treated on the lumbar muscle and acupuncture points, 3 times per week for 2 weeks with a frequency of 8.56 kHz; versus placebo, the PEMF group showed better results for pain but not quality of life. Also, Omar et al[14] have evaluated the effect of PEMF in the management of patients with LBP in 40 patients randomly assigned: 20 in a study group who received PEMF therapy, and 20 patients in a control group who received placebo treatment. The authors concluded that PEMF should be effective for conservative treatment of lumbar radiculopathy caused by lumbar disc prolapse and seems effective in reducing nerve root compression as evidenced by the improvement of somatosensory evoked potentials (SSEPs) parameters after treatment. The results are in line with the review by Andrade et al[15] in which the authors underline how PEMF can reduce pain and increase functionality in patients with different LBP conditions, when added to standard therapy, it seems not to add any beneficial effect.

Using a different approach, Giombini et al[37] randomized 45 patients to 3 groups with chronic neck pain. Groups A and B (control groups) used an NBS-DM2/RW (neck balance system-Del Monte 2/regular weight) and NBS-DM2/NW (neck balance system-Del Monte 2/negligible weight) helmet systems with balancing weight, respectively, whereas Group C (treatment group) underwent electromagnetic therapy with whole-body PEMF in supine position with a low frequency of 5–25 Hz and very low intensity of 5–70 μT. The authors concluded that PEMF therapy has no significant effect on reducing pain and disability in chronic mechanical neck pain. According to these results, Wu et al[71] showed that PEMFs are useless for reducing pain and improving function in cervical OA, as there is no evidence that PEMFs act on reducing the formation of osteophytes, which may induce nerve root compression that can lead to deterioration of pain and function.

Based on our review, PEMFs in whole-body mode have found innovative and unique use, especially in complex and widespread musculoskeletal chronic pain conditions, such as FM.

Multanen et al[17] analysed the effects on FM of low-energy PEMF therapy, with a signal that consisted of 5 sessions of pulses of half-wave-shaped sinusoidal variations, with a range of intensities of 0–150 μT and a frequency of 33.3Hz, in a sample of 108 women (47±10) who were randomized to 2 groups (TG, CG) in a crossover study. They found that treatment with an active device elicited no significant improvement in pain, stiffness, or FIQ index over sham treatment. Also, there was no correlation between the frequency of using the device and the decrease in pain with active ($r = -0.11$, 95% CI [−0.31, 0.10]) or sham treatment ($r = -0.10$, 95% CI [−0.31, 0.12]).

In contrast, Paolucci et al[18] described the efficacy of administering extremely-low-frequency magnetic fields (not pulsed ELF) to the entire body in FM patients in decreasing chronic pain. Thirty-seven (N=37) women (50.33±10.94) were randomized to 2 groups (TG1, TG2) in a crossover study. One group was first exposed to systemic ELF-MF therapy (100 μT, 1 to 80 Hz) and then sham therapy, and the other group received the opposite sequence of interventions. Regarding the primary outcome, ELF-MF treatment significantly lowered pain (p=0.001), which rose after the end of treatment but remained significantly lower than baseline levels (p=0.001) in both groups. Short-term benefits were also observed in terms of the secondary outcome measures, but the medium-term effects were less significant; FAS and FIQ scores generally declined by 40% for scores between pre-and post-ELF-MF versus sham treatment.

Also, Sutbeyaz et al[40] analysed the effects of PEMF on pain in 56 patients with FM, administered to the entire body using a mat with a mean intensity of 40 μT and

frequency that ranged from 0.1 to 64 Hz. For pain, VAS scores in the TG improved significantly from baseline (73.3±14.0) to after treatment (38.07±16.9) and at the follow-up (59.4±9.8). In contrast, in the CG, VAS scores improved significantly only from baseline (68.4±12.1) to after the treatment (63.4±13.8), not at the follow-up (67.4 ±11.8). Also, FIQ scores in the TG were enhanced at the end of therapy compared with baseline and were significant than in the CG at the end of therapy.

The three groups used very different protocols in FM: Paolucci et al[18] used a non-pulsed field, administered once per day, whereas Multanen et al[17] and Sutbeyaz et al[40] administered a pulsed-field twice daily. In addition, the results of Paolucci et al[18] and Sutbeyaz et al[40] should be interpreted with caution due to the small sample sizes in each treatment arm. However, there is evidence that exposure to electromagnetic fields affects pain, nociception, and opiate-mediated analgesia.[12] However, all three groups used frequencies lower than 100 Hz and very low intensities between 0 and 150 μT.

In the literature, the duration of disease in FM directly influences the efficacy of the treatment, because drugs and rehabilitation treatment are less sensitive to the placebo effect. This finding implies that the longer a person has FM, the more entrenched the condition becomes, the lower the patient expectancy is, and the harder it is to improve outcomes by active treatment or placebo or other factors that govern contextual responses.[72]

Conclusion

In conclusion, this systematic review suggests that electromagnetic field therapy relieves pain and improves function in patients with various pain musculoskeletal diseases. Electromagnetic field therapy is well tolerated with no reported negative side effects in the analyzed studies. Then, it could be a helpful component during drug therapy for chronic and acute pain in musculoskeletal disease. A limitation of our study is that the included studies analysed have high-level criticism about the standardized protocols especially with respect to the length and exposition time and Hz frequency of the magnetic field applied. PEMFs at the low weak intensity and low frequency (from 1 Hz up to 100 Hz) are the most commonly used and most effective in resolving pain, but when other physical therapies, such as TENS, US, and hot pack are added, no additive beneficial effect is observed.

Finally, further studies are needed to examine the use of more standardized protocols respect to the length and exposition time and frequency characteristics of the magnetic field, applied to specific pathologies to resolve with relatively safe and conservative treatment the musculoskeletal pain.

Disclosure

The authors report no conflicts of interest in this work.

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Nº 2

Peripheral Magnetic Stimulation

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Peripheral Magnetic Stimulation

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Continuing Education Activity

Peripheral magnetic stimulation (PMS) or so-called transcutaneous magnetic stimulation is a non-invasive method of delivering a rapidly pulsed, high-intensity magnetic field to the periphery other than the brain. Interest in the research and clinical applications has increased over the last three decades as it is considered a novel, painless, and easy approach for many neurological and musculoskeletal conditions. This activity reviews peripheral magnetic stimulation and discusses the role of the interprofessional team in educating patients on when this therapy might be considered.

Objectives:

- Describe peripheral magnetic stimulation as a therapeutic intervention.
- Identify the conditions in which peripheral magnetic stimulation may be considered as a treatment.
- Explain the use of peripheral magnetic stimulation in the stimulation of peripheral nerves.
- Outline peripheral magnetic stimulation and discusses the role of the interprofessional team in educating patients on when this therapy might be considered.

Access free multiple choice questions on this topic.

Introduction

Peripheral magnetic stimulation (PMS) or so-called transcutaneous magnetic stimulation is a non-invasive method of delivering a rapidly pulsed, high-intensity magnetic field to the periphery other than the brain. Interest in the research and clinical applications has increased over the last three decades as it is considered a novel, painless, and easy approach for many neurological and musculoskeletal conditions.[1]

Humankind has been trying to use magnetism to treat illness for more than thousands of years. Almost 190 years ago, Faraday discovered that a time-varying current creates a magnetic field that can induce another current in a nearby conductive medium.[2] Around 60 years ago, Kolin et al. first demonstrated that an alternating magnetic field could stimulate a nerve in an animal model.[3] In 1982, a group of researchers from the University of Sheffield was the first to report developing a practical magnetic peripheral stimulator and using it to stimulate human peripheral nerves.[4] This magnetic stimulator's main difference from the previously developed pulsed electromagnetic field device (PEMF) was its much higher peak magnetic field strength.

Function

Physiology

The time-varying current flow passing to the coil creates the magnetic field around the coil. When the pulse of the magnetic field passes into the body, it will induce a voltage difference between any two points. This creates an electric field and induces electrons to flow between these two points. Unlike electrical stimulation, magnetic stimulation does not need a traverse of electric current through electrodes, skin, and tissue interface. The magnetic field acts as the

vehicle to induce ions to flow, and it does not stimulate the nervous tissue itself. However, once the ion flow is created, the mechanism of both electrical and magnetic stimulation at the neural level is the same; these are axon depolarization and the initiation of the action potential.[4] Because of the higher stimulation threshold of the cell bodies, peripheral magnetic stimulation will stimulate axons rather than cell bodies.[1]

The magnetic field provides many advantages. First, the magnetic field can pass any medium, even a vacuum space, without attenuation of energy. This allows penetration to deep tissue such as spinal nerve roots or deep muscles. The magnetic field only decreases inversely proportional to the distance away from the generator coil. Owing to this characteristic, no mechanical contact is necessary, making it applicable to patients with extreme hypersensitivity or allodynia to skin touch. Similarly, because the magnetic field can pass through clothing, the patient does not need to undress. Moreover, due to no charged particles being injected into the skin and superficial tissue and the weak recruitment ability of cutaneous sensory afferent fiber, magnetic stimulation rarely causes pain during clinical practice.[4]

Possible Mechanisms of Action

Many researchers have been trying to identify the mechanisms of action underlying the effect of peripheral magnetic stimulation; however, no clear conclusion has been made. The one strong postulate is that peripheral magnetic stimulation can recruit peripheral afferents, potentially influencing cerebral activation and neuroplasticity. Peripheral magnetic stimulation is thought to be another useful method to induce proprioceptive afferents resembling movement therapy that has already been demonstrated to increase motor control in stroke patients. Peripheral magnetic stimulation triggers massive proprioceptive afferents when applied to muscles via two pathways.[1] The first pathway is the direct activation of sensorimotor nerve fibers. The other is the indirect activation of mechanoreceptors in the muscle fiber. Evidence shows an increase in regional cerebral blood flow by PET scan of the premotor cortex, parietal areas, and motor cingulum in the lesioned hemisphere in stroke patients after applying peripheral magnetic stimulation on the paretic muscles. Peripheral magnetic stimulation is also shown to normalize the activation patterns of the frontoparietal networks of motor planning and leads to some functional improvement. Other supporting findings include that peripheral magnetic stimulation might have effects on the homeostasis of cortical excitability. Additional possible underlying mechanisms for using peripheral magnetic stimulation in many applications such as spasticity reduction, strength improvement, and pain control are still being investigated. Interestingly, spasticity reduction is consistently reported after peripheral magnetic stimulation application over both spinal nerve roots and muscles.[5]

Device

The equipment consists of a high current pulse generator able to produce a large electric discharge current (several thousand amperes).[1] The current flows through a stimulating coil, generating magnetic pulses with field strength up to several Teslas. Heat is an unavoidable by-product derived from magnetic pulse generation; therefore, the coil must be contained in an air- or oil-cooling system.

Many types of coils have been manufactured. Two frequently used are the round coil and figure-8 coil. The choice of the coil depends on the focality and depth of penetration on the target. The round coil is less focal but produces a deeper magnetic field with a stimulated area equivalent to its diameter. The figure-8 coil produces a stronger magnetic field at the center with an accurate focus. When the coil is distant from the target, the magnetic field from the figure-8 coil declines faster than the round coil. The orientation of the coil also matters. Placing the coil in a flat, tangential orientation with the longitudinal axis of the conductive structure is the most effective way to stimulate structures beneath.[6][7]

Parameter

Different parameters have been speculated to create different preferential activation. Until now, there is no consensus regarding a standardized protocol of peripheral magnetic stimulation. The following are common parameters for peripheral magnetic stimulation:

Duty Cycle: On and Off Periods

Two different protocols regarding the duty cycle include (1) the continuous protocol (only “on” during the whole treatment session), which is hypothesized to briefly inhibit overactive spinal circuits of muscle spasticity, and (2) the

intermittent protocol, which imitates physiological muscle contraction and relaxation and generates proprioceptive afferent inducing neuroplasticity. However, the optimal length of the "on" and "off" period in the intermittent protocol has not been determined. The increase in the "off" period during treatment may reduce the risk of excessive heating originated from the coil.[5]

Total Number of Stimuli

For transcranial magnetic stimulation (TMS), the total number of magnetic pulses obtained is one important factor to determine effectiveness; however, its role in peripheral magnetic stimulation has not been determined.[5]

Frequency

As is the case with the total number of stimuli, frequency is another major factor of TMS. Low-frequency stimulation (less than 1 Hz) has inhibitory effects, while high-frequency stimulation (more than 5 Hz) initiates excitatory effects in the brain.[8] Its influence on the effect of peripheral magnetic stimulation remains inconclusive.[5]

Intensity

Peripheral magnetic stimulation intensity is indicated by using tesla units or a percentage of the maximal stimulator output. But the real magnetic field strength that reaches the target structure cannot be determined. Factors affecting the strength are the type of coil used for stimulation, depth of target tissues, and geometry of the area beneath the coil. Therefore, the intensity is roughly measured by observing whether there is a muscle contraction, and it would be reported as subthreshold and suprathreshold stimulation. Almost all studies used for suprathreshold stimulation are based on the rationale that muscle contraction would produce proprioceptive afferents to induce neuroplasticity.[5]

Issues of Concern

Unlike TMS, the safety data regarding peripheral magnetic stimulation remain insufficient. Since both peripheral magnetic stimulation and TMS have similar physics properties, safety data of TMS is referenced.

Safety Considerations

Heating

The temperature increase is affected by the coil type, its cooling system, target tissue positions relative to the coil, and stimulation parameters. Different tissues have different thresholds to thermal damage, depending on exposure time and temperature. Most tissues can tolerate minutes of heat up to 43 degrees Celsius. Concerning excessive heat, the manufactured coils always have heat sensors that will automatically stop the coils when the temperature reaches around 40 degrees Celsius. Implants can heat as well and might cause thermal damage to surrounding tissues. No specific data has been provided on how peripheral magnetic stimulation heats certain kinds of implants. It is advisable to first measure the heating with planned parameters outside the body if it is still uncertain. Furthermore, applying peripheral magnetic stimulation over tumors is contraindicated.[9]

Force and Magnetization

The magnetic field emitted from the coil exerts an attractive force on ferromagnetic objects, meaning that the object can be moved by the magnetic force. A study indicated that stainless steel aneurysm clips in the brain were barely moved by TMS less than 0.0003 mm. Thus, this shift has no clinical significance. There are no safety data of peripheral magnetic stimulation applying over these kinds of ferromagnetic objects. Some experts suggest that principles of MRI safety for patients with implants can be adapted as a guide for peripheral magnetic stimulation.[9]

Induced Voltage

The magnetic field pulse can potentially damage the circuits of electronic implants such as deep brain stimulation and cochlear implant. Based on previous TMS studies, it appears safe to apply TMS to patients with implanted stimulators with some distance between the coil and the internal pulse generator. However, there is no comprehensive information about safe distance, even for TMS. Some TMS guidelines even suggest that life-sustaining implants anywhere in the body, like prosthetic cardiac valves, are absolute contraindications. Any electronic devices carried by both operators and patients should be removed to prevent possible damage.[9] The heart is also a conductive structure. There was a concern that the magnetic field would interfere with the cardiac electrical conduction; however, stimulating the

cardiac muscles requires extremely high energy. Two mechanisms are proposed: (1) First; the magnetic stimulators produce current with a shorter duration which cannot stimulate cardiac muscles. (2) The second reason relates to the distance of the heart away from the coil. The current produced by the magnetic field decreases with an increased distance from the stimulating coil. Also, the location of the heart makes it hard to stimulate.[3]

Adverse Effects

Peripheral magnetic stimulation is considered a painless approach. Some pain and discomfort were reported in studies that used triple stimulation techniques deploying suprathreshold peripheral magnetic stimulation. These adverse effects are likely associated with the intensity of peripheral magnetic stimulation.[5]

Considerations on Patient Selection

Pediatric Patients

TMS safety guidelines concluded that single-pulse and paired-pulse TMS is safe for children aged 2 years and older, although there are few studies of peripheral magnetic stimulation conducted in children. One study deployed peripheral magnetic stimulation to five cerebral palsy patients with a mean age of 8 years old to evaluate spasticity reduction. The study did not state any adverse effect after stimulation of tibial and common peroneal nerves by peripheral magnetic stimulation.[9]

Pregnancy

It is suggested that direct magnetic stimulation on the lumbar spine should be avoided. Women who are pregnant should stay at least 70 cm away from the coil.[9]

Clinical Significance

Many studies demonstrated peripheral magnetic stimulation to be advantageous in many medical conditions. However, more evidence is needed for proving the effectiveness of peripheral magnetic stimulation in certain clinical settings. The following are possible indications for the use of peripheral magnetic stimulation:

Myofascial Pain Syndrome

Smania et al. reported significantly better long-term (follow up after 3 months) outcomes in both subjective and objective clinical evaluations of peripheral magnetic stimulation in treating upper trapezius myofascial pain compared to TENS and sham ultrasound therapy.[10]

Traumatic Brachial Plexopathy

A study conducted by Khedr et al. showed significant improvement of electrophysiologic parameters, handgrip strength, and pain scores by applying both suprathreshold and subthreshold peripheral magnetic stimulation over upper trapezius muscle in comparison with sham treatments.[11]

Post-traumatic Peripheral Neuropathic Pain

A case series reporting four patients with neuromas and one patient with inguinal nerve entrapment was treated with a course of low frequency (0.5 Hz) peripheral magnetic stimulation. Allodynia was resolved after treatment. A reduction of 60% to 100% of pain scores was observed after treatment.[12]

Acute Low Back Pain

A pilot study was carried out by Lim et al. Immediate pain relief after peripheral magnetic stimulation application on patients' most tender points was reported. The study also showed better results of functional questionnaires after ten sessions of peripheral magnetic stimulation compared to sham.[13]

Chronic Low Back Pain

Several studies were conducted to investigate the effects of peripheral magnetic stimulation in patients with chronic low back pain. The investigators successfully showed relations between the use of peripheral magnetic stimulation and reactivation of short-interval intracortical inhibition of the primary motor cortex, which is usually absent in

patients with chronic pain. They also emphasize that a combination of peripheral magnetic stimulation and motor training has a positive outcome in pain, function, and lumbopelvic spine motor control.[14][15]

Spasticity Reduction

Many studies with varying protocols aimed to identify the antispastic effect of peripheral magnetic stimulation. Some studies applied peripheral magnetic stimulation over spinal nerve roots, while others applied over spastic muscles. All studies reported consistent results that spasticity decreased after each peripheral magnetic stimulation session. Nevertheless, understanding how peripheral magnetic stimulation could reduce spasticity needs further investigation.[1][16]

Increase Muscle Strength

A recently published study investigated the effect of peripheral magnetic stimulation over vastus lateralis muscles in patients after hip replacement surgery. After 15 sessions of peripheral magnetic stimulation, muscle strength improved but without a significant difference compared with the sham treatment. However, other functional outcomes seemed to be better in the peripheral magnetic stimulation group. The author explained that it might be related to the proprioceptive effect of peripheral magnetic stimulation on the brain.[17]

Dysphagia

Eight patients with stroke and dysphagia (7 out of 8 patients had subcortical strokes) were reported to have some reduction in penetration-aspiration episodes after applying additional peripheral magnetic stimulation to swallowing exercises for a week. Although, no single patient could change their mode of nutritional intake.[18]

Enhancing Healthcare Team Outcomes

Peripheral magnetic stimulation (PMS) or so-called transcutaneous magnetic stimulation is a non-invasive method of delivering a rapidly pulsed, high-intensity magnetic field to the periphery other than the brain. Interest in the research and clinical applications has increased over the last three decades as it is considered a novel, painless, and easy approach for many neurological and musculoskeletal conditions.[1] The technique can be used by any healthcare professional, but solid evidence for its efficacy is still lacking. For patients with mild to moderate pain due to the musculoskeletal system, one may try PMS, but patients should be warned that the benefits are often not immediate, and the therapy may require multiple sessions.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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N° 3

Repetitive Magnetic Stimulation for the Management of Peripheral Neuropathic Pain: A Systematic Review

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REVIEW

Repetitive Magnetic Stimulation for the Management of Peripheral Neuropathic Pain: A Systematic Review

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ABSTRACT

Introduction: Repetitive magnetic stimulation (rMS) is a safe and well-tolerated intervention. Transcranial magnetic stimulation (TMS) is used for the treatment of depression and for the treatment and prevention of migraine. Over the last few years, several reports and randomised controlled studies of the use of rMS for the treatment of pain have been published. The aim of this systematic review was to identify the available literature regarding the use of rMS in the treatment of peripheral neuropathic pain.
Methods: After a systematic Medline search we identified 12 papers eligible to be included in this review.
Results: The majority of the studies were on patients with phantom limb pain, followed by radiculopathy, plexopathy, post-traumatic pain and peripheral neuropathy. The treatment protocols vary significantly from study to study and, therefore, pooling the results together is currently difficult. However, rMS has a definite immediate effect in pain relief which, in the majority of studies, is maintained for a few weeks.
Conclusion: rMS seems to be a promising intervention in the treatment of peripheral neuropathic pain. Further research is in the field is needed. Use of neuronavigation might increase the precision of stimulation and subsequently its effectiveness.

Keywords: Neuropathic pain; Peripheral; Repetitive magnetic stimulation; TMS

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Key Summary Points
Both peripheral and central repetitive magnetic stimulation have been employed for the treatment of peripheral neuropathic pain.
Repetitive magnetic stimulation has potential in the treatment of peripheral neuropathic pain.
Use of neuronavigation might increase the precision of stimulation and subsequently the effectiveness of repetitive magnetic stimulation.
Assessment of brain networks might be the way forward to developing an objective means of studying the effect of repetitive magnetic. stimulation.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique based on the principle of electromagnetic induction of an electric field in the brain [1]. Anthony T. Barker was the first to explore the use of magnetic fields to alter electrical signalling within the brain, in Sheffield, and the first stable TMS devices were developed in 1985 [2].

The therapeutic utility of repetitive TMS (rTMS) has been demonstrated in a variety of neurological [3] and psychiatric conditions [4] and has already been approved as a treatment for depression and migraine in many countries. TMS is a safe and well-tolerated intervention whilst serious adverse events during TMS are rare [5].

Neuropathic pain is a common presenting complaint of patients with peripheral neuropathy (PN) and is considered one of the most detrimental aspects of the condition with regards to patients' quality of life [6–13]. It is therefore imperative for robust pain therapeutic interventions to be innovated, improved and implemented.

Over the years, increasing reports of the clinical utility of magnetic stimulation (MS) in the management of peripheral neuropathic pain and in particular rMS delivered either through a peripheral or transcranial route have been attempted with promising results.

The aim of this work was to systematically review the current literature regarding the use of rMS for the management of peripheral neuropathic pain. We aimed to describe the different treatment protocols that have been used and their efficacy in order to establish the therapeutic utility of rMS in the management of peripheral neuropathic pain.

METHODS

Search Strategy

A systematic computer-based literature search was conducted on 12 June 2019 using the PubMed database. We evaluated all articles published between the dates of 1 January 1999 and 12 June 2019. For the search, we used three Medical Subject Heading (MeSH) terms that had to be present in the title or the abstract. Term A was "neuropathy" or "phantom limb" or "polyneuropathy" or "peripheral" or "neuronopathy" or "radiculopathy" or "polyradiculopathy" or "dorsal" or "low back". Term B was "magnetic stimulation" or "magnetic therapy" or "electromagnetic". Term C was "pain" or "painful". No filters were applied to our search.

Inclusion and Exclusion Criteria

In order to be included in this review articles were required to meet the following criteria: (1) be original articles; (2) involve study of human subjects; (3) be written in the English language; (4) refer to transcranial magnetic stimulation or peripheral magnetic stimulation; (5) refer to pain because of peripheral nervous system involvement. The exclusion criteria for the articles were as follows: (1) book chapters, reviews, meta-analyses, systematic reviews,

letters to the editor and editorials not providing new data and study protocols; (2) articles which did not discuss magnetic or electromagnetic stimulation as a management option; (3) articles with a lack of individual results for the management of painful peripheral neuropathies, even if those subjects were included in the study; (4) articles not referring to patients with painful peripheral neuropathies.

Synthesis of Results

The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [6]. Where studies did not provide raw values in graphically displayed results, an open-source programme was used to extract raw data (Engauge Digitizer, http://markummitchell.github.io/engauge-digitizer). A database was developed using the Statistical Package for Social Sciences, version 24 for Mac. Pooled frequencies and descriptive characteristics of demographic parameters were extracted.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Our literature search strategy identified 332 articles. Of these, 12 met the inclusion criteria and were included and analysed in this review. Of them five were randomised controlled trials (RCTs), two were small case series and five single case reports. The majority of the papers (50%) tested the use of rMS in phantom limb pain, followed by radiculopathy (17%), brachial plexopathy (17%), post-traumatic pain (8%) and peripheral neuropathy (8%).

The PRISMA chart displays the process of article selection (Fig. 1). Table 1 summarizes the characteristics of the papers included and gives a detailed summary of the treatment protocols and outcomes.

PHANTOM LIMB PAIN

Phantom limb pain (PLP) is difficult to treat and often responds poorly to conventional pain management [15, 16]. Phantom limb sensations can be experienced following amputation. Phantom limb-like sensations can also be seen in patients with spinal cord injury, nerve avulsions and with congenital limb aplasia [17]. In PLP, maladaptive plasticity and reduced connectivity in interhemispherical and sensorimotor networks play a major role in pain. rTMS has been tested in PLP as a tool for blocking maladaptive plasticity in the sensorimotor cortex and has shown analgesic effects when used on the motor cortex, through modulating cortical reorganisation [18]. One particular study has shown that amputees with PLP have a significantly greater activation in the primary motor cortex and supplementary motor cortex of the affected hemisphere compared to those without pain, likely due to increased excitability after limb amputation [19].

Malavera et al. studied the effects of rTMS in the treatment of PLP in a randomised double-blinded placebo-controlled study [16]. Fifty-four patients underwent real or sham rTMS of the primary motor area contralateral to the amputated limb. The analgesic effect of the treatment was significant for the first 15 days; however, it was not after 30 days. The analgesic effect found in this study can possibly be explained by the effect of rTMS over the central pathophysiological mechanisms relating to PLP. After a traumatic amputation, maladaptive reorganisation of the sensorimotor cortex involves a reduction in intracortical inhibition mechanisms, an imbalance between γ-aminobutyric acid (GABA) and glutamate and an increase in excitability of corticospinal neurons. High frequency rTMS over the motor cortex enhances its excitability leading to the indirect activation of inhibitory projections towards the thalamus, resulting in the modulation of pain signalling pathways [16].

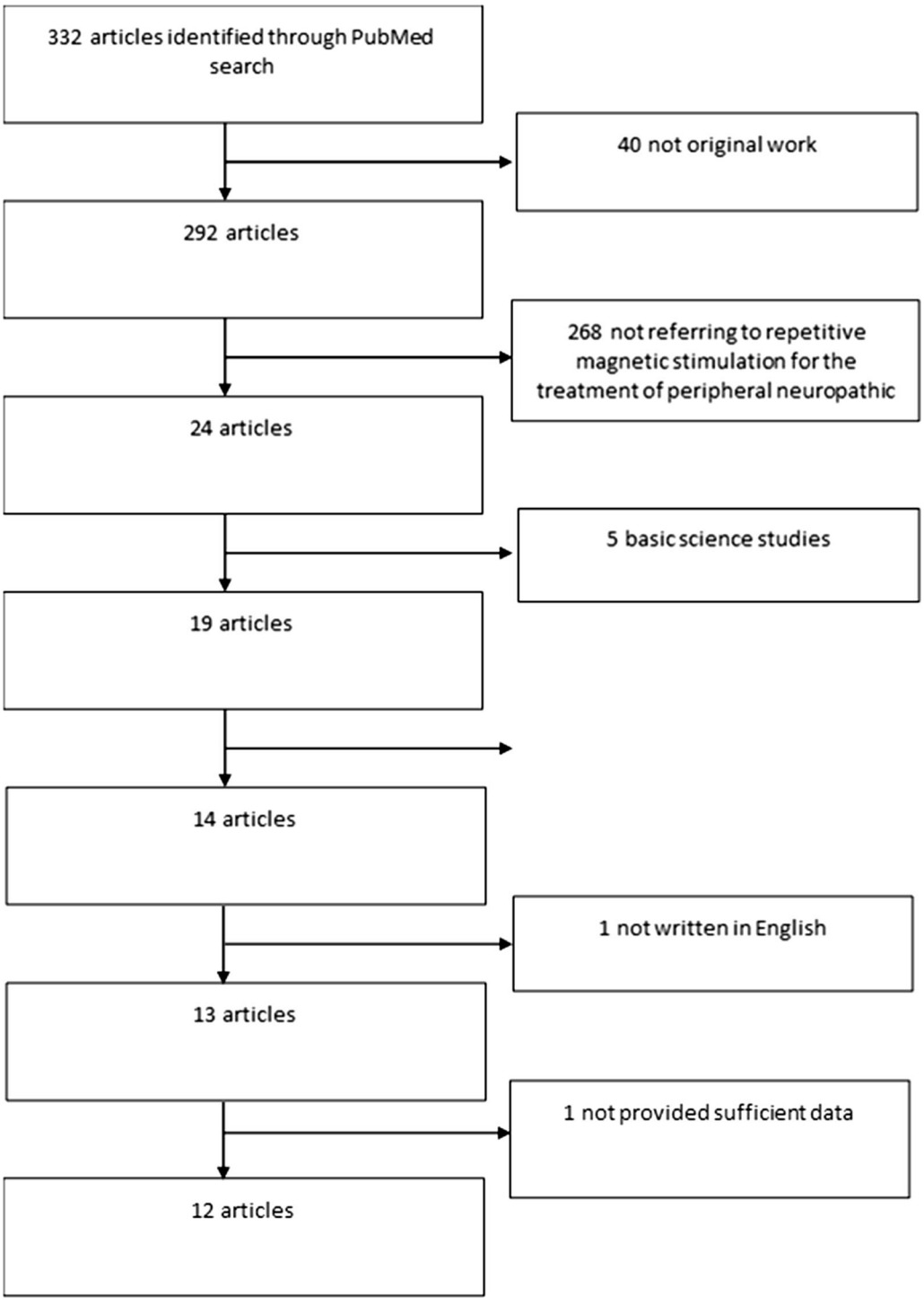

Fig. 1 PRISMA chart

In contrast to the RCT conducted by Malavera et al., a study by Ahmed et al. showed a significant and prolonged reduction of pain in patients with PLP receiving real rTMS versus sham. The authors randomised patients to receive either real rTMS (n = 17) or sham rTMS

Table 1 Description of protocols and outcomes reported in the studies included in this review

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Malavera (2016)	RCT	Phantom limb pain	54	Brain: hemisphere contralateral to the pain	Magstim Rapid 2 (Magstim, Whitland, UK)	No	Double	10 daily sessions over 2 weeks Primary motor area was stimulated at 10 Hz, with an intensity of 90% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 60 pulses (6 s). Interval between bursts was 54 s. In total, 1200 pulses were delivered in each session	70% of patients had a clinically significant pain reduction (> 30%) in the active group compared to 41% in the sham group 15 days after completion of treatment. This effect was not significant 30 days after treatment
Ahmed (2011)	RCT	Phantom limb pain	27	Brain: hemisphere contralateral to the pain	Mag-Lite r25 stimulator (Dantec Medical, Skovelund, Denmark	No	Double (90 mm)	Five consecutive daily sessions Primary motor area was stimulated at 20 Hz, with an intensity of 80% of the resting motor threshold. Each session had 10 bursts. Each burst consisted of 200 pulses (10 s). Interval between bursts was 50 s. In total, 2000 pulses were delivered in each session	Significant pain reduction in the active rTMS group compared to sham; 55% pain reduction at completion of treatment which remained reduced by 52% at 1 month after completion of treatment and reduced by 39% at 2 months after completion of treatment
Scibilia (2018)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Nexstim NBS system 4.3 (Nexstim Oy, Finland)	Yes	Not specified	30 consecutive daily sessions Primary motor area and dorsolateral prefrontal cortex were stimulated at 10 Hz, with an intensity of 120% of the resting motor threshold. Each session had 75 bursts. Each burst consisted of 40 pulses (4 s). Interval between bursts was 26 s. In total, 3000 pulses were delivered in each session Primary sensory area was stimulated at 1 Hz, with an intensity of 100% of the resting motor threshold. Each session had 77 bursts. Each burst consisted of 26 pulses (26 s). Interval between bursts was 4 s. In total, 2002 pulses were delivered in each session	55% pain reduction at 1 month after completion of treatment and remained at 6 months

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Grammer (2015)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Not specified	No	Double	2 rounds over 6 weeks (in total 28 daily sessions) First round: primary sensory area (five sessions) was stimulated at 1 Hz, with an intensity of 100% of the resting motor threshold. Each burst consisted of 26 pulses (26 s). Interval between bursts was 4 s. In total, 2000 pulses were delivered in each session Second round: alternating pattern between sessions as per round 1 and stimulation of the dorsolateral prefrontal cortex as follows Dorsolateral prefrontal cortex was stimulated at 10 Hz, with an intensity of 120% of the resting motor threshold. Each burst consisted of four pulses (4 s). Interval between bursts was 26 s. In total, 3000 pulses were delivered in each session Supplementary motor complex (2nd to 6th rounds) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session	60% pain reduction after three low frequency sessions stimulating the primary sensory area and 90% pain reduction after completion of all 28 sessions

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Lee (2015)	Case report	Phantom limb pain	1	Brain: hemisphere contralateral to the pain	Magstim Rapid 2 (Magstim, Whitland, UK)	Yes	Double (70 mm)	Six rounds, each consisting of 10 daily sessions over 2 weeks (varying intraround interval) Primary motor area (1st round) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session Supplementary motor complex (2nd to 6th rounds) was stimulated at 1 Hz for 800 s, with an intensity of 85% of the resting motor threshold. In total, 800 pulses were delivered in each session	Significant pain relief was reported after using low frequency rTMS over the supplementary motor complex, but not over the primary motor area
Di Rollo (2011)	Case report	Phantom limb pain	1	Brain: hemisphere ipsilateral to the pain	Magstim Rapid (Magstim, Whitland, UK)	No	Double (70 mm)	15 daily sessions over 3 weeks Primary motor area was stimulated at 1 Hz, with an intensity of 80% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 20 pulses (20 s). Interval between bursts was 10 s. In total, 600 pulses were delivered in each session	33% pain reduction at completion of treatment and remained reduced by 25% at the end of week 1 after completion of treatment and 17% at the end of week 3 after completion of treatment
Attal (2016)	RCT	Radiculopathy	36	Brain: hemisphere contralateral to the pain	MagPro X100 (Magventure, Farum, Denmark)	No	Double	Three consecutive daily sessions Primary motor area was stimulated at 10 Hz, with an intensity of 80% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 100 pulses (10 s). Interval between bursts was 20 s. In total, 3000 pulses were delivered in each session	43% of patients had a clinically significant pain reduction (> 30%) in the active repetitive transcranial magnetic stimulation (rTMS) group compared to 22% in the active transcranial direct current stimulation (tDCS) and 17% in the sham group. The superiority of rTMS was demonstrated for at least 5 days after treatment

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Töpper (2003)	Case series	Radiculopathy	2	Brain: hemisphere contralateral to the pain	Magstim Rapid (Magstim, Whitland, UK)	No	Double (90 mm)	Two rounds. Each round consisted of 15 daily sessions over 3 weeks (in total 28 daily sessions). The two rounds were separated by 4–6 weeks First round: Parietal cortex was stimulated at 10 Hz, with an intensity of 110% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 20 pulses (2 s). Interval between bursts was 1 min. In total, 400 pulses were delivered in each session Second round: Parietal cortex was stimulated at 1 Hz, with an intensity of 110% of the resting motor threshold. Each session a single burst lasting for 12 min. In total, 720 pulses were delivered in each session	Pain reduction only lasted for 10 min after the end of treatment
Leung (2014)	Case series	Post-traumatic pain	5	Peripheral: over the site of trauma, where neuroma developed	Not specified	No	Double	3–4 daily sessions over 2 months Stimulation frequency was 0.5 Hz. In total, 400 pulses were delivered in each session	85% pain reduction after 3–4 sessions Limitation due to lack of information about intensity of each treatment

Table 1 continued

Study	Type of paper	Type of pain	Number of patients	Site of stimulation	Device	Navigation	Coil	Protocol	Outcome
Khedr (2012)	RCT	Brachial Plexopathy	34	Peripheral: over the superior trapezius muscle	Magstim model 200 (Magstim, Whitland, UK)	No	Double (70 mm)	10 daily sessions over 2 weeks. Two protocols were applied (10 min apart) For pain relief: stimulation at 15 Hz, with an intensity of 100% of the resting motor threshold was applied. Each session had seven bursts. Each burst consisted of 150 pulses (10 s). Interval between bursts was 20 s. In total, 1050 pulses were delivered in each session For strength increase: stimulation at 3 Hz, with an intensity of 70% of the resting motor threshold was applied. Each session had 50 bursts. Each burst consisted of 30 pulses (10 s). Interval between bursts was 30 s. In total, 1500 pulses were delivered in each session	Real rMS led to a significant reduction of the VAS compared to sham rMS, which lasted for at least 1 month after completion of treatment
Lefaucheur (2004)	Case report	Brachial Plexopathy	1	Brain: hemisphere contralateral to the pain	Super-Rapid Magstim (Magstim, Whitland, UK)	No	Double (70 mm)	One session per month Primary motor area was stimulated at 10 Hz, with an intensity of 80% of the resting motor threshold. Each session had 20 bursts. Each burst consisted of 100 pulses (5 s). Interval between bursts was 55 s. In total, 2000 pulses were delivered in each session	Satisfactory reduction of pain (mean VAS score reduction of more than 5/10) was achieved with active rTMS. The effect lasted for at least 1 week and faded away at 4 weeks
Onesti (2013)	RCT	Peripheral Neuropathy	25	Brain	Magstim Rapid 2 (Magstim, Whitland, UK)	No	H-coil	5 consecutive daily sessions Primary leg motor areas were stimulated at 20 Hz, with an intensity of 100% of the resting motor threshold. Each session had 30 bursts. Each burst consisted of 50 pulses. Interval between bursts was 30 s. In total, 1500 pulses were delivered in each session	Real rTMS led to a significant reduction of the VAS compared to sham rTMS, which lasted for up to 3 weeks after completion of treatment

(n = 10). Sham rTMS involved elevating and angling the magnetic coil away from the cortex. The authors found a 55% reduction in pain in the treatment group immediately following the fifth session. This effect was still seen at 2 months follow-up [20]. Interestingly the percentage of pain reduction was higher in patients with upper limb phantom pain compared to patients with lower limb phantom pain. Whilst the results reported are positive, there are multiple drawbacks in the methodology within this study including non-standard randomisation criteria, small sample size and unequal group allocation. Additionally, the study recruited a heterogenous population of patients affected by PLP, in both upper (n = 11) and lower limbs (n = 16).

Navigated TMS employs conventional TMS combined with sophisticated neuronavigational software providing precise anatomical information necessary for anatomically controlled cortical stimulation. It can be used to stimulate highly selected areas in the brain in PLP. It promotes the modulation of brain connectivity to induce its rearrangement in chronic pain syndromes. In a patient with PLP, Scibilia et al. used high frequency stimulation (10 Hz) of the primary motor area and the dorsolateral frontal cortex contralateral to the pain, and low frequency (1 Hz) stimulation of the primary somatosensory area contralateral to the pain, using navigated TMS [21]. Using resting state functional magnetic resonance, they showed that rTMS promoted cortical and subcortical plasticity, which led to an associated pain reduction. After treatment, the patient experienced a significant reduction of 5 points on the visual analogue scale (VAS) in terms of pain. This suggests that high frequency stimulation of the motor cortex contralateral to site of PLP can induce an analgesic effect. As this was a single case report, larger cohort studies are warranted to validate these findings.

In cases such as motor function recovery post stroke, stimulation with low frequency rTMS in the unaffected hemisphere has shown beneficial results [22]. Di Rollo et al. reported the effect of stimulating the hemisphere ipsilateral to the PLP in a single patient [15]. The patient showed a 33% reduction in pain at the end of the third week of treatment and a decrease of 17% at the follow-up visit which was 3 weeks after the last session.

Lee et al. described a case report of PLP treated with rTMS of the supplementary motor cortex and the primary motor cortex, using neuronavigation. Magnetic therapy dramatically reduced the pain intensity when directed over the supplementary motor cortex; however, there was no reduction in pain with therapy directed over the primary motor cortex [23]. The authors postulate that this is due to a reported greater activation of the supplementary motor cortex in amputees with PLP than those without [24]. These results, however, are to be taken with caution, owing to the patient receiving one round of treatment to the primary motor cortex, versus five rounds to the supplementary motor cortex.

Grammer et al. reported a patient with upper extremity PLP. Over 6 weeks they delivered 28 sessions of rTMS to the dorsolateral prefrontal cortex and primary sensory area contralateral to the side of pain. The sessions were of low frequency (1 Hz) for the first five sessions, thereafter alternating between low frequency (1 Hz) and high frequency (10 Hz). This protocol led to an 80% decrease in pain as rated on the VAS [25].

RADICULOPATHY

Attal et al. studied the efficacy of rTMS in patients suffering from neuropathic pain secondary to unilateral lower lumbar radiculopathy in an RCT. In tandem with this they compared the efficacy of rTMS to transcranial direct current stimulation (tDCS), which applies low intensity electrical currents directly, rather than the magnetic field employed in rTMS [26]. In an altered crossover methodology, they randomised 36 patients to receive either active rTMS and tDCS or sham rTMS and tDCS, with a 3-week period between either modality. Results showed that rTMS was more effective than tDCS and sham (tDCS and rTMS), after the third and final stimulation session. Repetitive magnetic stimulation maintained its efficacy over sham when pain was measured 5 days after the final

session, but not in comparison to tDCS. The study was limited by its relatively short treatment and follow-up period.

Töpper et al. evaluated the use of rTMS in two patients with PLP-like syndrome who had suffered cervical nerve root (C7 and C8) injuries secondary to road traffic collisions [27]. The authors investigated two separate protocols of rTMS directed over the posterior parietal cortex contralateral to the symptomatic side. The first included high frequency stimulation (10 Hz) and the second low frequency (1 Hz). The two protocols were separated by at least 4 weeks. Whilst the authors reported a significant reduction in pain measured with VAS during the rTMS treatment, this effect was seen only for up to 15 min after therapy. The study is, however, limited by its small number of participants.

Brachial Plexopathy

In an RCT of 34 patients with traumatic brachial plexopathy, Khedr et al. evaluated the efficacy of rTMS as an adjuvant intervention to physical therapy, consisting of electrical stimulation, ultrasound, heat therapy and therapeutic/active exercises [28]. Magnetic stimulation was directed over the superior trapezius muscle, using stimulation at both 3 Hz (aiming to increase strength) and 15 Hz (aiming to relieve pain). The authors reported a significant reduction in the VAS score in patients receiving real therapy compared to sham therapy. This effect was seen both at the end of the therapy and at 1-month follow-up. The study is limited by the fact that the sham protocol was substandard as the authors used an active coil that was elevated away from the muscle, rather than a sham coil applied directly over the muscle [29].

In a case report of a 37-year-old patient with brachial plexopathy, Lefaucheur et al. assessed the efficacy of high frequency rTMS targeting the precentral gyrus [30]. Over a treatment period of 16 months, they found that rTMS provided a statistically significant reduction in VAS scores. Whilst the study provides evidence of long-term use of rTMS, it is limited by being a single patient report with no matched control.

POST-TRAUMATIC NEUROPATHIC PAIN

Peripheral nerve injury can lead to the formation of a neuroma which results from abnormal nerve regeneration, which is often refractory to medications and invasive interventions. In a small case series reported by Leung et al., five patients tolerated well low frequency TMS over the site of the neuroma formation and showed long-term pain relief [31]. This is in line with other studies demonstrating that low frequency rTMS provides an inhibitory effect on neuronal activities. However, this study is limited by its small sample size, lack of control and unclear frequency of treatment sessions.

PERIPHERAL NEUROPATHY

Peripheral neuropathy is common amongst the diabetic population [32]. In a cross-over RCT Onesti et al. were the first to investigate the effect of deep rTMS, achieved by using the H-coil in 25 patients with diabetic neuropathic pain. The H-coil allows safe access to deep cortical areas which otherwise could not be accessed [33] and has been proven to be effective in the management of major depressive disorder, bipolar disorder and focal dystonias [34–36]. In this study the authors used deep real or sham rTMS of the lower limb motor cortex. The authors reported that real rTMS at 20 Hz reduces chronic drug-resistant distal diabetic neuropathic pain for 3 weeks.

CONCLUSIONS

Chronic pain perception has been found to propagate through central brain sensitisation, particularly involving the prefrontal cortex and the thalamus, in comparison to acute pain scenarios primarily recruiting the spinothalamic pathways [37]. This presents an opportunity to identify therapeutic interventions that are able to target this central processing of pain. Magnetic stimulation exerts its effect by the magnetic field generated inducing a subsequent electrical field that is able to depolarise axons

and therefore modulate active neural networks within the cortex [38]. This effect may differ depending on factors such as the magnetic pulse waveform, the intensity, frequency and pattern of stimulation [38]. There is consensus in the literature that low frequency stimulation (< 1 Hz) and high frequency stimulation (> 5 Hz) are responsible for suppression and facilitation of corticospinal excitability, respectively [39]. There is some consensus that high frequency rather than low frequency stimulation is able to illicit an analgesic effect in neuropathic pain [38]. Indeed, a similar conclusion may be drawn from the studies that have been included in this review.

On a molecular level, rTMS has been reported to induce endogenous opioid release, with one study demonstrating a reduction of the analgesic effect when stimulating the primary motor cortex in subjects administered naloxone. The authors did not find this to be the case when rTMS was applied to the dorsolateral prefrontal cortex [40]. It is important to note, however, that naloxone is known to play a role in reducing the perceived analgesic effect derived through placebo [41]. Various other neurochemicals have been reported to be implicated during rTMS therapy, including GABA, glutamate and dopamine. Glutamate *N*-methyl-D-aspartate (NMDA) receptors are known to be responsible for synaptic plasticity and have been reported to be associated with the long-term analgesic effect of rTMS [42]. In the context of PLP in particular, high frequency rTMS may indirectly activate inhibitory thalamic projections, thereby modulating ascending nociceptive pathways [43]. Neuropathic pain of diverse aetiologies has been shown to be associated with decreased intracortical inhibition (ICI) and interestingly rTMS therapy has been correlated with increased ICI in tandem with pain relief, particularly in patients with drug-resistant neuropathic pain [44]. Functional magnetic resonance imaging has revealed that rTMS of the motor cortex results in subsequent activity within the ipsilateral thalamus and putamen, structures known to be linked to the sensorimotor cortex, implicated in the centralisation of pain [45].

This review identified five RCTs, highlighting a paucity in the literature of well-designed placebo-controlled trials evaluating rMS for relief of peripheral neuropathic pain. Although the majority of the studies included in this review show that rMS has potential for the treatment of peripheral neuropathic pain, there is a need for further studies in the field. Whilst its efficacy is still debated, rMS has been demonstrated to be a safe and tolerated intervention, with no serious adverse effects noted in the studies included in this review. Furthermore, there is a need to create consensus regarding optimum stimulation protocols and procedures [46]. The use of neuronavigation might increase the precision of stimulation and subsequently its effectiveness; however, this requires further robust assessment as current evidence is lacking. Finally, assessment of brain network function, with techniques such as functional magnetic resonance or appropriate TMS-compatible EEG recordings, with various quantitative EEG metrics, might be the way forward to developing an objective means of studying the effect of rMS on widely distributed brain network constituents involved in the generation and persistence of neuropathic pain.

Limitations

- As in all studies measuring pain with the VAS, a self-reported questionnaire, there is potential for an inherent response bias when reporting the nature and extent of the pain.
- The variations in treatment protocols between studies and the limited number of studies eligible for inclusion make it impossible to use a meta-analytic approach.
- A more comprehensive search using databases other than PubMed alone might have identified a greater number of articles suitable for analysis.

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N° 4

The Effectiveness of the Functional Magnetic Stimulation Therapy in Treating Sciatica Syndrome

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The Effectiveness of the Functional Magnetic Stimulation Therapy in Treating Sciatica Syndrome

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Abstract

Introduction: Degenerative or traumatic causes are most common in generating sciatica syndrome, which is normally treated with well-known physical therapy methods. A relatively new way of treating sciatica problems is so-called functional magnetic stimulation (FMS), whose principle is based on electromagnetic field inducing electrical field inside the body. Electrical field triggers action potential of nerve cells and that way stimulates peripheral motor nerve system. Aim: Aim of this study is to measure and estimate the effectiveness of implementing therapy with functional magnetic stimulation in regular physical treatment of sciatica syndrome. Materials and Methods: 28 male patients aged between 30 and 55 with back problem were recruited on an outpatient basis. FMS therapy was performed with TESLA Stym® device (Iskra Medical d.o.o., Slovenia) treating lumbosacral region equally on both sides of the spine. Physical examination was performed to evaluate tree parameters: the mobility of the lumbar spine in flexion and extension, together with the straight leg raise test (Lasegue sign). We estimated patients' progress, comparing angle values of mobility from the first examination day with other examination days. Results: In FMS treated group of patients, lumbosacral flexion, extension and Lasegue test angle were significantly higher compared to day 0 on the first physical examination day (day 3) ($p < 0.05$). In control group such increase of a measured angle was not noticed until a second physical examination day (day 5) or a third physical examination day (day 8) ($p < 0.05$). Discussion: Results in this study showed that applying FMS therapy along with other standard physical therapy methods rapidly increased effectiveness of the treatment of sciatica syndrome (*lat. ischialgia*). It suggests that functional magnetic therapy could be suggested as a regular physical therapy method in treating this kind of pain syndromes.

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Keywords

Sciatica Syndrome, Lasegue Sign, Functional Magnetic Stimulation, FMS

1. Introduction

Functional magnetic stimulation (FMS) of peripheral nerves and muscles is based on the principle of electromagnetic induction. Functional magnetic field is generated by a pulse of current created through a wire inside a coil in the applicator of TESLA Stym® device [1]. Dynamic magnetic field up to 1.5 T inside the body induces electric current that is responsible for triggering action potential on motor nerve system [2]. This direct stimulation of motor neurons [3] results in contraction of the muscle or a group of muscles, depending on the number of axons affected. Key advantage of direct nerve stimulation is in inducing its metabolism, perineural circulation and nutrition. Therefore, FMS is a suitable option for treating neuropathic diseases, radiculopathies and plexopathies [4]. FMS induced muscle stimulation can be used for preventing muscle atrophy while it simultaneously increases blood circulation [5].

Sciatica syndrome (SS) (low back pain, *lat. ischialgia*) represents a collective term for various symptoms like: low back pain, severe muscle spasm, reduced mobility of lumbosacral region, radicular pain, positive Lasegue sign, paresthesia in specific dermatome, reduced sense for touch, and sometimes even paresis and hypotrophy of a muscle [6]. Degenerative or traumatic causes are most common in generating sciatica syndrome. Causes can be: disk protrusion or extrusion, osteochondrosis and osteophytosis, anterolisthesis and retrolisthesis, spondylosis, osteoporosis and malformation of lumbosacral vertebrae, fractures, neoplastic infiltrations, compressive tumors and infections [7]. Mechanical or musculoskeletal problems are defined as the cause in almost 90% of the cases [8] [9], while 75% of them do not have a specific cause identified, but are thought to be due to muscle strain or injury to ligaments [8] [9]. Other causes such as fibromyalgia and somatoform disorders are not diagnosed so often as the ones previously mentioned [9].

Low back pain is a very common symptom around the world. When we look at the global picture, about 40% of people experience low back pain at some point in their lives [10], with estimates as high as 80% of people in the developed countries [11]. It is estimated that 9% to 12% of people (around 632 million) have low back pain at any given point in time, while 23.2% of them report having it at some point over any one-month period [10] [12]. This common symptom usually manifests between 20 and 40 years of age [13]. Sciatica syndrome is most commonly diagnosed at age between 40 and 80, with the overall number of individuals affected expected to increase as the population ages [10]. This is why developing modern and more efficient therapeutic approaches for sciatica syndrome is very important.

Standardized medical approach to this problem consists of complete and qualitative diagnostics, physical treatment, and then, if needed, surgical procedure.

Standard physical treatment of the SS is a set of therapies of few combined well-known physiotherapy procedures: diadynamic current (DDC), interference current (IFC), ultrasound (US), laser, electromagnet, massage, traction, IR lamp, application of fixed and mobile ventouses and kinesiotherapy. High field magnetic therapy has already been shown as an effective alternative method in back pain treatment [14] [15].

Aim of this study is to measure and estimate the effectiveness of implementing therapy with functional magnetic stimulation in regular physical treatment of sciatica syndrome.

2. Material and Methods

Twenty-eight male patients aged between 30 and 55 with back problem were recruited on an outpatient basis. Patients were treated in Center of physical medicine and rehabilitation “CIM” in Novi Sad, Serbia during the time period from November 2013 until March 2014. All the patients included in the analysis were diagnosed with *sy. lumbale ac.ishialgia l. dex*. More detailed characteristics are shown in **Table 1**.

Patients were randomly divided into two groups. Each patient received personally adapted physical therapy consisting of 12 consecutive daily sessions. The therapy comprises a combination of three therapy procedures (DDC, IFS, US, lasers, massage, traction, IR lamps, fixed suction cups, kinesiotherapy). Control group of 14 patients received regular physical therapy on daily basis. FMS treated group of 14 patients received 20 minutes of

FMS therapy every other day in addition to the daily regularly physical therapy. The therapeutic scheme for both groups of patients is represented in **Table 2**. FMS therapy was performed with TESLA Stym® device (Iskra Medicald. o.o., Slovenia) using the large movable applicator, treating lumbosacral region equally on both sides of the spine. Specific combination of amplitudes and frequencies, named as "Program no. 2" on this device was used in treatments. This combination was used since the most patients subjectively found it as the most relaxing.

Physical examination was performed to evaluate tree parameters: the mobility of the lumbar spine in flexion and extension, together with the straight leg raise test (Lasegue sign). These three parameters (flexion, extension, Lasegue test) were assessed in *angles*, measured with goniometer [16] [17]. Follow-up examinations were performed on the 3rd, 5th, 8th and 12th day of therapy and included the same tests [**Table 2**]. Patients were instructed not to consume painkillers, non-steroidal anti-inflammatory drugs, opioids or other anti-rheumatic drugs during the 12 days of therapy. We estimated patients' progress, comparing angle values of mobility measured on the first examination day (examination before the beginning of the therapy) with values measured on the examination performed on the 3rd, 5th, 8th and 12th day of therapy. We compared it using statistical t-test and one-way ANOVA on each examination day. Statistical analyses were performed using Statistica version 10 software (StatSoft, USA) [18].

The study was study was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients before the first treatment.

3. Results

3.1. Flexion in Lumbosacral Region

Figure 1 indicates lumbosacral flexion measurement on a daily basis. Firstly, there was no difference between the control and FMS treated group on day 0, before the first treatment. In FMS treated group of patients, lumbosacral flexion angle was significantly higher compared to day 0 on the first physical examination day (day 3). In control group such increase of a measured angle was not noticed until a second physical examination day (day 5).

3.2. Extension in Lumbosacral Region

Figure 2 represent measured angles in lumbosacral extension after the therapy. Again, there was no difference between the control and FMS treated group on day 0, before the first treatment. In FMS treated group of patients, lumbosacral flexion angle was significantly higher compared to day 0 on the second physical examination day (day 3). In control group such increase of a measured angle was not noticed until a third physical examination day (day 8).

3.3. Lasegue Sign. Strait Leg Test (Flexion)

Measured angles by performing Lasegue test showed noticeable increase in motion in the FMS treated group.

Table 1. Summarized characteristics of patients enrolled in this study.

	Diagnose	Number of patients	Age	Sex
Control group	sy. lumbale ac. ischalgial.dex.	14	42.4 ± 6.99	Male
FMS group	sy. lumbale ac. ischalgial.dex.	14	43 ± 6.27	Male

Table 2. Therapy schedule scheme. *Orange colour* represents days with regular physical therapy for control and FMS treated group; *Red colour* represents 20 minutes of FMS therapy (FMS treated group only); *Blue colour* represents physical examination (control and FMS treated group).

Days	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Standard physical therapy												
FMS therapy												
Physical examination												

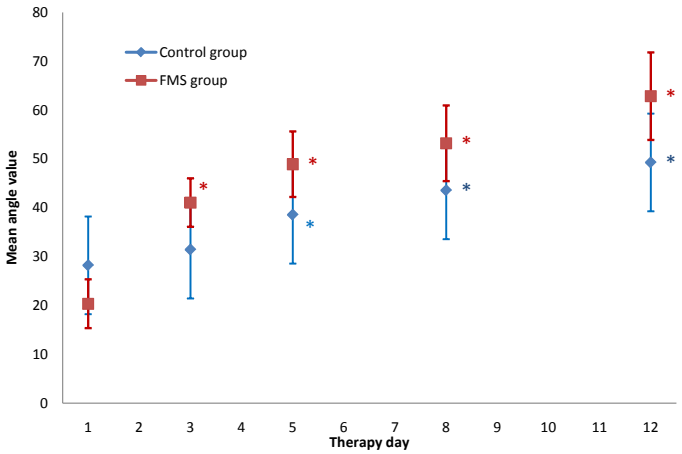

Figure 1. Lubmosacral flexion angle for control and FMS treated group for every day of therapy. Statistical significance is marked with *($p < 0.01$).

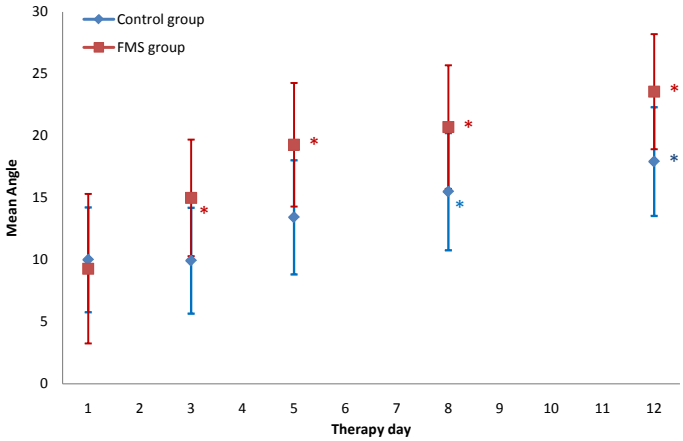

Figure 2. Extension in Lubmosacral region for control and FMS treated group for every day of therapy. Statistical significance is marked with *($p < 0.05$).

Statistical t-test showed significant difference in second group of patients already on the first examination after first physical examination day (day 3) while significant increase in motion was measured on second physical examination day (day 5) in the control group (**Figure 3**).

4. Discussion

Since the first achievements in training and counteracting atrophy [19]-[21], neuromuscular electrical stimulation has opened up several additional fields for applications. Today, it plays an indispensable role in rehabilitation, physiotherapy [22] and treatment of chronic low back pain [23]. Ratajczak B *et al.* (2011) showed that diadynamic currents (DDC) and transcutaneous electrical nerve stimulation (TENS) have analgesic effect in treating sciatic syndrome (*lat. ischialgia*) [24]. However, electrical stimulation shows several crucial drawbacks. A number of issues reflect badly on this very promising and potent method: not only the stimulation-related pain [25], but also the limited force response, electrochemical degradation effects near the electrodes [26] [27] and limited penetration of the current into the muscle because of the parallel paths through the surface tissue layers. In contrast, functional magnetic neuromuscular stimulation (FMS) is less painful and allows profound activation

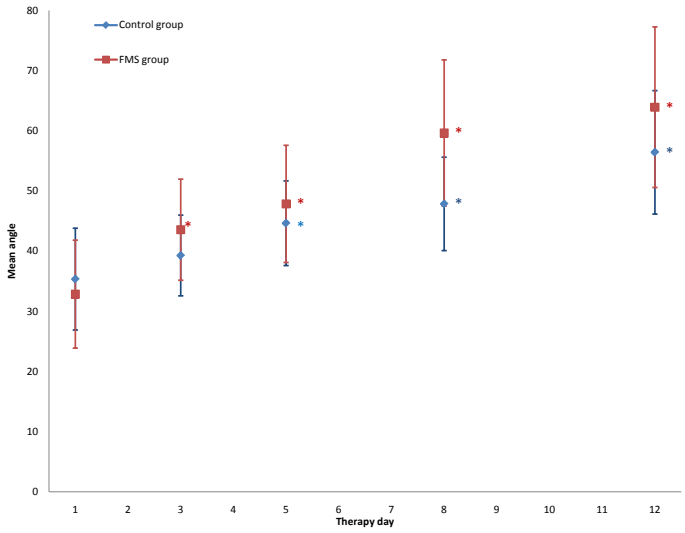

Figure 3. Lasague test angle for control and FMS treated group for every day of therapy. Statistical significance is marked with $^{*}(p < 0.05)$.

of muscles at the level approaching maximal voluntary contraction [28]. The aforementioned regularly used physical procedures have a limited effect on all local structures and surface tissues due to the basic underlying principles of electricity, ultrasound and light in human tissue. Their effects depend on skin resistance, moisture and resistance of other tissues, tissue water content and many other factors. Due to all these, these physical procedures only achieve effects at limited depths.

On the other hand, FMS works by the principle of magnetic field, whose intensity does not depend on the characteristics of the local tissue. FMS propagation depth is up to 7 - 10 cm deep inside the tissue. FMS therapy can also be used similar like electrotherapy with various positive noticeable effects like muscle training, increased circulation, oxygenation and rehabilitation process of nerve and muscles, reduced muscle spasms and inflammatory processes.

Analyzing values measured in this study, we have compared values within the group, but not between the groups, since every group of patients has their own characteristics and individual progress. Statistics followed each group of patient's own mobility improvement during the therapy time. Significant statistical results show that improvements of patient's mobility are more rapidly achieved by adding functional magnetic stimulation to the regular physical therapy treatment.

There are reports on multiple acute and chronical locomotors system problems being relieved or solved using FMS. These include tissue regeneration after muscular or tendon injuries, relieving pain effect, preventing and reducing muscular and nerve atrophy, muscle spasms, reducing intra-articular calcifications and foremost treating conditions due to pelvic floor muscle problems. In the literature, there are reports showing significant improvement due to conditions of female stress and urge incontinence [29]-[31]. The success in treating symptoms of female urge incontinence additionally shows [31] [32] that functional magnetic field is also affecting smooth muscles structures during few weeks of therapy. Further studies are expected to show more profound knowledge of FMS effect on vegetative nervous system. FMS effect of directly depolarizing nerve cell in transcranial magnetic stimulation (TMS), using similar magnetic fields, is used for decades in diagnostic as well as therapeutic application in treating neurological and psychiatric disorders [33]. Use of the magnetic muscle stimulation in locomotory system stimulation was long hindered by overheating of the devices within minutes of their continuous use [34]. Applications in physical therapy and rehabilitation require magnetic stimulators with capability of continuous use for hour(s) while imitating output signal parameters used in electrical neuromuscular stimulation. Such magnetic stimulators have only recently been available; therefore further studies are needed to rigorously determine true potentials of FMS.

Results in this study showed that applying FMS therapy along with other standard physical therapy methods

rapidly increased effectiveness of the treatment of sciatica syndrome (*lat. ischialgia*). Most of the patients also have reported significant low back pain relief already after first therapy with FMS (TESLA Stym®). This leads us to the conclusion that functional magnetic therapy could be suggested as a regular therapy method in treating sciatica syndrome and similar medical conditions.

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Nº 5

Integrating Ultrasound-Guided Multifidus Injections with Repeated Peripheral Magnetic Stimulation for Low Back Pain: a Feasibility Study

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CASE SERIES

Integrating Ultrasound-Guided Multifidus Injections with Repeated Peripheral Magnetic Stimulation for Low Back Pain: A Feasibility Study

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Background: Low back pain is a globally prevalent musculoskeletal issue. Repetitive peripheral magnetic stimulation (rPMS) is emerging as a promising modality for managing musculoskeletal pain, while ultrasound-guided lumbar facet/multifidus injections are a potential therapeutic option for low back pain. This study explores the feasibility of combining these two treatments for managing low back pain.

Materials and Methods: Ultrasound-guided injections were administered using 5 mL of 50% dextrose and 5 mL of 1% lidocaine. Bilateral injections targeted the L4/L5 and L5/S1 facet joints with 1 mL at each site, and the remaining 8 mL was distributed over the multifidus muscles using peppering techniques. Following injections, rPMS therapy was conducted with the TESLA Stym® device, targeting the bilateral lumbosacral region over 12 sessions. Pain intensity was measured using the visual analog scale (VAS), and disability was assessed with the Oswestry disability index (ODI) at baseline, after six sessions, and after 12 sessions of rPMS.

Results: Three participants were enrolled. Baseline VAS and ODI scores were 8.33 ± 0.29 cm and 49.63 ± 1.28%, respectively. After six rPMS sessions, VAS and ODI scores changed to 4.33 ± 3.75 cm and 21.48 ± 19.42%, respectively. After 12 sessions, VAS decreased to 0.83 ± 1.44 cm and ODI to 5.19 ± 8.98%. Significant differences were observed between baseline and final assessments.

Conclusion: Combining ultrasound-guided lumbar facet/multifidus injections with rPMS shows promise for treating low back pain. However, long-term efficacy and comparison with conventional treatments require further investigation through prospective randomized controlled trials.

Keywords: Magnetic field therapy, lumbar vertebrae, paraspinal muscles, ultrasonography, interventional procedures

Introduction

Low back pain (LBP) is a prevalent musculoskeletal issue worldwide.[1] Its age-standardized point prevalence in 2017 was 7.5%, with the number of affected individuals reaching approximately 577 million. This condition tends to escalate with age, peaking notably between 80 to 89 years of age. Various environmental and individual factors have been linked to heightened risk of LBP such as older age, poor general health like smoking, physical stressors such as vibration, and psychological stress including depression.[2] LBP can stem from diverse causes including muscle strain, disc problems, spinal stenosis, arthritis, or traumatic injuries. Prognostic factors for nonspecific chronic LBP have been reported as maladaptive behaviors, anxiety, functional limitations during episodes, smoking, and physical labor.[3] Non-pharmacological treatments like exercise therapy and physiotherapy are recommended as initial approaches, particularly for chronic LBP or high-risk patients.[4] Cognitive behavioral therapy, often combined with physical therapy, is suggested for improving pain management. Pharmacological interventions encompass oral treatments, topical lidocaine patches, and spinal epidural injections.[4] Despite the efficacy of various treatment modalities, a significant proportion of patients remain resistant to these strategies.

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Repeated peripheral magnetic stimulation (rPMS) shows promise as an effective treatment for various types of musculoskeletal pain. It involves the application of a rapidly pulsed, high-intensity magnetic field to peripheral areas of the body, excluding the brain.[5] Unlike electrical stimulation, rPMS bypasses the need to use electrodes for delivering electric current through the skin to the target tissue. The equipment typically comprises a high-current pulse generator and a stimulating coil. rPMS has shown efficacy in treating conditions like myofascial pain syndrome, traumatic brachial plexopathy, post-traumatic peripheral neuropathic pain, and spasticity.[5] Recent studies, included in a 2023 meta-analysis, highlight its potential in alleviating LBP.[6] Moreover, advancements in ultrasound (US) imaging allow for precise visualization of the musculoskeletal structures in the thoracic and lumbar spine.[7] Given the involvement of lumbar facet joints and adjacent muscles like the multifidus in LBP, US-guided multifidus injections seem to have a potential therapeutic avenue.[8]

Chen et al[8] compared the effects of US-guided prolotherapy with 5% dextrose in water in the multifidus muscle to US-guided mechanical needling and sterile water injections for treating lumbar spinal stenosis. They evaluated LBP, leg pain, and gait ability using the Visual Analogue Scale (VAS) and walking distance at six different time points. Of the 211 older patients with lumbar spinal stenosis, 104 received US-guided mechanical needling and sterile water injections over four weeks, while 107 received a single session of dextrose injection into the multifidus muscles. Both intervention groups showed significant improvements in chronic LBP, radiating pain, and walking ability at 1 and 3 months post-treatment compared to baseline. The authors concluded that prolotherapy with dextrose in the multifidus muscle has a moderate effect lasting up to three months.

To date, no research has explored the feasibility of combining ultrasound-guided lumbar facet joint or multifidus injections with rPMS for LBP. While US-guided injections provide targeted pain relief, rPMS offers a broader effect on pain relief beyond the site of local injection. Given these complementary mechanisms, we hypothesized that combining these therapies could result in rapid and sustained relief of LBP. This study was designed to address this gap and investigate the potential synergistic effects of these modalities in pain management.

Materials and Methods

Participants and Study Flow

Participants were sourced from the outpatient clinic of the Department of Physical Medicine and Rehabilitation at National Taiwan University Hospital, Bei-Hu Branch. The eligibility of all candidates who completed the baseline questionnaire concerning LBP was assessed. The study utilized retrospective patient data from the clinic's registry, which did not require approval from the hospital's institutional review board for a case report involving three or fewer cases. According to the institutional review board's regulations for a case report, patient informed consent was not required for the retrospective review of electronic medical records, as confidentiality was maintained in accordance with the Declaration of Helsinki. Based on a meta-analysis by Diao et al in 2023,[6] patients with acute or chronic low back pain, lumbosacral spondylotic changes, and lumbar radiculopathy are potential candidates for rPMS treatment. Therefore, our inclusion criteria encompassed (1) age exceeding 18 years, (2) experiencing non-specific LBP for a minimum of six weeks within the past 12 months, and (3) provision of available data for analysis. Exclusion criteria consisted of back trauma/surgery within the preceding three months. A control group would not be included for analysis if the required scoring scales were lacking. Enrolled participants underwent US-guided injection for bilateral lumbar facet joints and adjacent multifidus muscles. Subsequently, they received 12 sessions of rPMS over a 6-week period. Assessments were done at baseline, after six and 12 sessions of rPMS (Figure 1).

Application of rPMS

rPMS therapy involved the utilization of the TESLA Stym® device (Iskra Medicald. o.o., Slovenia) which is equipped with a spacious movable applicator specifically designed to target the bilateral lumbosacral region symmetrically. The simulation protocol was adapted from the study by Radaković et al,[9] which used the same rPMS machine as ours to treat 28 male patients with sciatica. This treatment regimen relied on a tailored combination of amplitudes and frequencies, known as the "Chronic Pain Back Pelvic II" program, operating in accordance with Faraday's law of magnetic induction.

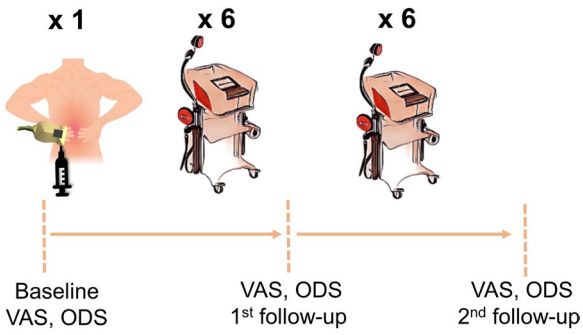

Figure 1 Flowchart for implementing interventions and measuring outcomes of studies.
Abbreviations: VAS, visual analogue scale, ODI, Oswestry disability index.

Through the application of magnetic pulses, nerves were stimulated, and paraspinal muscle activity was modulated - resulting in the repeated activation of motor nerve fibers and motor end plates, thus enhancing muscle strength and endurance. The stimulator generated symmetric magnetic gradients of up to 2.5 Tesla/sec. Each rPMS treatment session lasted for 20 minutes, conducted three times weekly over four consecutive weeks. The stimulus intensity level commenced at 20% of the maximal stimulator output and increased gradually by 2%. The final intensity was adjusted to the maximum level that elicited appropriate contraction of the paraspinal muscles while remaining within the patient's tolerable range.

US-Guided Injection

A convex transducer (i10CX1) operating at a center frequency of 5.0 MHz, integrated within the Aplio i600 platinum platform (Canon Medical Systems, Tokyo, Japan) was employed to guide the injections. Participants were positioned prone, with a pillow placed over their abdominal region for comfort. Scanning commenced from the midline, where the peak of the spinous process and the median sacral crest were clearly visualized. Subsequently, the transducer was adjusted laterally to observe the laminae, which appeared as straight bone planes separated by the inter-lamina space, represented by the dura and ligamentum flavum.[10] Upon adjusting the transducer laterally, the facet column emerged, characterized by its mountain-range-like structure, with the inferior articular process connecting cranially and the superior articular process connecting caudally. Once the longitudinal plane of the facet column was identified, a 21 G 7-mm NIPRO needle was introduced through an in-plane, caudal to cranial approach. A mixture of 5 mL of 50% dextrose and 5 mL of 1% lidocaine was used. L4/L5 and L5/S1 facet joints were targeted with administering 1 mL of injectate in each, whereby the remaining 8 mL was distributed over the multifidus muscles using peppering injection techniques (Figure 2). If the patient presented bilateral symptoms, bilateral paraspinal muscles would be injected.

Outcome Evaluation

Assessments encompassed VAS to gauge pain intensity and the Oswestry disability index (ODI). The former is a widely recognized method for subjectively evaluating pain intensity.[11] Participants indicated their pain level on a scale of 0 to 10 cm, spanning from "no pain" to "worst pain imaginable." The distance from the "no pain" end to their marked point was measured, offering a quantifiable representation of pain intensity.

The ODI comprises ten sections, each targeting various daily activities impacted by LBP, such as lifting, walking, sitting, standing, and sleeping.[12] Respondents rated their degree of disability on a scale from 0 to 5 for each section, where 0 signifies no disability and 5 signifies maximal disability. These scores across all sections were then aggregated to derive an overall disability score, typically ranging from 0 to 50 or expressed as a percentage.

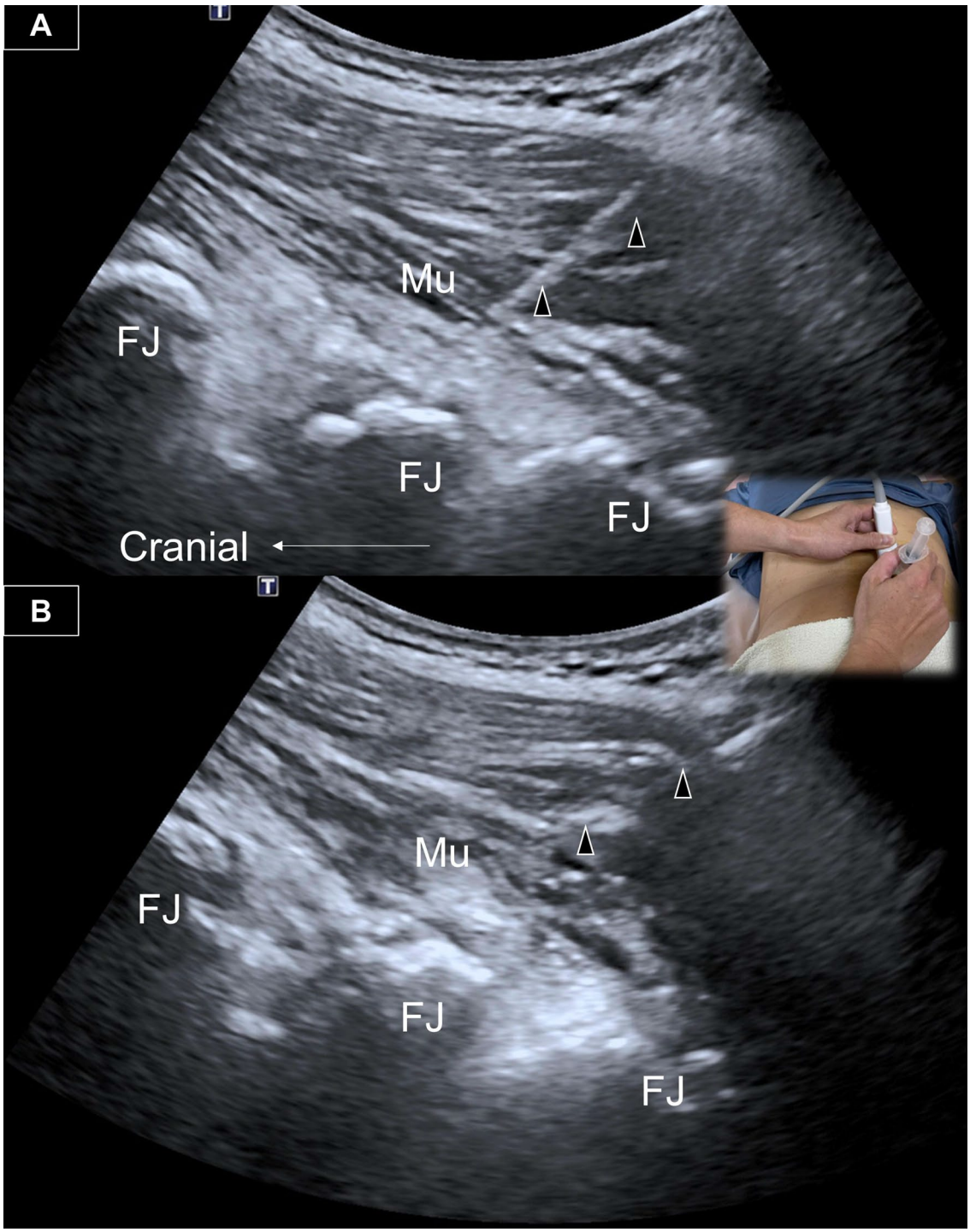

Figure 2 Ultrasound-guided (**A**) lumbar facet joint (FJ) and (**B**) lumbar multifidus (Mu) muscle injection. Arrowhead, needle trajectory.

Statistical Analysis

We employed the Shapiro–Wilk test to assess the normality of continuous variables. If the variables followed a normal distribution, we proceeded with univariate analysis using either one-way analysis of variance or the Mann–Whitney

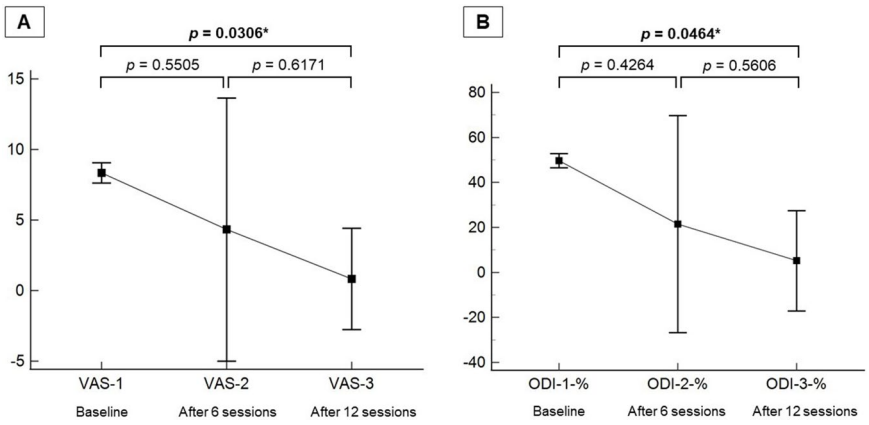

Figure 3 Line graphs showing the changes in (**A**) visual analogue scale (VAS) and (**B**) Oswestry disability index (ODI).
Notes * indicates $p<0.05$.

U-test. For categorical data comparison, the chi-square test was applied, with Fisher's exact test utilized for small cell counts. Repeated measure analysis of variance was employed to compare means across various time points within groups. All statistical analyses were conducted using SPSS 21.0b software, with a significance level set at $P < 0.05$.

Results

Three participants (2 F and 1 M) were enrolled in the study. Their ages ranged from 36 to 72 years, with an average of 56.33 ± 18.45 years (95% confidence interval [CI], 10.51–102.16). Heights varied between 156.3 and 170 cm, averaging 162.10 ± 7.09 cm (95% CI, 144.49–179.71). Body weights ranged from 47 to 61.6 kg, with an average of 51.97 ± 8.34 kg (95% CI, 31.24 to 72.69). Lumbar spondylosis was identified on the plain film in two participants.

Initially, baseline VAS in cm and ODI in percentage were recorded at 8.33 ± 0.29 (95% CI, 7.62 to 9.05) and 49.63 ± 1.28 (95% CI, 46.45 to 52.81), respectively. Following US-guided injections and six sessions of rPMS, VAS and ODI (%) values changed to 4.33 ± 3.75 (95% CI, −4.99 to 13.66) and 21.48 ± 19.42 (95% CI, −26.75 to 69.72), respectively. After an additional six sessions of rPMS, VAS and ODI (%) further decreased to 0.83 ± 1.44 (95% CI, −2.75 to 4.42) and 5.19 ± 8.98 (95%CI, −17.13 to 27.50), respectively (Figure 3). Significant statistical differences were observed for both VAS and ODI (%) between the baseline and final follow-up assessments (Table 1). No side effects were reported during or within three months after the treatment.

Table 1 Clinical Outcome After Peripheral Magnetic Stimulation Treatment

	Patients (n = 3)
VAS (cm)	
Baseline	8.33 ± 0.29 [a] (7.62 to 9.05)
After 6 sessions	4.33 ± 3.75(−4.99 to 13.66)
After 12 sessions	0.83 ± 1.44[a] (−2.75 to 4.42)
ODI (%)	
Baseline	49.63 ± 1.28[a] (46.45 to 52.81)
After 6 sessions	21.48 ± 19.42 (−26.75 to 69.72)
After 12 sessions	5.19 ± 8.98[a] (−17.13 to 27.50)

Notes: Scores are given as mean ± standard deviation (95% confidence interval of mean). [a] Significant difference between baseline and after the 12th session.
Abbreviations: VAS; visual analogue scale, ODI; Oswestry disability index.

Discussion

The results of this preliminary investigation showed that the integration of US-guided facet and multifidus muscle injections with 12 sessions of rPMS significantly decreased LBP and increased the functional performance - without any adverse effects.

In 2023, Diao et al[6] conducted a comprehensive meta-analysis investigating the effects of rPMS on pain intensity, functional mobility, and kinesiophobia in individuals affected by LBP. Employing a meticulous approach, they systematically scoured databases such as PubMed, Physiotherapy Evidence Database, Embase, Cochrane Library, and Web of Science. Eligible randomized controlled trials meeting specific criteria regarding the population suffering from low back pain, the intervention of rPMS, and outcomes associated with pain intensity, functional mobility, and kinesiophobia were considered for inclusion. Comparisons were drawn between participants subjected to rPMS and those in sham or alternative control groups pertaining to six randomized controlled trials (out of 733 studies) encompassing 139 participants. The findings revealed that rPMS exhibited noteworthy effectiveness in reducing both pain intensity and functional disability when contrasted with sham rPMS or other therapeutic approaches. However, the analysis did not discern any significant variance in kinesiophobia between the studied groups. The authors cautiously concluded that while rPMS may offer promise in alleviating pain intensity and enhancing functional disability among individuals with LBP, the evidence supporting this assertion ranged from very low to low quality. Nonetheless, the impact of rPMS on kinesiophobia remains uncertain based on the available data.

The understanding of mechanisms behind the effects of magnetic stimulation on LBP is yet incomplete. According to the gate-control theory,[13] the electrical field produced by magnetic stimulation primarily targets large-diameter myelinated Aβ afferent fibers, hindering the depolarization of smaller Aδ and C nerve fibers. This inhibition may trigger descending inhibition, leading to increased central β-endorphin release, hyperpolarization at the motor end plate, and subsequent muscle relaxation, potentially impeding the transmission of pain perception to the brain. Stimulation of large-diameter fibers also has potential in reducing nociceptive signaling in spinal dorsal horns. Furthermore, rPMS offers advantages such as localized targeting and the activation of efferent fibers in mixed nerves, resulting in physiologic muscle contraction without significant discomfort.[14] In patients with LBP, paraspinal muscles might become atrophic,[15] and activation of the atrophic muscles might be helpful to restore their muscle mass. Additionally, when applying rPMS, suprathreshold stimulation operates under the assumption that muscle contraction will activate proprioceptive afferents, thus aiding neuroplasticity.[16] Another plausible explanation involves the immediate activation of a descending inhibitory pathway, possibly by activating brain stem areas like the rostral ventral medulla and periaqueductal gray.[5]

Numerous individuals experiencing LBP often exhibit myofascial trigger points within the paraspinal muscles, particularly the multifidus. Freeman et al[17] emphasized the crucial role of the lumbar multifidus muscles as stabilizers of the trunk. Dysfunction in these muscles strongly correlates with LBP, resulting in pain inhibition originating from the spine. Persistent dysfunction in the lumbar multifidus muscles presents as atrophic replacement by fat, a condition best visualized through magnetic resonance imaging. Hence, administering injections into the multifidus muscle could potentially alleviate LBP.

In 2021, Kanamoto et al[18] conducted a cohort study involving 75 patients diagnosed with acute LBP based on physical and imaging findings. They performed hydro-release of the multifidus muscle at the L4/5 level. Statistical analysis of VAS scores before and five minutes after hydro-release demonstrated significant improvement. The injection technique mirrored that proposed by Chen et al[8] who advocated an in-plane approach from lateral to medial, enabling sequential targeting of the lumbar facet joint, medial branches, and short axis of the multifidus with a single needle entry portal. In contrast, our adapted method involves inserting the needle along the long axis of the spine to target the multifidus and two levels of the facet joints (L4/L5 and L5/S1). This modification broadens the scope of potential pain sources, leading to enhanced pain relief outcomes. The combination of US-guided lumbar facet/multifidus muscle injection followed by rPMS offers several advantages. Of note, US guidance enables clear identification of the deeply situated multifidus muscle, ensuring safe injection without the risk of injuring intrathecal structures. In areas where muscle fibers are prone to disorganization and exhibit focal hypoechoic echotexture, trigger points are more prevalent and can be effectively relieved through repeated needle release.[19] This process

significantly enhances local blood flow, addressing the energy crisis within the myofibrils associated with myofascial pain.[20] Once the energy crisis is resolved, subsequent rPMS can help modify pain perception in the low back region and adjust the local pain threshold. Additionally, the atrophic or inactive paraspinal muscle may potentially be activated or strengthened through rPMS sessions, leading to improved functional recovery from disability caused by LBP.

Moreover, the rationale for administering the injection before rPMS is based on the promptness of treatment effects and the number of sessions required. US-guided injections for affected muscles can result in significant pain reduction after just one session, as shown by a recent narrative review on the use of US imaging and guidance in managing myofascial pain syndrome.[21] In contrast, rPMS requires multiple sessions to achieve significant benefits for patients with LBP, as demonstrated by the meta-analysis by Diao et al.[6] Therefore, to provide patients with rapid and sustained pain relief, we first administer US-guided injections for the multifidus muscle, followed by rPMS.

The current investigation is constrained by several limitations. First, the retrospective design had been applied on the present research, whereas recall bias and participant self-selection might be a potential source of bias. Second, the inclusion of only three cases limits the study's representativeness, so the data should be interpreted with caution. Third, the study only includes one treatment (and no control) arm, therefore it cannot exclude pain relief solely to natural recovery. Moving forward, there is a critical need for a prospective randomized controlled trial comparing intervention with a control (or placebo) arm to provide clearer insights. Furthermore, if a randomized controlled trial will be conducted in the future, a sample size calculation is necessary to ensure the adequate power to detect the difference between our developed combination therapy and the controlled treatment.

Conclusion

Utilizing US-guided lumbar facet/multifidus muscle injection alongside rPMS presents a viable approach for the management of LBP. Herewith, assessing the sustained efficacy of this combined therapy in the long term and comparing it with conventional non-operative treatments require prospective randomized controlled trials to offer more definitive insights.

Data Sharing Statement

The data generated or analyzed during the study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study utilized retrospective patient data from the clinic's registry, which did not require approval from the hospital's institutional review board (eg National Taiwan University Hospital) for a case report involving three or fewer cases. According to the institutional review board's regulations for a case report, patient informed consent was not required for the retrospective review of electronic medical records, as confidentiality was maintained in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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FMS

FUNCTIONAL MAGNETIC STIMULATION

Intensive Care Units

Nº 1

Functional Magnetic Neuromuscular Stimulation vs. Routine Physiotherapy in the Critically Ill for Prevention of ICU Acquired Muscle Loss: A Randomised Controlled Trial

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Article

Functional Magnetic Neuromuscular Stimulation vs. Routine Physiotherapy in the Critically Ill for Prevention of ICU Acquired Muscle Loss: A Randomised Controlled Trial

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Abstract: *Background and Objectives*: Muscle loss is a known complication of ICU admission. The aim of the study was to investigate the effect of neuromuscular functional magnetic stimulation (FMS) on quadriceps muscle thickness in critically ill patients. *Materials and Methods*: Among ICU patients one quadriceps was randomized to FMS (Tesla Stym, Iskra Medical, Ljubljana, Slovenia) stimulation and the other to control care. Quadriceps thickness was measured by ultrasound (US) in transversal and longitudinal planes at enrolment, Days 3–5, and Days 9–12. The trial stopped early following an interim analysis comparing muscle thickness differences between groups using repeated measures ANOVA. *Results*: Of 18 patients randomized, 2 died before completing the trial. The final analysis reported included 16 patients (female 38%, age 68 ± 10 years, SOFA 10.8 ± 2.7). Three mild skin thermal injuries were noted initially, which were later avoided with proper positioning of FMS probe. Primary outcome comparison showed that quadriceps thickness in transversal and longitudinal planes decreased in the non-stimulated legs and, but it did not change in FMS legs (−4.1 mm (95%CI: −9.4 to −0.6) vs. −0.7 mm (95%CI: −4.1 to −0.7) (p = 0.03) and −4.4 mm (95%CI: −8.9 to −1.1) vs. −1.5 mm (95%CI: −2.6 to −2.2) (p = 0.02), respectively) (ANOVA difference between groups p = 0.036 and 0.01, respectively). *Conclusions:* In the critically ill, neuromuscular FMS is feasible and safe with precautions applied to avoid possible skin thermal injury. FMS decreases the loss of quadriceps muscle thickness.

Keywords: functional magnetic stimulation; skeletal muscle; ICU acquired weakness; muscle ultrasound

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1. Introduction

In critical illness, intensive-care-unit-acquired weakness (ICU-AW) is a known complication [1,2] with an estimated 50% rate of muscle weakness [3,4]. Patients with ICU-AW stay longer on mechanical ventilation. It causes persistent functional impairment, lasting even after hospital discharge [5,6]. The cause of ICU-AW is multifactorial form systemic inflammation, sepsis, immobilisation, sedation, hyperglycaemia, and exposure to neuromuscular blocking agents and corticosteroids [7,8], which all lead to decreases in muscle mass and strength [9]. There are different strategies to ameliorate the ICU-AW including passive mobilisation [10,11], shorter time of depth sedation and adequate analgesia for promoting faster awakening allowing active movements [12].

The ICU physiotherapy also includes peripheral transcutaneous electrical stimulation [13], something that has been found effective in non-critically ill patients [14]. Despite electrical stimulation is a method for preventing ICU-AW, it has some important limitations [13]. It is effective in critically ill patients when the stimulation starts within the first seven days of admission and is not effective in very acute conditions [15]. Electrical stimulation can induce visible muscle contractions in 75–80% of patients, probably due

to tissue oedema over the muscles acting as insulation [16]. Electrical stimulation is also painful, what is difficult to assess and avoid in the critically ill [17]. Thus, an alternate approach is needed.

Transcutaneous neuromuscular functional magnetic stimulation (FMS) differs from electrical stimulation. FMS uses a magnetic applicator instead of electrodes for muscle tissue stimulation [18] and is known to be less painful [17]. An electric coil installed in the applicator generates a magnetic field that propagates into the human body, inducing electric currents [18]. These induced currents artificially propagate a signal along neurons inducing muscle contraction. Despite transcutaneous electrical stimulation and FMS have the same triggering mechanism in the nerve cell, they differ in the method of energy delivery [13]. Unlike electrical stimulation, which rarely reaches structures more than 12 mm deep, FMS penetrates deeper into the body without direct contact of the applicator with the skin. That is why FMS can be performed through clothing and bandages [19]. FMS also causes little or no pain, because it does not cause a high concentration of electric current at the point of entry into the body through the skin [16]. It was shown that FMS can prevent inactivation atrophy of skeletal muscles in the mobilised limb of rats [20]. It was also shown that in humans transcutaneous FMS of the quadriceps is a safe and painless method [21]. In patients with COPD quadriceps FMS was successfully applied and it increased size of slow-twitch muscle fibres, increased contraction force by 17% and improved quality of life [22,23]. It was previously also shown that lumbar repetitive peripheral magnetic stimulation in lumbar region fosters nerve regeneration and motor recovery in patients with lumbar radiculopathy [24].

In the above background, the primary purpose of the study was to evaluate the effect of FMS in critically ill patients to prevent quadriceps atrophy.

2. Materials and Methods

2.1. Study Design

The current study was a single-centre, parallel, two-arm, open-label, randomised controlled trial. It was conducted in an 11-bed, level 3, medical ICU at the General and Teaching Hospital Celje, Slovenia during a 6-month period (from December 2023 to April 2024). The study was approved by the Institutional Review Board of General Hospital Celje (No. 61/2023/3, 25 October 2023). It was prospectively registered (NCT06368908, 16 April 2024). Informed consent was signed by relative carers before inclusion and confirmed by the patient after gaining conciseness. The trial is reported according to CONSORT guidelines [25].

2.2. Participants

Critically ill patients after 2 to 3 days of ICU admission, whose treatment was expected to require at least 10 days in the ICU, were included in the study when the muscle ultrasound team (A.S., M.P.) was available. Exclusion criteria were as follows: age < 18 years of age, implanted electrical devices affected by magnetic fields, expected ICU survival of less than 5 days, pregnancy, bone and tissue injuries of legs where standard physiotherapy cannot be performed, high-dose corticosteroid application (equivalent to >300 mg hydrocortisone per day), continuous or intermittent muscle relaxants use, obesity (BMI over 40 kg/m^2) or cachexia (BMI less than 20 kg/m^2 or loss of 5% body weight over 12 months), brain death, and inability to obtain informed consent.

2.3. Randomisation and Baseline Data

After the recruitment of the patient, the right or the left leg was randomised to transcutaneous FMS while the other leg was allocated to control care. Research Randomizer (Research Randomizer, www.randomizer.org (accessed on 15 September 2024)) was used to create the allocation sequence. Allocation data for each consecutive patient was saved in separate closed envelope. Trial investigators enrolling the participants were kept blind to the random allocation until after the consent was obtained. ICU and 28-day basic demographic data, ethology, and severity of disease outcome data were collected from the

hospital electronic database BIRPIS21 (SRCInfonet, Kranj, Slovenia). Laboratory analysis on admission was carried out in the laboratory of our institution. The worst of the first 24 h SOFA (sepsis-related organ failure assessment) [26] and APACHE II (acute physiology and chronic health evaluation) [27] score were used.

2.4. Transcutaneous Neuromuscular Functional Magnetic Stimulation

Skeletal muscle FMS was performed above randomised quadriceps using a magnetic stimulator (Tesla stym, Iskra Medical, Ljubljana, Slovenia). For FMS, a predefined ICU program was used (pulse trains (30 Hz) with power ranging from 0.5 to 2.5 (100%) T, 6 s long stimulation trains, and a duty cycle varying from 1:1 to 1:10). Muscles were stimulated with a magnetic field intensity that triggers touchable and visible contraction. For touchable detection of muscle contraction, the investigator's hand was put on the skin over the contracting muscle close to stimulation probe. The stimulation was performed for 55 min per randomised selected limb 5 days per week. The percent of maximal power of magnetic stimulation used for each stimulation and the number of stimulations per patient were recorded. FMS (frequency: 30 Hz, power: 1.6 T) can generate approximately 72 $\pm$ 5% of the maximal spontaneous contraction force of the quadriceps [22].

Temperatures of the working head of magnetic stimulator, connecting cables, skin under working head of stimulator at the end of stimulation cycle and temperature of contralateral not stimulated skin were measured with IR camera (GTC 600C, Bosch, Gerlingen, Germany) in one patient after AE detection.

2.5. Routine Treatment and Physiotherapy

Treatment data (i.e., maximal noradrenaline dose, duration of mechanical ventilation) was collected from the intensive care information system (Centricity Critical Care, GE healthcare, Chicago, IL, USA). The feeding of the patients according to European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines was at discretion of the treating physicians [28]. The physiotherapy of the patients according to current recommendations was at the discretion of the ward physiotherapists [29]. Twice per day, classical physiotherapy was performed (passive stretching), followed by active bed exercising with both legs, sitting, and early mobilisation as soon as possible.

2.6. Quadriceps Muscles Thickness Measurement by Ultrasound and Strength Testing

Measurements of quadriceps thickness and cutaneous/subcutaneous tissues were taken three times on each leg (first: upon enrolment in the study; second: between Days 3–5 after enrolment; and third: between Days 9–12 after enrolment) at the measuring point, which was set as follows. The patient was in the supine position, leg in a neutral position, knee extended with fingers pointing up. On the thighs, the transversal measurement line was marked circumferential at the lower 1/3 of the distance between the spino-iliac point and the medal of the patella. The longitudinal measurement line was set, where the rectus femoris, vastus intermedius and femur were centrally located in the transversal plane. All further measurements we performed at the crossing of transversal and longitudinal measuring line, marked with a permanent marker [30]. Ultrasound (US) (Vivid 70, GE Healthcare, Chicago, IL, USA) examination was performed with a linear probe of 8–12 MHz; ultrasound settings (frequency 12 Hz, gain: 55 dB, dynamic range: 75) were kept constant for all patients, with depth adjusted only in the case of larger muscle thickness. Measurements were performed in transverse and longitudinal muscle sections with minimal compression of the US probe, the probe was perpendicular to get the shortest distance to avoid oblique scanning. Quadriceps thickness (both rectus femoris and vastus intermedius together) was defined as the distance between the superior border of the muscle and the cortex of the femur. US measurements were performed by A.S. and M.P, who are educated to perform US in different body regions of critically ill including muscles. To avoid subjectivity in measurement, the videos and measurements were reevaluated by both operators together

on EchoPack ultrasound analysis software v206 (GE Healthcare, Chicago, IL, USA) to reach the consent on the final measurement.

2.7. Outcomes and Monitoring of Side Effects and Adverse Effects

Primary outcome was the effectiveness of the FMS on quadriceps thickness in critically ill patients. Secondary outcome was the muscle strength between FMS stimulated and not-stimulated leg. At the end of the study, in patients who were able to cooperate (Ramsay Sedation Scale: 2 or 3 points) [31], the muscle strength of both legs was tested according to the Medical Research Council (MRC) [32]. The test was performed by a trained physiotherapist (A.J.). ECG monitoring (CarescapeB850, GE Healthcare, USA) was observed to detect interactions between FMS and monitoring signals. Possible local skin changes as redness of the skin and local burns under FMS probe were visually detected and recorded. Skin redness and blisters < 2 cm, up to superficial second degree burns, were defined as mild adverse effects (AE) according to burs classification [33]. Severe adverse effects (SAE) were all higher-grade thermal injuries of the skin and subcutaneous tissue compared to mild AE. The AE were independently individually reviewed and treated by two team-nurses, who had additional education of wound management (post-registration qualification of wound management—European qualification framework level 6, Slovenian Wounds Management Society, dors.si) and two intensivists with more than 5 years ICU working experience including also surgical ICU.

2.8. Sample Size Estimation and Statistical Analysis

The indicated sample size in the trial registry was 20. The sample size was estimated on previous data [29], assuming the mean difference of muscle thickness between the FMS and control groups at the end of the study of 5 mm with standard deviation of 5 mm. At this level of effect, 17 patients would have been required in the study with type I error level of 0.05 (p-value threshold 0.05) and a type II error of 0.20 (power 80%), we added 3 patients due to potential loss of patients after recruitment. There were mild thermal skin injuries noted initially in the 3 (2nd, 4th, and 5th) of the first 5 patients recruited. Thus, it was decided that interim analyses after additional inclusion of 6 patients should be carried out to maximise safety. The trial was stopped earlier than planned, due to the interim analysis showing statistically significant effects on quadriceps thickness.

Normality of data distribution was tested by the D'Agostino–Pearson test. Normally distributed data are presented as mean (±standard deviation) for metric variables, absolute and relative frequencies for categorical variables. Not-normally distributed data is presented as median (95%CI). The Mann–Whitney test for independent samples or the Wilcoxon test for paired samples were used to compare two groups. The effect of treatment compared to control on repeated measurements of quadriceps thickness during the study was analysed by repeated measures ANOVA. MedCalc ver. 12.5 (MedCalc Software Ltd., Ostend, Belgium) was used for sample size estimation and statistical analysis. A p-value < 0.05 was considered to define statistical significance.

3. Results

There were 18 patients randomised, of whom 2 patients died before completing the study. The flow of participants through each stage of a randomized trial is presented in Figure 1. The primary outcome data were available for 16 patients.

Demographic data, severity of disease, treatment and outcome of patients is presented in Table 1. In all patients FMS induced palpable quadriceps contractions, confirming feasibility of FMS in critically ill patients. Initial power of FMS was 100% (95%CI; 94–100). During study period 10 (95%CI: 9–10) FMS were performed in each patient. Median cutaneous/subcutaneous tissue was not different between FMS compared to non-stimulated leg (12.8 mm (95%CI: 5.0–15.8) vs. 11.9 mm (95%CI: 6.2–16.1), $p = 0.6$).

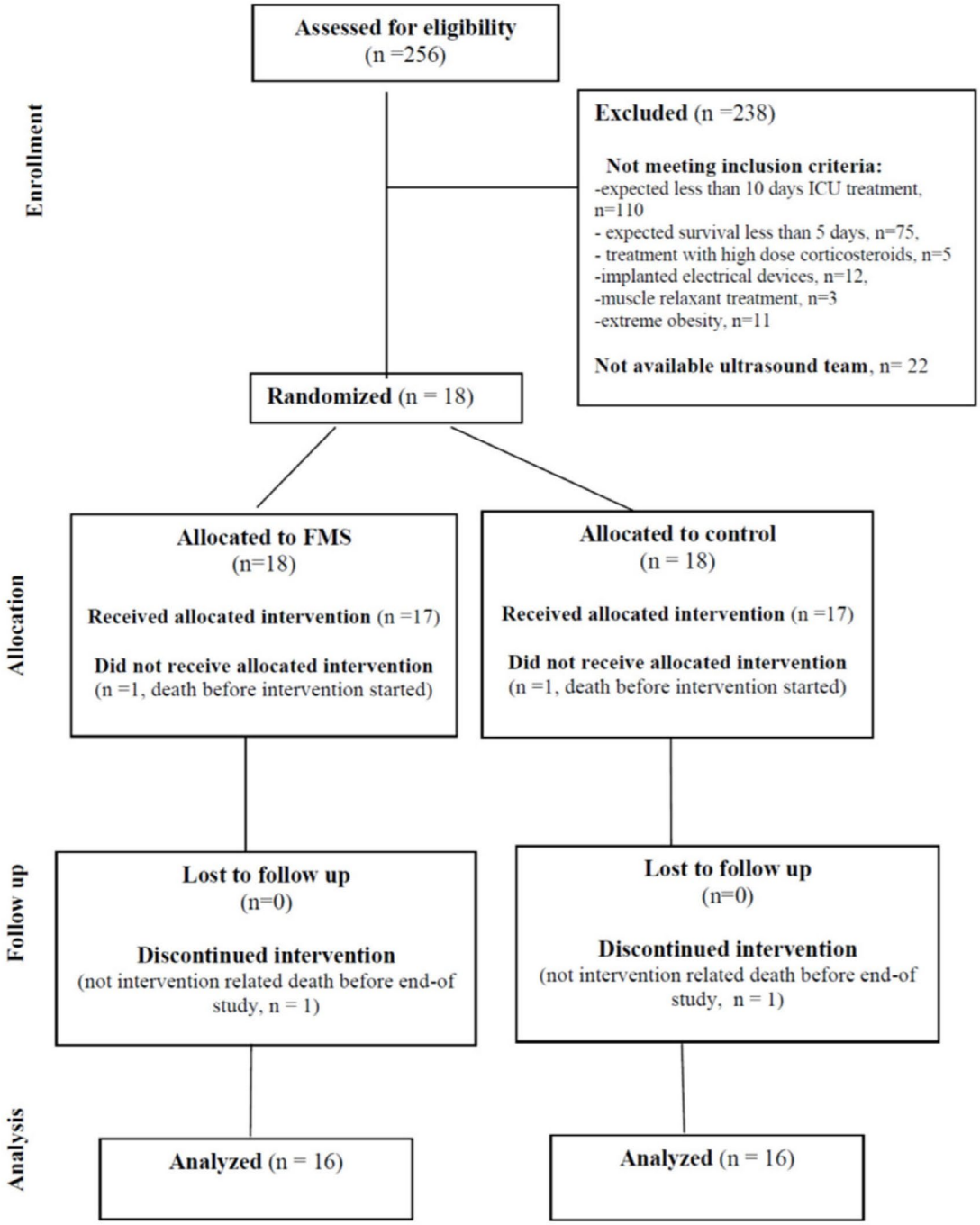

Figure 1. The CONSORT diagram showing the flow of participants through each stage of a randomised trial.

Table 1. Demographic data, severity of disease, treatment and outcome.

	Values (n = 16)
Gender (female/male), n (%)	6/10 (37/63)
Age, years	68 ± 10
BMI, kg/m^2	31.5 ± 6.3
WHO performance at home, points	1.0 ± 0.9
Severity of disease and treatment	
Septic shock/sepsis, n (%)	10/6 (63/37)
Acute respiratory failure, n (%)	15 (94)
Acute renal failure, n (%)	14 (88)
Acute circulatory failure, n (%)	7 (44)
Acute liver failure, n (%)	3 (19)
SOFA score at admission, points	10.8 ± 2.7
APACHE II at admission, points	26.0 ± 7.2
Lactate at admission	2.2 [95%CI: 1.7–3.2]
Maximal noradrenalin dose, µg/kg/min	0.41 ± 0.21
Haemodialysis support, n (%)	4 (25%)
Duration of mechanical ventilation, days	8.2 ± 5.6
Duration of ICU stay, days	12.7 ± 6.2
Outcome	
ICU survival, n (%)	15 (94)
28-day survival, n (%)	8 (50)

APACHE II—acute physiology and chronic health evaluation II, BMI—body mass index, ICU—intensive care unit, WHO—world health organization. SOFA—sepsis-related organ failure assessment.

Quadriceps thickness in transversal plane decreased in the non-stimulated legs, but it did not change in FMS legs (−4.1 mm (95%CI: −9.4 to −0.6) vs. −0.7 mm (95%CI: −4.1 to −0.7) (p = 0.03)) (repeated measurements ANOVA difference between groups F = 3.52, p = 0.036) (Figure 2).

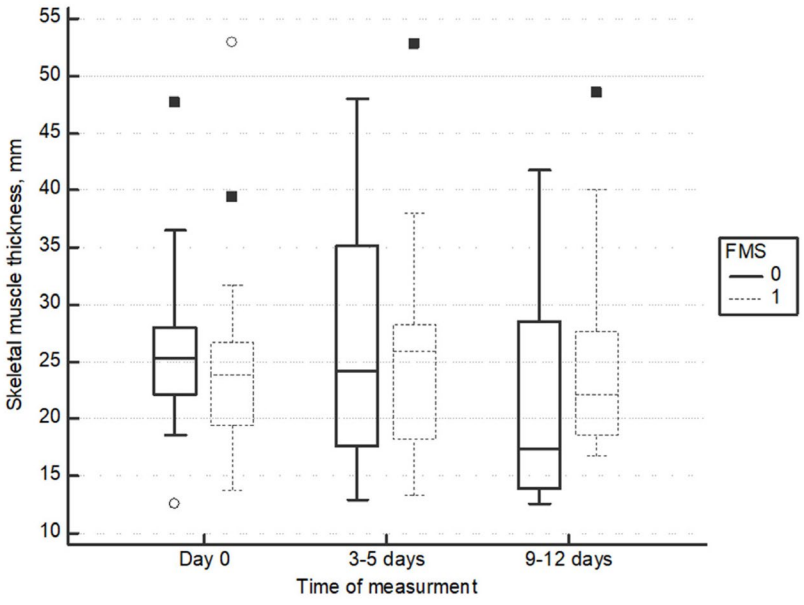

Figure 2. Change of quadriceps thickness in transversal plane.

Quadriceps thickness in longitudinal plane decreased in the non-stimulated legs, but it did not change in FMS legs (−4.4 mm (95%CI: −8.9 to −1.1) vs. −1.5 mm (95%CI: −2.6 to −2.2) (p = 0.02)) (repeated measurements ANOVA difference between groups F = 5.06, p= 0.01) (Figure 3). Details of quadriceps thickness measurements is available in Table 2.

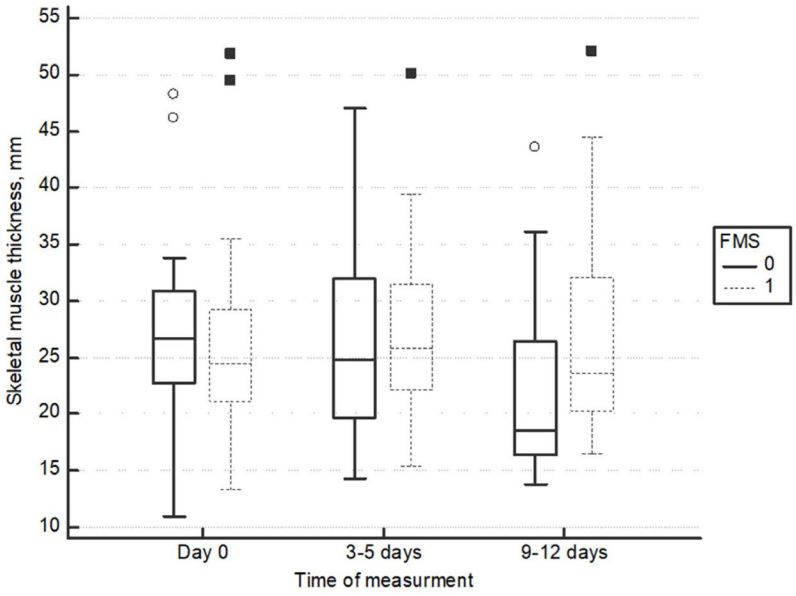

Figure 3. Change of quadriceps thickness in longitudinal plane.

Table 2. Quadriceps muscle thickness.

		Day of Measurement			Statistics		
Ultrasound Plane		**Day 0**	**Day 3–5**	**Day 9–12**	**Day 0 vs. Day 3–5 *p*-Value**	**Day 0 vs. Day 9–12 *p*-Value**	**Day 3–5 vs. Day 9–12 *p*-Value**
Transversal plane	No-FMS	25.3 [22.4–27.8]	24.3 [17.7–35.1]	17.4 [13.7–27.7]	0.78	0.003 *	0.001 *
	FMS	23.9 [19.5–26.6]	25.9 [18.5–28.3]	22.2 [18.8–27.5]	0.5	0.6	0.5
Longitudinal plane	No-FMS	26.6 [23.0–30.4]	24.9 [19.8–31.8]	18.5 [16.4–26.2]	0.6	0.002 *	0.002 *
	FMS	24.5 [21.3–29.2]	25.9 [22.4–31.1]	23.7 [20.4–31.6]	0.9	0.6	0.9

Data are presented in millimetres as median (95CI: interval), n = 16, * statistically significant difference $p < 0.05$.

At the end of the study, in 8 cooperative patients (Ramsay Sedation Scale: 2 or 3 points), leg muscle strength was tested (Table 3). Hip flexion, knee extension, and ankle dorsiflexion strength were higher on FMS-stimulated legs.

Table 3. Muscle strength assessment according to the Medical Research Scale.

	No FMS (n = 8)	**FMS (n = 8)**	**Statistics *p***
Hip flexion	3.0 (95%CI: 1.0–3.4)	3.5 (95%CI: 2.0–5.0)	0.03 *
Knee extension	3.0 (95%CI: 1.8–4.0)	4.0 (95%CI: 3.0–5.0)	0.02 *
Ankle dorsiflexion	3.0 (95%CI: 1.8–3.2)	4.0 (95%CI: 2.8–5.0)	0.02 *

FMS—functional magnetic stimulation, * statistically significant difference $p < 0.05$.

Concerning adverse reactions/events, during FMS there were stimulation spikes detected on the ECG signal on the bed-side monitoring system, but there was no triggering of any alarms. All other signals (i.e., invasive arterial pressure, frequency of respiration, arterial haemoglobin oxygen saturation) were undisturbed. The stimulation probe and connecting cable are heated due to high current induction, the probe is cooled by specially designed air channels and ventilator on the top of the probe (detained thermal analysis of probe/connecting cable/skin after stimulation with IR camera is available in the Supplementary Materials). At the beginning of study, in the first 5 patients, the FMS stimulation head was put above the thigh, which was covered by a towel. There were mild thermal skin injuries noted initially in the 3 (2nd, 4th, and 5th) of the first 5 patients recruited. In the 2nd recruited patient, we detected redness of the skin directly under the stimulation head, which disappeared by local cooling. In the 5th patient, the probe was accidentally covered with the sheet by nursing staff, the redness of skin and blister < 2 cm was detected. The blister was left alone, and the area was cooled and covered with hydrocolloid dressing (Granuflex, ConvaTec, Bridgewater, NJ, USA). The side-effect was classified as mild AE. FMS was continued the next day on a slightly different spot so that the thermal injury was not under the stimulation head. In the 4th patient, a blister < 2 cm on the sole of the foot was found, it has been retrospectively connected with the injury due to connection cable between probe and stimulator. The treatment was conservative with hydrocolloid dressing (Granuflex, ConvaTec, USA) and it was classified as mild AE. In the continuum of the study, the position of the stimulation head and connecting cable during stimulation were changed; the head was put on specially designed holder, a few millimetres above the towel covering the quadriceps, the connecting cable was not in contact with the patient anymore (Figures S1 and S2). No further thermal injuries were detected to the end of the study.

4. Discussion

The current study confirmed that neuromuscular FMS in critically ill patients is feasible and safe with precautions used to avoid thermal skin injuries. FMS decreases the loss of quadriceps thickness. There was also a difference in leg muscle strength as a secondary outcome in favour of FMS, but the muscle strength testing was performed only in 8 cooperative patients. Transcutaneous skeletal muscle FMS could become an additional therapeutic modality to ameliorate quadriceps atrophy influencing the short- and long-term outcomes of the critically ill.

We registered the trial prospectively and reported according to CONSORT guidelines [25]. Our study stopped early, but this was due to the demonstration of a statistically significant difference in effectiveness, not due to safety concerns. The interim analysis was not originally planned in the registered protocol. However, in any trial involving human subjects, safety is the primary ethical concern. As terminal injury had been initially observed, interim analyses were introduced for monitoring. The changes made to the intervention protocol eliminated the thermal injury concern. However, as the interim analysis showed a significant effect on muscle thickness, the registered primary outcome, the trial was stopped early. Muscle thickness was registered as the primary outcome because a recent study had confirmed that every 1% loss of quadriceps thickness over the first week of critical illness is associated with 5% higher odds of 60-day mortality [34]. In rehabilitation, neuromuscular FMS serves to counteract muscle atrophy and to support relearning of movement sequences; orthodromic 4 signals travelling from the periphery back to the central nervous system seem to trigger supportive neuroplastic effects [35]. Given the relationship of muscle atrophy with mortality, it was not ethically justifiable to continue the trial as the control group would have experienced a worse outcome compared to intervention in the remaining sample size after the interim analysis had demonstrated effectiveness for the primary outcome.

The major advantage of skeletal muscle FMS compared to electrical stimulation is that it is known to be less painful [16,36]. In our study, stimulation FMS protocol used a similar protocol as electrical stimulation in a previous study and was already predefined in

the stimulation apparatus [15,16,36,37]. Significantly greater muscle strength and shorter weaning from mechanical ventilation was reported in patients who received electrical stimulation in addition to standard rehabilitation treatment in comparison to patients who receive only standard rehabilitation treatment [15]. Electrical stimulation alters muscle fibres proportions; changes depend on the selected stimulation parameters, stimulation duration, and muscle innervation. This decreases the proportion of fast, glycolytic fibres (type II), which are seen dominantly in less active individuals, and increases the proportion of more endurance-oriented, slow-contracting muscle fibres (type I) [15]. Similar changes in skeletal muscle architecture were detected in critically ill patients during ICU stay [38]. The effect of FMS on different types of muscle fibres in critically ill patients is currently unknown.

In our trial, leg muscle strength at the end of the study in a sub-group of cooperative patients was different between FMS and not-stimulated legs, in favour of FMS. The difference in quadriceps thickness can implicate the possibility of increased strength as was shown in a recent report [39]. Measuring maximal muscle strength with magnetic stimulation is currently not validated for the critically ill [40].

There are different approaches to assessing the skeletal muscles using ultrasound in the critically ill [41]. In the current study, quadriceps thickness was measured; we measured quadriceps rectus femoris and vastus intermedius together. Fivez T et al., using the same methodology as in our study, confirmed ultrasound as a reliable tool for early detection of muscle mass wasting in critically ill adults (median absolute inter-observer variability 0.5 mm (IQR: 0.3–0.9), absolute intra-observer accuracy 95%CI: 2.2 mm) [30]. Other studies confirmed excellent intra-observer and inter-observer reliability of quadriceps thickness measurements [42–44].

In our study, the muscle thickness measurements were done while applying minimal compression of the US probe to avoid possible measurement errors [41]. Compression, especially maximal, can alter the appearance of myofascial structures and has been shown to compromise the validity of US muscle parameters [45,46]. The trend of quadriceps thickness change during our study on the non-stimulated leg are in limits as previously observed [47]. Special care was taken so that US skeletal muscle measurements were performed while the patient was supine with knee in extension and toes pointing to the ceiling to ensure that measurements were taken at the same muscle location in subsequent evaluations [45]. Dual energy X-ray absorptiometry, computer tomography scanning, and magnetic resonance imaging could be used in further skeletal muscle FMS studies to independently confirm our observations, preservation of muscle volume/thickness.

Heat is produced during magnetic field generation in a magnetic stimulator, which was used in our study. The excessive heat is removed by a special design. Despite this, the stimulation head temperature at the end of stimulation reached around 40 °C (Figures S3–S5 in Supplementary Materials). This high temperature increases the skin temperature under the stimulation head. This is especially important in fragile, not-moving, critically ill patients without verbal contact, where the skin thermal injury can be induced, as was the case in the beginning of the current study. Before starting the stimulation, the stimulation head should not lay directly on the skin; we placed a towel on the skin first; a few millimetres above the towel, there was a stimulation head fixed by a specially designed holder. There should not be any contact between the patient and the stimulation head or connecting cable to avoid skin thermal injury.

The pathophysiology of ICU-AW is complex, including not only muscle changes but also to long-term neural impairment [48]. Lumbar repeated peripheral magnetic stimulation improves nerve regeneration in lumbar radiculopathy [24]. Further research should explore the effects of combined therapy of FMS and lumbar repeated peripheral magnetic stimulation to enhance corticospinal excited motor recovery during or after ICU care. This combination could offer a more comprehensive approach to patient rehabilitation.

Further independent studies need to confirm our results and to find optimal stimu2lation protocols of FMS (i.e., duration of stimulation, frequency of stimulation) for the critically ill.

In the future, the effect of FMS should be tested on different skeletal muscle groups and different magnetic coil designs should be applied [49].

5. Conclusions

Skeletal muscle FMS is feasible in the critically ill. Precautions should be applied to avoid possible skin thermal injury. FMS decreases the loss of quadriceps thickness. FMS could be a promising additional method to classical physiotherapy, electrical stimulation, and early mobilisation for ameliorating muscle atrophy in the critically ill.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina60101724/s1, CONSORT 2010 checklist of information to include when reporting a randomised trial; Figure S1. Application of stimulation head, before special holder for stimulation head was applied; Figure S2. Application of stimulation head after use of special holder; Figure S3. Thermal imaging of stimulation head immediately after FMS; Figure S4. Thermal imaging of stimulation head holder during FMS, Figure S5. Thermal imaging of connection cable during FMS.

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Institutional Review Board Statement: The study was carried out in accordance with the ethical principles and the Helsinki Declaration. The study protocol was approved by the ethics committee of the General Hospital Celje, Slovenia (No. 61/2023/3, 25 October 2023).

Informed Consent Statement: Informed consent was signed by relative carers before inclusion and confirmed by the patient after gaining consciousness.

Data Availability Statement: The data that support the findings of this study are not openly available due to the reason of patient privacy and are available from the corresponding author upon request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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FMS

FUNCTIONAL MAGNETIC STIMULATION

Aesthetic Medicine

Nº 1

The effects of functional magnetic stimulation (FMS) on the rectus abdominis muscle size and abdominal subcutaneous adipose tissue thickness

The effects of functional magnetic stimulation (FMS) on the rectus abdominis muscle size and abdominal subcutaneous adipose tissue thickness

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ABSTRACT

Objective The aim of this prospective study was to investigate safety and efficiency of using functional magnetic stimulation technology for abdominal muscle toning, shaping, and strengthening.

Methods Ten participants (4 men, 6 women) received 10 sessions of repetitive magnetic stimulation, using the Tesla Former prestige device. Efficacy was evaluated through waist circumference, MRI imaging and patient satisfaction.

Results On the 10-week follow-up we observed a waist circumference reduction of -2.76 ±1.37 cm, as compared to the baseline. On the patients that have undergone MRI imaging, the *rectus abdominalis* muscles thickness was increased by 5.98±1.87 mm and subcutaneous abdominal fat thickness was decreased by -4.35±2.80 mm.

Conclusion FMS magnetic stimulation seems to be an effective and safe method for muscle toning and body shaping, resulting in an increase in muscle mass in the treated area as well as a decrease in subcutaneous fat, resulting with visible improvement in abdominal body shape and very high patient satisfaction rates.

INTRODUCTION

Pulsed magnetic stimulation using high intensity magnetic fields has been introduced in the 1980's by Barker and colleagues[1] and has firstly been recognized as a tool for diagnostic and therapeutic nerve stimulation and muscle contraction. Recently, it is becoming increasingly popular as a non-invasive method for muscle strengthening and body shaping.

High intensity magnetic stimulation works by inducing currents in the biological tissue, leading to nerve stimulation. The induced action potentials in the efferent nerves results with a contraction of the targeted muscles [2]. Magnetic stimulation is especially suitable for this sort of application, as the magnetic field is able to easily penetrate through skin and can also affect deeper lying nerves and muscles. Traditionally, transcutaneous electrical stimulation has been used to induce nerve stimulation and muscle contraction, although its limitations are low penetration and pain at stimulation intensity levels needed for efficient muscle contraction. The magnetic field is able to propagate deep inside the tissue without stimulating the pain receptors in the upper layers of the skin; therefore the treatment is not painful and can be easily tolerated at higher intensities[3]. Due to this advantage, the popularity of magnetic stimulation in the field of muscle toning is rising as opposed to electrical stimulation.

Recent studies have shown that treatment of abdominal muscles using high intensity magnetic muscle stimulation resulted in increased muscle size and strength additionally it even decreased the subcutaneous fat layer [4,5].

The aim of this prospective study was to investigate safety and efficiency of using functional magnetic stimulation technology for abdominal muscle toning, shaping and strengthening. We also aimed to investigate whether the intensive muscle contractions result in changes of the subcutaneous fat and abdominal muscle thickness.

METHODS

10 participants (4 men, 6 women) took part in the clinical study, with an average age of 32.7 years old.

The study was done according to the Declaration of Helsinki, including healthy volunteers, all of whom signed the informed consent form.

Abdominal muscle stimulation treatment

All patients received 10 sessions of repetitive magnetic stimulation, using the Tesla Former prestige device (Iskra Medical, Slovenia). The treatments were performed using two large FMS applicators that have been connected together side by side and attached to the abdomen using the fixing straps. The intensity of the treatments can vary between 2 and 100% of the total device magnetic field intensity of 3 T. The intensity was set to fit the individual tolerability level of each participant. The treatment was 30 minutes long, with several steps including different frequency modulations in order to achieve stimulation of different muscle fibers. The preset program called Abdomen 2 was used for the stimulation. 10 sessions were performed altogether, with 2 days in between each session. Potential adverse events during or after the treatment were monitored in all patients.

Evaluation methodology

All participants were weighed at baseline and at each follow-up to check for changes in body weight that could affect the final visual result. Waist circumference was measured at baseline and at follow-ups 10 weeks after the last treatment session. Waist circumference was measured at the level of anterior superior iliac spine (ASIC) as well as 3 cm above ASIC and 3 cm below ASIC.

Patient satisfaction was recorded using an original questionnaire, which included questions about the satisfaction with muscle appearance, strength and the perceived muscle contraction strength during muscle stimulation, which was evaluated on a 1-5 scale (1 = none; 2 = low; 3 = moderate, 4 = high, 5 = very high). The patients were also asked about the willingness to repeat and recommend the treatment to others. three randomly chosen patients that have been included in the study have also undergone magnetic resonation imaging (MRI) to determine the extent of any potential changes in the muscle and/or the subcutaneous fat layer thickness. The image acquiring and the analysis of cross-sectional MRI images was performed by an expert radiologist.

Statistical evaluation

Anonymized data was entered into an Excel spreadsheet. Descriptive and comparative statistics were analyzed using standard spreadsheet software (Microsoft Excel, USA).

RESULTS

The responses from the patient questionnaire indicated high patient satisfaction. The patient's perceived improvement in abdominal body shape was 4.3 on a 1-5 scale (Table 1). The average weight change from baseline to the 10-week follow-up was -0.6±1.35 kg and which is clinically irrelevant. There was a significant decrease ($p<0.001$) in waist circumference of -2.76 ±1.37 cm, as compared to the baseline.

The results from cross-sectional MRI analysis show an increase in thickness of rectus abdominis muscle of 40.6±17.5%; and a decrease

in subcutaneous fat layer above the rectus abdominis muscle of 25.9±5.7% (Figure 1).

There were no reported adverse events during or after the therapy.

Table 1 – The results of the patient questionnaire for each patient.

Patient No.	Sex	Patient's perceived muscle contraction intensity during treatment (1-5 scale)	Patient's perceived improvement in muscular strength (1-5 scale)	Patient satisfaction with body shape (1-5 scale)
1	F	4	3	4
2	F	4	5	5
3	M	5	4	4
4	M	5	5	5
5	M	3	3	4
6	F	3	3	3
7	F	4	5	4
8	M	5	5	5
9	F	4	4	5
10	F	4	4	4
	average	4.1	4.1	4.3
	SD	0.73	0.87	0.67

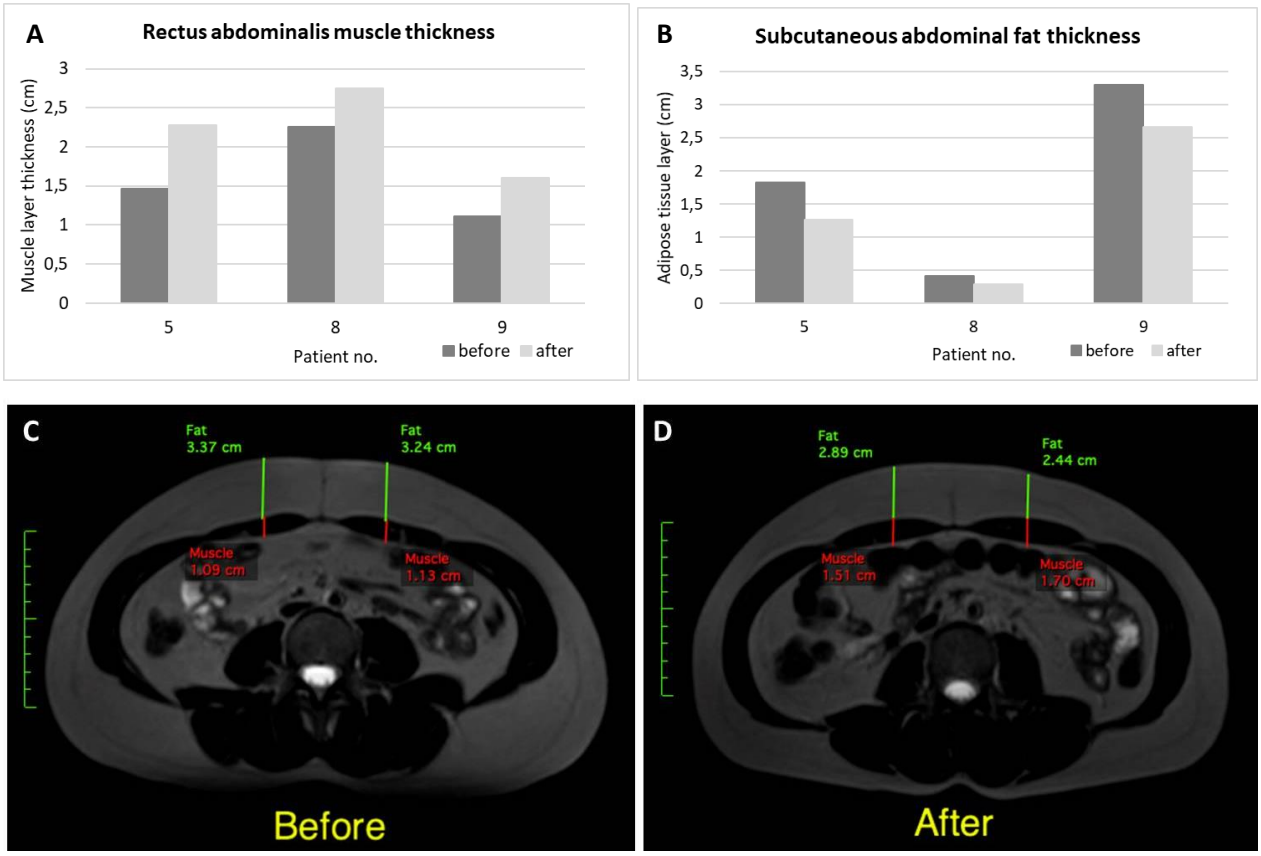

Figure 1. A - Measured change in rectus abdominis muscle thickness before and 10 weeks after the FMS treatment, taken form MRI transverse abdominal sections from 3 patients; **B** Measured change in abdominal subcutaneous fat muscle thickness before and 10 weeks after the FMS treatment, taken form MRI transverse abdominal sections from 3 patients; **C and D** – example of an MRI image of patient No. 9 taken before (A) and 10 weeks after (D) FMS treatment

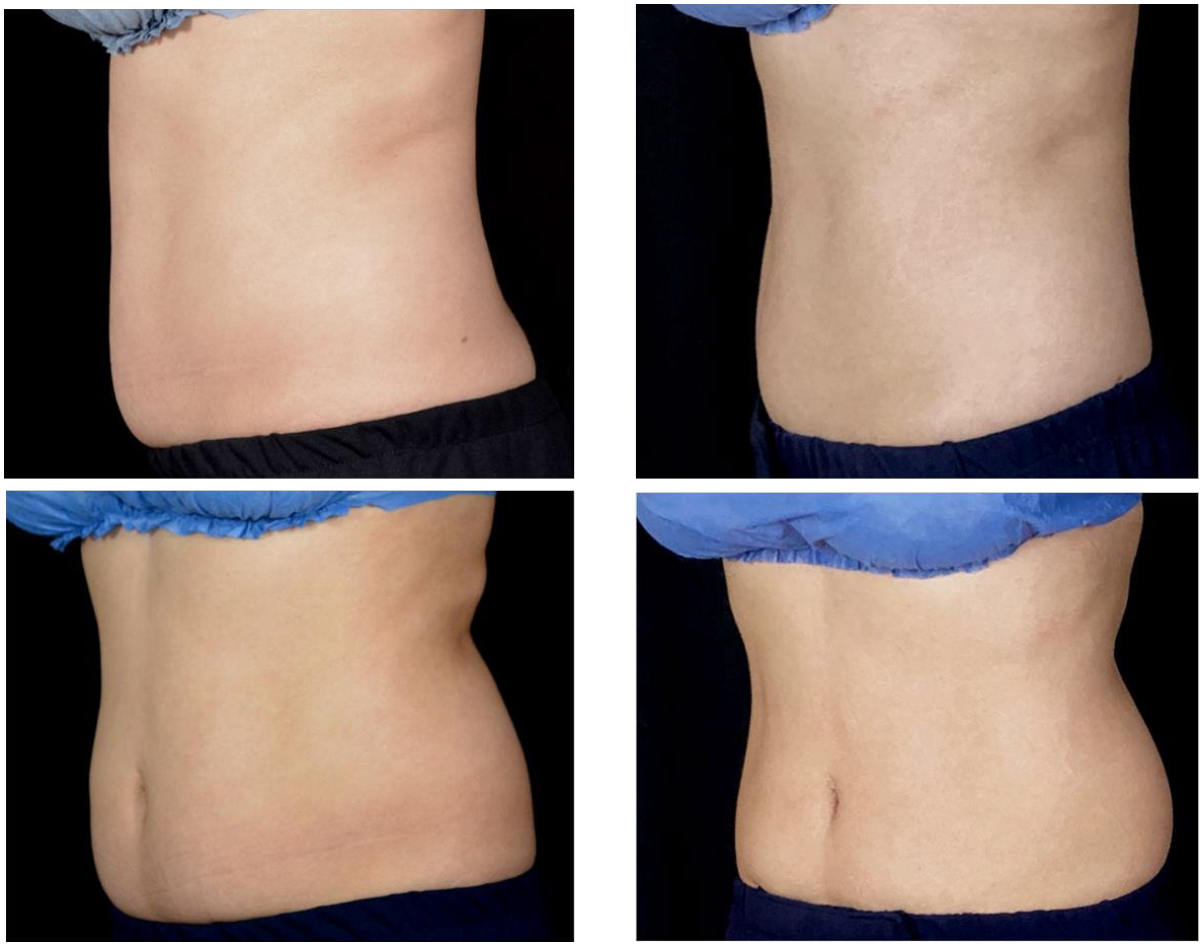

Figure 2 Before (left) and after (right) photograph of patient No. 9 (see Figure 1C and 1D for an MRI image from the same patient) with evident abdominal body shape aesthetic improvement.

DISCUSSION

Our study has shown that magnetic stimulation is an effective treatment for abdominal muscle toning and body shaping. Analysis of MRI images revealed an increase in abdominal muscle thickness and a decrease in subcutaneous fat 2.5 months following magnetic stimulation treatment. There was a significant decrease in waist circumference (up to 3cm on average), which was not connected to weight fluctuations, as the patient's weight did not significantly change. Visual improvement in abdominal muscle toning and body shape, as determined by the patient satisfaction questionnaire, was evident in all treated patients. The patients were very satisfied with visual as well as functional (perceived muscle strength) improvement, which was measured 10 weeks after the last treatment session.

The intensity of the magnetic field in the device used in this study was high enough to induce the current in the underlying neurons and cause muscle contraction. Muscle hypertrophy is most optimally achieved when repeated contractions of above 60% maximum voluntary contraction (MVC) are elicited in resistance training[6]. Since high intensity magnetic

stimulation is painless, it can be used at higher intensities, enabling stronger muscle contractions than when electrical stimulation is used. For example in a study by Kremenic et al.[7], an average MVC of 72% was elicited by magnetic stimulation of the quadriceps femoris muscle. A study using electrical stimulation of the same muscle has reported much lower achieved MVC values, which were limited by the discomfort felt by the patient when increasing the current intensity [8]. In this study we did not measure MVC values but have asked the patients to assess the strength of perceived muscle contraction. They have rated the strength of abdominal muscle contraction as 4.1 on a 1-5 scale, indicating a high achieved MVC value, which was evident also from the observed visual changes and improvement in perceived muscular strength. By using a range of frequencies during the treatment protocol, both slow- and fast- twitch muscle fibers are activated, resulting with uniform muscle contraction of all motor units, some of which would normally require high-intensity exercise to be activated[9]. Alon et al [10] have compared differences in muscle strength in 3 groups – i) exercise alone; ii) electrical stimulation alone; or iii) combination of exercise and electrical stimulation. They have shown that electrical stimulation in combination with exercise produced the highest increase in isometric muscle strength, while electrical stimulation alone produced better results than exercise alone. Magnetic stimulation shares some of the mechanism of action as electrical muscle stimulation, without the downsides of applying transcutaneous electrical currents which can cause pain. As the magnetic stimulation is able to reach deep muscles structures this method could be an excellent complementary muscle shaping method in addition with exercise; as well as an excellent option to increase muscle strength in less active individuals.

The increase in muscle thickness of rectus abdominis muscle of 40.6±17.5% was evident from the analysis of cross-sectional MRI images taken from 3 patients at baseline and at 3 months follow-up. At the same time, an overall decrease in subcutaneous fat was observed from the cross-sectional MRI image, as well as from the measurements of subcutaneous fat layer thickness above the rectus abdominis muscle, which showed a decrease of 5.9±5.7%. This is consistent with the results of previous studies that used magnetic muscle stimulation. These results corroborate previously published data using similar technologies[4,5,11].

In two studies by Kinney et al[4,11] muscle thickness evaluation after abdominal magnetic stimulation was performed using MRI[4], with follow up of 12 months[11]. Analysis of MRI slices showed significant average increase in muscle thickness of 19.05% (1.89 ± 0.88 mm) and reduction in fat of 14.63% (2.97 ± 2.11 mm).

Decrease in fat layer thickness following magnetic stimulation was also measured in two studies using ultrasound evaluation, which have shown a similar pattern of significant increase in muscle thickness and decrease in subcutaneous fat layer post abdominal magnetic stimulation [12,13]. Since a human histological study[14] found no fat cell injury or inflammatory response 3–17 days following a single session of magnetic muscle stimulation, it can be speculated that the fat layer may be reduced by increased catabolic fat metabolism due to contraction of large muscles following magnetic stimulation or due to synergistic changes in diet and/or physical activity, which cannot be observed histologically. The limitations of this study are a small study population, lack of a control group and a short follow-up period. The optimal treatment number and maintenance schedule still needs to be determined and should be the subject of further clinical research.

CONCLUSIONS

FMS magnetic stimulation seems to be an effective and safe method for muscle toning and body shaping, resulting in an increase in muscle mass in the treated area as well as a decrease in subcutaneous fat, resulting with visible improvement in abdominal body shape and very high patient satisfaction rates.

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Nº 2

The Combination of Functional Magnetic Stimulation and Low-Frequency Therapeutic Ultrasound for Body Shaping: Preliminary Case Reports

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Open Access Case Report

The Combination of Functional Magnetic Stimulation and Low-Frequency Therapeutic Ultrasound for Body Shaping: Preliminary Case Reports

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Abstract

Functional magnetic stimulation (FMS) is commonly used to accelerate the healing process and alleviate pain. Recently, it has been shown to be useful for non-invasive body-shaping techniques. Low-frequency therapeutic ultrasound has been proven to be a safe, non-invasive alternative to liposuction. This report discusses a few cases to compare the effects of FMS with the combination of FMS with low-frequency therapeutic ultrasound on muscle thickness, volume, and subcutaneous adipose tissue thickness which can increase muscle strength and loss of unwanted fat.

Four healthy Caucasian female volunteers aged between 42 and 45 years received 10 sessions of FMS using the Tesla Former prestige device (Iskra Medical, Otoče, Slovenia). Additionally, three volunteers (out of four) received four sessions of low-frequency therapeutic ultrasound with the Sonic Shaper device (Iskra Medical). The efficacy of the treatments was evaluated through ultrasound imaging and tensiomyography (TMG). Patients 1 and 2 received the application of FMS on the gluteal area and Sonic Shaper on the gluteal adipose tissue. However, patient 4 received the combination treatment on the rectus abdominalis, and patient 3 received only FMS treatment on the gluteus maximus (GMx) and gluteus medius (GMe) instead.

The measurements collected after the last session showed significant improvements in each patient. Post-treatment measurement of left/right gluteus maximus diameter for patients 1, 2, and 3 showed an increase compared to the baseline. Patient 4, who received combination treatment on the rectus abdominis muscle (RAb), also showed an increase in rectus abdominis diameter. The study shows that FMS increases muscle volume, whereas low-frequency therapeutic ultrasound reduces localized subcutaneous adipose tissue thickness. Combining these two non-invasive treatments may be a promising, safe, and effective intervention for body shaping and countering.

Categories: Public Health, Healthcare Technology, Therapeutics
Keywords: body shaping, cavitation, functional magnetic stimulation, gluteus, ultrasound

Introduction

Electric stimulation of muscles and nerves has existed since 1896 when d'Arsonval used a strong, time-varying current to stimulate living tissue. His experiments showed the potential of nerve stimulation to contract muscles, and research on the subject was carried out throughout the 20th century. In 1965, the first successful muscle twitching was obtained, and, 10 years later, transcranial magnetic stimulation was applied for clinical purposes [1]. The last two decades have witnessed an upswing in the popularity of gluteal reconstructive surgery, with personalized exercises for strengthening the gluteal muscles and specific exercises all prescribed for the treatment of the lower back as well as lower extremities. This increase in demand and interest has influenced aesthetic norms and physical exercise and is attributed to refined and improved contouring techniques [2]. As a fast-growing field, many new surgical procedures have been adapted to achieve satisfactory and refined outcomes. However, increased engagement in physical activities, such as leisure time and professional sports, can lead to sport-related injuries [3]. Therefore, many prefer the use of augmentation techniques as a safer alternative [4-6].

Muscle size increases when a person continually challenges the muscles to deal with higher levels of resistance or weight. This process is known as muscle hypertrophy. Muscle hypertrophy occurs when the fibers of the muscles sustain microdamage or injury. The body repairs damaged fibers by fusing them, which increases the mass and size of the muscles. Certain hormones, including testosterone, human growth hormone, and insulin growth factor, also play a role in muscle growth and repair [7]. They may also be used and frequently prescribed for the treatment of lower back and lower extremity pathology [4, 8].

Traditionally, functional magnetic stimulation (FMS) has been used in gynecology and physiotherapy to accelerate the healing process and alleviate pain by strengthening the pelvic floor muscles [9-11]. Recently,

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FMS has been used as a non-invasive body-shaping technique [12-14]. The preceding technique, i.e., electromyostimulation, is sometimes used for voluntary exercise in athletes to improve their fitness. However, it does not penetrate deep enough, rarely produces satisfactory results, and provides the best results only if the whole body is subjected to treatment [15]. Most literature documenting FMS as a body-shaping technique uses cooperative standardized images, patient satisfaction questionnaires, or circumference measurements as their method for monitoring the results.

To our knowledge, no previous study has investigated the cumulative effects of FMS and low-frequency therapeutic ultrasound on outcomes. It is known that low-frequency therapeutic ultrasound delivers an energy signature through the skin for adipose tissue disruption. Adipose tissue disruption releases triglycerides into the extracellular spaces and bloodstream. The released triglycerides are now readily available for metabolic processes. This has been proven to be a safe, non-invasive alternative to liposuction and an efficient way to reduce the circumference of the treated area [16]. We hypothesized that combining FMS and low-frequency therapeutic ultrasound will improve body shaping by strengthening the skeletal muscles and removing localized adipose tissue build-up [10,15,16].

This case report aimed to explore the effects of FMS and the combination of FMS and low-frequency therapeutic ultrasound on muscle thickness and volume, as well as subcutaneous adipose tissue thickness. We also aimed to investigate the safety and efficiency of both treatment methods in body shaping.

Case Presentation

Four healthy female volunteers took part in the case study, with an age range from 42 to 45. Three patients received FMS and ultrasound treatments. Of these three patients, two received treatment on the gluteus and one on the abdomen. One patient received only FMS on the gluteus muscle. A written, informed consent was obtained from the participants before the study. The study was conducted according to the Declaration of Helsinki.

Gluteus and hamstring muscle magnetic stimulation

All patients received FMS 45 minutes a day, every second day (three times a week) for 10 sessions, using the Tesla Former prestige device (Iskra Medical, Otoče, Slovenia). During the treatment, two XXL applicators were placed on the gluteal area and two XL applicators were placed on the hamstring area. The program Muscle Strengthening II was used, which concurrently activated the gluteus applicators at the frequency of 30 Hz, followed by the hamstring applicators simultaneously at 30 Hz. One patient received FMS on the abdomen. An XL applicator was placed on the abdomen for this patient and two XL applicators were placed on the thighs. The program Abdomen Thighs I was used. The applicators were connected to the body using fixing straps. The intensity was set to fit the individual tolerability level of each participant. All individuals were able to painlessly handle 100% of the total device magnetic field intensity of 3 T at every session for the entire duration. Potential adverse events during or after the treatment were monitored in both participants.

Low-frequency therapeutic ultrasound of the gluteus and hamstring area

In addition to the 10 FMS sessions, three participants received low-frequency therapeutic ultrasound treatment. Patients 1 and 2 were treated for 40 minutes on the gluteus maximus and 20 minutes on each thigh, once a week spanning four sessions, using the Sonic Shaper device (Iskra Medical, Otoče, Slovenia). Patient 3 was treated with Sonic Shaper for 40 minutes on the abdomen, 20 minutes on each side, once a week for four sessions. Both the FMS and the Sonic Shaper treatments started on the same day. The treatment was carried out using a large Sonic Combo applicator. The parameters were set to 100% of low-frequency ultrasound intensity, and the vacuum pulsed between 60 and 120 hPa. Potential adverse events during or after the treatment were monitored.

Evaluation methodology

All participants were subjected to diagnostic ultrasound impinging of the treated areas. The diagnostic ultrasound was carried out at KLANMEDIC d.o.o., - Diagnostični in Terapevtski Center, Slovenia. The muscle diameter and adipose tissue thickness were measured using the diagnostic ultrasound, with MyLab9 exp Esaote linear probe (Esaote SpA, Genoa, Italy), from L4-L15, set to operate at 4-15 MHz. The ultrasound measurement was repeated twice before the start of treatment and once after all the treatments were completed.

The participant treated only with FMS was also subjected to tensiomyography (TMG) using a TMG device (TMG d.o.o, Ljubljana, Slovenia) to observe the difference in maximal displacement of the probe. The increase in deviation amplitude points to increased muscle volume and the ability to activate a more significant number of motor units during contracting.

Findings

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The measurements taken with a diagnostic ultrasound are summarized in Table 1. Figure 1 shows the before and after images following the combined treatment.

		Baseline diameter (mm)	End diameter (mm)	Difference betwwen end/baseline (%)
Gluteus maximus - L	Patient no. 1	42	54	28
	Patient no. 2	25	42	68
	Patient no. 3	38	48	26
Gluteus maximus - R	Patient no. 1	33	48	45
	Patient no. 2	22	38	53
	Patient no. 3	33	41	24
Gluteus medius - L	Patient no. 1	22	25	14
	Patient no. 2	18	22	22
Gluteus medius - R	Patient no. 1	20	27	35
	Patient no. 2	20	26	30
Rectus abdominalis - L	Patient no. 4	11	14	19
Rectus abdominalis - R	Patient no. 4	10	13	25
Adipose tissue - L	Patient no. 1	23	17	- 26
	Patient no. 3	25	17	-30
	Patient no. 4	18	13	-24
Adipose tissue - R	Patient no. 1	28	27	- 4
	Patient no. 3	18	14	-20
	Patient no. 4	14	12	-10

TABLE 1: Results of diagnostic ultrasound measurements of the gluteus area and abdomen

Patients 1, 3, and 4 were treated with the combination of FMS and Sonic Shaper, and the patient two was treated with FMS only. Patients one, two and three were treated on the gluteal area. Patient four was treated on the abdomen

FMS: functional magnetic stimulation; L: left; R: right

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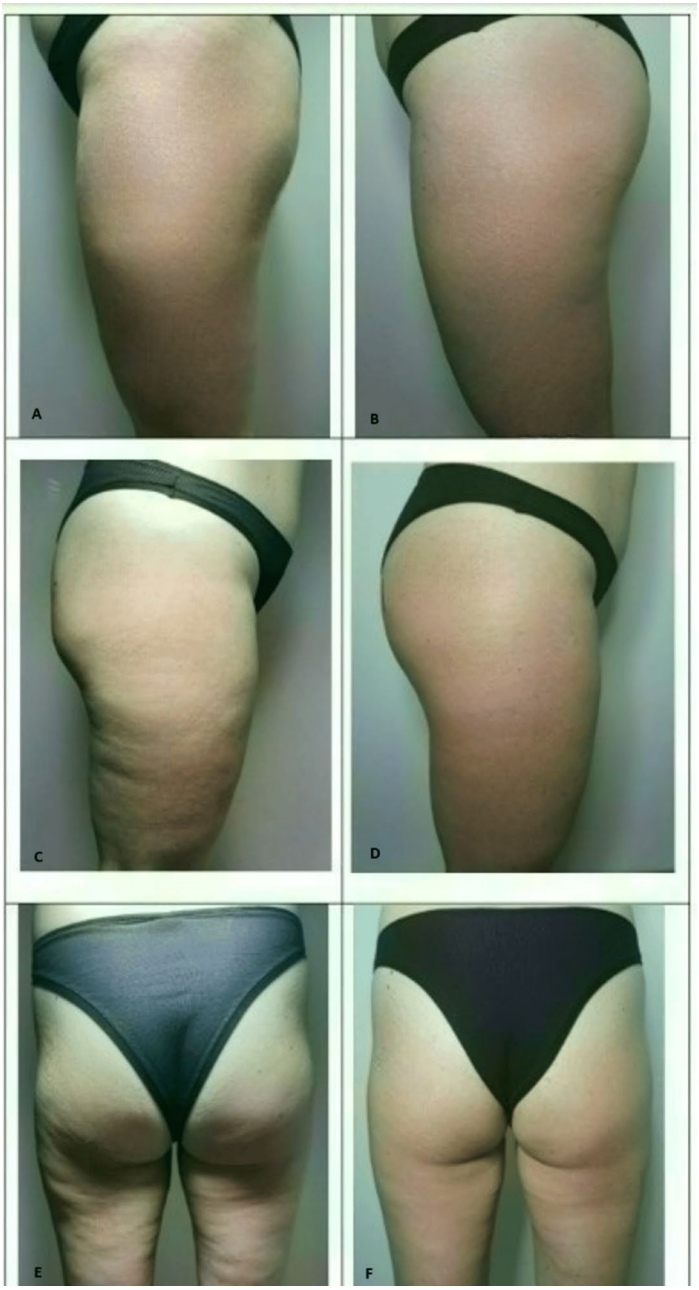

FIGURE 1: Comparison of images of the patient treated with both FMS and Sonic Shaper at the baseline and at the end of the protocol

Baseline (A, C, and E). At the end of the protocol (B, D, and F)

FMS: functional magnetic stimulation

Patient 1 received a multimodal treatment of FMS and Sonic Shaper. The devices were applied on the gluteus maximus (GMx) and gluteus medius (GMe) muscles. Measurements before treatment of the muscle diameter were 42 mm for the left GMx, 33 mm for the right GMx, 22 mm for the left GMe, and 20 mm for the right GMe. After the last session, new measurements were taken. The left Gmx was measured at 54 mm, which indicated a 12 mm (or 28%) increase, right GMx was at 48 mm, a 15 mm (or 45%) increase, left GMe was at 25 mm, a 3mm (or 14%) increase, and finally the right GMe was measured at 27 mm, a 7 mm (or 35%) increase in diameter.

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Patient 2 received a multimodal treatment of FMS and the Sonic Shaper on her gluteal area, more accurately on the GMx. Starting measurements of the muscle diameter were 25 mm on the left GMx and 22 mm on the right GMx. The diameter of adipose tissue on the left buttock was 25 mm, while it was 18 mm on the right. The final result was 42 mm (17 mm or 68% increase) on the left GMx, 34 mm (12 mm or 53% increase) on the right GMx for the muscle diameter, and 17 mm (8 mm or -30% decrease) for the left and 14 mm (4mm or -20% decrease) for the right side of adipose tissue.

Patient 3 received only FMS applications on both sides of GMx and GMe. Starting measurements that were taken before treatment were 38 mm for the left GMx, 33 mm for the right GMx, 18 mm for the left GMe, and 20 mm for the right GMe. After the last treatment, new measurements were taken, which were as follows: 48 mm (10 mm or 26% increase) on the left GMx, 41 mm (8 mm or 24% increase) in the right GMx, 22 mm (4 mm or 22% increase) for the left GMe and 26 mm (6 mm or 30% increase) for the right GMe.

Patient 4, on the other hand, received a multimodal treatment of FMS and Sonic Shaper on the abdominal area, more accurately on the rectus abdominis muscle (RAb). Baseline measurements were as follows: 11 mm for the left side and 10 mm for the right side of the muscle; adipose tissue was measured at 18 mm for the left and 14 mm for the right side. The results were as follows: 14 mm (3 mm or 19% increase) on the left RAb and 13 mm (3 mm or 25% increase) on the right RAb regarding muscle diameter and 13 mm (5 mm or 24% decrease) on the left side RAb and finally 12 mm (2 mm or 10% decrease) for the right RAb regarding the adipose tissue.

Figure 2 presents the ultrasound images at the baseline and at the end of the protocol.

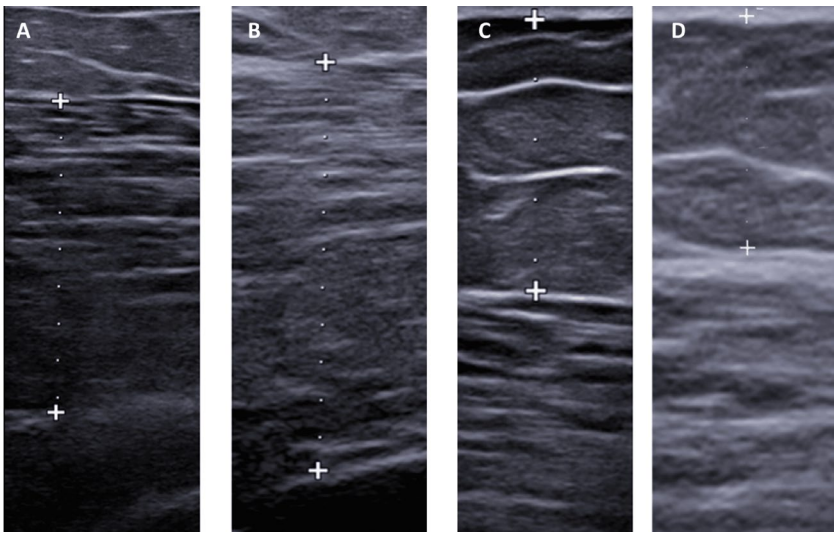

FIGURE 2: Diagnostic ultrasound images at the baseline and at the end of the protocol

Diagnostic ultrasound images of the left gluteus maximus of the patient treated with both FMS and Sonic Shaper at the baseline (A) and at the end of the protocol (B); the plus signs and the white dots mark the diameter of the gluteus maximus. Diagnostic ultrasound images of the subcutaneous adipose tissue over the left gluteus maximus of the patient treated with both FMS and Sonic Shaper at the baseline (C) and at the end of the protocol (D); the plus signs and the white dots mark the thickness of the subcutaneous adipose tissue

FMS: functional magnetic stimulation

Discussion

The findings of this case series highlight the potential efficacy of combining FMS and low-frequency therapeutic ultrasound (Sonic Shaper) for body shaping, with the results indicating significant improvements in muscle diameter and reductions in localized adipose tissue. These preliminary outcomes align with previous studies, such as those by Jacob et al. (2020) [17], which reported favorable outcomes following high-intensity focused electromagnetic stimulation for postpartum abdominal wall toning. The absence of significant side effects in our cases further endorses the safety profile of this approach.

The increase in muscle diameter observed across all patients, ranging from 14% to 68%, suggests that FMS facilitates muscle hypertrophy. Notably, patients who underwent the combined treatment of FMS and Sonic

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Shaper showed superior muscle growth compared to those receiving FMS alone. For instance, patient 1 achieved a 45% increase in the right GMx, while patient 2 achieved a 68% increase in the left GMx, demonstrating the added benefit of low-frequency ultrasound in enhancing the outcomes of FMS. This enhancement may be attributed to the synergistic effect of the Sonic Shaper, which improves local circulation and optimizes tissue conditions for muscle development.

Localized adipose tissue reduction in patients treated with both FMS and Sonic Shaper further underscores the potential of this multimodal approach. For example, patient 2 experienced a 30% reduction in left gluteal adipose tissue thickness, while patient 4 exhibited a 24% reduction in left abdominal adipose tissue thickness. These results are in line with the known effects of low-frequency ultrasound, which enhances lipolysis by delivering mechanical vibrations that disrupt adipocyte membranes without damaging surrounding tissues. The absence of necrosis or apoptosis supports the safety of this technique, offering a compelling alternative to more invasive procedures like liposuction. Interestingly, patient 3, who underwent FMS alone, still showed substantial muscle growth (e.g., a 26% increase in left GMx). This indicates that while FMS alone is effective in promoting muscle hypertrophy, the addition of low-frequency ultrasound significantly amplifies the outcomes, particularly for combined muscle toning and adipose tissue reduction.

Our results also align with findings from TMG, which demonstrated increased maximal displacement in muscles treated with FMS, further confirming muscle hypertrophy and improved neuromuscular function. These results suggest that FMS-induced muscle contractions mimic the effects of high-intensity resistance training, leading to enhanced muscle volume and function. Previous studies have also supported these findings [18,19].

While the outcomes of this case series are promising, the small sample size and lack of a control group limit the generalizability of the findings. A larger-scale, double-blind randomized controlled trial is required to validate the efficacy and safety of this combined approach. Such a trial should ideally include three groups: a placebo group (sham FMS and sham ultrasound), an FMS-only group (real FMS and sham ultrasound), and a combined treatment group (real FMS and real ultrasound). This design would allow for a more robust comparison of the relative contributions of each modality.

Conclusions

This report provides preliminary evidence that the combination of FMS and low-frequency therapeutic ultrasound is a safe and effective non-invasive method for body shaping. FMS appears to promote muscle hypertrophy, while low-frequency ultrasound effectively reduces localized adipose tissue. Together, these modalities offer a synergistic approach that could serve as an alternative to traditional surgical interventions. Future research with larger sample sizes and rigorous study designs is warranted to confirm these findings and further explore the mechanisms underlying this promising multimodal treatment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ana Kristina Klancic, Marko Klancic

Acquisition, analysis, or interpretation of data: Ana Kristina Klancic, Marko Klancic

Drafting of the manuscript: Ana Kristina Klancic

Critical review of the manuscript for important intellectual content: Marko Klancic

Supervision: Marko Klancic

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. KlanMedic Diagnostic and Therapeutic Center Ethics Committee issued approval No. DIR/KDT-EC/202419. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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FMS

FUNCTIONAL MAGNETIC STIMULATION

Inside The Technology

Nº 1

Characteristics of Functional Magnetic Stimulation

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Characteristics of Functional Magnetic Stimulation

(Submitted for presentation at the 3rd LA&HA Super Symposium 2020; online Sept/Oct 2020)

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SUMMARY

a) Introduction

Functional magnetic stimulation (FMS) devices [1] work by creating a pulsed magnetic field, which means that the magnetic field density changes with time. A pulsed magnetic field induces electrical potential inside body tissue. The electrical potential causes electric current to flow, thus exciting the neurons in the body. A single action potential is then triggered by the excited neurons. When the excited neuron is a motor neuron, the triggered action potential causes the corresponding motor units in the muscle to contract.

b) Muscle contractions

The above principle can be used to achieve muscle contraction if two conditions are fulfilled. First, the electrical current that is induced in the body must be greater than a threshold value, and second, the motor neuron and consequentially the human muscle must not be in its refractory period. A refractory period is the time during which an action potential cannot be excited. The refractory period of a healthy human skeletal muscle is roughly 1-4 ms [2-4]. Theoretically, this principle can be applied for an unlimited amount of time and the muscle will behave identically as it did the first time a contraction was triggered. To be certain of achieving a muscle contraction every time a stimulus is triggered, we must deliver pulses with a pulse repetition frequency no higher than about 100 Hz, or one pulse every 5 ms.

Top performance magnetic devices (for example, Tesla Former, manufactured by Iskra Medical d.o.o., Slovenia) can deliver high pulse repetition frequencies, e.g. 80 Hz. Ideally, to trigger 50 000 contractions in 30 minutes, where the active time is 1 s and the pause time is also 1 s (50% duty cycle), a frequency of 56 Hz must be used. A frequency of 56 Hz delivers a trigger pulse every 18 ms, which is more than the muscle refractory period. Therefore, each trigger pulse will excite at least one muscle unit contraction. In the previously mentioned 80 Hz stimulation, with 1 s active time and 1 s passive time, 72 000 contractions can be achieved.

A logical question arises about what happens at such high frequencies (50 Hz or higher) after long-term stimulation (15 minutes or more), as muscle fatigue is a well-known phenomenon after prolonged stimulation. As muscles become fatigued, the muscle response decreases. A recent study has shown that even at high frequencies of about 100 Hz, muscle response was still present after a 15-minute stimulation period [5]. Based on the trend of response reduction by the minute as reported in the above study (Figure 1), we can deduce that even after a 30-minute stimulation period there will be considerable muscle response present at frequencies used by the Tesla Former device.

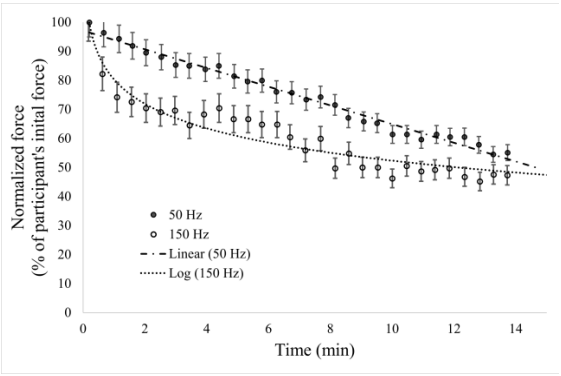

Fig 1: Curve fitting pattern of normalized stimulated force values obtained during a 15-minute fatigue test under all stimulation conditions. Data are presented as mean. Error bars represent standard error of mean. Adapted based on source: ref [5].

c) Fat burning

The body's energy demand is dramatically increased in periods of increased physical activity [6]. Muscle contraction requires energy in the form of the body's universal energy currency – the ATP molecule. ATP production for muscle contraction is derived from two main energy storages: carbohydrate and fat. Carbohydrates are stored in the form of glycogen, which is broken down to glucose, while fat is stored in the form of triglycerides, which are broken down to fatty acids.

The metabolism of both glucose and fatty acids both converge at a common metabolite, the acetyl-coenzyme A, which is a key substrate for ATP production in the mitochondria, the cells' power plants.

As the body's carbohydrate reserves are precious and limited, their utilization is tightly regulated. In the

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periods of increased demands for energy - e.g. from extensive muscle contraction, the utilization of energy stored in the body's fat reserves is intensified.

The main fat reserve molecules are triglycerides, which are broken down to glycerol and fatty acids. The fatty acids can be further utilized to produce ATP for muscle contraction in the metabolic process of ß oxidation, which produces the acetyl coenzyme A molecule - the main substrate for mitochondrial ATP production. The fatty acids used as fuel for muscle contractions are mainly derived from the adipose tissue reserves and plasma VLDL.

d) Conclusions

In conclusion, functional magnetic stimulation (FMS) is a non-invasive treatment in which a pulsed magnetic field is applied to a localized part of the body. The magnetic field stimulates muscles and causes them to contract. These contractions may result in increased strength and endurance of muscles in the targeted body area. Depending on the magnetic pulse repetition rate, up to (or even more than) 50 000 contractions can be induced during a short 30-minute therapy session. Additionally, the increased muscle activity during the session increases catabolic processes that ensure ATP production from fatty acids. The functional muscle stimulation can therefore, along with diet and exercise, increase the rate of fat burning.

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N° 2

End User Survey on the Use of High Intensity Tesla Stimulation (HITS®) Magnetic Devices

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End User Survey on the Use of High Intensity Tesla Stimulation (HITS®) Magnetic Devices

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ABSTRACT

HITS® magnetic stimulation devices can be applied for multiple indications for use and for a variety of types of patients.

AIM: The aim of the end-user survey was to acquire information from end users about frequency of use of magnetic stimulation devices for particular indications, the specifics of their treatments, and to obtain information on side effects observed with the use of magnetic stimulation devices in their practice.

METHODS: The survey was prepared in electronic form. The online survey platform 1ka.si was used to design the survey and to gather the responses. In the first part of the survey, information about the end-user – name (optional), country, length of experience with the device, type of device and accessories used – was collected together with questions about satisfaction with the instructions for use and user interface. Afterwards, the end-users were asked about indications they use the device for, their estimate of efficacy, the procedures used, the number of patients treated, body areas treated and observed side effects.

RESULTS: Of the 96 valid responses, 81% of respondents listed the indications for which they use magnetic stimulation devices. Of those, 81% of respondents reported using it for muscle strengthening/body toning, 67% for treatment of incontinence, 26% for rehabilitation and 33% for treatment of sports injuries. Effectiveness was evaluated on a 5-point scale (1-very poor, 5-very good) and the average rating was above 4 for all indications. Most users rated the effectiveness as "good" or "very good". The end-users reported an average of 5–12 patients treated per week per indication with one device. Responses about known possible side effects and adverse events were mostly rated "never observed" or "uncommon" (<1% of treated patients). The most commonly observed were muscle soreness and muscle pain. Night-time palpitations were suggested as an additional side effect by one user. No other new side effects were reported.

CONCLUSIONS: The results from this survey have recognized HITS® treatments as very effective and safe. The gathered data provides important information on practice patterns, clinical outcomes, safety profiles and other end-user insights. A continuation with future surveys is important to gain information on possible changes and trends in this field.

Key words: magnetic stimulation, muscle toning, incontinence.

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I. INTRODUCTION

Magnetic stimulation is a non-invasive treatment method that can penetrate through skin to stimulate deeper conductive structures in a painless manner. When delivered peripherally, magnetic stimulation can generate electrical stimulation of selected motor nerves, inducing muscle contraction, which is utilized in treatments of muscle toning or strengthening; as well as sensory nerve stimulation, inducing the relay of sensory information to the central nervous system, which is mostly utilized in rehabilitation and pain management. These treatments are also known as functional magnetic stimulation (FMS), repetitive peripheral magnetic stimulation (rPMS), or as the recently introduced High-Intensity Tesla Magnetic Stimulation (HITS®). HITS® denotes a proprietary magnetic technology developed by Fotona d.o.o. and Iskra Medical. Although this technology shares a similar mechanism of action to functional electrical stimulation, magnetic stimulation has a deeper tissue penetration at intensities that do not activate skin pain receptors, making it a more efficient and comfortable method for nerve activation and muscle contraction than electrical stimulation.

It has been demonstrated that magnetic stimulation is an effective tool for stimulation of pelvic floor musculature for the purpose of rehabilitation of weak pelvic muscles and restoration of neuromuscular

control for the treatment of male and female urinary incontinence and other pelvic floor disorders [1–3]; for improvement of motor control after disease or injury [4, 5]; for muscle strengthening and/or body toning/shaping [6, 7] and also for alleviating musculoskeletal pain [8, 9]. In various studies conducted since 1995, there have been almost no adverse events reported. Thus, HITS® can be considered as a treatment method with a high level of tolerance and safety.

The advantages of non-invasive body shaping solutions, such as HITS®, over invasive body shaping treatments are: increased safety, faster treatments, no downtime, and the absence of any incision-induced permanent tissue damage. Because of these reasons, the popularity of non-invasive solutions is constantly growing. HITS® treatment of urinary incontinence has similar benefits to those of non-invasive body shaping, leading to a high level of interest in non-invasive treatment of urinary incontinence. Numerous different approaches that are more invasive have been in use for treatment of urinary incontinence, and although they have been greatly refined over the years, complications can still occur[10].

With our end-user survey, we aimed to acquire information directly from the end-users of Iskra Medical's HITS® devices.

There were two primary goals of the present end-user survey. The first goal was to obtain information that would allow for an estimation of the number of patients treated for particular indications. Therefore, the end users were asked which HITS® magnetic stimulation device they use, which indications they treat, and how many patients they see for a particular indication. We also asked the end users how often they use magnetic stimulation devices for particular indications and about the effectiveness of the device for particular indications; The second goal was to obtain more detailed post-market safety data for magnetic stimulation devices. The end users were asked to report any observed side effect for every performed indication, as well as about their frequency.

II. MATERIALS AND METHODS

This study was conducted using a web-based survey (1ka, Version 21.02.16, Fakulteta za družene vede, Ljubljana). An invitation to respond to the survey was sent to registered users of Iskra Medical magnetic devices. Data collection took place from 19.10.2020 to 7.3.2021. Responses were automatically recorded and analysed using an online software program (1ka, Version 21.02.16, Fakulteta za družene vede, Ljubljana).

The following metrics were calculated/reported:
-Global distribution of respondents.
-The distribution of respondents according to starting year of use of a magnetic stimulation device.
-For each question the proportion of respondents who answered the question.
-The proportion of respondents who use a particular Iskra Medical magnetic stimulation device.
-The proportion of respondents who use a particular accessory with their Iskra Medical magnetic stimulation device.
-For each indication for use the average number of treated patients per week.
-The proportion of end-user respondents who perform specific indications.
-For each indication of use, the average estimate of effectiveness.
-The proportion of respondents who treat a specific body area.
-For each listed possible side effect, the average estimate of frequency.

III. RESULTS

A total of 96 practitioners from 22 different countries responded to the survey. The average duration of use of a magnetic stimulation device was three years. Out of 66.7% (n=64) of respondents who provided information on the devices they use, 70.3% (n=45) reported owning only one Iskra Medical magnetic stimulation device, whereas 29.7% of the respondents (n=19) reported owning more than one Iskra Medical FMS device. The most frequently used device was the TESLA Former (18%), followed by the TESLA Stym (15%), TESLA Former prestige (15%), Magneto STYM (13%), TESLA Care prestige (9%), FMS Former (7%), TESLA Stym prestige (5%), FMS Stym (4%), TESLA Care (4%), Magneto STYM prestige (3%), FMS Former prestige (3%), FMS Stym prestige (1%), FMS Care (1%) and FMS Care prestige (1%).

81% (n=78) of all respondents provided information on indications for which they use their magnetic stimulation device. The most performed indication was strengthening of healthy muscle, i.e. muscle toning (81%), followed by urinary incontinence (67%), sports injuries (33%) and rehabilitation after immobilization (27%). Other listed indications that users reported to perform but were not listed in the survey were: *neuropathic pain, cosmetic, neurological pathology, v. complete rehabilitation, pelvic pain, radicular pain, pains, anal incontinence, low backache, edema, erectile dysfunction.*

The reported mean effectiveness score was very

high for all indications - 4.3 or more (on a 1-5 scale, 5 representing maximum effectiveness), with rehabilitation after immobilization having the highest score of 4.6 (Table 1). The highest number of patients per week were treated for muscle toning (n=12), followed by rehabilitation after immobilization (n=11), and sport injuries (n=8) and urinary incontinence (n=5), (Table 1).

The most frequently used programs for muscle strengthening (muscle toning) and urinary incontinence are presented in Figures 1 and 2. Due to heterogeneity of the answers regarding the program used for rehabilitation after immobilization and sports injuries, quantitative analysis was deemed inappropriate and was not included in the analysis.

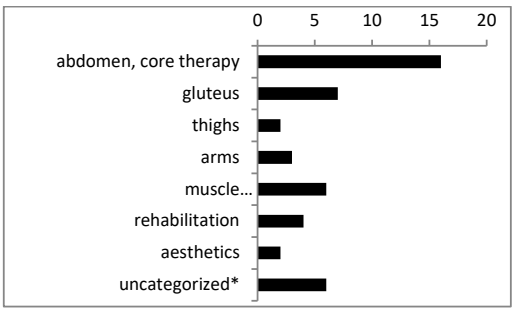

Figure 1: Most frequently used programs for muscle toning (n=31).

Multiple categories per single user were possible. Results are presented as number of respondents. *uncategorized answers: per requirements, various programs, medium, manual, many different

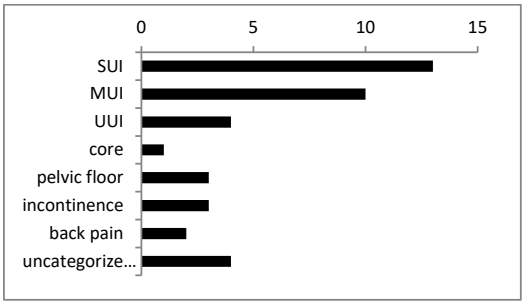

Figure 2: Most frequently used programs for urinary incontinence (n=29).

Per single user, multiple categories are possible. Results are presented as number of respondents. * uncategorized answers: different/many different, as per requirements programs for incontinence

Users have reported using magnetic intensity ranges from 2 to 100%. The most frequently used magnetic intensity range for muscle toning was from 72 to 100%; for urinary incontinence from 62 to 70%; for rehabilitation after immobilization from 42 to 70%; and for sport injuries from 62 to 70%.

The most frequently targeted body areas on which users have used the HITS® device are presented in Fig 3.

Table 1: Effectiveness of Iskra Medical magnetic stimulation devices for specific indications; estimation of the number of patients treated per week per indication per device; mean number of sessions. ***[i] Percentage of active users performing a specific indication. [ii] Mean effectiveness, calculated on the basis of effectiveness scores provided by respondents[iii]. N_p=Estimated number of patients treated per practitioner per year (number of weeks=52).***

Indication	Mean effectiveness [ii]	SD	Number of respondents[iii]	Number of patients treated per week	Number of respondents [i]	N_p	Mean number of sessions				
							1–5	6–10	11–15	16–20	21–25
Strengthening of healthy muscle, e.g. muscle toning	4.3	0.68	n=63	12	n=44*	624	25.0%	67.5%	12.5%	2.5%	0.0%
Urinary incontinence	4.3	0.69	n=49	5	n=34*	260	20.6%	61.8%	17.6%	11.8%	2.9%
Rehabilitation after immobilization	4.6	0.6	n=20	11	n=10*	572	30.0%	60.0%	20.0%	0.0%	0.0%
Sports injuries	4.4	0.75	n=26	8	n=14*	416	42.9%	50.0%	21.4%	0.0%	0.0%
Other: neurological pathology, pain, radicular pain etc.	4.1	0.9	n=7	2	n=3	104	66.7%	33.3%	0.0%	0.0%	0.0%

*One respondent excluded from analysis due to invalid value.

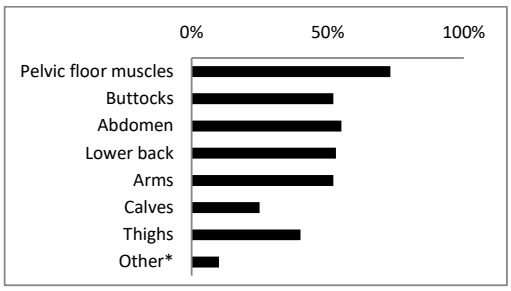

Figure 3: Most frequently targeted body areas (n= 60).
* Other: deltoids, arti, diaphragm, shoulders, upper back

A majority, 61% (n=59), of all users answered the question about known side effects following the magnetic stimulation treatment. Known possible side effects were mostly rated as "never observed" or "uncommon". The most commonly observed side effects were delayed onset muscle soreness (24%) and muscle pain (22%) (Table 2). Palpitations were suggested as an additional side effect by one user. No other new side effects were reported.

IV. DISCUSSION

Contemporary lifestyle and healthcare trends are strongly moving towards treatment personalization, so it is essential to consider not only technological and clinical aspects during the product and service development cycle, but also the users' experiences and demands. In this context, the end-user surveys can provide important information on attitudes, beliefs, practice patterns, behaviors and concerns of health care providers and patients. An additional benefit of conducting end-user surveys is obtaining real world safety and effectiveness data from every-day clinical practice.

The results of this user survey offer valuable insights into the most frequently performed HITS® procedures and their effectiveness, as well as the most commonly used parameters for performing HITS® treatments. The end-user respondents reported positive clinical outcomes from HITS® treatments without treatment-related complications.

The data obtained through this survey allowed us to estimate the numbers of patients and the frequency of use of the surveyed HITS® magnetic stimulation devices for particular indications for use. Based on the number of patients treated per week per specific indication, the estimated number of patients treated was highest for muscle toning (n=624 patients per practitioner per year) followed by rehabilitation after immobilization (n=572 per practitioner per year). Although the number of patients per week was higher for rehabilitation than for pelvic floor strengthening, rehabilitation was reported to be performed by fewer users, indicating that while rehabilitation might be a niche application for a smaller group of HITS® device users, it appears to attract a high number of patients to their practices.

When looking only at the number of respondents that reported to perform specific indications, the highest number of correspondents reported to perform muscle toning treatments, followed by pelvic floor strengthening (urinary incontinence). This confirms that these indications share the highest demand from patients, which is useful information for current and future device users. The effectiveness of the HITS® treatments was evaluated on a 5-point scale (1-very poor, 5-very good) and the average rating was above 4 for all indications. Most users rated the effectiveness as "good" or "very good". Users reported a high degree of effectiveness for all indications. As a possible option to further increase the effectiveness and success rate of the treatments, further emphasis should be made on appropriate patient selection.

We have also collected important real-world data about the number of treatment sessions used for specific treatment groups. Similar average numbers of sessions

Table 2: Side effects and estimation of their frequency.

Side effect	Number of respondents		Answers				Mean score (max. 4)	SD	Median
			Never observed	Uncommon (< 1%)	Common (1–10%)	Very common (> 10%)			
Skin burns	100%	n=59	75%	17%	8%	0%	1.3	0.6	1
Paresthesia	98%	n=58	79%	14%	7%	0%	1.3	0.6	1
Delayed onset muscle soreness	98%	n=58	41%	33%	24%	2%	1.9	0.9	2
Muscle pain	100%	n=59	32%	44%	22%	2%	1.9	0.8	2
Skin redness	98%	n=58	59%	28%	12%	2%	1.6	0.8	1
Other	18%	n=18	89%	6%	6%	0%	1.2	0.5	1

were reported across all indications. For muscle toning, urinary incontinence and rehabilitation, the mean number of sessions was 6-10 in 60% or more of cases. For treating sports injuries, 6-10 sessions were performed in 50% of cases and 1-5 sessions in 43% of cases.

Although there is still no consensus about the optimal number of sessions for the treatment of urinary incontinence, the existing literature reports the range of 8-16 sessions, and also shows that the beneficial effects improve with an increasing number of sessions[11]. Although the published clinical trials often used high session numbers, the data from our survey has revealed that only 6-10 sessions are usually performed, and only in 17.6% cases the mean number of session is 11-15. Although the number of sessions was often lower than reported in published clinical trials, the effectiveness reported by the users was high; indicating that wider clinical use in daily practice results in an optimization of the number of sessions.

Another important insight from this user survey was the range of most-often-used treatment intensities, which revealed that the highest intensities are being used for muscle toning treatments.

In addition, the HITS® treatments have been confirmed to have an excellent safety profile. Previously known listed side effects were mostly rated as "never observed" or "uncommon" (<1% of treated patients) by the survey respondents. The most commonly observed side effects were muscle soreness and muscle pain. Night-time palpitations were suggested as a potential side effect by one user. Palpitations have been previously identified as a potential rare side effect through the manufacturer's clinical evaluation.

Proactive gathering of the safety data, such as this end-user survey, is very important, since users usually do not regularly report device-related side effects, especially when these are minor and transient, as is mostly the case with HITS® therapy. Furthermore, some more serious side effects (such as e.g. burns) are often not reported, since they may be caused by user error. Proactive gathering of anonymized end-user data, such as with this survey, can paint a better and much clearer picture of the treatments' safety profile.

The collected real-world data in our study gives important insights and builds a more comprehensive picture of the frequency of specific treatments and their efficacy and safety in every day clinical practice. This will allow the manufacturers, clinicians and patients to better understand the effectiveness and safety of HITS® treatments in a larger pool of patients, for a longer period of time, and enable more informed decision-making at all levels.

V. CONCLUSIONS

Results from this survey have confirmed HITS® treatments as very effective and safe. The gathered data provides important information on practice patterns, clinical outcomes, safety profiles and other end-user insights. A continuation with future surveys is important to gain information on possible changes and trends in this field.

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