



## Electromagnetic transduction therapy and shockwave therapy in 86 patients with rotator cuff tendinopathy: A prospective randomized controlled trial

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### ABSTRACT

Rotator cuff (RC) tendinopathy is the most common cause of shoulder pain. The effectiveness of electromagnetic transduction therapy (EMTT), a high energetic pulsed electromagnetic field therapy in this field has not been tested yet in combination with extracorporeal shock wave therapy (ESWT).

A total of 86 patients with RC tendinopathy were randomized to undergo three sessions of ESWT in combination with 8 sessions of EMTT or sham-EMTT. Both intervention groups experienced significant and clinical relevant decrease of pain at all follow-up visits, and the functionality of the shoulder evaluated by the Constant Murley score increased significantly as well. The combination of EMTT + ESWT produced significantly greater pain reduction in the visual analogue scale compared to ESWT with sham-EMTT after 24 weeks, during which the Constant Murley score improved significantly when the combination of ESWT and EMTT was employed.

In patients with RC tendinopathy, electromagnetic transduction therapy combined with extracorporeal shock wave therapy significantly improves pain and function compared to ESWT with sham-EMTT.

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EMTT; PEMF; ESWT; rotator cuff tendinopathy; electromagnetic; transduction



## Introduction

Shoulder pain is one of the most common musculoskeletal disorders in patients over 40 years, with a prevalence between 4 and 36% (Murphy & Carr, 2010; Tekavec et al., 2012). Rotator cuff (RC) tendinopathy is the most common cause for shoulder pain and affects females in 70% of cases, typically during their 5th decade of life (Lewis, 2009). The pathogenesis of RC tendinopathies is unclear, and extrinsic and intrinsic factors, or a combination of both, are involved. Extrinsic factors include irritation or compression of the superior aspect of the tendons under the coraco-acromial arch, or of the articular side of the tendons from internal impingement onto the glenoid labrum (Harrison & Flatow, 2011). Tendinopathy is usually as a consequence of overuse or overload (Abate et al., 2009). Increase and change in collagen, proteoglycans, vascularity and tenocytes have been described (Abate et al., 2009). Intrinsic changes within the RC are the principal factors in the pathogenesis of RC tears (Hashimoto et al., 2003). RC

tendinopathy persists or recurs in 40 to 50% of individuals within one year after initial presentation, and leads to marked functional loss and decreased quality of life (Chard et al., 1991; Van Der Windt et al., 1996).

The initial management of RC tendinopathy is typically conservative, including physiotherapy, nonsteroidal anti-inflammatory drugs and subacromial corticosteroid injections (Green et al., 1998; Tolstykh et al., 2013). Nevertheless, the evidence of efficiency for these therapies is limited (Gerdesmeyer et al., 2003; Rosso et al., 2015; Varani et al., 2008). If conservative management fails, open or arthroscopic debridement are widely used but again with lack of evidence for their use (L. Gerdesmeyer et al., 2005; Louwerens et al., 2014; Rosso et al., 2015). However, surgery is costly, has peri- or postoperative complication and needs long rehabilitation (Balke et al., 2012; Clement et al., 2015).

Extracorporeal shock wave therapy (ESWT) has been used as an effective nonsurgical alternative in patients with shoulder tendinopathy for the past 20 years (Loew et al., 1995), and subsequent level 1a

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studies have corroborated these results (Gerdesmeyer et al., 2003; Hsu et al., 2008; Ioppolo et al., 2013; Rompe et al., 2001). ESWT is effective in other chronic tendinopathies, including plantar fasciitis, insertional and non-insertional Achilles tendinopathy, greater trochanteric pain syndrome and tennis elbow (Gerdesmeyer et al., 2008; 2015; Lee et al., 1997; Thiele et al., 2015).

Pulsed electromagnetic field therapy (PEMF) is another non-surgical option in the management of tendinopathies, but the evidence from randomized controlled trials is by far not as strong as for ESWT. The most common reasons for failure of such modality are low electromagnetic field power of less than 10 mT, and the missing dynamic oscillating physical property of each impulse (Denaro et al., 2011; Page et al., 2016; Pienkowski et al., 1992). Long acting low level high frequency electromagnetic impulses or high energy static single magnetic impulses have no clinical, biological and clinical relevant effects (Denaro et al., 2011; Page et al., 2016). This has determined this technology to be abandoned over the last two decades. Nowadays, technical advances allow to manufacture devices with high electromagnetic field power and a string oscillating magnetic power of every single impulse. Up to 80 mT and oscillating frequencies of up to 20 kHz can be reached with modern electromagnetic transduction technologies. These directly interact with biological electromagnetic induced pathways (Green et al., 1998; Rosso et al., 2015; Sackett, 1997). This mechanism is described as electromagnetic transduction therapy (EMTT). EMTT requires an electromagnetic field power of at least 80 mT and an oscillating frequency of 20 kHz of each single impulse. Impulses that fail to have these strong physical characteristics are known as PEMF. EMTT impulses are produced by a high-speed generator to build up a voltage up to 30 kV which is released in nanoseconds with an impulse release frequency of 3 Hz. The very short duration of each impulse ensures full electrophysical reactions without any temperature increase or mechanical effect within the treatment zone. EMTT interacts at all electromagnetic gradients which are found along every electrophysical gradient within cells, intercellular space, inflammation induced ion shifts and occur in most all energy consuming biochemical pathways. The various proteins, receptor mediated pathways and metabolic pathways respond to electromagnetic impulses if a threshold higher than 10 mT is applied (Pienkowski et al., 1992; Semenov et al., 2013; Tolstykh et al., 2013; Wolf-Goldberg et al., 2013). Experimental studies demonstrated some effects in osteoarthritis, pseudarthrosis, chronic pain from different musculoskeletal disorders and healing of tendon injuries (Guerkov et

al., 2001; Nicolakis et al., 2002; Osti et al., 2015a, 2015b; Prato et al., 2005; Strauch et al., 2006). Recent randomized controlled trials reported excellent effects of EMTT in chronic low back pain and in Achilles tendinopathy (Gerdesmeyer et al., 2017; Krath et al., 2017). Lower energy levels mostly failed to show a significant effect. To our knowledge, clinical Level 2a randomized controlled trials on electromagnetic field beyond 10 mT have not been published.

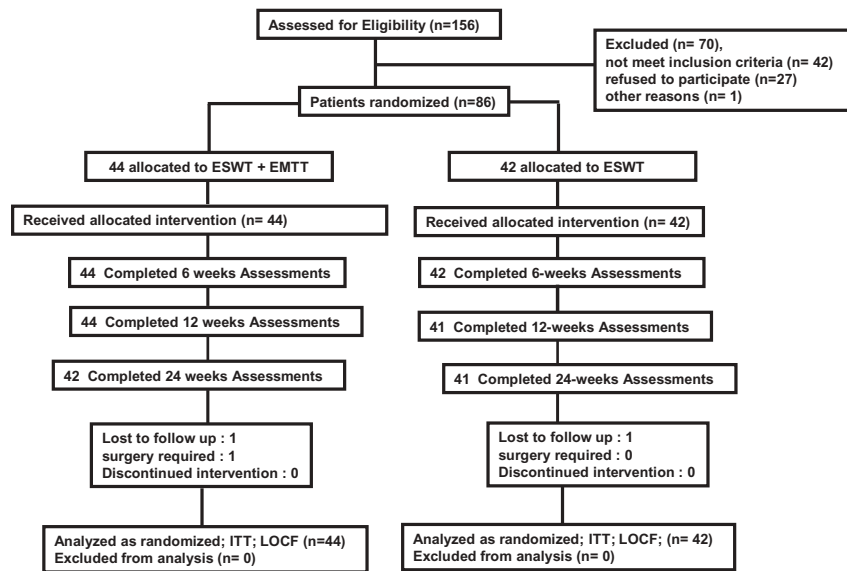
ESWT and EMTT act via different mechanisms. The present investigation analyses whether ESWT and EMTT have synergistic effects in the management of RC tendinopathies in a prospective randomized controlled study.

## Material and methods

Within a 12-month period patients with diagnosed non-calcific RC tendinopathy were enrolled into this trial. All patients received plain radiography and MRI of the shoulder to document increased signal intensity of the RC and to exclude calcifications and full thickness RC tears. All patients have failed to conservative management, including non-steroidal anti-inflammatory drugs and physiotherapy (twice a week) for at least 3 months. A total of 86 patients were randomly assigned to receive either ESWT and sham-EMTT or a combination of ESWT and EMTT (Figure 1) with concealed allocation in permuted blocks of four to eight with the use of a computer-generated random list. Concealment of randomization was guaranteed by non-transparent envelopes. The treating physician was not blinded, but both participants and evaluating physicians were blinded to randomization. The trial was in accordance with the standardized guidelines of good clinical practice from the International Conference on Harmonization. The study was registered in the German Clinical Trial register (DRK S 00011054), and approved by the Ethics Committee. All patients provided written informed consent. Inclusion and exclusion criteria are listed in Table 1.

## Treatment

Focused ESWT was administered to the point of maximum tenderness via patients feedback, with an ultrasound coupling gel used to ensure transmission of the shock wave from the hand-piece to the painful area. No radiographic or ultrasound guidance was used. Two thousand impulses of the assigned intervention were delivered per session, and the intervention was repeated with a total of three sessions at 2 week intervals. In the ESWT group, 2000 impulses of focused shock waves



**Figure 1.** Flow chart of a the randomized controlled trial in accordance to the CONSORT statement.

**Table 1.** Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>• Symptomatic rotator cuff tendinopathy</li> <li>• At least a 3-month duration of symptoms</li> <li>• Must complete and failed to conservative treatment with:               <ul style="list-style-type: none"> <li>○ Physiotherapy</li> <li>○ Systemic NSAID's</li> </ul> </li> <li>• NSAIDs treatment washout period of 1 weeks</li> <li>• No calcific tendinitis</li> <li>• No clinically relevant rotator cuff tear</li> <li>• Signed informed consent</li> <li>• VAS pain score &gt; 4</li> <li>• Age greater than 18 years</li> </ul>	<ul style="list-style-type: none"> <li>• Glenohumeral or acromioclavicular joint arthrosis</li> <li>• Previous surgery of the painful shoulder</li> <li>• Infection ortumor of the shoulder</li> <li>• Shoulder Instability/clinically significant complete rotator cuff lesion of the shoulder</li> <li>• Pathological neurological findings</li> <li>• VAS Pain score &lt; 5</li> <li>• Significant coagulation disturbance</li> <li>• Previous unsuccessful ESWT</li> </ul>

with an energy flux density of  $0.32 \text{ mJ/mm}^2$  and a rate of 4 impulses per second (Hz) were applied at each session. Focused shock waves were generated electromagnetically with the Duolith SD1 shock wave device (Storz Medical AG, Tägerwilten, Switzerland) according to the shoulder treatment recommendations (Gerdesmeyer et al., 2003; Ongaro et al., 2012).

EMTT was administered twice per week for a total of eight session. The MT1 device (Figure 2) was used to perform EMTT (Storz Medical AG, Tägerwilten, Switzerland). Each treatment lasted 20 min at 80 mT, impulse frequency of 3 Hz, discharge voltage of 30 KV. No local anesthesia was used either in ESWT or EMTT. Sham-EMTT was

applied by using an inactivated original EMTT device which produced same sound as the active one but no EMTT impulse.

The participants were allowed to use a standardized rescue medication throughout the entire study (2 g of paracetamol per day for up to 14 d following the last intervention; thereafter, 2 g of paracetamol per week). No other therapies were allowed.

### Primary outcome measures

The primary outcome measure was the change of functional outcome and pain, using the age and gender adapted Constant Murley score (CMS) and change in subjective pain sensation quantified by scoring on the 10 point visual analogue rating scale (VAS). This was measured by the percentage change of the CMS and VAS at the primary endpoint 6 month (24 weeks) after the last intervention compared to baseline.

The change in pain was defined as change of shoulder pain while performing daily activities, scored at the same time point at the end of the day. The 10 point pain visual analogue scale was used to quantify the change 24 weeks after the last intervention compared to baseline.

To keep the multiple level of alpha, both primary efficacy criteria had to be statistically significant. Primary outcome measures were analyzed with last value carried forward (LVCF) technique and correction for interfering analgesic therapy.



**Figure 2.** EMTT device.  
The Theracell® device was used to perform EMTT

The primary endpoint was pain 24 weeks after the last intervention. A clinically relevant effect size was defined as at least 60% reduction in pain. Both groups underwent identical physiotherapy with shoulder stabilization techniques only, no other concomitant therapy to control shoulder pain was allowed accepted the rescue medication.

### Secondary outcome measures

The secondary outcome measure was the change of functional outcome and pain using the age and gender adapted CMS and change in subjective pain sensation quantified by scoring on the 10-point VAS measured by the percentage change of the CMS and VAS at the secondary endpoints 6 and 12 weeks after the last intervention compared to baseline.

All subjects with at least one intervention either ESWT or EMTT were included in the safety population. Patients were followed throughout the study and all local tissue effects and adverse events were recorded.

### Statistical analysis

All analyses were performed with SigmaPlot 12.5. The sample size calculation was based on the model of stochastic superiority within the Wilcoxon-Mann-Whitney test for the primary outcome measure “percentage change of VAS composite score”. The following stipulations were made: relevant effect size  $MW = 0.64$ , alpha (one-sided) = 0.025, and beta (power) = 0.10. To account for attrition, dropping out, etc., the sample size was increased to  $N = 44$  per group.

To keep the multiple level of alpha, efficacy of the combined therapy ESWT + EMTT is confirmed if both primary criteria of effectiveness (CMS as well as VAS score) showed a statistically significant result. A value of  $p < 0.025$  (one-sided) was considered statistically significant.

### Results

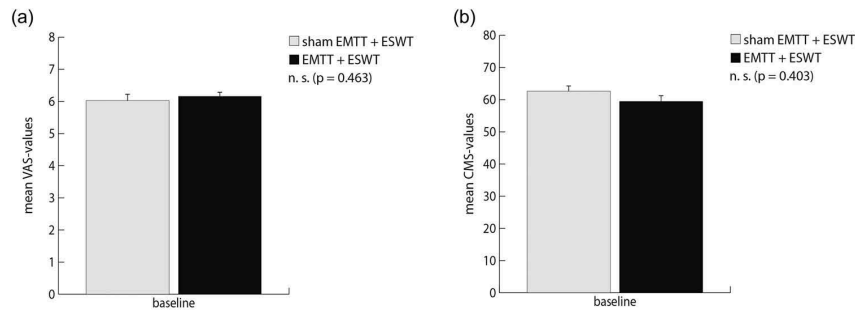
A total of 86 participants with shoulder tendinopathy were randomized according to the study protocol to receive either sham-EMTT/ESWT or EMTT/ESWT (Figure 1). Three patients (3.5%) were lost to follow-up during the study period (two in the sham-EMTT/ESWT group and one in the EMTT/ESWT group). Missing data were replaced by the LVCF technique. All patients were treated as allocated and randomized. The required number of pulses was achieved in all treatments.

To analyze the homogeneity of the two groups at baseline, we used the Wilcoxon-Mann-Whitney test. Across the two groups, no significant difference was found with regards to primary criteria VAS values ( $p = 0.403$ ) nor for CMS values at baseline ( $p = 0.463$ ) as well as biometric data (Figure 3, Table 2).

At 6, 12 and 24 weeks after the last intervention, follow-up evaluations were performed, including physical examination and measurement of VAS and CMS score. The results of the sham-EMTT/ESWT group are presented in Figure 4. The subjective pain perception significantly improved at all follow-up points compared to baseline. 24 weeks after the last intervention, the VAS score had decreased by 41.6% to  $1.88 \pm 0.268$ , but even after 6 weeks the means dropped from  $6.0 \pm 0.2$  at baseline to  $3.5 \pm 0.18$  ( $p \leq 0.001$ ).

Within the same 24 week period, the CMS increased significantly by 32.1% from  $62.62 \pm 1.73$  to  $82.70 \pm 2.11$  ( $p \leq 0.001$ ). The CMS had also improved significantly after 6 ( $72.91 \pm 1.50$ ) and 12 weeks ( $78.659 \pm 2.12$ ).

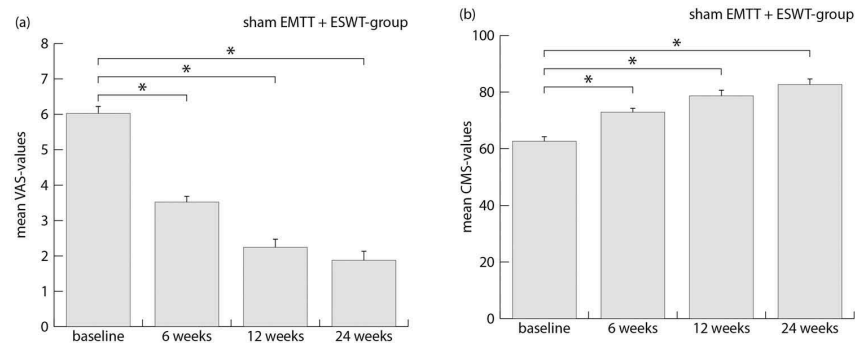
The combination of ESWT and active EMTT showed significant and clinically relevant improvement at all follow-up visits, with a peak of improvement 24 weeks after the last intervention (Figure 5). The VAS values



**Figure 3.** VAS and CMS score at baseline. No differences were determined between sham EMTT/ESWT and EMTT/ESWT at baseline.

**Table 2.** Demographic data at baseline.

Subject Demographics	ESWT + sham-EMTT	ESWT + EMTT	<i>p</i> Value
No Pts	42	44	
Female	22	23	> 0.05
Age (years)	49.21 ± 7,3	50.21 ± 8,5	> 0.05
Afflicted site right	22	23	> 0.05
CMS	60.62 ± 11.2	59.44 ± 12,5	> 0.05
VAS	6.0 ± 1.4	6.16 ± 0,9	> 0.05



**Figure 4.** VAS and CMS values at baseline, 6, 12 and 24 weeks after sham EMTT/ESWT. Whereas VAS values (a) decreased after ESWT, CMS values (b) increased significantly. ( $p \leq 0.001$ ;  $n = 42$ )

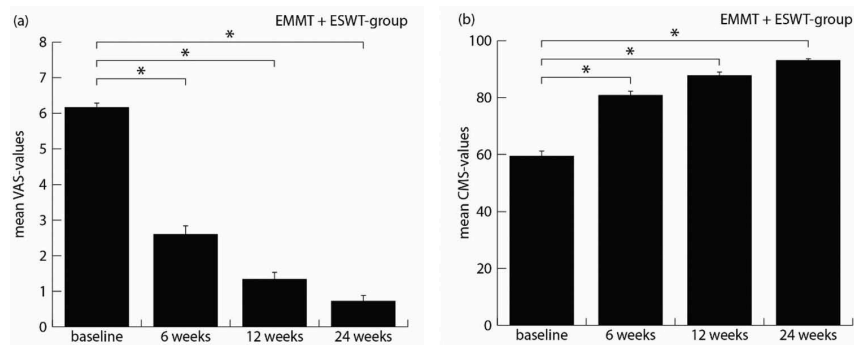
decreased significantly by 88.2% from  $6.16 \pm 0.13$  at baseline to  $0.725 \pm 0.245$  after 24 weeks. Compared to baseline, the CMS increased significantly by 56.6% within 24 weeks after EMTT/ESWT (baseline  $59.44 \pm 1.91$  to week 24  $93.10 \pm 0.69$ ). At all follow-up visits, the improvement was statistically significant.

Finally, the analysis of ESWT + sham-EMTT versus ESWT + EMTT showed a better outcome in favor for the combined ESWT + active EMTT (Figure 6), with statistically improved functional outcomes measured by the CMS value as well as the pain during daily activities score by the VAS scoring system. Statistical significance level was tested by Wilcoxon-Mann-Whitney test. At each follow-up visit, the ESWT + EMTT group performed significantly better compared to ESWT alone

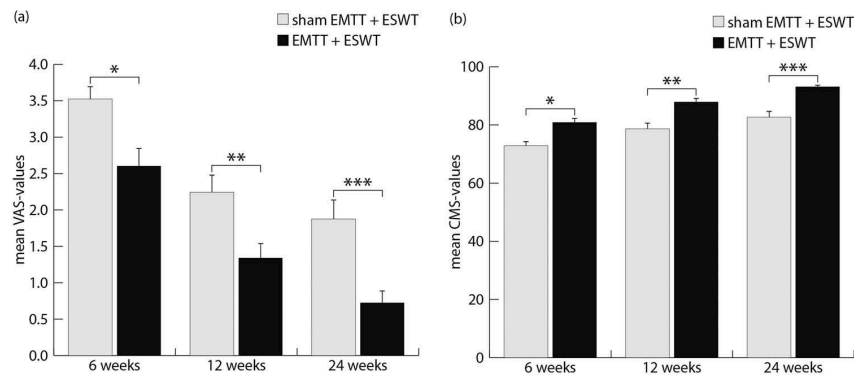
(Figure 6 a). Twenty-four weeks after the last intervention, the VAS pain score decreased from  $6.02 \pm 0.21$  to  $1.87 \pm 0.27$  in the ESWT group, and decreased from  $6.16 \pm 1.3$  at baseline to  $0.73 \pm 1.67$  after 24 weeks. The improvement was significantly greater in the ESWT + EMTT group compared to ESWT alone at all follow-up visits.

The statistically significant difference in VAS change from baseline to follow-up visits in between the treatment groups was 0.9 pts after 6 weeks, 0.9 after 12 weeks, and 1.1 after 24 weeks in favor of the combined therapy ESWT+ EMTT.

The functional outcome comparing combined ESWT + EMTT versus ESWT + sham EMTT was superior in the combined therapy option. The



**Figure 5.** VAS and CMS values at baseline, 6, 12 and 24 weeks after EMTT/ESWT. After EMTT/ESWT pain reduced significantly, but the functionality was enhanced at all time points. ( $p \leq 0.001$ ;  $n = 44$ )



**Figure 6.** sham EMTT/ESWT versus EMTT/ESWT 6, 12 and 24 Weeks after treatment. Patient had less pain (A) and enhanced functionality after combined treatment of EMTT and ESWT compared to patients which received sham EMTT/ESWT.  $*p \leq 0.1$ ;  $**p \leq 0.01$ ;  $***p \leq 0.001$

functional improvement measured by increased CMS value was significantly better after combined therapy ESWT plus EMTT. Both groups did better compared to baseline, but, again, shock wave therapy as a single treatment did not perform as well as when it was combined with EMTT.

In the ESWT + EMTT group, the CMS improved from  $59.4 \pm 1.9$  at baseline to  $93.1 \pm 0.7$  after 24 weeks. After ESWT + sham-EMTT alone, the CMS value improved from  $62.6 \pm 1.7$  to  $82.7 \pm 2.1$  after 24 weeks. The statistically significant difference in change from baseline to follow-up visits in between the treatment groups was 7.9 points after 6 weeks, 9.1 after 12 weeks and 10.4 after 24 weeks in favor of the combined therapy ESWT + EMTT (Figure 6 b).

No severe adverse events were reported for either intervention group. Some clinically irrelevant petechiae, small cutaneous hematoma or erythema were reported immediately after the treatment by seven patients after ESWT and by nine patients after ESWT + EMTT. They

all disappeared within 24 hours. Other clinically significant adverse events such as neurologic disorders, tendon rupture, infection or necrosis were not observed in any of the patients at any time.

## Discussion

RC tendinopathy is common and challenging, especially when conservative treatments have failed. Surgical interventions carry risks such as infection or soft tissue, nerve and vessel damage.

ESWT is a validated modality in the management of tendinopathies (Gerdesmeyer et al., 2003; Ongaro et al., 2012), with the best evidence in calcific tendinopathy of the shoulder (Moya et al., 2015). Also, level 1 evidence in favor of ESWT has been published for Achilles tendinopathy, plantar fasciitis, greater trochanter pain syndrome, and jumper's knee (Gerdesmeyer et al., 2008, 2015; Thijs et al., 2016).



Shock waves act via mechanotransduction (Huang et al., 2013). Several biochemical pathways are activated by ESWT, including recruitment of stem cells, neovascuogenesis and release of growth factors and improvement of blood supply (Haake et al., 2002; Leone et al., 2012). The treatment area is small, as the focal zone of shock wave devices is up to 8 mm in diameter (Haake et al., 2002). Electromagnetic impulses, such as EMTT, work in a different way. Shock waves act mechanically via mechanotransduction within a small treatment area around the focus zone. EMTT acts via electromagnetic transduction within a much larger treatment area up to 30 cm in diameter (Krath et al., 2017).

EMTT is characterized by electromagnetic exposure, which leads to a change of the electric potential of the cell membrane, and migration of calcium ions ( $\text{Ca}^{2+}$ ) into the cell. Furthermore, electromagnetic energy enhances the binding of  $\text{Ca}^{2+}$  to calmodulin, which catalyses nitric oxide release and leads to a secretion of growth factors (Colomer & Means, 2007; Korhonen et al., 2005). Chronic tendinopathy could be mediated by inflammatory mediators such as proinflammatory cytokines which are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$  are involved in the process of neuroinflammation process.

Further, substance P, vascular endothelial growth factor (VEGF) and cyclooxygenase type II (COX2) (Rees et al., 2014) are involved in tendinopathies. Electromagnetic fields such as EMTT influence multiple different pathways, including the ligand-independent activation of members of the tyrosine kinase family (Wolf-Goldberg et al., 2013) and the upregulation of adenosine receptors in human neutrophils, chondrocytes and synoviocytes. This results in a decrease of proinflammatory cytokines such as IL-6 and IL-8, and in inhibition of the release of the key regulator of inflammatory responses NF- $\kappa$ B (Ongaro et al., 2012; Varani et al., 2008). Furthermore, Heredia-Rojas et al. detected electromagnetic-responsive DNA sequences in the Hsp70 promoter, suggesting that electromagnetic energy directly modulates gene expression of specific proteins (Heredia-Rojas et al., 2010). Taken together, electromagnetic energy may well activate tenocytes firstly by limiting the catabolic effect of proinflammatory molecules, and secondly increasing the production of extracellular matrix and cell proliferation (Rosso et al., 2015).

To effectively use EMTT in the management of soft tissue injury, specific physical parameter and thresholds have to be reached. The most important one is defined

as magnetic field strength, measured in Millitesla (mT). Earlier, different devices and technologies were designed to undertake a form of magnetic therapy named PEMF. Most clinical trials failed to demonstrate efficacy, and basic sciences research produced conflicting results, as the strength of the electromagnetic field was not high enough to induce significant biological reaction and activate repair mechanism. Galace de Freitas et al. determined PEMF and exercises in patients with shoulder impingement syndrome (Galace De Freitas et al., 2014), but could not show significant superiority compared to placebo group. One reason might be the weak magnetic field strength. At least 10 mT energy have to be reached to initiate significant biological effects (Pienkowski et al., 1992; Urnukhsaikhan et al., 2016; Wuschech et al., 2015). EMTT reaches up to 80 mT, and is therefore appropriate to induce beneficial soft tissue regeneration.

However, we stress that the electromagnetic energy level is just one parameter. Other parameters, such as a high oscillating frequency with a single EMTT impulse, are necessary. The still in use single static rectangular impulses miss the physical parameter needed to induce healing. The MT1 device used in this prospective randomized controlled trial fulfils all the presently known criteria needed to perform electromagnetic transduction.

This study has some limitations. First, it remains unclear which treatment parameter of EMTT is the most clinically important. Further studies have to test different treatment protocols to optimize the use of this technology and to evaluate economic aspects including costs and time effectiveness. Second, we did not include in our investigation a group receiving placebo treatment or EMTT treatment alone. Therefore, we cannot infer the pure EMTT-induced effect. ESWT and EMTT have different mechanism of action, and mechanotransduction and electromagnetic transduction may have synergistic effects in tendinopathies.

We acknowledge that the follow-up period of six months is short- and long-term data are needed to analyze the relevant long acting effects of EMTT. However, this was a pragmatic trial: it is unlikely that, in clinical practice, patients would accept to be monitored for two years following treatment if this had not produced amelioration of their symptoms.

## Conclusion

The present study reports high level of evidence in favor of the combined use of EMTT and ESWT to manage RC tendinopathy. The two treatment modalities have a favorable synergetic effect and EMTT significantly improves the results after ESWT. Further

studies will determine whether changes in treatment parameters impact on outcome. Furthermore, studies also should focus on tendinopathies in other locations to ascertain the place of EMTT, alone or in combination with ESWT, in the management of such ailments.

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## Declaration of Interest

The authors declare no conflict of interest.

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