Electromagnetic transduction therapy and shock wave therapy in sports related rotator cuff tendinopathy: a prospective randomised controlled trial

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Abstract

Background

Rotator cuff tendinopathy is the most common cause of shoulder pain. Level I clinical trials have documented the effectiveness of extracorporal shock wave therapy (ESWT) to treat Rotator cuff tendinopathy. The effectiveness of pulsed electromagnetic field therapy such as electromagnetic transduction therapy (EMTT) in this field has not been proven yet.

Hypothesis

There is no difference in effectiveness between ESWT and a combination of ESWT and EMTT in the management of Rotator cuff tendinopathy.

Study design

Randomized, controlled trial; Level of evidence: 2a

Methods

88 patients with sports related rotator cuff tendinopathy were either treated with three interventions of ESWT (0.32 mJ/mm^2; 2000 impulses) alone or in combination with 8 sessions of EMTT (80mT; 3 Hz; 30kV). Primary endpoints were at least 60% reduction of pain in visual analogue scale from baseline to 24 weeks' follow-up. Secondary endpoints were single changes in visual analogue scale scores and Constant Murley score 6, 12 and 24 weeks after last interventions.

Results

Both intervention groups revealed significant decrease of pain at all follow-up visits, and the functionality of the shoulder tested by Constant Murley score increased significantly. The combination of EMTT + ESWT produced significantly greater reduction of the visual analogue scale composite score compared to ESWT alone (88.2% vs 41.6% (P = 0.001)) after 24 weeks. Within the same period, the Constant Murley score improved significantly (56.6% versus 32.1%). No side effects were observed.

Conclusion

In patients with rotator cuff tendinopathy, electromagnetic transduction therapy together with extracorporeal shock wave therapy significantly improves pain and function compared with ESWT alone.

Clinical Relevance

The addition of electromagnetic transduction therapy to extracorporeal shock wave therapy enhances pain reduction and functionality in patients with rotator cuff tendinopathy.

Key terms: ESWT, EMTT, PEMF, shoulder tendinopathy, rotator cuff

What is known about the subject:

ESWT is effective in the conservative management of rotator cuff tendinopathy. Electromagnetic transduction therapy is a novel treatment modality in rotator cuff tendinopathy, but so far, research has not verified biologically relevant effects, as the physical parameters needed to reach to induce significant biological reaction and activate repair mechanism are not identified yet.

What this study adds to existing knowledge:

The combination of electromagnetic transduction therapy with extracorporeal shock wave therapy produces better outcome in the treatment of rotator cuff tendinopathy than extracorporeal shock wave therapy, with patients reporting significantly less pain and superior function compared to treatment with ESWT alone.

Introduction

Shoulder pain is one of the most common musculoskeletal disorders in patients over 40 years of age, with a prevalence between 4 and 36% [23, 37]. Shoulder tendinopathy is a generic term which describes tendon pathology and tendon driven pain without aetiological, biochemical or histological implications. The pathogenesis of rotator cuff (RC) tendinopathies is mostly divided into extrinsic and intrinsic factors or combinations of both. 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. Intrinsic tendinopathy is defined as tendon pathology that originates within the tendon, usually as a consequence of overuse or overload such as tendon impingement. Increases and changes in collagen, proteoglycans, vascularity and cells have been described in tendon pathology. Intrinsic changes within the rotator cuff are the principal factors in the pathogenesis of rotator cuff tears [13]. 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 [2, 42].

The initial management is typically conservative, including physiotherapy, nonsteroidal anti-inflammatory drugs and subacromial corticosteroid injections [10, 40]. Nevertheless the evidence of efficiency for this therapies is limited [9, 33, 43]. If conservative management fails, open or arthroscopic debridement, subacromial decompression or cuff repair techniques are widely used: they as well have limited scientific evidence for their use [7, 21, 33]. However, surgery is costly, might provoke peri- or postoperative complication and needs longer rehabilitation [1, 3].

Extracorporeal shock wave therapy (ESWT) was first used as a nonsurgical alternative in patients with shoulder tendinopathy 20 years ago [20], and subsequent level 1a has corroborated these results [9, 15, 17, 32]. ESWT has been proved to be effective in other chronic tendinopathies, including plantar fasciitis, insertional and non-insertional Achilles tendinopathy, greater trochanteric pain syndrome and tennis elbow [6, 8, 38].

Pulsed electromagnetic field therapy (PEMF) is another non-surgical option in the management of tendinopathies, but the evidence from randomized controlled trials is not as strong as for ESWT. The most discussed reasons of failing to show significant effects are low electromagnetic field power of at least 10 mT and the missing dynamic oscillating physical property of each impulse [5, 28, 29]. Long acting low level electromagnetic impulses have no clinical, biological and clinical relevant effects [5, 28]. This has determined this technology to be abandoned over the last 2 decades. Nowadays, technically advanced knowledge has renewed the option to manufacture devices which electromagnetic field power and a string oscillating power of every single impulse. Up to 80 mT and oscillating frequencies of 220 kHz

can be reached with modern technologies. This level directly interacts with biological electromagnetic induced pathways [10, 33, 34]. This mechanism is described as electromagnetic transduction therapy (EMTT). EMTT requires an electromagnetic field power of at least 80mT and an oscillating frequency of 220 kHz of each single impulse. Impulses that fail to have these physical characteristics are widely known as PEMF. EMTT impulses were emitted by a high-speed generator to build up a voltage up to 30 kV which is released in nanoseconds and an impulse release frequency of 3 Hz. The very short duration of each impulse ensures full electrophysical reactions without any temperature increase in the tissue. 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 most energy consuming reactions act to electromagnetic impulses if a higher than 10 mT threshold is applied [29, 35, 40, 44]. Experimental studies demonstrated some effects in osteoarthritis, pseudoarthrosis, chronic pain from different musculoskeletal disorders and healing of tendon injuries [11, 24, 26, 27, 30, 36]. Lower energy levels mostly failed to show a significant effect. Clinical randomized controlled trials at Level 2a investigation electromagnetic field beyond 10mT have not been published so far.

Mechanotransduction by extracorpopreal shock wave therapy (ESWT) and electromagnetic transduction therapy (EMTT) acts via different mechanisms. Good outcomes after ESWT can further be improved if EMTT is applied in combination with ESWT. The aim of the study was to analyse if ESWT and EMTT have synergistic effects in treatment of shoulder tendinopathies in a prospective randomized controlled study.

Methods

Within a 12 month period patients undertaking moderate sport activity (3 hour per week) such as tennis, basketball, volleyball, swimming and other shoulder related sports activities were enrolled into this trial. A total of 86 patients were randomly assigned to receive either ESWT 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 unblinded, and 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 of Ärztekammer Schleswig-Holstein, Germany. All patients provided written informed consent. Inclusion and exclusion criteria are listed in table 1.

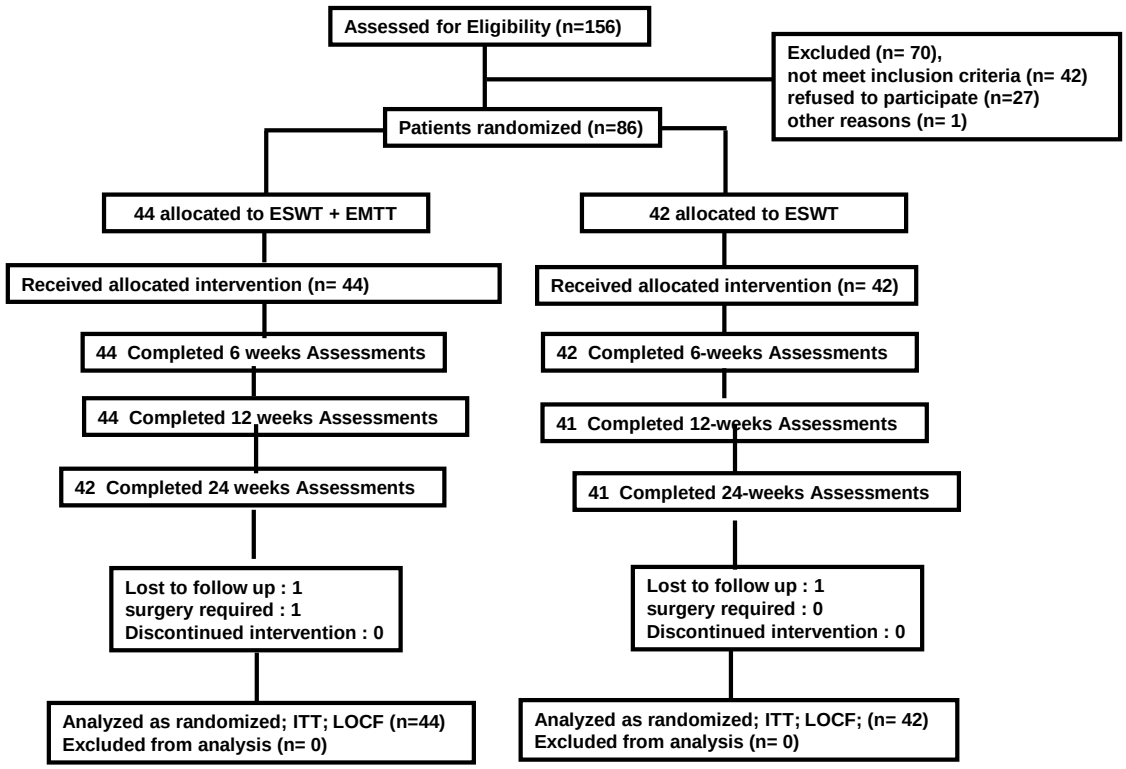


Figure 1: Flow chart of a the randomized controlled trial in accordance to the CONSORT Statement

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria

• Symptomatic rotator cuff tendinopathy
• At least a 3-month duration of symptoms
• Must complete and failed to conservative treatment with:
  ○ Physical therapy *and*
  ○ physiotherapy
  ○ Systemic NSAID´s
• NSAIDs treatment washout period of 1 weeks
• No calcific tendinitis
• Signed informed consent
• VAS pain score > 4
• Age greater than 18 years
	• Glenohumeral or acromioclavicular joint arthrosis
	• Previous surgery of the painful shoulder
	• Bursitis/ infection/ tumor of the shoulder
	• Shoulder Instability/ clinically significant complete rotator cuff lesion of the shoulder
	• Pathological neurological findings
	• VAS Pain score < 5
	• Significant coagulation disturbance
	• Previous unsuccessful ESWT

Focused ESWT was administered to the point of maximum tenderness, 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. 2000 impulses of the assigned intervention were delivered per session, and the intervention was repeated up to a total of three sessions at 2 week intervals. In the ESWT group, 2000 impulses of focused shock waves with a total energy flux density of 0.32 mJ/mm² 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, Tägerwilen, Switzerland) according to the shoulder treatment recommendations[9, 25].

Subjects in the ESWT and EMTT combination group received identical ESWT intervention. The intervention was performed by placing the tip of the applicator to the most tender point at the insertion area of the rotator cuff, determining proper placement by patient-controlled feedback and adjusted during treatment if necessary.

EMTT was administered twice per week for a total of 8 session. The MT1 device was used to perform EMTT (Storz Medical AG, Tägerwilen, Switzerland). Each treatment lasted 20 minutes at 80mT, impulse frequency of 3 Hz, discharge voltage of 30 KV. No local

anaesthesia was used either in ESWT or EMTT.

The participants were allowed to use a standardized rescue medication throughout the entire study (2g of paracetamol per day for up to 14 days following the last intervention; thereafter, 2g 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 sensation was defined as change of shoulder pain while performing daily activities. The 10 point pain visual analogue scale was used to quantify the change 24 weeks after last intervention compared to baseline. The pressure level that just elicited unbearable pain was related to a VAS score 10.

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), replacement of missing values and correction for interfering analgesic therapy.

The primary endpoint was pain 24 weeks after the last intervention. At this point, the decision was also made whether the subject had sufficient treatment response to continue the study. Sufficient response was considered at least 60% reduction in pain on CMS or VAS. Both groups underwent identical physiotherapy with shoulder stabilization techniques only, no other concomitant therapy to control shoulder pain was allowed.

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, 12 and 24 weeks after the last intervention compared to baseline.

Safety criteria

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. Due to usual ambiguities of the study (dropout etc.) the sample size for the study was increased to N = 44 per group.

In order 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 ESWT or EMTT/ESWT (Figure 1). Three patients (3.5%) were lost to follow-up during the study period, two in the ESWT group and one in the EMTT/ESWT group. Missing data were replaced by the last value carried forward technique (LVCF). 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 treatment groups, 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 2, table 2).

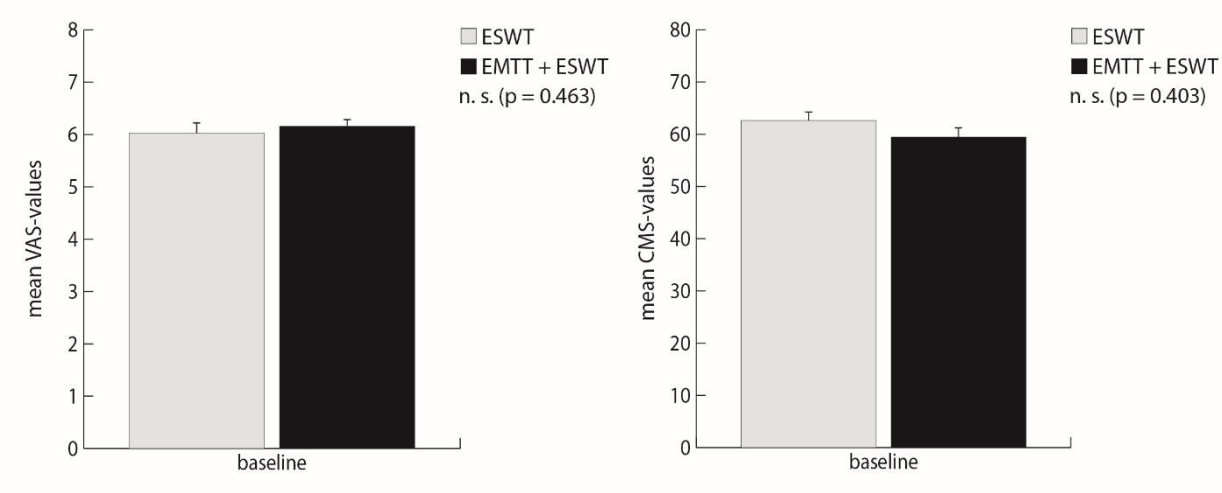


Figure 2 VAS and CMS score at baseline

No differences were determined between ESWT and EMTT/ESWT at baseline.

Table 2: Demographic data at baseline

Subject Demographics			
	ESWT	ESWT+EMTT	p-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

At six, 12 and 24 week after the last intervention, follow-up evaluations were performed, including physical examination and measuring VAS and CMS score. The results of the ESWT group are presented in figure 3. The subjective pain perception was analyzed and found to improve at all follow up points significantly compared to baseline. 24 weeks after the last intervention, the VAS score decreased by 41.6% to 1.88 ± 0.268, but even after 6 weeks the means dropped from 6.0 ± 0.2 at baseline to 3.5(± 0.18 (p≤0.001).

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

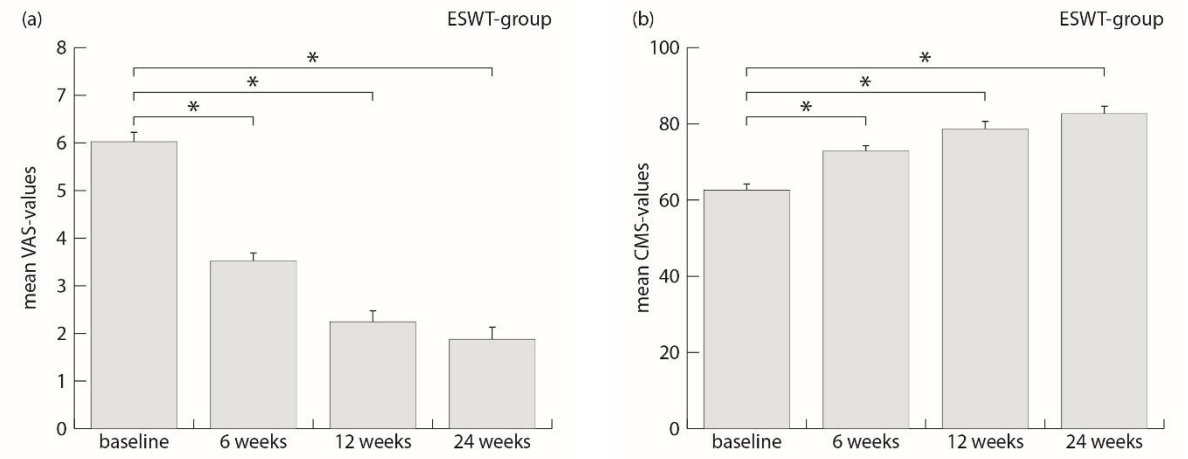


Figure 3 VAS and CMS values at baseline, 6, 12 and 24 weeks after ESWT

Wheras VAS values (a) decreased after ESWT, CMS values (b) increased significantly. (p≤0.001; n=42)

The combination of ESWT and EMTT showed significant and clinically relevant improvement at all follow up visits, with a peak of improvement 24 weeks after the last intervention (Figure 4). The VAS values decreased significantly by 88.2% from 6.16 ± 0.13 at baseline to 0.725 ± 0.245 after 24 weeks. Compared to baseline, the CMS increased significantly by 56.6% within 24 weeks after EMTT/ESWT (baseline 59.44 ± 1.91 to week 24 93.10 ±0.69). At all follow up visits, the improvement was statistically significant.

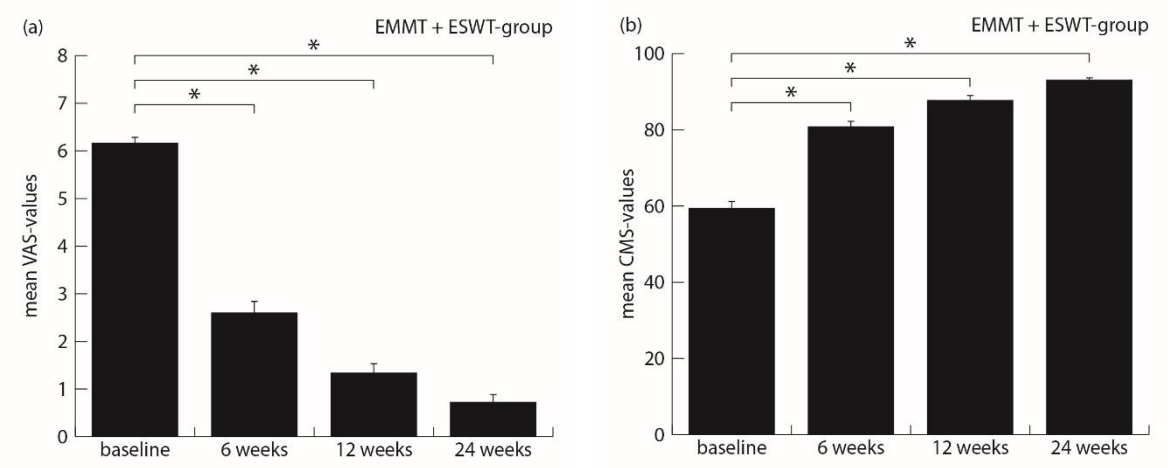


Figure 4 VAS and CMS values at baseline, 6, 12 and 24 weeks after EMTT/ESWT

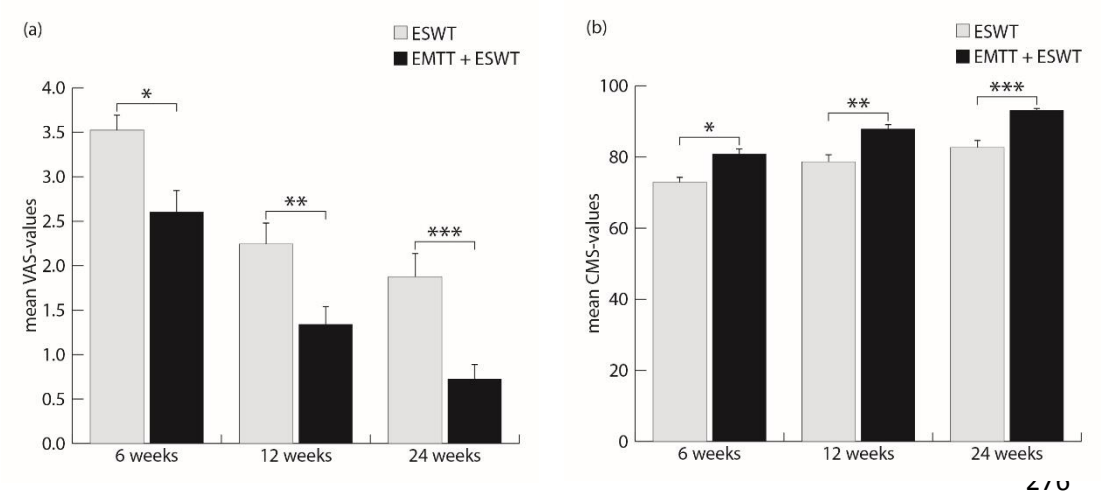
After EMTT/ESWT pain reduced significantly, but the functionally was enhanced at all time points. (p≤0.001; n=44)

Finally, the analysis of ESWT versus ESWT+EMTT showed clearly a better outcome for the combined ESWT+EMTT (Figure 5),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 fared significantly better compared to ESWT alone (Figure 5 a). 24 weeks after last intervention, the VAS pain score decreased from 6.02 ± 0.21 to 1.87 ± 0.27 in the ESWT group, and decreased from 6.16 ± 1.3 at baseline to 0.73 ± 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 favour of the combined therapy ESWT+EMTT.

The functional outcome comparing combined ESWT+EMTT versus ESWT alone was superior in the combined therapy option. The functional improvement measured by increased CMS value was significantly better after combined therapy ESWT plus EMTT. Both groups

261 did better compared to baseline, but again, shock wave therapy as a single treatment
262 performed was not as good as when combined with EMTT.

263 In the ESWT+EMTT group, the CMS improved from 59.4 ± 1.9 at baseline to 93.1 ± 0.7 after
264 24 weeks. After ESWT alone, the CMS value improved from 62.6 ± 1.7 to 82.7 ± 2.1 after 24
265 weeks. The statistically significant difference in change from baseline to follow up visits in
266 between the treatment groups was 7.9 pts after 6 weeks, 9.1 after 12 weeks and 10.4 after
267 24 weeks in favour for the combined therapy ESWT+EMTT (Figure 5 b).



277 **Figure 5 ESWT versus EMTT/ESWT 6, 12 and 24 Weeks after treatment**

278 Patient had less pain (A) and enhanced functionality after combined treatment of EMTT and
279 ESWT compared to patients which received ESWT only. * p≤0.1; **p≤0.01; ***p≤0.001

280

281 No severe adverse were reported after combined ESWT+EMTT or ESWT alone. Some
282 clinically irrelevant petechiae, small cutaneous hematoma or erythema were reported
283 immediately after the treatment by 7 patients after ESWT, and by 9 patients after
284 ESWT+EMTT. They all disappeared within 24 hours. Other clinically significant adverse
285 effects such as neurologic disorders, tendon rupture, infection, or necrosis were not
286 observed in any of the patients at any time.

Discussion

Rotator cuff 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 valid modality in the management of tendinopathies [9, 25], with the best evidence in calcific tendinopathy of the shoulder [22]. However, level 1 evidence in favour of ESWT has been published Achilles tendinopathy, plantar fasciitis, greater trochanteric pain syndrome, and jumper`s knee [6, 8, 39]. Shock waves act via mechanotransduction [16]. Several biochemical pathways are activated by ESWT, including recruitment of stem cells, neovasculogenesis, release of growth factors and improvement of blood supply [12, 19]. The treatment area is small, as the focal zone of shock wave devices is up to 8 mm in diameter [12]. Electromagnetic impulses, such as EMTT, work in a different way. As shock waves act mechanically via mechanotransduction, EMTT act via electromagnetic transduction, resulting in a much larger treatment area up to 30 cm in diameter.

Electromagnetic exposure leads to a change of the electric potential of the cell membrane, and migration of calcium ions (Ca^{2+}) into the cell. Furthermore, electromagnetic energy enhances the binding of Ca^{2+} to calmodulin, which catalyses nitric oxide release and leads to a secretion of growth factors [4, 18]. Chronic tendinopathy could be mediated by inflammatory mediators such as substance P, vascular endothelial growth factor (VEGF) and cyclooxygenase type II (COX2) [31]. PEMF influence multiple different pathways, including the ligand-independent activation of members of the tyrosine kinase family [44] and the upregulation of adenosine receptors in human neutrophils, chondrocytes and synoviocytes. This results in a decrease of proinflammatory cytokines like IL-6 and IL-8, and in inhibition of the release of the key regulator of inflammatory responses NF-κB [25, 43]. Furthermore, Heredia-Rojas et al. detected electromagnetic-responsive DNA sequences in the Hsp70 promotor, suggesting that electromagnetic energy directly modulates gene expression of specific proteins [14]. 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 [33].

To effectively use electromagnetic transduction therapy 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 proof 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. At least 10mT energy have to be reached to initiate significant biological effects [29, 41, 45]. 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 (figure 6). 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.

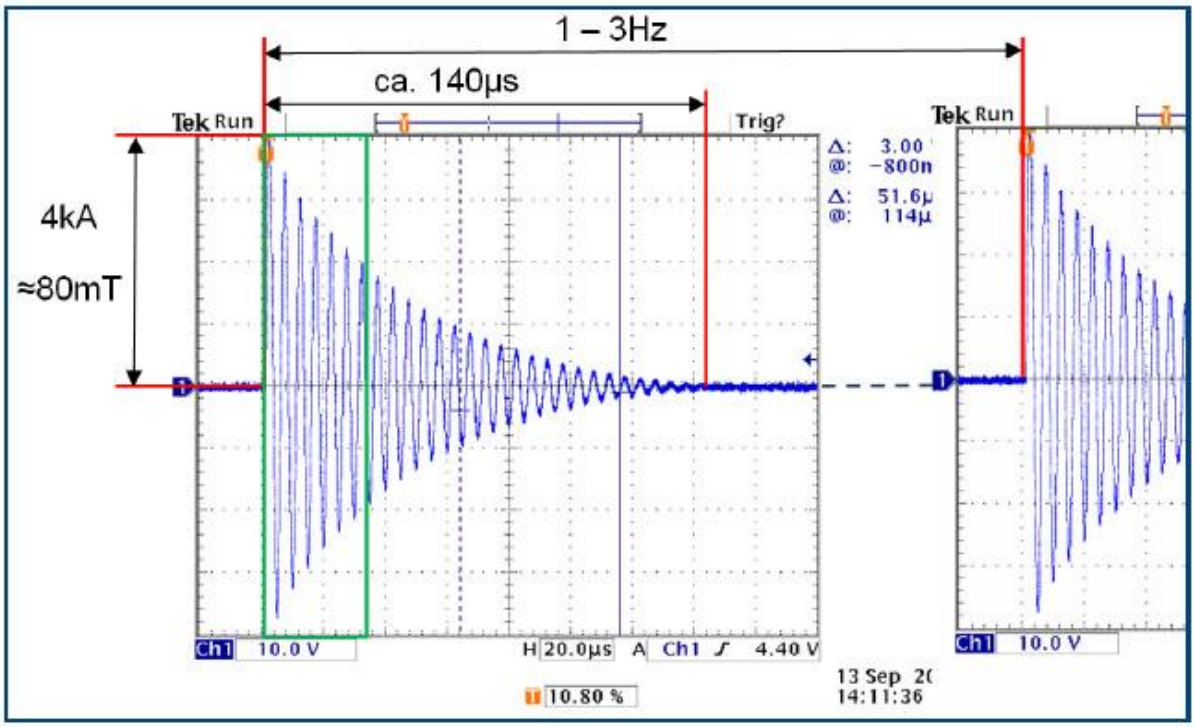


Figure 6: physical characteristics of a single EMTT impulse

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 optimise the use of this technology. Secondly, we did not include in our investigation a group receiving placebo treatment. Therefore, we cannot infer the pure EMTT-induced effect.

We acknowledge that the follow up period of six months is short and long term data are needed to analyse 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.

The present study reports for the first time high level of evidence in favour of the combined use of EMTT and ESWT to manage rotator cuff tendinopathy. The two treatment modalities

have a favourable 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.

Acknowlegement

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