

## Accepted Manuscript

Ultrasound-Guided Application of Percutaneous Electrolysis as an Adjunct to Exercise and Manual Therapy for Subacromial Pain Syndrome: a Randomized Clinical Trial

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PII: S1526-5900(18)30183-4  
DOI: [10.1016/j.jpain.2018.04.017](https://doi.org/10.1016/j.jpain.2018.04.017)  
Reference: YJPAI 3585

To appear in: *Journal of Pain*

Received date: 26 November 2017  
Revised date: 17 April 2018  
Accepted date: 30 April 2018

Please cite this article as: Lorena de-Miguel-Valtierra PT PhD student , Jaime Salom-Moreno PT, PhD , César Fernández-de-las-Peñas PT, PhD, DMSc , Joshua A. Cleland PT, PhD , José L. Arias-Buría PT, PhDa , Ultrasound-Guided Application of Percutaneous Electrolysis as an Adjunct to Exercise and Manual Therapy for Subacromial Pain Syndrome: a Randomized Clinical Trial, *Journal of Pain* (2018), doi: [10.1016/j.jpain.2018.04.017](https://doi.org/10.1016/j.jpain.2018.04.017)



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**Highlights**

- We examine the effects of US-guided percutaneous electrolysis in subacromial pain syndrome.
- Percutaneous electrolysis was not associated to better outcomes in disability and pressure sensitivity
- Positive findings for some secondary outcome warrant further study.

ACCEPTED MANUSCRIPT

## Ultrasound-Guided Application of Percutaneous Electrolysis as an Adjunct to Exercise and Manual Therapy for Subacromial Pain Syndrome: a Randomized Clinical Trial

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**Abstract word account:** 250 words

**Main text word account:** 3,900 words

**Reference account:** 39

**Table account:** 5

**Figure account:** 4

**Disclosures:** The authors have no conflicts of interest to declare. No funds were received.

## Abstract

This randomized clinical trial compared the effects of adding US-guided percutaneous electrolysis into a program consisting of manual therapy and exercise on pain, related-disability, function and pressure sensitivity in subacromial pain syndrome. Fifty patients with subacromial pain syndrome were randomized into manual therapy and exercise or percutaneous electrolysis group. All patients received the same manual therapy and exercise program, one session per week for 5 consecutive weeks. Patients assigned to the electrolysis group also received the application of percutaneous electrolysis at each session. The primary outcome was Disabilities of the Arm, Shoulder and Hand (DASH). Secondary outcomes included pain, function (Shoulder Pain and Disability Index-SPADI) pressure pain thresholds (PPTs) and Global Rating of Change (GROC). They were assessed at baseline, post-treatment, and 3, and 6 months after treatment. Both groups showed similar improvements in the primary outcome (DASH) at all follow-ups ( $P=0.051$ ). Subjects receiving manual therapy, exercise, and percutaneous electrolysis showed significantly greater changes in shoulder pain ( $P<0.001$ ) and SPADI ( $P<0.001$ ) than those receiving manual therapy and exercise alone at all follow-ups. Effect sizes were large ( $SMD>0.91$ ) for shoulder pain and function at 3 and 6 months in favour of the percutaneous electrolysis group. No between-groups differences in PPT were found. The current clinical trial found that the inclusion of US-guided percutaneous electrolysis in combination with manual therapy and exercise resulted in no significant differences for related-disability (DASH) than the application of manual therapy and exercise alone in patients with subacromial pain syndrome. Nevertheless, differences were reported for some secondary outcomes such as shoulder pain and function (SPADI). Whether or not these effects are reliable should be addressed in future studies

**Key words:** Subacromial pain, percutaneous electrolysis, manual therapy, exercise.

**Trial registration:** <http://www.clinicaltrials.gov>, ClinicalTrials.gov, NCT02569281.

## **Perspective**

This study found that the inclusion of US-guided percutaneous electrolysis into a manual therapy and exercise program resulted in no significant differences for disability and pressure pain sensitivity than the application of manual therapy and exercise alone in patients with subacromial pain syndrome.

## Introduction

Subacromial pain syndrome, as a main cause of shoulder pain is a significant health problem and has a point prevalence ranging from 7% to 26% in the general population depending on the diagnostic criteria used in the study [23]. The annual costs of shoulder pain symptoms is estimated to be 345€ million per year in primary health care [22].

Shoulder pain is the third most common reason for consulting a physical therapist [24]. Conservative treatment is usually the first therapeutic option for subjects suffering from subacromial pain syndrome [16]; however, the most appropriate treatment remains to be elucidated. Several therapeutic interventions, e.g., injection, oral medications, manual therapy, and exercise are proposed in clinical guidelines to manage this condition [11]. Among all the interventions, exercise probably exhibits the highest level of evidence [12,17,33] However, meta-analysis support that the combination of exercise with other treatments, e.g., manual therapy, exhibits a trend toward better effectiveness than exercise alone [12,33]. Therefore, multimodal approaches are advocated for subacromial pain syndrome.

Needling therapies have been recently advocated for the treatment of shoulder pain. In fact, a recent study found that deep dry needling plus exercise was effective for subacromial pain syndrome [4]. Others have suggested the use of galvanic current through the needle, a technique called percutaneous electrolysis [30]. This technique consists of the combination of mechanical (needle) and electrical (galvanic current) stimulation as a method to provide a controlled micro-trauma to the targeted tissue, usually the tendon. The needle is inserted in the tendon under proper ultrasound visualisation (US) [30]. Preliminary evidence suggests that percutaneous electrolysis is effective for individuals with patellar [1] or elbow [34] tendinopathy; however these studies did not include a control group. The only study with a comparative group

investigating the effectiveness of US-guided percutaneous electrolysis was conducted in rotator cuff tendinopathy [5]. Results showed that the combination of US-guided percutaneous electrolysis with exercise was more effective than exercise alone at short-term [5]. However, this study only assessed outcomes immediately after treatment and the isolated application of exercise does not represent real clinical practice. Therefore, the objective of this randomized clinical trial was to compare the effects of adding US-guided percutaneous electrolysis to a manual therapy and exercise program on pain, disability, function, and pressure pain sensitivity in subacromial pain syndrome. We hypothesized that subjects receiving US-guided percutaneous electrolysis combined with manual therapy and exercise would exhibit greater improvements in pain intensity, disability, function, and pressure sensitivity than those receiving only manual therapy and exercise.

## **Methods**

### **Study Design**

This randomized, parallel-group clinical trial compared 2 treatments in patients with subacromial pain syndrome: manual therapy and exercise versus manual therapy exercise plus US-guided percutaneous electrolysis. Since shoulder related-disability is the strongest predictor for physical therapy interventions [9], the primary end-point was 6-month changes in shoulder pain related-disability. Secondary outcomes were mean, worst and lowest shoulder pain intensity, function, pressure pain sensitivity and the self-perceived improvement. This report follows the Consolidated Standards of Reporting Trials (CONSORT) extension for clinical trials [39].

The study design was approved by the Institutional Review Board of Universidad Rey Juan Carlos (URJC 08-2015), and the clinical trial was registered (ClinicalTrials.gov: NCT02569281).

### **Participants**

Consecutive individuals with shoulder pain presenting to a health care centre in Madrid (Spain) from October 2015 to November 2016 were screened for eligibility criteria. Subacromial pain syndrome was defined and diagnosed following the Dutch Orthopedic Association Clinical Practice Guideline where a cluster of tests have been proposed. To be included in the trial, subjects had to satisfy the following criteria: 1, unilateral shoulder pain for at least 3 months; 2, an intensity of at least 4 on an 11-point numerical pain rating scale (NPRS) during arm elevation; 3, a positive painful arc test during abduction (positive LR: 3.7, 95%CI 1.9-7.0) [17]; and, 4, at least one positive of the following tests: Hawkins-Kennedy test (+LR 1.70, 95%CI 1.29-2.26), Neer's sign (+LR 1.86, 1.49-2.31), empty can test (specificity 0.62), drop arm test (specificity 0.92), or lift-off test (specificity 0.97) [3]. Participants were excluded if they exhibited: 1, bilateral shoulder symptoms; 2, were younger than 18 or older than 65 years of age; 3, had a history of shoulder fracture; 4, had a diagnosis of cervical radiculopathy; 5, had previous interventions with steroid injections to the shoulder; 6, had fibromyalgia syndrome; 7, had a previous history of shoulder or neck surgery; or, 8, any type of intervention for the neck-shoulder area during the previous year. All subjects signed an informed consent prior to their participation in the study.

### **Randomization and masking**

Patients were randomly assigned to receive manual therapy and exercise alone or manual therapy and exercise with US-guided percutaneous electrolysis. Concealed allocation was conducted using a computer-generated randomized table of numbers

created by an external statistician not involved in subject recruitment. Individual and sequentially numbered index cards with the random assignment were prepared, folded, and placed in sealed opaque envelopes. The treating therapist opened the envelopes and proceeded with allocation. Patients were unaware of the real objective of the study in that they were aware of the clinical implications without revealing the real intervention that was being evaluated. Further, all participants were naïve in relation to US-guided percutaneous electrolysis. All subjects were informed of the true nature of the study at the end of the trial.

### **Interventions**

Both groups received the same manual therapy and exercise program during a one weekly session over a period of 5 weeks applied by a physical therapist with more than 10 years of experience in the management of shoulder pain patients. Research suggests that manual therapy is more effective than placebo and when combined with exercise is better than exercise alone for patients with shoulder pain [33]. In the current study, patients received passive joint mobilizations targeting the gleno-humeral joint, acromioclavicular joint, sternoclavicular joint and scapulothoracic joint, and associated soft tissues structures.

A similar exercise program to previous trials was used in this study [4,5]. There currently exists no consensus on the frequency and the type of exercise for individuals suffering from subacromial pain syndrome; although it has been recommended that they should be specific and of low intensity and high frequency [7]. Briefly, the program consisted of 3 exercises focusing on supraspinatus, infraspinatus, and scapular stabilizer muscles. Each exercise was performed in 3 sets of 12 repetitions. Each repetition included first the concentric phase followed by the eccentric phase of the exercise. The exercise program was instructed by an experienced physical therapist in the 1st session

and therefore monitored in subsequent 4 sessions, once per week during the treatment period. Each session lasted approximately 40-45min. Patients were asked to perform the exercises on an individual basis twice every day for 5 weeks. Subjects were monitored during the treatment period for proper adherence to the exercise program for obtaining a 90% rate of daily practice. During the follow-up period, participants were asked to continue with the exercise program and this was monitored on subsequent follow-up assessments.

Subjects assigned to the electrolysis group also received five sessions (once per week during their respective treatment session) of US-guided percutaneous electrolysis by a second physical therapist with 10 years of clinical experience in this therapeutic approach. The technique was applied using a specifically developed medically certified device (EPTE®V01, classification IIa, Ionclinics, Valencia, Spain), which produces modulated galvanic electricity through the negative electrode cathodic flow. The galvanic current is applied using acupuncture needles. In the current study we used a 0.30\*25 mm needle (Agupunt®, Barcelona, Spain). The EPTE® is usually pain-free applied to the patient; therefore, in the current trial we used an intensity of 350µA for a total of 90 seconds. The technique was applied under US guidance (US system hand-carried colour Doppler Mindray® M7) on the clinically relevant area, i.e., supraspinatus tendon as follows: the patient lied in supine with the affected shoulder placed in internal rotation. The shoulder area was sterilised with isopropyl alcohol and the sonographic transducer, enclosed in a sterile cover over sterile (Tegaderm™ Film 3M 10 cm x 12 cm) applied gel, was placed at the projection of the supraspinatus tendon (**Fig. 1**). The needle was inserted at an 80° angle to the skin with the needle tip directed towards the supraspinatus tendon (**Fig. 2**).

## Outcome Measures

Outcomes were assessed at baseline (before), one week after the last session (post-intervention), and 3 and 6 months after the last treatment session. The examining assessor was blinded to the patient's group allocation. Shoulder related-disability, the primary outcome, was assessed with the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire [19]. The DASH is a 30-items upper extremity specific questionnaire assessing disability and symptoms in subjects with musculoskeletal pain disorders of the upper extremity. Briefly, this questionnaire assesses different domains: 1, degree of difficulty during the preceding week in performing several physical activities because of problems in a upper extremity (21 items); 2, severity of each pain symptom, activity-related pain, tingling, weakness, and stiffness (5 items); 3, the problem's effect on social activities, work, and sleep, and its psychological impact (4 items). Each item is answered on a 5-points scale ranging from 1 (no difficulty to perform, no symptom, or no impact) to 5 (unable to do, very severe symptom, or high impact). All responses are summed to form a raw score that is converted to a 0 to 100 score where higher score reflect greater disability. In the current study, the Spanish version of the DASH, which has shown high internal consistency and excellent test-retest reliability [19], was used. Franchignoni et al found that the minimal clinically important difference (MCID) for the DASH was 10.81 points [14].

Secondary outcomes included the intensity of shoulder pain, function, pressure pain sensitivity and self-perceived improvement. A 10-point Numerical Pain Rating Scale (NPRS 0: no pain, 10: maximum pain) was used to assess the mean current, the worst and the least level of pain experienced in the preceding week [21]. The MCID for the NPRS in patients with shoulder pain has been estimated to be 1.1 points [26].

Shoulder-related disability and function was assessed with several questionnaires [30]. As secondary outcome measures, function was assessed with The Shoulder Pain and Disability Index (SPADI). The SPADI consists of a 13-item shoulder functional index assessing pain and function related to the shoulder [27]. Each item is scored on a numeric rating scale ranging from 0 (no pain/no difficulty) to 10 (worst pain imaginable/so difficult it required help). The total score ranges from 0 to 100 points where a higher score indicates worse function [27]. The Spanish version of the SPADI has exhibited high internal consistency and excellent test-retest reliability [25], and therefore, was used in the current trial. It has been reported that MCID for the SPADI ranges from 8 to 13 points [28].

Pressure pain thresholds (PPT), defined as the amount of pressure applied for the pressure sensation to first change to pain [35], were assessed with a mechanical pressure algometer (Pain Diagnosis and Treatment Inc, New York). Participants were instructed to press a switch when the sensation changed from pressure to pain. The mean of 3 trials was calculated and used for the main analysis. A 30 second resting period was allowed between each measure. The reliability of pressure algometry has been found to be high, at least in the neck [37]. PPTs were assessed bilaterally over the C5-C6 zygapophyseal joint, the deltoid muscle, the second metacarpal, and the tibialis anterior muscle. Since no side to side differences were found, the mean of both sides was used for the analysis.

Finally, self-rated improvement was assessed with a 15-points Global Rating of Change (GROC) score from -7 (a very great deal worse) to +7 (a very great deal better). Scores of +4 and +5 on the GROC are indicative of moderate changes whereas scores of +6 and +7 indicate large changes in the self-perceived status of the patient [38].

### **Adverse events**

All participants were asked to report any adverse events that they experienced during the study. An adverse event was defined as sequelae of medium-term in duration with any symptom perceived as distressing and unacceptable and that required further treatment [8].

### **Sample Size Determination**

The sample size was calculated using Ene 3.0 software (Autonomic University of Barcelona, Spain). The calculations were based on detecting differences of 11 points in the primary outcome (DASH) at follow-up (MCID), assuming a standard deviation of 12 points, a 2-tailed test, an alpha level ( $\alpha$ ) of 0.05, and a desired power ( $\beta$ ) of 80%. The estimated desired sample size was calculated to be 20 individuals per group. A dropout percentage of 20% was expected, so 25 patients were included on each group.

### **Statistical Analysis**

Statistical analysis was performed using SPSS statistical software, version 21.0, and was conducted according to the intention-to-treat analysis by using the Expectation-Maximization process whereby missing data was computed using regression equations [29]. The Expectation-Maximization algorithm starts by estimating the expected values of missing data from observed data (from the same patient) and then repeats the process using both the observed data and the estimated missing values until the values stabilize. Mean, standard deviations and/or 95% confidence intervals were calculated for all variables. The Kolmogorov-Smirnov test showed a normal distribution of the data ( $P > 0.05$ ). Baseline data were compared between groups using independent Student t-tests for continuous data and  $\chi^2$  tests of independence for categorical data.

A 4x2 repeated measured analysis of covariance (ANCOVA) with time (baseline, post-treatment, 3 months, or 6 months) as the within-subjects factor, and group (manual therapy/exercise vs. manual therapy/exercise/electrolysis) as the between-subjects factor and adjusted for baseline data was used to determine the effects of the intervention on related-disability (DASH), pain intensity (NPRS), function (SPADI) and PPTs. Separate ANCOVAs were performed for each outcome. The main hypothesis of interest was the Group \* Time interaction with a Bonferroni-corrected alpha of 0.017 (3 moments). To enable comparison of between-group effect sizes, standardized mean score differences (SMDs) were calculated by dividing mean score differences between groups by the pooled standard deviation. We used  $\chi^2$  tests to compare self-rated improvement (GROC) at each follow-up period. Numbers needed to treat (NNT) and 95% confidence intervals (CI) were also calculated at 3 and 6 months follow-ups using the definition for a successful outcome ( $\geq 5$  in the GROC).

## Results

Sixty consecutive patients with shoulder pain were screened for eligibility criteria. Fifty patients (mean  $\pm$ SD age: 54 $\pm$ 7 years; 54% female) satisfied the eligibility criteria, agreed to participate, and were randomized into manual therapy/exercise (n=25) or the manual therapy/exercise plus electrolysis (n=25) group. At 6 months, two patients in the manual therapy/exercise group were lost to follow-up. The reasons for ineligibility can be found in **Fig 3**, which provides a flow diagram of patient recruitment and retention. Baseline features between groups were similar for all variables (**Table 1**). Six (24%) patients within the percutaneous electrolysis group experienced muscle soreness after the first 2 treatments, which resolved spontaneously at 24-36 hours.

Adjusting for baseline outcomes, the mixed-model ANCOVA did not reveal a significant Group\*Time interaction for DASH ( $F=4.088$ ;  $P=0.051$ ). Subjects receiving manual therapy, exercise plus percutaneous electrolysis achieved higher improvements in related-disability at 3 ( $\Delta -2.8$ , 95%CI -7.8 to 2.2) and 6 months ( $\Delta -9.9$ , -20.0 to 0.2), but not at post-treatment ( $\Delta 1.7$ , 95%CI -0.3 to 3.7) than those receiving manual therapy and exercise alone, but these differences were not statistically significant (**Fig. 4**). Between-group effect sizes were small at 3 months (SMD: 0.2) and moderate (SMD: 0.41) at 6 months in favor of the US-guided percutaneous electrolysis group.

The 4x2 mixed model ANCOVA revealed significant Group\*Time interactions for the mean level of shoulder pain ( $F=14.12$ ;  $P<0.001$ ), the least level of shoulder pain ( $F=11.532$ ;  $P<0.001$ ), the worst level of shoulder pain ( $F=10.509$ ;  $P<0.001$ ), and SPADI ( $F=17.189$ ;  $P<0.001$ ): patients receiving US-guided percutaneous electrolysis in addition to manual therapy and exercise exhibited higher improvements in pain intensity and function at all follow-ups (**Table 2**). Between-groups effect sizes were moderate for mean, worst and lowest pain intensity at post-treatment (SMD<0.80) and large at 3 and 6 months periods (SMD>0.91), and large for SPADI at all follow-ups (SMD>1.06) in favour of the percutaneous electrolysis group (**Table 3**).

No statistically significant Group\*Time interaction for PPT at any location was observed: C5-C6 joint ( $F=0.348$ ,  $P=0.55$ ), deltoid muscle ( $F=0.380$ ,  $P=0.540$ ), second metacarpal ( $F=1.108$ ,  $P=0.297$ ), and tibialis anterior ( $F=1.478$ ,  $P=0.230$ ). There was a significant main effect of time for all tested sites with both groups experiencing similar increases in PPT after the intervention (all,  $P<0.001$ ). **Table 4** provides data of PPTs in both groups throughout the trial.

Based on the cut-off score of  $\geq 5$  on the GROC, significantly more patients in the US-guided percutaneous electrolysis group achieved a successful outcome compared to the non-percutaneous electrolysis group at 3 ( $X^2=18.182$ ;  $P=0.006$ ) and 6 ( $X^2=21.727$ ;  $P<0.001$ ) months (**Table 5**). Therefore, based on this cut-off considered as a successful outcome, the NNT was 2.77 (95%CI 1.68, 6.79) and 2.09 (95%CI 1.44, 3.71) in favor of the US-guided percutaneous electrolysis group at 3 and 6 months, respectively.

## Discussion

This is the first study investigating the effect of adding US-guided percutaneous electrolysis to a multimodal treatment approach including manual therapy and exercise for the treatment of patients with subacromial pain syndrome. This randomized clinical trial found that inclusion of US-guided percutaneous electrolysis into a manual therapy and exercise program did not provide significant differences in disability and pressure pain sensitivity than the application of manual therapy and exercise alone in patients with subacromial pain syndrome. However, the inclusion of US-guided percutaneous electrolysis lead to improvements in secondary outcomes such as pain intensity and function.

The Dutch clinical guideline supports the use of manual therapy and exercise for the management of subacromial pain syndrome [11]. This recommendation is based on the conclusion made by systematic reviews and meta-analysis supporting the effects of exercise [12,17,33] and manual therapies [10] for this population. The results of our study may also support the effectiveness of manual therapies and exercises for the management of individuals with subacromial pain syndrome since within-group change scores and their 95% confidence intervals reached the respective MCID for each

outcome. However, it is important to consider that no consensus exists on which kind of exercise, general or specific, is the best for the management of subacromial pain [32].

The novelty of this clinical trial was the inclusion of US-guided percutaneous electrolysis into a multimodal therapeutic program for the management of subacromial pain syndrome. There is preliminary evidence suggesting that the combination of US-guided percutaneous electrolysis and exercise seems to be more effective at short term than exercise alone in subjects with rotator cuff syndrome [5]. This trial is the first to add percutaneous electrolysis into a multimodal approach including manual therapy and exercise for patients with subacromial pain syndrome, reflecting common clinical practice. Surprisingly, for related-disability (DASH), the primary outcome, both groups exhibited similar improvements at all follow-up periods. This may be related to the fact that the DASH assesses generalized function of the upper extremity, but it is not a shoulder-specific outcome such as SPADI (secondary outcome). It is also possible that the lack of significant differences in the primary outcome of the trial would be related to the fact that the study was underpowered for detecting modest treatment effect sizes that would seem to be clinically meaningful for this pain population. In fact, between-groups differences for changes in pain intensity (NPRS) and function (SPADI) exceeded the reported MCID for pain (1.1 points) and function (13 points) at all follow-ups in favour of the US-guided percutaneous electrolysis group, which deserve future trials. However, it should be considered that MCID scores used in our trial were based on within-patient improvements; therefore, their direct extrapolation to between-group differences should be considered with caution [13]. Further, the NNT suggests that for every 2 patients treated with combination of manual therapy, exercise and US-guided percutaneous electrolysis, rather than manual therapy and exercise alone, one additional patient with subacromial pain syndrome will achieve clinically important reductions in pain, and

function at 3 and 6 months. Based on the current results, we could anticipate a clinical benefit of adding US-guided percutaneous electrolysis to manual therapy and exercise for individuals with subacromial pain syndrome, although we should recognize that lower bound of confidence intervals falls over MCID at some follow-up periods and further studies are needed.

We also observed similar hypoalgesic effects, expressed by significant changes in PPTs at the neck, the shoulder, the hand, and tibialis anterior muscle, in both groups. A recent systematic review found moderate evidence indicating that manual therapy is able to increase PPTs in patients with musculoskeletal pain [36]. These results confirm the neuro-physiological effects of manual therapy and exercise in the central nervous system as previously suggested [6]. Nevertheless, our trial reported that the inclusion of US-guided percutaneous electrolysis did not exert such effect since any between-group differences were observed in widespread pressure pain sensitivity.

The exact therapeutic mechanism by which percutaneous electrolysis exerts its effects are not completely understood, and both mechanical and biochemical effects are suggested. The theoretical framework for the application of percutaneous electrolysis is to induce an inflammatory response by inducing a non-thermal electrolytic reaction in the tendon through a cathodic flow [2]. This controlled local inflammatory response may facilitate an organic reaction leading to a phagocytosis and posterior regeneration of the tendon [30]. Therefore, it is possible that the inclusion of a biological approach such as percutaneous electrolysis, combined with biomechanical (eccentric exercises) and neuro-physiological (manual therapy) interventions increases the therapeutic effect.

The results of this trial should be considered according to the potential strengths and limitations. Major strengths included that the trial was prospectively registered, adhered to strict CONSORT guidelines, used blinded outcome assessment, concealed

allocation, and intention-to-treat analysis. Among the limitations, first we recruited from a single health care centre which may reduce the generalizability of our results. Second, we did not include a control group without any intervention, so it cannot be determined if changes observed in both groups can be attributed to interventions or simply the passage of time; although this is unlikely. Third, the influence of the placebo effect is unknown as we did not include a group receiving a sham-percutaneous electrolysis intervention [15]. In fact, although we tried to blind patients by including those naïve to US-guided percutaneous electrolysis, it is possible that individual's expectation for the needling intervention may also affect the results. Similarly, it was not possible to blind therapists administering each treatment due to the nature of the interventions; therefore, it is also feasible that therapist's expectations can also play a potential role in the results. Finally, the current trial was conducted in just one center and only one dosage was studied. In fact, the most effective dosage of exercise and US-guided percutaneous electrolysis remains to be elucidated. Therefore, we do not know if a greater number of sessions will reveal greater changes in outcomes or differences between interventions. Future trials including different treatment dosages, multiple therapists/sites and sham-percutaneous electrolysis group should be conducted to determine the best therapeutic option for management of subacromial pain syndrome.

## **Conclusions**

The results of this trial suggest that the inclusion of US-guided percutaneous electrolysis into a treatment approach including manual therapy and exercise resulted in no significant differences in related-disability and pressure pain sensitivity in subjects with subacromial pain syndrome. Future trials investigating the underlying mechanisms and potential clinical effects of US-guided percutaneous electrolysis are now needed.

**Contributors:** All authors contributed to the study concept and design. LdMV did the statistical analysis. JIAB and CFdIP contributed to analysis and interpretation of data. JIAB, JSM, JAC contributed to drafting the paper. CFdIP and JSM provided administrative, technical and material support. CFdIP and JAC supervised the study. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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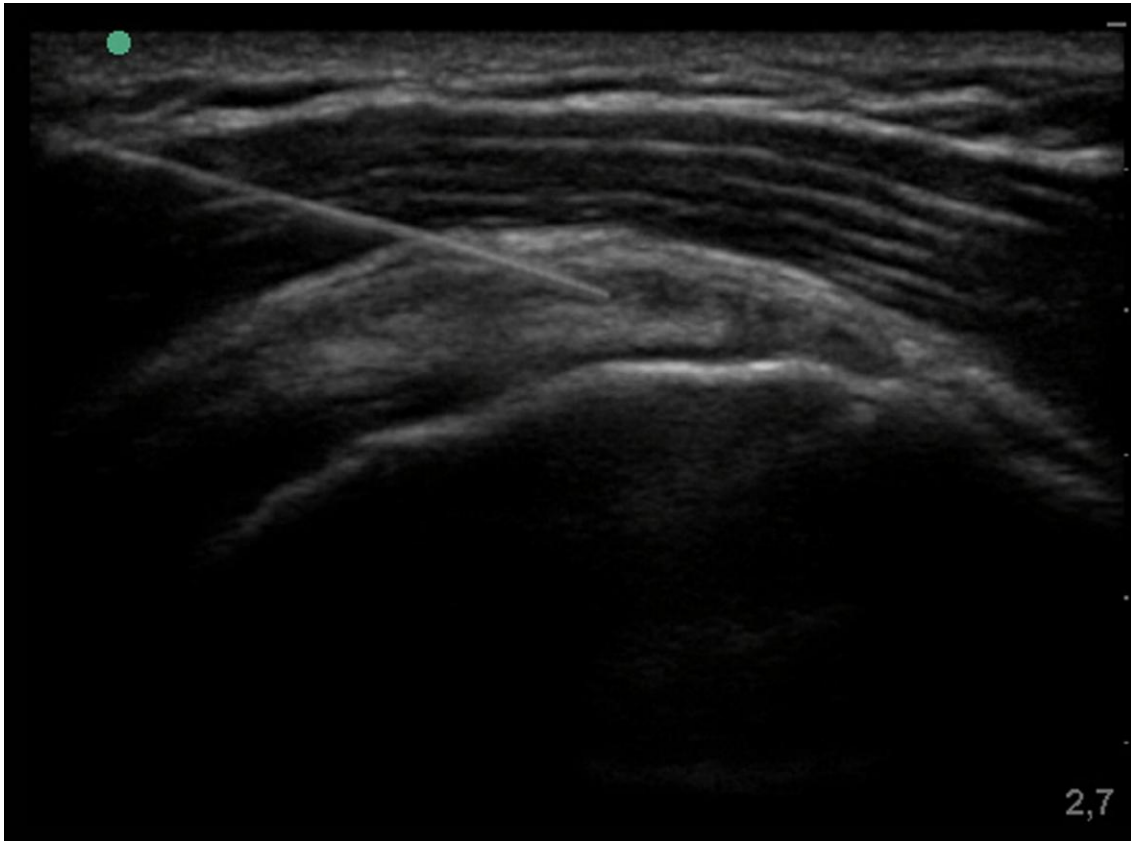
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### Legend of Figures



**Figure 1:** Needle approach during the application of US-guided percutaneous electrolysis. The transducer is placed on the supraspinatus tendon and the needle is inserted in the centre of the transducer in a long axis position at an angle of about  $45^\circ$  to the skin surface, depending on the target area, and then advanced parallel to the sound beam.



**Figure 2:** Long-axis grey-scale ultrasound image displaying the supraspinatus tendon during needle placement showing the echogenic needle during the application of US-guided percutaneous electrolysis

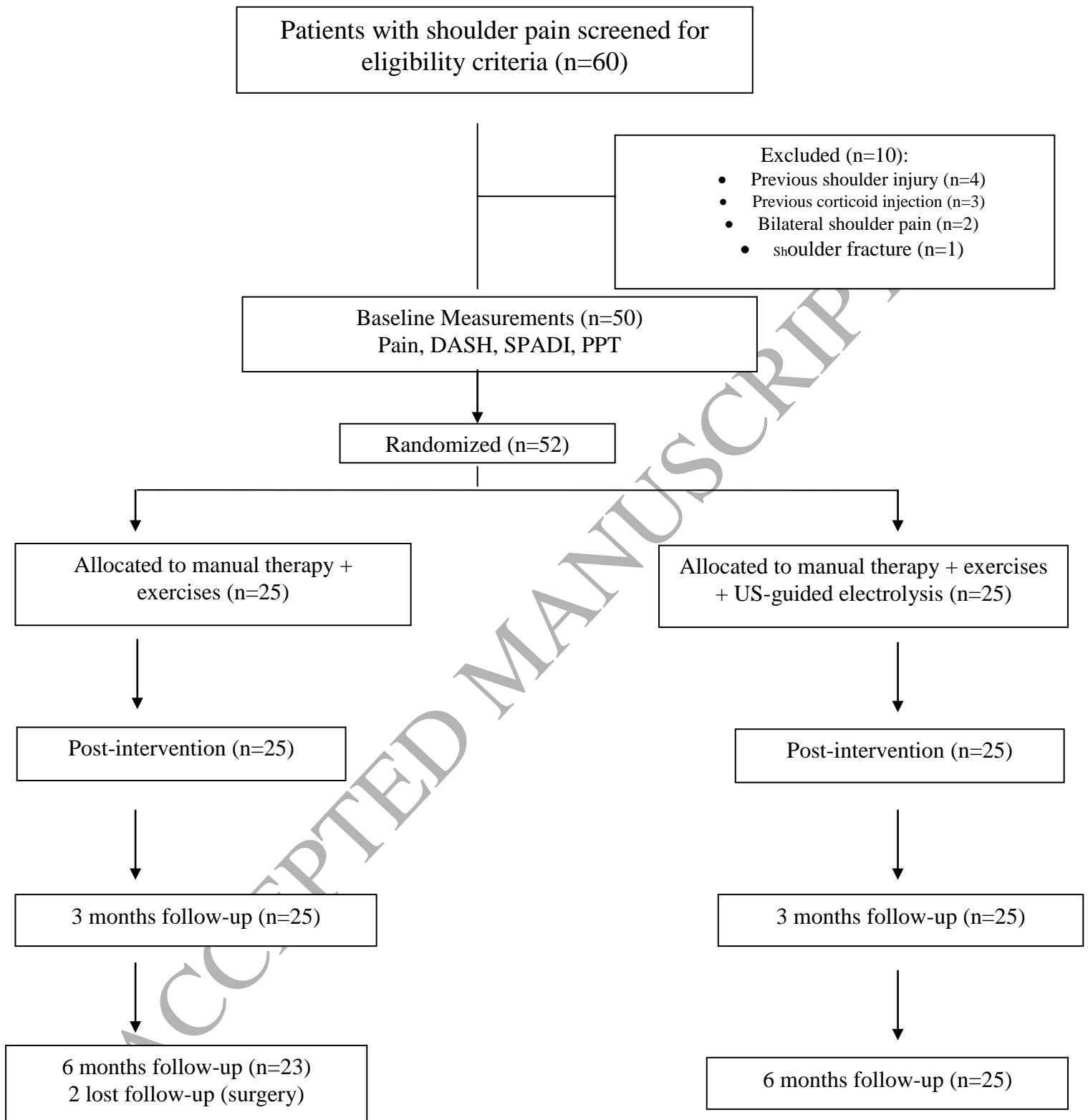
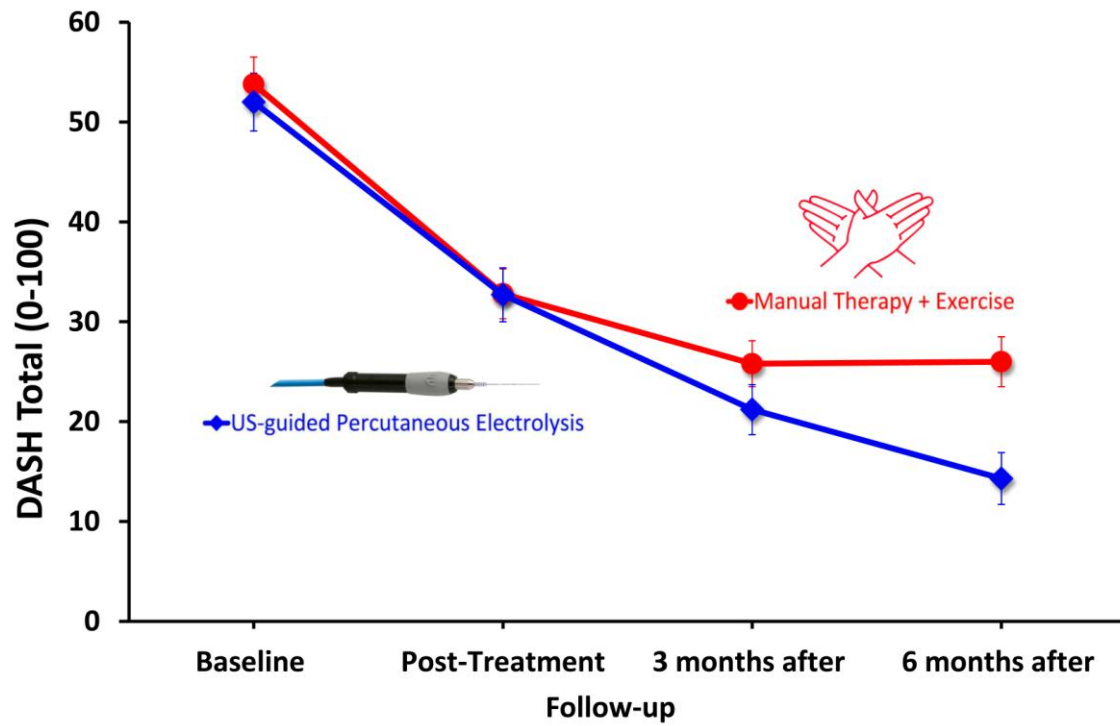


Figure 3: Flow diagram of patients throughout the course of the study



**Figure 4:** Evolution of all the DASH throughout the course of the study stratified by randomised treatment assignment. Data are means (SE)

**Table 1:** Baseline characteristics by treatment assignment

Baseline Variable	Manual Therapy + Exercise (n=25)	Manual Therapy + Exercise + US-guided Percutaneous Electrolysis (n=25)
Gender (male/female)	12/13	11/14
Age (years)	55.3 ± 11.1	54.9 ± 13.7
Affected shoulder (left/right)	12/13	14/11
Months with shoulder pain	11.2 ± 10.6	12.6 ± 14.4
Mean intensity of shoulder pain (NPRS, 0-10)	6.8 ± 1.9	6.9 ± 1.6
Least intensity of shoulder pain (NPRS, 0-10)	4.2 ± 1.7	4.4 ± 1.7
Worst intensity of shoulder pain (NPRS, 0-10)	8.5 ± 0.7	8.9 ± 1.0
DASH (0-100)	53.8 ± 15.4	52.0 ± 13.1
SPADI (0-100)	57.6 ± 16.9	57.4 ± 14.7
<b>Pressure Pain Thresholds (PPT, kg/cm<sup>2</sup>)</b>		
C5-C6 Zygapophyseal Joint	4.0 ± 1.6	3.8 ± 1.4
Deltoid Muscle	5.8 ± 2.5	5.6 ± 2.0
Second Metacarpal	6.2 ± 2.6	6.2 ± 1.6
Tibialis Anterior Muscle	8.2 ± 3.0	8.3 ± 2.1

Data are mean (SD) except for gender and medication intake. NPRS: Numeric Pain Rating Scale, 0-10, lower scores indicate less pain; DASH: Disabilities of the Arm, Shoulder and Hand; SPADI: The Shoulder Pain and Disability Index

**Table 2:** Mean, lowest and worst intensity of shoulder pain, and function (SPADI) at baseline, post-intervention, 3-months and 6 months after treatment as well as within-group and between-groups mean scores by randomized treatment assignment

Outcomes	Timeline Scores: Mean $\pm$ SD (95% CI) Within-Group Change Scores: Mean (95% CI)		Between-Group Differences: Mean (95% CI)
	MT + EX	MT + EX + US-guided	
<b>Mean current of shoulder pain (NPRS, 0-10)</b>			
Baseline	6.8 $\pm$ 1.9 (6.1, 7.5)	6.9 $\pm$ 1.6 (8.1, 9.3)	
After intervention	4.8 $\pm$ 2.4 (4.0, 5.6)	3.5 $\pm$ 1.4 (4.8, 6.0)	
Change baseline $\rightarrow$ after intervent.	-2.0 $\pm$ 2.1 (-2.8, -1.2)	-3.4 $\pm$ 2.0 (-4.2, -2.6)	-1.4 (-2.4, -0.4)*
<b>3 months</b>	4.9 $\pm$ 2.8 (4.1, 5.7)	2.2 $\pm$ 2.0 (2.9, 3.9)	
Change baseline $\rightarrow$ 3 months	-1.9 $\pm$ 2.3 (-2.7, -1.1)	-4.5 $\pm$ 2.7 (-5.9, -3.1)	-2.6 (-4.0, -1.5)*
<b>6 months</b>	4.1 $\pm$ 3.4 (3.1, 5.1)	1.5 $\pm$ 1.8 (2.3, 3.3)	
Change baseline $\rightarrow$ 6 months	-2.7 $\pm$ 3.1 (-3.9, -1.5)	-5.4 $\pm$ 2.4 (-6.4, -4.4)	-2.7 (-4.2, -1.2)*
<b>Least intensity of shoulder pain (NPRS, 0-10)</b>			
Baseline	4.2 $\pm$ 1.7 (3.6, 4.8)	4.4 $\pm$ 1.7 (3.7, 5.1)	
After intervention	4.0 $\pm$ 2.3 (3.2, 4.8)	2.4 $\pm$ 1.4 (1.6, 3.2)	
Change baseline $\rightarrow$ after intervent.	-0.2 $\pm$ 1.2 (-0.9, 0.5)	-2.0 $\pm$ 1.8 (-2.9, -1.1)	-1.8 (-2.6, -1.0)*
<b>3 months</b>	3.8 $\pm$ 2.4 (3.1, 4.5)	1.0 $\pm$ 1.6 (0.2, 1.8)	
Change baseline $\rightarrow$ 3 months	-0.4 $\pm$ 1.3 (-1.2, 0.4)	-3.4 $\pm$ 1.5 (-4.2, -2.6)	-3.0 (-4.2, -1.8)*
<b>6 months</b>	3.1 $\pm$ 2.1 (2.4, 3.8)	0.5 $\pm$ 0.8 (0.2, 0.8)	
Change baseline $\rightarrow$ 6 months	-1.1 $\pm$ 2.1 (-2.3, 0.1)	-3.9 $\pm$ 1.7 (-4.5, -3.3)	-2.8 (-3.6, -2.0)*
<b>Worst intensity of shoulder pain (NPRS, 0-10)</b>			
Baseline	8.5 $\pm$ 0.7 (8.3, 8.7)	8.9 $\pm$ 1.0 (8.6, 9.2)	
After intervention	6.0 $\pm$ 2.9 (5.1, 6.9)	5.1 $\pm$ 1.9 (4.1, 6.1)	
Change baseline $\rightarrow$ after intervent.	-2.5 $\pm$ 2.2 (-3.6, -1.4)	-3.8 $\pm$ 1.9 (-4.5, -3.0)	-1.3 (-2.0, -0.6)*
<b>3 months</b>	6.6 $\pm$ 2.9 (5.7, 7.5)	3.8 $\pm$ 2.3 (2.7, 4.9)	
Change baseline $\rightarrow$ 3 months	-1.9 $\pm$ 1.8 (-2.8, -1.0)	-5.1 $\pm$ 2.6 (-6.2, -4.0)	-3.2 (-3.8, -2.6)*
<b>6 months</b>	5.9 $\pm$ 3.1 (4.8, 7.0)	3.2 $\pm$ 2.4 (2.1, 4.3)	
Change baseline $\rightarrow$ 6 months	-2.6 $\pm$ 1.9 (-3.7, -1.5)	-5.7 $\pm$ 2.5 (-6.7, -4.7)	-3.1 (-3.6, -2.6)*
<b>SPADI (0-100)</b>			
Baseline	57.6 $\pm$ 16.9 (51.7, 63.5)	57.4 $\pm$ 14.7 (51.0, 63.8)	
After intervention	36.1 $\pm$ 17.2 (30.6, 41.6)	23.4 $\pm$ 11.2 (17.5, 29.3)	
Change baseline $\rightarrow$ after intervent.	-21.5 $\pm$ 11.6 (-25.9, -17.1)	-34.0 $\pm$ 11.9 (-38.9, -29.1)	-12.5 (-18.9, -6.1)*
<b>3 months</b>	30.6 $\pm$ 17.6 (25.3, 35.9)	13.5 $\pm$ 8.9 (7.8, 19.2)	
Change baseline $\rightarrow$ 3 months	-27.0 $\pm$ 16.7 (-33.4, -20.6)	-43.9 $\pm$ 12.9 (-49.3, -38.5)	-16.9 (-25.2, -8.6)*
<b>6 months</b>	27.6 $\pm$ 17.1 (22.7, 32.5)	10.1 $\pm$ 6.5 (4.7, 15.5)	
Change baseline $\rightarrow$ 6 months	-30.0 $\pm$ 16.0 (-36.0, -24.0)	-47.3 $\pm$ 13.8 (-53.0, -41.6)	-17.3 (-25.5, -9.1)*

**Table 3:** Between-group effect sizes (SMD) in favor of the US-guided Percutaneous Electrolysis group when compared to the combination manual therapy and exercise

Outcome	DASH	SPADI	Mean Pain	Worst Pain	Least Pain
Post-treatment weeks	---	1.06	0.65	0.56	0.79
3 months	0.20	1.08	0.91	1.18	1.15
6 months	0.41	1.18	1.03	1.29	1.05

Large effect size:  $SMD \geq 0.8$ . Medium effect size:  $0.79 \geq SMD \geq 0.21$ . Small effect size:  $SMD \leq 0.20$ .

DASH: Disabilities of the Arm, Shoulder and Hand; SPADI: The Shoulder Pain and Disability Index

**Table 4:** Pressure Pain Thresholds (PPT,  $\text{kg}/\text{cm}^2$ ) at baseline, post-intervention, 3-months and 6 months after treatment as well as within-group and between-groups mean scores by randomized treatment assignment

Outcomes	Timeline Scores: Mean $\pm$ SD (95% CI) Within-Group Change Scores: Mean (95% CI)		Between-Group Differences: Mean (95% CI)
	MT + EX	MT + EX + US-guided	
<b>Pressure Pain Thresholds over the cervical spine (kg/cm<sup>2</sup>)</b>			
<b>Baseline</b>	4.0 $\pm$ 1.6 (3.5, 4.5)	3.8 $\pm$ 1.4 (3.3, 4.3)	
<b>After intervention</b>	5.2 $\pm$ 2.1 (4.5, 5.9)	5.0 $\pm$ 1.8 (4.3, 5.7)	
Change baseline $\rightarrow$ after intervent.	1.2 $\pm$ 1.6 (0.7, 1.7)	1.2 $\pm$ 1.0 (0.8, 1.6)	0.0 (-0.5, 0.5)
<b>3 months</b>	5.3 $\pm$ 2.0 (4.6, 6.0)	5.3 $\pm$ 1.4 (4.7, 5.9)	
Change baseline $\rightarrow$ 3 months	1.3 $\pm$ 1.4 (0.7, 1.9)	1.5 $\pm$ 1.3 (1.0, 2.0)	0.2 (-0.1, 0.5)
<b>6 months</b>	5.7 $\pm$ 2.0 (5.0, 6.4)	5.4 $\pm$ 1.8 (4.6, 6.2)	
Change baseline $\rightarrow$ 6 months	1.7 $\pm$ 1.8 (1.0, 2.4)	1.6 $\pm$ 2.1 (1.0, 2.2)	-0.1 (-0.3, 0.1)
<b>Pressure Pain Thresholds over the deltoid muscle (kg/cm<sup>2</sup>)</b>			
<b>Baseline</b>	5.8 $\pm$ 2.5 (5.0, 6.6)	5.6 $\pm$ 2.0 (4.7, 6.5)	
<b>After intervention</b>	7.1 $\pm$ 2.6 (6.2, 8.0)	7.0 $\pm$ 2.3 (6.0, 8.0)	
Change baseline $\rightarrow$ after intervent.	1.3 $\pm$ 1.8 (0.6, 2.0)	1.4 $\pm$ 1.4 (0.9, 1.9)	0.1 (-0.7, 0.9)
<b>3 months</b>	7.0 $\pm$ 2.5 (6.1, 7.9)	6.8 $\pm$ 2.3 (5.8, 7.8)	
Change baseline $\rightarrow$ 3 months	1.2 $\pm$ 1.9 (0.5, 1.9)	1.2 $\pm$ 1.6 (0.5, 1.9)	0.0 (-0.9, 0.9)
<b>6 months</b>	7.3 $\pm$ 2.3 (6.4, 8.2)	7.2 $\pm$ 2.5 (6.2, 8.2)	
Change baseline $\rightarrow$ 6 months	1.5 $\pm$ 1.9 (0.7, 2.3)	1.6 $\pm$ 1.8 (1.0, 2.2)	0.1 (-0.9, 1.1)
<b>Pressure Pain Thresholds over the second metacarpal (kg/cm<sup>2</sup>)</b>			
<b>Baseline</b>	6.2 $\pm$ 2.6 (5.2, 7.2)	6.2 $\pm$ 1.6 (5.3, 7.1)	
<b>After intervention</b>	7.1 $\pm$ 2.3 (6.4, 7.8)	7.0 $\pm$ 1.7 (6.2, 7.8)	
Change baseline $\rightarrow$ after intervent.	0.9 $\pm$ 1.8 (0.2, 1.6)	0.8 $\pm$ 1.2 (0.4, 1.2)	-0.1 (-0.9, 0.7)
<b>3 months</b>	6.5 $\pm$ 2.1 (5.8, 7.2)	6.4 $\pm$ 1.8 (5.6, 7.2)	
Change baseline $\rightarrow$ 3 months	0.3 $\pm$ 2.2 (-0.5, 1.1)	0.2 $\pm$ 1.3 (-0.5, 0.9)	-0.1 (-1.0, 0.8)
<b>6 months</b>	6.7 $\pm$ 1.8 (6.2, 7.2)	6.5 $\pm$ 1.5 (5.8, 7.2)	
Change baseline $\rightarrow$ 6 months	0.5 $\pm$ 2.1 (-0.2, 1.2)	0.3 $\pm$ 1.2 (-0.4, 1.0)	-0.2 (-0.8, 0.4)
<b>Pressure Pain Thresholds over the tibialis anterior muscle (kg/cm<sup>2</sup>)</b>			
<b>Baseline</b>	8.2 $\pm$ 3.0 (7.2, 9.2)	8.3 $\pm$ 2.1 (7.3, 9.3)	
<b>After intervention</b>	9.7 $\pm$ 2.9 (8.8, 10.6)	9.4 $\pm$ 2.0 (8.5, 10.3)	
Change baseline $\rightarrow$ after intervent.	1.5 $\pm$ 2.0 (0.8, 2.2)	1.1 $\pm$ 1.7 (0.7, 1.5)	-0.4 (-1.4, 0.6)
<b>3 months</b>	9.1 $\pm$ 2.5 (8.2, 10.0)	8.7 $\pm$ 2.5 (7.7, 9.7)	
Change baseline $\rightarrow$ 3 months	0.9 $\pm$ 2.7 (-0.2, 2.0)	0.4 $\pm$ 1.7 (-0.4, 1.2)	-0.5 (-1.8, 0.8)
<b>6 months</b>	9.7 $\pm$ 2.2 (9.0, 10.4)	9.2 $\pm$ 2.3 (8.3, 10.1)	
Change baseline $\rightarrow$ 6 months	1.5 $\pm$ 2.4 (0.6, 2.4)	0.9 $\pm$ 2.0 (0.0, 1.8)	-0.6 (-2.1, 0.9)

**Table 5:** Self-perceived improvement with Global Rating of Change (GROC) in both groups [n (%)]

<b>Global Rating of Change (GROC, -7 to +7)</b>	<b>MT + EX</b>	<b>MT + EX + US-guided</b>
<b>Post-intervention</b>		
<b>Moderate changes (+4 / +5)</b>	3 (12%) / 8 (32%)	3 (12%) / 11 (44%)
<b>Large changes (+6 / +7)</b>	0 (0%) / 1 (4%)	5 (20%) / 1 (4%)
<b>3 months follow-up</b>		
<b>Moderate changes (+4 / +5)</b>	0 (0%) / 10 (40%)	0 (0%) / 6 (24%)
<b>Large changes (+6 / +7)</b>	1 (4%) / 2 (8%)	8 (32%) / 6 (24%)
<b>6 months follow-up</b>		
<b>Moderate changes (+4 / +5)</b>	1 (4.5%) / 7 (30%)	0 (0%) / 6 (24%)
<b>Large changes (+6 / +7)</b>	0 (0%) / 5 (22%)	7 (24%) / 11 (44%)