Extracorporeal Shock-Wave Therapy for Supraspinatus Calcifying Tendinitis: A Randomized Clinical Trial Comparing Two Different Energy Levels

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Background. Extracorporeal shock-wave therapy (ESWT) represents a valid intervention in the treatment of people with supraspinatus calcifying tendinitis (SCT), but there is limited evidence for the useful range of ESWT doses.

Objective. The aim of this study was to compare 2 different ranges of energy flux density in treatment of SCT with ESWT.

Design. This study was designed as a single-blind randomized clinical trial.

Setting. This study was performed in a university hospital.

Patients. Forty-six patients with SCT were randomly assigned to 2 groups that received different therapeutic energy doses of ESWT: (1) group A received ESWT at an energy level of 0.20 mJ/mm^2, and (2) group B received ESWT at an energy level of 0.10 mJ/mm^2.

Intervention. The treatment protocol consisted of 4 sessions performed once a week.

Measurements. The change in mean Constant Murley Scale (CMS) scores at 3 and 6 months was the primary endpoint. The change in the mean visual analog scale (VAS) scores from baseline to 3 and 6 months after the intervention and radiographic change in size of calcium deposits were evaluated as secondary endpoints. At 12 months, pain relief was assessed using a numeric rating scale.

Results. Significant clinical improvement based on mean CMS scores was observed after 6 months in group A ($\overline{X}$=79.43, SD=10.33) compared with group B ($\overline{X}$=57.91, SD=6.53). Likewise, after 6 months, a significant decrease in VAS scores was found in group A ($\overline{X}$=2.09, SD=1.54) compared with group B ($\overline{X}$=5.36, SD=0.78). Calcific deposits disappeared in the same percentage of patients in both groups.

Limitations. The small sample size and lack of a control group were limitations of the study.

Conclusions. In ESWT for SCT, an energy level of 0.20 mJ/mm^2 appears to be more effective than an energy level of 0.10 mJ/mm^2 in pain relief and functional improvement.

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Supraspinatus calcifying tendinitis (SCT) represents an acute or chronic disease caused by inflammation around calcium deposits situated upon tendons, with particular involvement of the supraspinatus tendon in its proximal portion of the humerus. It is most common among people between 30 and 50 years of age.[1] The prevalence of SCT has been reported to range from 7% to 36% of the population,[2] and the incidence is estimated to be between 2.5% and 20%.[1,3] Clinical features of this disease are pain-triggering loss of muscular strength, decrease in range of motion (ROM), and disability of the shoulder. Furthermore, pain localized in the deltoid region is more often present during the night, when calcium undergoes reabsorption.[4] This phase can last from 2 weeks in its acute form to up to 3 months in its chronic form.[5]

According to Bosworth et al,[6] calcium deposits can be divided into 3 categories according to size and clinical impairment: tiny (<0.5 cm), medium (0.5–1.5 cm), and large (>1.5 cm). Gartner and Simons[7] classified these calcifications in relation to their radiological features: (1) type 1=pasting and not clear in radiographs, (2) type 2=pasting and clear in radiographs, and (3) type 3=without clear limits and with a high tendency toward spontaneous resolution. The mechanisms underlying the etiology of intratendinous deposits of carbonated apatite are not fully understood.[8]

Uhthoff et al[5] demonstrated that SCT is a dynamic phenomenon in which calcium goes through a cyclical process of formation, reabsorption, and remodeling. Treatment of people with SCT may be conservative or surgical.[9] Conservative treatment[10] includes therapeutic exercise,[11] analgesic and nonsteroidal anti-inflammatory drugs, transcutaneous electrical nerve stimulation,[12] steroid injections,[13] and shock-wave therapy (SWT).[14–17] During the chronic state, arthroscopic-guided surgical resection of the calcification is indicated.[18] *Shock waves*, defined as a sequence of single sonic pulses characterized by high peak pressure (100 mPa), a fast rise in pressure (<10 nanoseconds), and a short life cycle (10 microseconds), are conveyed by an appropriate generator to a specific target area. Short-wave therapy can be classified according to its energy levels.[19,20] A simpler classification distinguishes between low-energy SWT, having an energy flux density (EFD) of less than 0.12 mJ/mm^2, and high-energy SWT, having an EFD between 0.12 and 0.38 mJ/mm^2.[19–21]

During the last 10 years, extracorporeal shock-wave therapy (ESWT) has been used successfully in people with tendon and muscle tissue disease.[14,15,22] It was found that ESWT induces a long-term tissue regeneration effect in addition to having a more immediate antalgic and anti-inflammatory outcomes.[23] A "washout" of chemical inflammation mediators, a trigger to neovascularization, and a nociceptive inhibition (gate control theory) have been reported as the main biological effects of ESWT on tissues.[24,25]

To date, various molecular working mechanisms of shock waves have been demonstrated.[23,26–28] Two physical effects are produced by shock-wave application: (1) the stress-related phenomenon induced by an ultrashort rise time of about 5 nanoseconds and (2) cavitation bubbles produced at the interface between the solid and the surrounding liquid.[29] The latter effect induces vessel rupture and angiogenesis in soft tissues. In *in vitro* studies, ESWT at an EFD lower than 0.09 mJ/mm^2 is reported to produce a neoangiogenic effect by increasing expression of vascular endothelial growth factor

(VEFG) and its receptor Flt-1.[30] Several studies have shown that there is a direct relationship between dose and effect for ESWT.[31–33] Gotte et al[34] also demonstrated that ESWT induces a nonenzymatic production of nitric oxide and a subsequent suppression of NF-κB (nuclear factor-kappaB) activation responsible for the clinically beneficial action on tissue inflammation.

The number of cells destroyed (vacuolization) after ESWT increases in a way that is dose and number dependent. It would seem that the destruction of cells is a short-term effect of high shock-wave doses, whereas cells' stimulation is a medium-term effect.[35] On the other hand, a disorganization of matrix structure and changes in degraded collagen levels have been described in normal tendons after EWST and might represent the trigger for repair in chronic tendinopathy.[28]

Furthermore, side effects have been reported as consequences of the effect of ESWT on tissues.[25,36] Indeed, an EFD between 0.04 and 0.22 mJ/mm^2 has very few side effects, such as pain, local soft tissue swelling, cutaneous erosions, erythema, and local subcutaneous hematomas.[22,37] Only one case report of osteonecrosis of the humeral head has been published.[38]

To date, it is not yet clear which energy level is the most effective in pain relief and clinical improvement of shoulder function after ESWT.[24,39–41] Indeed, Gerdesmeyer et al[15] found that 2 sessions of 1,500 high-dose impulses (0.32 mJ/mm^2) appeared to be superior to 2 sessions of 6,000 low-dose impulses (0.08 mJ/mm^2) in terms of pain reduction, clinical improvement, and radiological calcium deposit resorption, although they stated that "threshold energy has yet to be defined." Schofer et al[42] found an increase in shoulder function and a reduction of pain in 2 groups treated with 6,000 impulses in 3 sessions. They used an energy level of 0.78 mJ/mm^2 in the first group and an energy level of 0.33 mJ/mm^2 in the second group, but did not observe any difference between groups.

Therefore, treatment parameters of ESWT remain empirical because there is no consensus on appropriate sessions and doses.[16,18,22,39] In our study, 2 different protocols were designed: one protocol bounded by the upper limit of low dose (0.04–0.12 mJ/mm^2) and the other protocol bounded by the lower limit of high dose (>0.12 mJ/mm^2). We tested low-energy procedures in our study because they do not require any kind of anesthesia, which generally was applied when high-energy protocols were used.[43] Moreover, it recently has been demonstrated that local anesthesia substantially alters the biological responses of ESWT.[25,44] It also been shown that both high- and low-energy protocol procedures are similarly effective if the total energy applied is approximately the same. Thus, with the low-energy protocol, more impulses had to be applied in more treatment sessions to achieve a similar result.[44] However, in our study, we chose to compare the effects of the 2 treatment protocols using the same impulses and number of sessions.

The Bottom Line

What do we already know about this topic?

Several studies suggest the effectiveness of extracorporeal shock-wave therapy (ESWT) as an intervention for reducing pain and improving shoulder function in people with supraspinatus calcifying tendinitis (SCT); however, there is limited evidence about the useful range of ESWT doses.

What new information does this study offer?

This study contributes to the standardization of treatment of SCT and can help clarify the most appropriate energy flux density (EFD) levels, number of sessions, and number of impulses of shock waves in SCT treatment. In this study, 2 different energy levels were tested: 0.10 mJ/mm^2 in the first group, and 0.20 mJ/mm^2 in the second group. The group that received the higher energy level showed a greater reduction in pain and a greater improvement in shoulder function than the other group. The study also revealed that the clinical improvement of patients was not related to the reabsorption of or a decrease in size of calcific deposits.

If you're a patient, what might these findings mean for you?

If you have SCT, the destruction of calcifications is not necessary to reduce your pain and improve your shoulder function.

Method

Design Overview

A single-blind randomized clinical trial with assessment at baseline (admission to the clinic) and at 3, 6, and 12 months after the end of the treatment was conducted.

Setting and Participants

Consecutive outpatients of the Department of Physical and Rehabilitative Medicine (School of Medicine, "La Sapienza" University of Rome) with clinical and radiological features of SCT from November 2008 to June 2010 were invited to participate in the study.

All patients had a current episode of shoulder pain that had been in progress for at least 4 to 6 months. A total of 68 consecutive patients affected by shoulder pain (40 women and 28 men) were screened for eligibility. If they had undergone previous conservative treatment with no visible clinical benefits, they were included in the study. Patients with medium and large calcific deposits according to the Bosworth classification[6] and with type I and II calcific deposits according to the Gartner classification[7] were included. Individuals with clinical signs of partial or complete tear of the rotator cuff (evaluated with Jobe and full can tests)[45] were excluded. Dinnes et al[46] reported that clinical examination has a sensitivity of 90% and a specificity of 54% in the detection of rotator cuff tears. Four patients were subjected to magnetic resonance imaging to eliminate doubts about supraspinatus tendon tears.

Moreover, patients with the presence of tiny calcific deposits according to the Bosworth classification[6] and type III calcific deposits according to the Gartner classification[7] were excluded because of the high probability of spontaneous resolution.[47] Further exclusion criteria were: age of less than 18 years, diabetes, coagulation diseases or undergoing anticoagulant therapy, tumors, bone infections, previous shoulder surgery, pregnancy, use of a pacemaker, acute bursitis demonstrated by ultrasound imaging, rheumatoid arthritis, or other connective tissue diseases.[48]

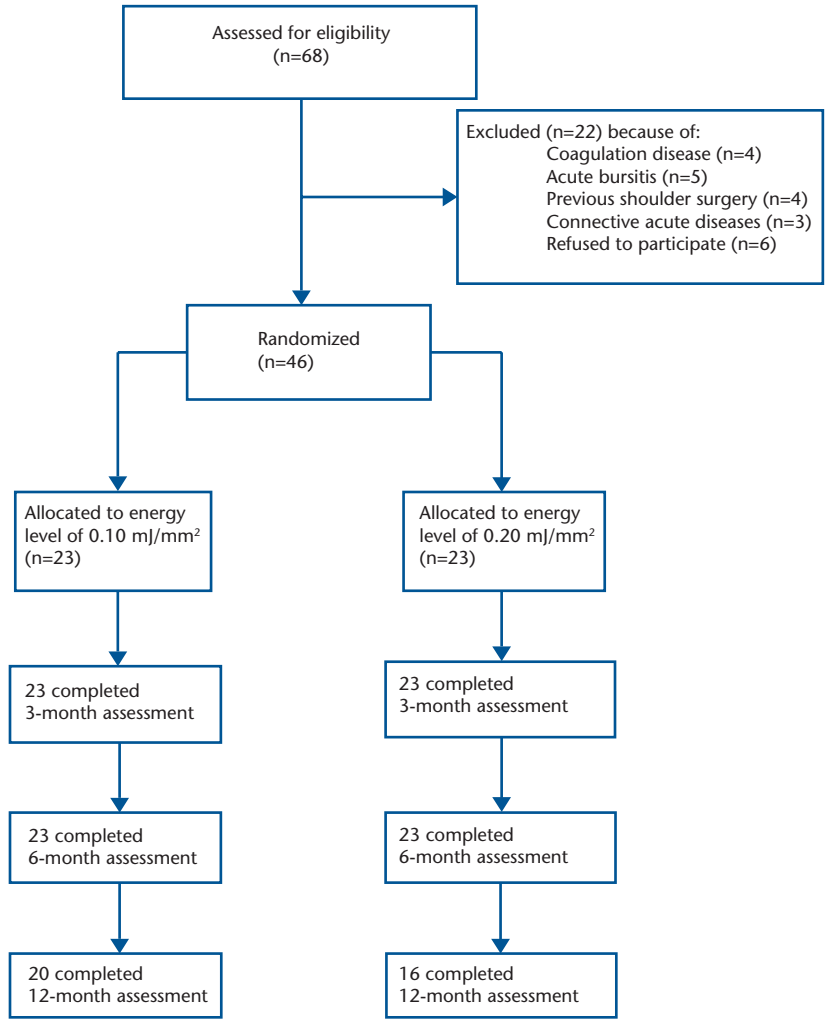

Figure 1.
Flow diagram of participants in the study.

At the end of the evaluation, 46 patients (31 women and 15 men; mean age=54.3 years, SD=14.8, range=29–78) fulfilled the selection criteria. They agreed to participate, signed informed consent statements, and were enrolled in the study. The right shoulder was affected in 70% of the participants, and the left shoulder was affected in 30%. The mean duration of condition at time of treatment was 7.1 months (SD=1.16, range=6–9). The enrolled patients did not receive any conservative treatment in the 4 weeks before ESWT, and this was the first time that they received ESWT. A flow diagram of participant recruitment and retention is shown in Figure 1.

Randomization and Interventions

Upon consenting to be involved in the study, patients were asked by an interviewer blinded general questions regarding age, symptom duration, current medicine intake, and average pain intensity over the previous week. A research assistant randomly assigned participants to study groups by the use of a computer-based 1:1 randomization scheme. Participants were randomly assigned to receive 1 of 2 treatment protocols: (1) group A received ESWT at an

Figure 2.
Participants underwent extracorporeal shock-wave therapy while lying on a bed with the affected arm positioned in adduction, the elbow flexed at 90 degrees, and the hand upon the abdomen.

energy level of 0.20 mJ/mm^2, and (2) group B received ESWT at an energy level of 0.10 mJ/mm^2. Both groups received 2,400 pulses once a week for 4 weeks. Baseline measurements were taken by a second interviewer who was blinded to ESWT dosage, and the participants completed the questionnaire administered. Treatment allocation was concealed in a numbered, opaque envelope, which subsequently was opened by the physician.

Participants were instructed to use oral nonsteroidal anti-inflammatory drugs (dexibuprofene, 400 mg) 1 hour before treatment to provide pain relief during treatment. Local anesthesia was not administered, as in previous studies.[25,49]

We utilized an ESWT device (Modulith SLK system, Storz Medical, Tagerwilen, Switzerland), with an electromagnetic extra-corporeal shock-wave generator equipped with an in-line ultrasound positioning system on the target zone. Participants underwent ESWT by lying on a bed with the affected arm positioned in adduction, the elbow flexed at 90 degrees, and the hand on the abdomen (Fig. 2).

Outcome and Follow-up

The Constant Murley Scale (CMS)[50] and a visual analog scale (VAS)[51] were administered before treatment and at 3 and 6 months after the end of the ESWT. The primary endpoint was the change in mean CMS scores from baseline to the 3- and 6-month follow-ups. Secondary endpoints were the change in VAS scores from baseline to the 3- and 6-month follow-ups and the numerical rating scale (NRS) score at the 12-month follow-up, as well as radiographic calcific deposit size at the 6-month follow-up.

The CMS evaluates shoulder function with high accuracy, test-retest reliability (intraclass correlation coefficient=.80), and reproducibility.[52] It is a cumulative scale, consisting of a 100-point scoring system, with assessment of patient-reported pain and function accounting for up to 35 points and quantitative assessment of ROM and strength accounting for up to 65 points. Its emphasis is on symptoms and functional difficulties, and the patient-report component documents pain and difficulty in activities of daily life, work, sports, and sleep. Higher scores reflect an improvement in shoulder function.

Shoulder pain was assessed using the VAS, which represents a valid measure of acute pain with a good construct validity.[53] It consists of a 10-cm horizontal line (with 0 cm referring to "no pain" and 10 cm referring to "worst pain ever") on which participants were invited to mark a line indicating pain intensity. The distance is measured, and pain is recorded on a 10-point scale.[54] In the acute pain setting, the VAS has been shown to have very good test-retest reliability (intraclass correlation coefficient=.99).[55]

Dworkin et al[56] suggested that raw score changes of approximately 1 point or percentage changes of approximately 15% to 20% represent the minimal clinically important difference (MCID) for the VAS and similar NRS measures (0–10) for pain intensity. All outcomes before ESWT and at the scheduled 3- and 6-month follow-ups were assessed by a third blinded independent observer.

To further assess pain relief in both groups, at 12 months, the third interviewer, who was blinded to the energy level of treatment, administered an 11-point NRS (group A: n=20; group B: n=16) by telephone. The NRS usually is an 11-, 21-, or (rarely) 101-point scale, with numbers in boxes that are anchored with 2 extremes at the ends of the scale.[57] The 11-point scale NRS consists of integers from 0 through 10, with 0 representing "no pain" and 10 representing "worst imaginable pain." The NRS recently has been demonstrated to possess good psychometric properties. High correlations were observed between the NRS and VAS scores. The patient acceptable symptomatic state (PASS) was 3.3.[58] Calcifications of each patient were first detected in a previous visit by radiography or ultrasound before treatment with a standardized technique in terms of position of the shoulder and arm, distance from

the radiographic film, and exposure. The size of the calcific deposit was defined as the difference in measurements at the 6-month follow-up compared with baseline values.

Statistical Analysis

Statistical analysis was performed according to the principle of intention to treat, with missing data imputed with the "last observation carried forward" technique. All analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). Computed *P* values were 2-sided, and $P<.05$ was used to determine statistical significance. Two-way analyses of variance (ANOVAs) for repeated measures of CMS and VAS scores were performed with group (treatments) as the between-subjects factor and time and group interactions × time as the within-subjects factors.

Preplanned time-repeated contrasts were done. Two-tailed unpaired *t* tests and the Fisher exact test were applied when appropriate. The participants' baseline characteristics are shown in the Table.

Sample Size

Sample size and power calculations were performed with nQuery Advisor 7 statistical software (Statistical Solutions, Saugus, Massachusetts). We computed that a sample size of 46 participants achieved a power over 80% to detect a 15% difference in CMS score. The statistical level of significance was set at alpha=.05, and the assumed standard deviation was set at 17.7 points based on the results of a study by Loew et al.[24]

Role of the Funding Source

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Table.

Baseline Demographic and Clinical Characteristics of Participants With Chronic Supraspinatus Tendinitis in Groups A and B[a]

Characteristic	Group A (n=23)	Group B (n=23)	*P*
Age (y)			.21[b]
$\bar{X}$	57.09	51.65	
SD	16.40	12.23	
Range	27–78	31–78	
95% CI	50.00–64.18	46.36–56.94	
Time since onset of pain (mo)			.44[b]
$\bar{X}$	6.95	7.22	
SD	1.06	1.20	
Range	6–9	6–10	
95% CI	6.49–7.41	6.69–7.74	
Sex (female/male)	15/8	16/7	1.00[c]
Treatment side (right/left)	16/7	14/9	.76[c]
Type of calcification[d]			
I	5	6	1.00[c]
II	18	17	1.00[c]
CMS score			.62[b]
$\bar{X}$	49.26	47.70	
SD	8.56	12.23	
95% CI	45.46–52.96	42.41–52.99	
VAS score			.68[b]
$\bar{X}$	8.45	8.36	
SD	0.67	0.78	
95% CI	8.17–8.74	8.03–8.69	

[a] Group A received extracorporeal shock-wave therapy (ESWT) at an energy level of 0.20 mJ/mm^2, and group B received ESWT at an energy level of 0.10 mJ/mm^2. 95% CI=95% confidence interval, CMS=Constant-Murley Scale (0–100 points), VAS=visual analog scale (0–10 points).
[b] As determined by an independent 2-sample *t* test.
[c] As determined by Fisher exact test.
[d] Gartner's classification.[7]

Results

All patients participated in the 3- and 6-month follow-ups. As shown in the Table, the baseline clinical and demographic characteristics of the participants were homogenous in the 2 groups.

Repeated-measures 2-way ANOVAs for CMS and VAS scores showed a significant effect of treatment (CMS: $F_{1,44}=25.04$, $P=.000$; VAS: $F_{1,44}=32.39$, $P=.000$) and a significant treatment-time interaction (CMS: $F_{2,88}=20.14$, $P=.000$; VAS: $F_{2,88}=46.23$, $P=.000$). A significant change in test performance over time also was observed in both groups (CMS: $F_{2,88}=72.52$, $P=.001$; VAS: $F_{2,88}=337.48$, $P=.000$).

Using preplanned contrasts, we observed a significant increase in CMS values compared with baseline values at 3 months in both treatment groups (time effect: $F_{1,44}=84.24$, $P=.000$), with no significant difference between treatment groups (interaction effect: $F_{1,44}=0.18$, $P=.672$). A further improvement

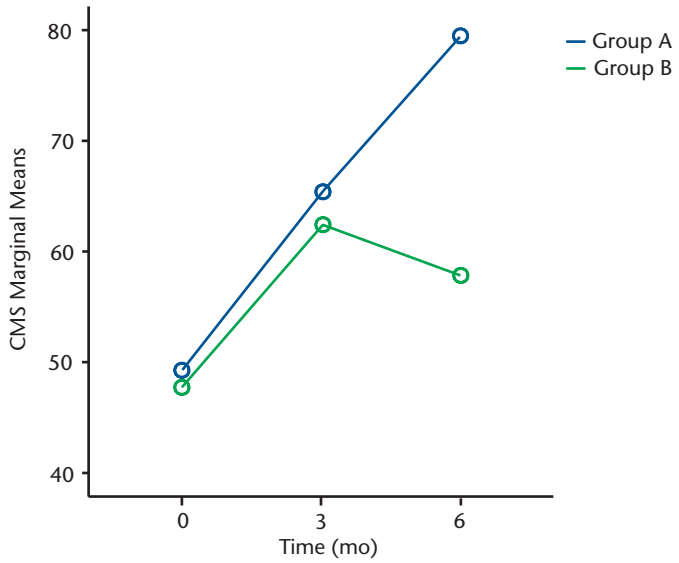

Figure 3.
Time course of Constant Murley Scale (CMS) scores at baseline (0) and at 3- and 6-month follow-ups. Data are expressed as marginal means. A significant increase in CMS values with respect to the baseline at 3 months in both treatment groups (time effect: $F_{1,44}$=84.24, *P*=.000), with no significant difference between treatment groups (interaction effect: $F_{1,44}$=0.18, *P*=.672), was observed using preplanned contrasts. A further improvment at the 6-month follow-up was observed in group A (time effect: $F_{1,44}$=11, *P*=.000) but not in group B (interaction effect: $F_{1,44}$=42.01, *P*=.000).

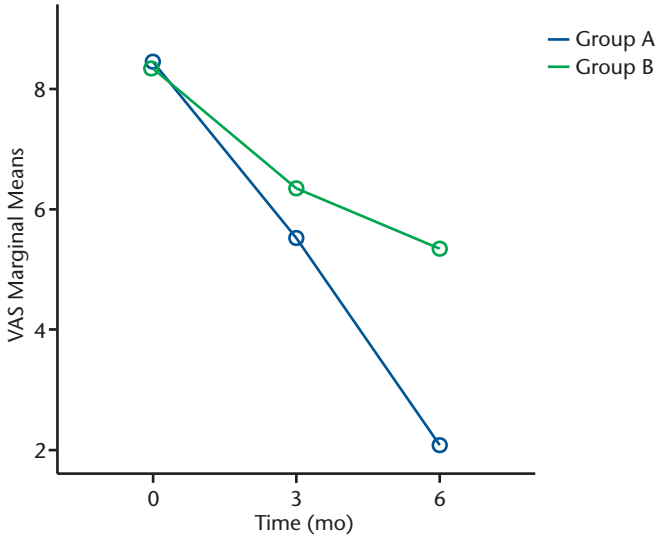

Figure 4.
Time course of visual analog scale (VAS) scores at baseline (0) and at 3- and 6-month follow-ups. Data are expressed as marginal means. Using preplanned contrasts, the decrease of pain was present at the 3-month follow-up versus baseline in both groups (time effect: $F_{1,44}$=174.92, *P*=.000), although it was more evident in group A than in group B (interaction effect: $F_{1,44}$=6.04, *P*=.018). At the 6-month versus 3-month follow-ups, the effect was still more obvious in group A (time effect: $F_{1,44}$=151.58, *P.*=000) than in group B (interaction effect: $F_{1,44}$=45.69, *P*=.000).

over the time at the 6-month follow-up was observed (time effect: $F_{1,44}$=11, *P*=.000); however, the improvement was present in group A but not in group B (interaction effect: $F_{1,44}$=42.01, *P*=.000) (Fig. 3).

The effect on pain relief was perceptible at the 3-month follow-up versus baseline in both groups (time effect: $F_{1,44}$=174.92, *P*=.000), although it was more evident in group A than in group B (interaction effect: $F_{1,44}$= 6.04, *P*=.018). Comparing scores obtained at the 6-month follow-up with those obtained at the 3-month follow-up, the effect was still more obvious in group A (time effect: $F_{1,44}$=151.58, *P*=.000; interaction effect: $F_{1,44}$=45.69, *P*=.000) (Fig. 4).

Furthermore, statistical analysis (2-tailed unpaired *t* test) of NRS scores obtained at 12 months showed a significantly lower level of pain (*P*=.045) in group A than in group B (group A: $\overline{X}$= 2.60, SD=2.1, 95% confidence interval [95% CI]= 1.62 to 3.58; group B: $\overline{X}$=4.56, SD=3.5, 95% CI=2.69 to 6.44). Moreover, 7 participants in group A and 10 participants in group B had NRS scores greater than 3.3, and 13 participants in group A and 6 participants in group B had NRS scores lower than 3.3.

The complete disappearance of calcification deposits was observed after 6 months in approximately 50% of the patients treated in both groups. In particular, we found that calcifications had disappeared in 23 (50%) of the 46 participants. Of these, 11 (47.8%) were in group A, and 12 (52.2%) were in group B. Furthermore, there was no difference (*t*-test value=.22) between treatments in mean change of calcific deposit size at 6 months from baseline (group A: $\overline{X}$=−135.91, SD= 71.69, 95% CI=−100.37 to −166.29; group B: $\overline{X}$=−109.73, SD=75.73, 95% CI=−50.69 to −134.44). No

correlation between clinical improvement and calcium deposit change was observed in either treatment group. Finally, no side effects were observed in participants after treatment or reported by participants afterward.

Discussion

According to the literature, when previous conservative treatment is not effective, ESWT is a valid alternative in the management of SCT because it reduces pain and improves the function of the shoulder joint.[39,59] There is no consensus as to the appropriate EFD, number of sessions, and impulses of SWT, and it is not known whether and, if so, to what degree a correlation exists between decreased pain and functional recovery, on the one hand, and the resorption of calcific deposits, on the other.

Peters et al[22] reported that therapy was more effective in the high-energy group (0.44 mJ/mm^2) than in the low-energy group (0.15 mJ/mm^2) in achieving clinical improvement and dissolving calcifications at 6 months from the end of treatment. Gerdesmeyer et al[15] also observed a better clinical response in the high-energy group (0.32 mJ/mm^2), with a rate of complete disappearance of calcific deposits of 60% at the 6-month follow-up and 86% at the 12-month follow-up. By contrast, in the low-energy group (0.08 mJ/mm^2), the rate of dissolution was 21% at 6 months and 25% at 12 months.

Albert et al[60] observed that a high-energy level of ESWT significantly decreased symptoms in individuals with SCT at a 3-month follow-up, but the results of our study indicated that clinical improvement was not related to resorption of calcific deposits. Indeed, the calcific deposits disappeared from the radiographs at 3 months in only 15% and 5% of the patients in the high-energy and low-energy groups, respectively.

The results of our study showed that the improvement in mean (SD, 95% CI) CMS scores was higher in group A: 79.43 (10.33, 74.97–83.90) than in group B: 57.91 (6.53, 55.09–60.74) at 6-month follow-up. Indeed, the change from baseline in 6-month CMS scores was 61% in group A: 49.26 (8.56, 45.56–52.96) and 21% in group B: 47.70 (12.23, 42.41–52.99).

To date, there are no studies providing data on the MCID for CMS scores. However, assuming a 30% increase in CMS score from baseline as clinically relevant improvement,[18] we could speculate that only an EFD of 0.20 mJ/mm^2 induced a clinically relevant improvement of shoulder function over time.

Both treatments produced a reduction of pain, although varying according to dose. At 6 months, the VAS score mean (SD, 95% CI) change was 75% in group A: 2.09 (1.54, 1.42–2.76) and 37% in group B: 5.36 (0.78, 5.03–5.70), from the respective baseline values (group A: 8.45 [0.67, 8.17–8.74]; group B: 8.36 [0.78, 8.03–8.69]), which was both statistically ($P<.001$) and clinically significant. Indeed, as described by Dworkin et al,[56] a reduction in chronic pain intensity of at least 10% to 20% appears to reflect minimally important changes. Furthermore, group A showed better effects for level of pain than group B at 12 months, assuming that an NRS score lower than 3.3 points is related to an acceptable state of pain.

Moreover, we found that clinical improvement was not related to the disappearance or reduction in size of calcifications, according to the current data,[61] because they were still detectable in approximately 50% of our participants in both groups after 6 months. Although some authors have emphasized the potential effects of ESWT for disintegrating calcified deposits upon the supraspinatus tendon, the real mechanisms remain unknown.[62,63]

The exact biological effects by which ESWT acts are still in question. A study conducted on rabbits showed that ESWT increases neovascularization at the tendon-bone junction through release of angiogenetic growth and proliferating factors such as VEFG and endothelial nitric oxide synthase, which stimulate increased blood flow in tendons and seem to relieve shoulder symptoms.[28] Another study carried out on rabbits showed some short-term tendon pathologies associated with ESWT energy levels of at least 0.6 mJ/mm^2.[64] However, neither tendons nor the cartilage of joints have been found to be injured by shock waves lower than this energy level. Despite a previous report,[42] the energy level used in our study was ranged in doses suitable for soft tissue diseases.[19–21] We did not observe any side effects in the participants in our study.

It also should be emphasized that these results were obtained using energy levels below those reported in the literature because we wanted to compare the effectiveness of 2 energy levels, ranging in the low levels. It can be hypothesized, on the basis of our findings, that at the low-energy level used in our study (0.10 mJ/mm^2), the ESW produces immediate analgesic and anti-inflammatory effects, washing out the inflammatory mediators and turning off the associated neoangiogenesis process. This efficacy possibly could be explained by an increased synthesis of nitric oxide, which has been shown to be produced *in vitro* by an EFD of 0.03 mJ/mm^2.[27] At 0.20 mJ/mm^2, ESWT probably led to integrated anti-inflammatory and regen-

erative actions on the different tissue components, and these combined mechanisms could explain the better clinical results observed in group A in our study. However, the limitations of the present study include the small sample size and the lack of a control group receiving a placebo. The efficacy of this therapy is better and longer lasting in patients treated with an energy level of 0.20 mJ/mm^2 than in those treated with an energy level of 0.10 mJ/mm^2.

So far, from what we know from the literature, this is the first study that used the same number of impulses and number of sessions in the range of low-energy levels in order to standardize a therapeutic protocol with better clinical results for SCT therapy. Certainly, it must be taken into account, as already stated, that the presence of a control group, as well as a larger sample size, would have allowed us to confirm the obtained results.

Nevertheless, in clinical practice the results of this study could be helpful to clarify the most appropriate EFD, number of sessions, and impulses of shock waves in SCT treatment, surpassing what is currently the most used empirical approach in clinical practice. In addition, many patients, and even some physicians, believe that the effect of treatment with EWST is due to the destruction of calcific deposits. On the contrary, our results, in line with those of the study by Albert et al,[60] showed that the destruction of calcifications is not necessary to reduce pain and improve function.

Further studies are needed to confirm the most appropriate energy threshold in ESWT to obtain the best results in reducing pain and improving shoulder function. The results of the present study are promising, but studies with larger samples, longer follow-up, and possible comparison with a control group are needed.

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