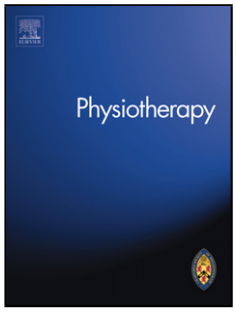

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PII: S0031-9406(15)03235-6
DOI: http://dx.doi.org/doi:10.1016/j.physio.2015.01.010
Reference: PHYST 819

To appear in: *Physiotherapy*

Received date: 6-6-2014
Accepted date: 13-1-2015

Please cite this article as: Merino LP, Briansó MCC, Alarcón GB, Martínez JF, López AEA, Pàmies RG, Batista MG, Ferran MR, Llort MRN, Evaluation of the effectiveness of three physiotherapeutic treatments for subacromial impingement syndrome: a randomised clinical trial, *Physiotherapy* (2015), http://dx.doi.org/10.1016/j.physio.2015.01.010

Evaluation of the effectiveness of three physiotherapeutic treatments for subacromial impingement syndrome: a randomised clinical trial

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Abstract

Objective To determine whether dexketoprofen administered by phonophoresis or iontophoresis is more effective for the treatment of subacromial impingement syndrome (SIS) than conventional ultrasound therapy

Design Randomised clinical trial.

Setting University hospital.

Participants Ninety-nine participants with SIS without a complete tear of the rotator cuff were assigned at random to three intervention groups.

Intervention groups Participants received ultrasound (*n*=32), phonophoresis with dexketoprofen (50 mg/session) (*n*=33) or iontophoresis with dexketoprofen (50 mg/session) (*n*=34). All participants completed 20 treatment sessions plus exercise therapy and cryotherapy.

Outcome measures A visual analogue scale (VAS), the Constant–Murley Scale (CMS) and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire were administered pre-treatment (baseline), post-treatment and 1 month post-treatment.

Results At baseline, there were no differences between the groups. Post-treatment, VAS score improved by -1.2 points and CMS score improved by 8.9 points in the ultrasound group compared with the iontophoresis group [95% confidence interval (CI) -0.2 to -2.2 and 95% CI 17.0 to 0.7, respectively]. CMS score improved by 7.1 points in the phonophoresis group compared with the iontophoresis group (95% CI 14.8 to -0.7). At 1 month post-treatment, no significant differences were detected between the groups. VAS, CMS and DASH scores of all groups improved post-treatment and at 1 month post-treatment.

Conclusion Ultrasound, iontophoresis with dexketoprofen and phonophoresis with dexketoprofen can improve pain, shoulder function, and physical functioning and symptoms in the upper limb in patients with SIS without a complete tear of the rotator cuff.

ClinicalTrials.gov registration number NCT01748188.

Keywords: Subacromial impingement syndrome; Ultrasound therapy; Phonophoresis; Iontophoresis; Dexketoprofen

<A>Introduction

Subacromial impingement syndrome (SIS) is a common source of shoulder pain and dysfunction caused by an impingement of the rotator cuff tendon [1] between the head of the humerus and the acromion or the coracoacromial ligament as a result of changes in the subacromial space [2].

Patients with SIS are assessed by means of medical history and physical examination. The patients' symptoms, such as pain, limited mobility and decreased strength, may lead to a diagnosis of SIS. However, these assessments should be reinforced with tests for more accurate and precise diagnoses [3]. Diagnostic imaging techniques can assess the rotator cuff accurately and confirm the diagnosis [4]. Ultrasonography of the shoulder is a sensitive and specific method that requires standardised examination and expertise for optimal analysis [5].

The initial treatment of patients with SIS is conservative [1], and includes analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), steroid injections and physiotherapy [6]. Physiotherapy aims to reduce inflammation in the tendons and strengthen the rotator cuff, eliminate pain and improve the patient's shoulder function [1]. It may include therapeutic exercise, mobilisation and manipulation, education and the application of physical agents such as ultrasound [7]. Ultrasound is among the most common treatments for SIS [8], but its effectiveness is debatable [6]. A recent study reported that ultrasound therapy is beneficial in the treatment of SIS, and is effective in decreasing pain and improving functionality [8]. Phonophoresis and iontophoresis combine the dual therapeutic action of physiotherapy and medication. In phonophoresis, a drug is used as a transmitter with ultrasound instead of the conventional conductor gel. Iontophoresis releases pharmaceuticals through the transcutaneous pathway using a low-intensity, low-voltage electric current. The three most common families of drugs

used are anaesthetics, anti-irritation agents and anti-inflammatories [9]. Ketoprofen is an NSAID in the propionic acid class, with analgesic, anti-inflammatory and mild antipyretic effects. The analgesic effect is due to the S (+)-enantiomer (dexketoprofen) [10].

Pain control is an essential component of a successful physiotherapeutic programme to treat SIS [1]. Clinically, the pain and inflammation caused by SIS can be diminished through the use of techniques such as ultrasound, phonophoresis and iontophoresis [11]. Additionally, initial pain management typically involves NSAIDs [1]. Oral NSAIDs seem to be more effective than placebo in reducing pain in the first weeks after onset, and are therefore recommended in the acute phase [5]. To the authors' knowledge, no studies to date have described the use of the NSAID dexketoprofen with phonophoresis and iontophoresis in the treatment of SIS. Systematic reviews have highlighted the need for high-quality clinical trials that combine different techniques to reflect common practice [12–14]. As such, this study aimed to evaluate the combination of different techniques in the treatment of SIS. It was hypothesised that physiotherapeutic treatments favouring the penetration of an anti-inflammatory and analgesic drug would lead to an improved response to the treatment of SIS. The main aim of this study was to determine whether dexketoprofen administered by phonophoresis or iontophoresis is more effective for the treatment of SIS than conventional therapy with ultrasound.

<A>Methods

A randomised, single-blind experimental clinical trial was developed, consisting of three treatment groups.

The sample size was determined using the GRANMO Version 7.11 sample calculator (March 2011), accepting an alpha risk of 5% (0.05) and beta risk of less than

20% (0.2) in a bilateral contrast. The power of the study was 80%. The calculations were based on detection of a difference of 12.2 points on the Constant–Murley Scale (CMS), assuming a standard deviation (SD) of 15.6 points and allowing for a 20% dropout rate. This generated a sample size of 33 subjects per group.

<B>Setting and participants

The study population was comprised of 99 patients diagnosed with SIS without a complete tear of the rotator cuff. The patients were recruited from the Rehabilitation, Physiotherapy and Speech Therapy Service of Sant Joan University Hospital, Reus, Spain. Participants were selected based on inclusion and exclusion criteria (Table A, see online supplementary material).

Assessments were made pre-treatment (baseline), post-treatment and 1 month post-treatment. All visits were attended to by the same blinded rehabilitation doctor using standardised protocols.

The baseline assessment consisted of medical history, physical examination, a visual analogue scale (VAS), the CMS, the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire and various diagnostic tests (Yocum test, Jobe test, palm-up test and drop-arm test).

The diagnosis was confirmed by ultrasonography. All scans were performed by an expert radiologist in shoulder pathology, who diagnosed the pathology as tendinitis, tendinosis or partial tear. Tendinitis is characterised by the presence of inflammatory mediators, whereas tendinosis involves a disorganised collagen structure and changes consistent with hypoxia [7]. A partial tear involves less than 50% of the thickness of the tendon.

Fig. A (see online supplementary material) shows the selection and recruitment of the study population, and the distribution of participants in treatment groups

<B>Randomising and interventions

Each participant was assigned to one treatment group, at random, using a numbered list generated through the random permuted blocks method, applied by a statistician. The statistician was not involved in data collection or analysis. The three treatment groups were: ultrasound with no drugs (comparison group), phonophoresis and iontophoresis. The treatment sequence for all three groups was exercises + physical agent + cryotherapy. The three groups underwent standardised exercise therapy and cryotherapy in order to obtain the greatest benefits for the patients, as exercise has proven to be very effective for the treatment of SIS [15,16], and cryotherapy after exercise can reduce the intensity of delayed muscle soreness [17]. In addition, cryotherapy reduces inflammation and increases the pain threshold, alleviates the pain associated with an acute injury and promotes the return of normal shoulder motion [11].

The ultrasound group received ultrasound of 1 MHz, with an effective radiation area (ERA) of 6 cm^2, in pulsed mode (10%) at an intensity of 2 W/cm^2 for 5 minutes. The phonophoresis group received phonophoresis with 50 mg of dexketoprofen (Enangel 12.5 mg/g) at 1 MHz, with an ERA of 6 cm^2, in pulsed mode (10%) at an intensity of 2 W/cm^2 for 5 minutes. The iontophoresis group received iontophoresis by galvanic direct current with 50 mg of dexketoprofen (Enantyum 50 mg/2 ml) at an intensity of 2 mA for 20 min.

Enangel was chosen as the conductor for the phonophoresis group because its gel formulation facilitates the use of ultrasound. Enantyum was used in the iontophoresis group as it was a solution.

The exercises consisted of seven standardised exercises for improving muscle strength and opening the subacromial space (Fig. B, see online supplementary material). Cryotherapy consisted of cooling using a cold air bundle at -32 ºC for 3 min.

All participants completed five sessions per week (total of 20 sessions). The treatments were provided by physiotherapists following standardised protocols. The physiotherapists did not collect data and did not evaluate the results.

No educational advice was provided, and participants were not given guidelines for performing exercises at home.

<B>Outcomes and follow-up

Sex, age, time from onset of injury, dominant or non-dominant affected side, type of injury (tendinitis, tendinosis or partial tear), VAS score, CMS score and DASH score were recorded at the baseline assessment. VAS, CMS and DASH scores, which were the study's main independent variables, were re-recorded at the post-treatment and 1 month post-treatment assessments.

The VAS assesses pain on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain.

The CMS was used to assess function of the affected shoulder. The CMS is a standardised clinical evaluation method [18] with a score ranging from 0 to 100 based on evaluation of four parameters: pain, daily life activities, active joint balance and muscle strength. The higher the CMS score, the better the shoulder function.

The DASH questionnaire assesses physical functioning and symptoms of the upper limb [19], and yields results expressed in percentages from 0% to 100%, with 0% being the best and 100% being the worst.

<B>Statistical analysis

Statistical Package for the Social Sciences Version 21 (IBM Corp., Armonk, NY, USA) was used to analyse the data, and a descriptive analysis of the study sample was conducted with minimum and maximum values, means, SDs and percentages of the variables collected. Kolmogorov–Smirnov test was used to assess normality of the distribution of each group. Repeated-measures analysis of variance (ANOVA) was used to assess the effectiveness of each treatment in each group over time, and ANOVA was used to compare the three treatment groups, followed by a post-hoc Scheffé test. $P<0.05$ was considered to indicate significance.

<A>Results

Data were collected between 2012 and 2013. No adverse events were documented in any of the treatment groups. At baseline, no differences in study outcome variables were found between the three groups, and all variables had normal distributions. The values are expressed as mean and SD.

Table 1 shows the baseline characteristics of the study participants, which were homogenous across groups.

<insert Table 1 near here>

<B>Comparison between treatments

Table 2 shows VAS, CMS and DASH scores at each assessment. VAS, CMS and DASH scores were similar for all three treatment groups at the baseline assessment.

<insert Table 2 near here>

Post-treatment, ultrasound improved the VAS score significantly compared with iontophoresis [-1.2 points; 95% confidence interval (CI) -0.2 to -2.2; *P*=0.012]. Ultrasound (8.9 points; 95% CI 17.0 to 0.7; *P*=0.025) and phonophoresis (7.1 points; 95% CI 14.8 to -0.7; *P*=0.049) improved the CMS score significantly compared with iontophoresis.

At 1 month post-treatment, the values were equal, and no significant differences were apparent between treatments.

<B>Comparison between visits

Table 3 shows differences in the values of the three variables in relation to the baseline values. Post-treatment, compared with the baseline assessment, ultrasound and phonophoresis improved VAS, CMS and DASH scores significantly and iontophoresis improved VAS and DASH scores significantly.

<insert Table 3 near here>

At 1 month post-treatment, significant improvements were documented for VAS, CMS and DASH scores for all three treatments compared with the baseline assessment.

<A>Discussion

Potential positive effects of exercises and cryotherapy were the same for all treatment groups, so the results obtained can only be due to differences between physical agents.

All the treatments applied in this study are effective for improving pain, shoulder function, and physical functioning and symptoms of the upper limb in patients with SIS. Post-treatment, all three treatments showed a significant improvement in these parameters compared with baseline, except for DASH score for phonophoresis and CMS score for iontophoresis. Between the post-treatment and the 1 month post-treatment assessments, the two treatments using dexketoprofen continued to improve pain, function, and physical functioning and symptoms of the upper limb, unlike ultrasound, which had poorer VAS, DASH and CMS scores at the 1 month post-treatment assessment. The benefits of ultrasound in improving pain, shoulder function, and physical functioning and symptoms of the upper limb therefore end after treatment, while iontophoresis and phonophoresis treatments with dexketoprofen improve these three variables for up to 1 month post-treatment. Ultrasound therefore has a more rapid and local effect for treatment of SIS, while the effects of phonophoresis and iontophoresis with dexketoprofen manifest later.

The same frequencies, intensities, modes and times were used for ultrasound and phonophoresis treatments. The time difference before the onset of clinical improvement may therefore be due to the conductor gel used and the mechanism of action of these physical agents. Many cream-based preparations used with phonophoresis do not permit adequate transmission of the ultrasonic acoustic wave. However, gel-based preparations appear to be superior in terms of wave transmission [20]. Dexketoprofen gel was used in this study, and it is believed that wave transmission was adequate. Souza *et al.* evaluated the use of phonophoresis with two anti-inflammatory drugs, and showed that the amount of ketoprofen that penetrated the skin was greater when applied with ultrasound compared with application without ultrasound, while the penetration of

diclofenac sodium decreased [21]. The properties of the drugs used with phonophoresis must therefore be taken into account.

The absorption of a drug depends on a number of physicochemical and pharmacological factors, including lipid solubility and the binding protein [20]. According to Beetge *et al.*, the partition coefficient is the most reliable variable to determine the transdermal absorption of a drug [22]. In the present study, the conditions were the same for all the participants in each group, so it was not possible to determine the transdermal absorption of the drugs used with phonophoresis and iontophoresis according to the partition coefficient, as no studies provide these data for the drugs used. The degree of ionisation is also involved in drug absorption. Dexketoprofen is an acid with a pKa of 5.02. Using this information and the pH of the drugs used with iontophoresis and phonophoresis, it was possible to calculate the degree of ionisation. The gel used with phonophoresis has a pH range of 4.5 to 6.5, and the solution used in iontophoresis has a pH of 6.5 to 8.5. Drugs with a lower pH result in better absorption with both treatments because dexketoprofen is an acid. Focusing solely on the molecular chemistry, the authors believe that penetration of the drug was easier with phonophoresis because the gel has a lower pH than the solution used the iontophoresis. This could explain the finding that phonophoresis with dexketoprofen was more effective than iontophoresis with dexketoprofen in improving shoulder function post-treatment.

Intermittent or continuous application of iontophoresis is another factor that affects transcutaneous release of the drug. After the application of intermittent iontophoresis treatment, the amount of drug in the stratum corneum decreases, indicating increased penetration of the drug, undoubtedly due to better skin hydration [23]. In this study, iontophoresis was applied continuously. This may explain why the

drug was released more slowly, thereby delaying the appearance of the effects of iontophoresis.

To the authors' knowledge, no other studies have been undertaken to evaluate the effectiveness of phonophoresis and iontophoresis with dexketoprofen. Several studies support the use of ultrasound and iontophoresis to facilitate the transdermal penetration of drugs [17,23]. NSAIDs applied with phonophoresis improve strength and pain significantly in patients with carpal tunnel syndrome [24]. Ketoprofen administered with iontophoresis is therapeutically effective in post-traumatic and postoperative pathologies accompanied by pain and functional limitation [25]. As for the efficacy of ultrasound, the results are sometimes conflicting. Kromer *et al.* concluded that ultrasound is no more effective than placebo, and did not recommend its use in the treatment of SIS [26], while another recent study found that ultrasound therapy is beneficial in the treatment of SIS [8]. Alexander *et al.*'s literature review concluded that the physiological response to ultrasound depends on the intensity and frequency used, and in order to obtain clinical benefits, >720 J of energy must be released per session, or an average of approximately 4228 J per session, and the total time of exposure should be less than 5 hours [7]. In the present study, the ultrasound and phonophoresis treatments released 3600 J of energy per session and the total exposure time was 1 hour and 40 minutes.

The authors have been unable to find any other studies comparing ultrasound, iontophoresis and phonophoresis. Başkurt *et al.* found that naproxen (10%) applied with phonophoresis and iontophoresis is equally effective for the treatment of epicondylitis [27]. Phonophoresis with ibuprofen vs continuous-mode ultrasound in knee arthrosis was effective after 10 treatment sessions, with no differences between them [28]. Continuous-mode ultrasound and phonophoresis with fluocinonide (0.05%) were

equally effective for the treatment of soft tissue injuries [29]. Phonophoresis with ketoprofen improved pain significantly compared with ultrasound and placebo ultrasound at 8 weeks post-treatment in carpal tunnel syndrome, with no differences between ultrasound and post-treatment phonophoresis [30], as in the present study.

Alexander *et al.* recommended creating homogeneous treatment groups in terms of diagnosis and disease chronicity [7]. In the present study, the groups were homogeneous not only for these variables but also for sex, age, affected shoulder and intake of analgesics, which gives greater weight to the results obtained.

The daily activities of the participants were not monitored during the study, and the histopathological state of tendon lesions was not considered between the treatment groups. Participants diagnosed with tendinitis, tendinosis and/or partial tears in the study were included. According to Alexander *et al.*'s review, the heterogeneous nature of the type of injury in study participants may explain the minimal scientific evidence regarding the use of therapeutic ultrasound in soft tissue pathology of the shoulder [7]. However, although the present study did not differentiate between tendinitis and tendinosis, the three groups were homogeneous in terms of this characteristic, and ultrasound was found to be effective for the treatment of SIS, as were phonophoresis and iontophoresis.

It would have been interesting to evaluate the three variables at different points during the 20 sessions in order to determine when patients started to notice an improvement. This would have enabled the authors to determine, and perhaps reduce, the number of sessions required to obtain these improvements, and thus increase the efficiency of the treatment.

In future studies, the first 10 ultrasound sessions should be evaluated to ascertain their immediate effects, followed by 10 sessions of phonophoresis with NSAIDs for

which the improvements would be maintained over time. Future studies should focus on finding the most effective and efficient treatment protocol for improving patients' clinical symptoms, with consideration given to cost-effectiveness, i.e. analysing the necessary duration of treatment and its long-term benefits.

<A>Conclusion

The results of this study support the use of ultrasound, phonophoresis with dexketoprofen and iontophoresis with dexketoprofen for the treatment of SIS. Although ultrasound proved to be more effective than the physical agents with drugs in improving pain and shoulder function immediately after treatment, all three physical agents were found to be equally effective at 1 month post-treatment. This is because the benefits of ultrasound cease after treatment, while phonophoresis and iontophoresis with dexketoprofen continue to improve pain, shoulder function, and physical functioning and symptoms in the upper limb. A conservative therapy combining techniques with and without drugs is proposed for the treatment of SIS.

<A>Acknowledgements

The authors wish to thank Manuel Montero, who performed the imaging tests; Arnau Besora, who created the database; and Neus Abajo, who attended to the participants. The drugs used in the study were donated by Menarini.

Ethical approval: Clinical Research Ethics Committee of Sant Joan University Hospital, Reus, Spain (Ref. 09-10-29/10proj2).

Conflicts of interest: None declared.

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Table 1

Demographic characteristics of study participants

	Ultrasound	Phonophoresis	Iontophoresis	*P*-value
Age, mean (SD) (years)	54.2 (10.5)	52.9 (9.6)	56.1 (8.1)	0.42
Men, *n* (%)	14 (44)	12 (36)	16 (47)	0.67
Time from onset of SIS, mean (SD) (months)	7.4 (6.1)	8.0 (8.8)	6.7 (8.0)	0.51
Dominant shoulder injury, *n* (%)	21 (66)	24 (73)	22 (65)	0.75
Tendinitis and tendinosis, *n* (%)	28 (88)	26 (79)	27 (79)	0.60
Partial tear, *n* (%)	4 (13)	7 (21)	7 (21)	0.60

SIS, subacromial impingement sundrome; SD, standard deviation.

Table 2

Comparison of visual analogue scale (VAS), Constant–Murley Scale (CMS) and Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) scores between groups at baseline, post-treatment and 1 month post-treatment

Variable	Visit	Ultrasound	Phonophoresis	Iontophoresis
VAS (points)	Baseline	5.7 (1.8)	5.7 (1.5)	6.3 (2.0)
	Post-treatment	3.6 (1.9)	4.2 (1.8)	5.0 (1.7)[a]
	1 month post-treatment	3.8 (2.1)	3.7 (2.4)	4.2 (2.0)
DASH (%)	Baseline	45 (17)	45 (18)	52 (18)
	Post-treatment	31 (18)	37 (16)	41 (24)
	1 month post-treatment	33 (19)	32 (19)	39 (23)
CMS (points)	Baseline	75.0 (10.7)	77.7 (7.8)	71.3 (13.3)
	Post-treatment	83.3 (12.1)	82.7 (8.0)	75.0 (13.2)[a,b]
	1 month post-treatment	82.2 (13.4)	85.3 (7.0)	78.8 (12.9)

Data are expressed as mean (standard deviation).

[a]Significantly different from ultrasound group.

[b]Significantly different from phonophoresis group.

Table 3

Differences in visual analogue scale (VAS), Constant–Murley Scale (CMS) and Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) scores in relation to the baseline values

Variable	Visit	Ultrasound		Phonophoresis		Iontophoresis	
		Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value
VAS (points)	Post-treatment	-1.9 (-2.9 to -0.9)	<0.001	-1.7 (-2.6 to -0.7)	0.002	-1.4 (-2.3 to -0.4)	0.008
	1 month post-treatment	-1.8 (-2.7 to -0.9)	<0.001	-2.0 (-3.0 to -1.0)	<0.001	-2.3 (-3.3 to -1.3)	<0.001
DASH (%)	Post-treatment	-12 (-16.1 to -7.5)	<0.001	-5 (-10.6 to 0.2)	0.027	-10 (-16.8 to -2.2)	0.004
	1 month post-treatment	-12 (-18.6 to -5.8)	<0.001	-8 (-15.1 to -1.6)	0.018	-12 (-17.6 to -7.1)	<0.001
CMS (points)	Post-treatment	5.5 (1.6 to 9.3)	<0.001	4.1 (1.1 to 7.1)	0.020	3.3 (-2.2 to 8.8)	0.101
	1 month post-treatment	5.1 (1.4 to 8.7)	0.007	6.4 (3.1 to 9.6)	0.002	6.5 (0.3 to 12.7)	0.024

CI, confidence interval.