# Ultrasound guided lavage with corticosteroid injection versus sham lavage with and without corticosteroid injection for calcific tendinopathy of shoulder: randomised double blinded multi-arm study

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## ABSTRACT

### OBJECTIVE

To compare treatment effects between ultrasound guided lavage with corticosteroid injection and sham lavage with and without corticosteroid injection in patients with calcific tendinopathy of the shoulder.

### DESIGN

Pragmatic, three arm, parallel group, double blinded, sham controlled, randomised, superiority trial with repeated measurements over 24 months.

### SETTING

Six hospitals in Norway and Sweden.

### PARTICIPANTS

220 adults with calcific tendinopathy of the shoulder, persistent for at least three months.

### INTERVENTIONS

Ultrasound guided deposit lavage plus subacromial injection of 20 mg triamcinolone acetonide and 9 mL 1% lidocaine hydrochloride (lavage+steroid); sham lavage plus subacromial injection of 20 mg triamcinolone acetonide and 9 mL 1% lidocaine hydrochloride (sham lavage+steroid); or sham lavage plus subacromial injection of 10 mL 1% lidocaine hydrochloride (sham). All patients received a physiotherapeutic treatment regimen consisting of four home exercises.

### MAIN OUTCOME MEASURES

The primary outcome was the result on the 48 point scale (0=worst; 48=best) of the Oxford Shoulder Score (OSS) at four month follow-up. Secondary outcomes included measurements on the short form of the Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH) and of pain intensity up to 24 months. The influence of the size of the deposit at baseline and of the persistence or disappearance of the deposit was investigated.

### RESULTS

Data from 218 (99%) participants were included in the primary analysis. Differences between groups on the OSS at four months were not significant: lavage+steroid versus sham 0.2 (95% confidence interval −2.3 to 2.8; P=1.0); sham lavage+steroid versus sham 2.0 (−0.5 to 4.6; P=0.35); lavage+steroid versus sham lavage+steroid −1.8 (−4.3 to 0.7; P=0.47). After four months, 143 patients with insufficient treatment effect received supplementary treatment. At 24 months, none of the study procedures was superior to sham. No serious adverse events were reported.

### CONCLUSIONS

This study found no benefit for ultrasound guided lavage with a corticosteroid injection or for sham lavage with a corticosteroid injection compared with sham treatment in patients with calcific rotator cuff tendinopathy of the shoulder.

### TRIAL REGISTRATION

NCT02419040EudraCT 2015-002343-34; Ethical committee Norway 2015-002343-34; Ethical committee Sweden 2015/79-31; Clinicaltrials.gov NCT02419040.

## WHAT IS ALREADY KNOWN ON THIS TOPIC?

Ultrasound guided deposit lavage together with a steroid injection or a steroid injection alone are frequently used in the treatment of calcific tendinopathy of the shoulder

The effectiveness of these interventions, however, is insufficiently investigated

A comparison with sham treatment has never been made

## WHAT THIS STUDY ADDS

This trial shows that treatment benefits from ultrasound guided lavage with a steroid injection or from a steroid injection alone are not superior to those from sham treatment

This questions their use as treatment measures for patients with calcific tendinopathy and should lead to a critical reconsideration of the role of these methods in treatment algorithms

## Introduction

Calcific tendinopathy is a painful disorder of the shoulder, characterised by the deposition of calcium hydroxyapatite crystals in the tendinous part of the rotator cuff. A prevalence of up to 7.8% in asymptomatic shoulders and up to 42.5% in symptomatic shoulders has been reported.[1] According to current theories, pain is caused by tendon inflammation at the periphery of the deposit, by a rise in intratendinous pressure, or by impingement of the deposit under the acromion.[2] The cause of the condition is unknown. Different theories have been proposed, including overuse,[3] local ischaemia,[3] tenocyte metaplasia,[4] mis-differentiation of stem cells,[5] and genetic predisposition.[6 7] The course of the disease is thought to be cyclic and often self-limiting and has been described in four distinct phases of varying length and symptom intensity (the formative, resting, resorptive, and reparative phases).[4] In many cases, the cycle ends with spontaneous resorption of deposit and pain relief after

a few months. The individual course of the disease, however, is unpredictable and delayed courses are not uncommon. Given the often limited period with symptoms, the primary treatment approach should be symptom relieving and non-operative by use of steroids, non-steroidal anti-inflammatory drugs, analgesics, and physiotherapy. Refractory cases may be considered for further treatment by ultrasound guided lavage, extracorporal shock wave therapy, or surgical treatment.

Over the past few years ultrasound guided lavage together with a steroid injection has gained increasing popularity and has become the preferred method for many orthopaedic surgeons, radiologists, and physical medicine physicians. It has the advantage of being an outpatient procedure and targets both the surrounding inflammation and the deposit itself. Several cohort studies have reported good results with the technique, but studies with an adequate control group are lacking.[8-12] Without comparison with a sham or a no-treatment group, whether reported improvements are due to the treatment itself, the natural history of the disease, or a placebo effect is unclear.

We designed this study to assess the true effect of ultrasound guided lavage with a steroid injection for patients with calcific tendinopathy. The primary study aim was to compare the four month results between the three study groups: lavage plus steroid versus sham lavage plus steroid versus sham. Our hypothesis was that in comparison with each other, the outcome would be best for lavage plus steroid and poorest for sham.

## Methods

### Trial oversight

This study reports the results of a pragmatic, multicentre, randomised, three arm, parallel group, double blinded, sham controlled superiority trial with a 24 month follow-up that was conducted at five hospitals in Norway and one in Sweden. Departments of orthopaedics, radiology, and physical medicine and rehabilitation were involved in the study. The recruiting sites were Martina Hansens Hospital, Sandvika; Helse Fonna Hospital, Stord; Haraldsplass Deaconess Hospital, Bergen; Vestfold Hospital, Stavern; Oslo University Hospital, Oslo (all Norway); and Linköping University Hospital, Linköping, (Sweden). The trial protocol has been published previously.[13] Written informed consent was obtained from all participants after study information was given orally and in writing. The study was conducted in compliance with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice and under consideration of national laws and regulations, and it is reported in accordance with the CONSORT guidelines.

### Participants

We recruited study participants among patients referred from primary care services in whom a specialist in physical medicine or orthopaedic surgery had diagnosed calcific tendinopathy. Eligibility was based on the inclusion and exclusion criteria given in box 1.

### Trial procedures

Demographic and baseline data were collected at the primary consultation. Standard shoulder radiographs (anterior-posterior, lateral, and acromioclavicular views) were obtained and the size of the calcification was measured in the anterior-posterior plane both vertically and horizontally within four weeks before the intervention. The deposit was classified according to Molé as a type A (sharply delineated, dense, homogenous), B (sharply delineated, dense, multiple fragments), or C (heterogenous, fluffy).[17] Experienced sonographers examined both shoulders sonographically according to a published examination protocol.[18] The anterior-posterior size of the deposit was measured sonographically on a short axis view and the medial-lateral size on a long axis view. Use of analgesics had to be terminated 48 hours before baseline. The intervention day was usually scheduled within six weeks after the primary consultation.

Before randomisation, patients filled in digital versions of the Oxford Shoulder Score (OSS)[19 20]; the short form of the Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH) upper extremity score[21 22]; the EuroQol-5D-5L (EQ-5D-5L) general health score[23 24]; the visual analogue scale (VAS) for pain at rest, at night, and during activity over the previous week, labelled 0 for no pain and 100 for worst imaginable pain; and the Stanford expectations of treatment scale (SETS).[25] We selected the study scores to allow a broad evaluation of shoulder function and therefore included a shoulder specific score (OSS), an upper extremity specific score (QuickDASH), and symptom specific scales (VAS for pain). The OSS has been validated for pathologies of the rotator cuff, including calcific tendinopathy, and exists in Norwegian and Swedish translation.[19 26 27] It ranges from 0 to 48 with a lower result indicating a greater degree of disability. The QuickDASH ranges from 0 to 100 with a higher score indicating greater disability. The EQ-5D-5L measures general health related quality of life, and results can be presented as an index value with a value of 1 representing a state of perfect health. The SETS measures positive and negative pre-treatment expectations, each on a scale from 1 to 7, with higher scores representing higher degrees of positive and negative expectations, respectively. An adverse event diary was handed out, and patients were instructed to note any change in their health condition that they perceived as an adverse event together with the type of the event, its date of occurrence, its severity, and whether treatment was needed.

### Randomisation

Randomisation to one of the three treatment options took place on intervention day by an online central randomisation system (web-CRF) developed and administered by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular

**Box 1: Eligibility criteria for participants**

**Inclusion criteria**

- Age ≥30 years
- Three months or more of shoulder pain
- Moderate to severe pain localised on the top and/or lateral side of the shoulder, exaggerated by activities above shoulder level
- Pain at night when lying on the affected shoulder
- A painful arc[14]
- A positive Hawkin's test[15] or Neer's sign[16] for impingement
- A finding of one or more calcifications ≥5 mm in diameter on a standard anterior posterior radiograph, localised proximally to the greater tubercle, taken not more than four weeks before the intervention
- A sonographic finding of one or more calcifications ≥5 mm in size on the short or long axis view, localised in the supraspinatus or infraspinatus tendon
- A morphological radiographic appearance of Molé type A, B or C[17]
- The ability to understand written and spoken Norwegian (Swedish)
- An existing expected cooperation of the patient for the treatment and the follow-up

**Exclusion criteria**

- The presence of clinical and radiological signs of a recent spontaneous release of the calcific deposit, such as a sudden change in size or density of the deposit on ultrasonography together with an acute onset of extreme shoulder pain
- Clinical signs of shoulder instability, glenohumeral arthritis, acromioclavicular joint pathology, inflammatory arthropathy, fibromyalgia, frozen shoulder, or cervical radiculopathy
- Sonographic signs of a rotator cuff tear (full thickness or partial thickness) or of a tear or a dislocation of the long head of the biceps tendon
- A history of surgery or barbotage of the relevant shoulder
- A subacromial injection with a corticosteroid or treatment by extracorporeal shockwave therapy during the last three months before inclusion
- Medical contraindications for any of the invasive procedures
- One of the following contraindications for the use of lidocaine 10 mg/mL: serious hypovolaemia, known cardiac conduction disturbances, epilepsy or porphyrias, or known serious dysfunction of the liver or the kidneys
- One of the following contraindications for the use of triamcinolone 20 mg/mL: systemic infections unless specific anti-infective therapy is used; local infection in the area of application; recent vaccination with live vaccines; or known diabetes mellitus, renal or cardiac insufficiency, ulcerating colitis, gastric ulcer, psychosis, idiopathic thrombocytopenic purpura, or ocular herpes simplex
- Concomitant medication with one of the following medicinal products:
  - Because of possible pharmacokinetic interactions with the study medicaments—antiarrythmics such as mexiletine or class III antiarrythmics (eg, amiodarone), muscle relaxants (eg, suxamethonium) or antipsychotics (eg, pimozide, sertindole, olanzapine, quetiapine, zotepine, tropisetrone, dolasetron), antibiotics such as quinopristin/dalfopristin
  - Because of an increased risk for haemorrhage or haematoma—anticoagulants such as warfarin (if international normalised ratio >2) or novel oral anticoagulants
- A history of previous allergic/hypersensitivity reactions related to the study medication
- Knowledge of an ongoing pregnancy (fertile women not using contraception and who are uncertain whether they are pregnant or not will have to perform a pregnancy test)
- Breastfeeding women

Medicine, University of Science and Technology, Trondheim, Norway. After registration, the patient's intervention group was displayed on-screen for the interventionalist only. Allocation was 1:1:1. We used block randomisation with varying block lengths and stratification according to hospital. The randomisation list remained at the University of Trondheim and, consequently, was inaccessible for the investigators, care providers, and outcome assessors at the study centres for the whole duration of the study.

### Intervention

Interventions were performed in an outpatient clinical setting by orthopaedic surgeons, physical medicine and rehabilitation physicians, and a radiologist, all with at least five years of experience with interventional ultrasonography. Specifications for the ultrasonography equipment in use are provided in supplementary table A. To ensure consistency, we sent a video of the procedure to all trial sites before the start of the study.[13] After sterile skin preparation, the subacromial-subdeltoid bursa was anesthetised (lidocaine hydrochloride 10 mg/mL with adrenaline 5 µg/mL). In the lavage plus steroid group, under sonographic monitoring, the deposit was punctured and then flushed, using a syringe with saline solution. Flushing was continued until the backflow became clear. If no material could be extracted, repeated perforation of the deposit was carried out. In the sham lavage plus steroid group and the sham group, the lavage procedure was mimicked for five minutes, which corresponds to the time needed for a lavage procedure. Finally, in all three groups, a new needle was introduced into the subacromial bursa and 1 mL of triamcinolone 20 mg/mL and 9 mL of lidocaine hydrochloride 10 mg/mL (in the two steroid groups) or 10 mL of lidocaine hydrochloride 10 mg/mL (in the sham group) were injected. A detailed description of the method is given in appendix 1.

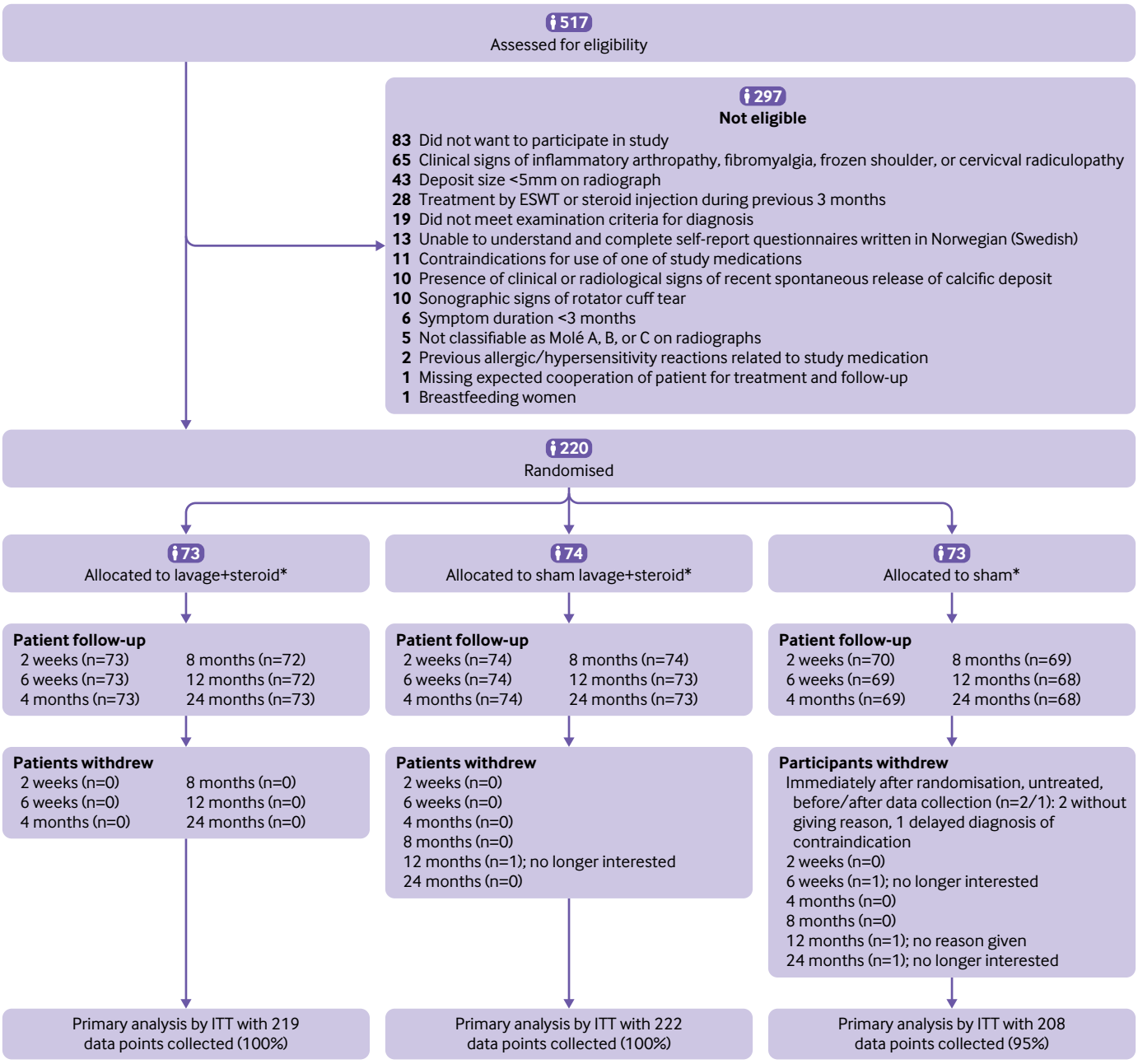


**Fig 1 | Trial flowchart. Screening, randomisation, and primary outcome population. ESWT=extracorporal shock wave therapy; ITT=intention to treat. *Protocol violations related to treatment (supplementary treatment was given) were noted before the 4 month follow-up for 14 participants (4 for lavage+steroid, 3 for sham lavage+steroid, 7 for sham) and after the 4 month follow-up for 129 patients (42 for lavage+steroid, 50 for sham lavage+steroid, and 37 for sham)**

### Post-intervention treatment

After the intervention, prescription-free analgesics and use of the shoulder for routine activities were permitted. Within one week after treatment, patients were instructed to start on a standardised home based physiotherapeutic treatment regimen, consisting of four shoulder exercises that had to be done twice daily. Exercises were presented on an illustrated instructional folder and as a video.[13 28] Before the start of the programme, a physiotherapist at each hospital showed the patients how to do the exercises correctly. Patients had to maintain a regular protocol over eight weeks, during which they had to record each training session with the date and number of exercises performed.

Change of treatment was avoided until the four month follow-up if possible. Patients who had symptoms sufficiently severe that they could not wait until four months were re-examined earlier by a blinded follow-up assessor. If secondary treatment was found to be indicated, patients were offered treatment measures such as ultrasound guided lavage, steroid injection, guided physiotherapy, or surgery, depending on findings and the patient's preferences.


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**Table 1 | Baseline characteristics of trial participants. Values are numbers (percentages) unless stated otherwise**

| Baseline characteristics | Lavage+steroid (n=73) | Sham lavage+steroid (n=74) | Sham (n=71) |
|---|---|---|---|
| Mean (SD) age, years | 50.5 (8.5) | 49.0 (8.8) | 49.3 (9.0) |
| Women | 51 (70) | 47 (64) | 46 (65) |
| Right shoulder affected | 43 (59) | 51 (69) | 35 (49) |
| Bilateral calcifications | 24 (33) | 30 (41)* | 26 (37)† |
| Mean (SD) duration of symptoms, months | 32 (26) | 32 (28) | 34 (43) |
| Shoulder demands‡ | 24 (33) | 31 (42) | 27 (38) |
| Earlier treatment: | | | |
| Physiotherapy | 22 (30) | 18 (24) | 25 (35) |
| Steroid injection | 8 (11) | 7 (10) | 4 (6) |
| ESWT | 4 (6) | 3 (4) | 1 (1) |
| Analgesics | 14 (19) | 17 (23) | 11 (15) |
| Physiotherapy and steroid injection | 9 (12) | 16 (22) | 12 (17) |
| Physiotherapy and ESWT | 4 (6) | 4 (5) | 2 (3) |
| No earlier treatment | 12 (16) | 9 (12) | 17 (24) |
| Non-smokers | 62 (85) | 55 (74) | 58 (82) |
| Molé classification[17]: | | | |
| Type A | 43 (59) | 45 (61) | 41 (58) |
| Type B | 25 (34) | 22 (30) | 25 (36) |
| Type C | 5 (7) | 7 (10) | 5 (7) |
| Mean (SD) deposit size on radiograph, anterior-posterior view, mm: | | | |
| Vertically | 6.4 (2.3) | 6.5 (2.9) | 7.1 (4.8) |
| Horizontally | 16.1 (7.6) | 15.2 (6.8) | 15.4 (5.7) |
| Mean (SD) deposit size on ultrasonography, mm: | | | |
| Anterior-posterior plane, horizontally | 11.4 (4.1) | 12.3 (4.3) | 12.2 (4.1) |
| Medial-lateral plane, horizontally | 12.3 (4.2) | 12.4 (4.2) | 12.6 (4.5) |
| Deposit location: | | | |
| Supraspinatus tendon | 31 (43) | 26 (35) | 25 (35) |
| Supraspinatus and infraspinatus tendon | 14 (19) | 20 (27) | 19 (27) |
| Infraspinatus tendon | 28 (38) | 28 (38) | 27 (39) |
| Mean (SD) distance to LHBT, mm | 13.1 (7.0) | 13.7 (7.0) | 13.5 (7.3) |
| Treating hospital: | | | |
| Martina Hansens Hospital | 29 (40) | 29 (39) | 29 (41) |
| Helse Fonna Hospital | 7 (10) | 7 (10) | 6 (9) |
| Oslo University Hospital | 4 (6) | 5 (7) | 5 (7) |
| Vestfold Hospital | 10 (14) | 11 (15) | 9 (13) |
| Haraldsplass Deaconess Hospital | 6 (8) | 5 (7) | 5 (7) |
| Linköping University Hospital | 17 (23) | 17 (23) | 17 (24) |
| Mean (SD) SETS points: | | | |
| Positive treatment expectations | 5.3 (1.2) | 5.3 (1.0) | 5.0 (1.1) |
| Negative treatment expectations | 2.9 (1.6) | 2.6 (1.6) | 3.1 (1.7) |

ESWT=extracorporeal shock wave therapy; LHBT=long head of the biceps tendon; SD=standard deviation; SETS=Stanford expectation of treatment scale (positive expectations: 1=minimal positive treatment expectations, 7=maximal positive treatment expectations; negative expectations: 1=minimal negative treatment expectations, 7=maximal negative treatment expectations).
*Three responses missing.
†One response missing.
‡Working with arms above the shoulders or repetitive lifting of heavy objects.

### Blinding

The study was conducted double blinded, with masking of patients and follow-up assessors for the patient's treatment allocation. During the intervention, patients were blinded by blocking their view on the ultrasonograph screen and the doctor's working space with opaque sheets and by mimicking barbotage in the sham lavage plus steroid and sham groups. The blinding effect was assessed by asking the patients directly after the treatment, and again after two and six weeks, which treatment they believed they had received. Response options were one of the three treatment groups or "I don't know." After study treatment was given, the interventionalists had no further contact with the patients. Follow-up was performed by blinded assessors, and statistical analyses were conducted blinded for treatment groups.

### Patient follow-up

Outcome data were collected two and six weeks and four, eight, 12, and 24 months after the intervention. The two week and six week follow-ups and the eight month and 12 month follow-ups were digital at-home follow-ups, whereas patients had to attend hospital after four months and 24 months for supplementary clinical follow-up, including registration of post-intervention use of prescription analgesics and radiographic examination. The primary outcome was the four month result on the OSS. Secondary outcomes were the results on the OSS at the other points of follow-up; the results on the QuickDASH score, on the VAS for pain at night, at rest, and during activity, and on the EQ-5D-5L at all follow-up points; and the number of patients in each treatment group who changed treatment. Before the start of the study, we planned to explore possible associations between the

**Table 2 | Summary of primary and secondary outcomes by treatment group. Values are mean (SD) score, unless stated otherwise**

| Outcome measures | Lavage+steroid¶** (n=73/73/73/73/73/72/73) | Sham lavage+steroid¶** (n=74/74/74/74/74/73/73) | Sham¶** (n=71/70/69/69/69/68/68) | Between group difference (95% CI)§ | | |
|---|---|---|---|---|---|---|
| | | | | Lavage+steroid v sham | Sham lavage+steroid v sham | Lavage+steroid v sham lavage+steroid |
| OSS | | | | | | |
| Baseline | 29.7 (7.4) | 29.6 (7.6) | 30.6 (6.3) | - | - | - |
| 2 weeks | 31.4 (10.0) | 35.5 (9.3) | 31.9 (8.0) | −0.03 (−2.58 to 2.52) | 4.12 (1.58 to 6.66)† | −4.15 (−6.66 to −1.64)† |
| 6 weeks | 36.1 (9.2) | 37.1 (8.9) | 33.0 (7.8) | 3.66 (1.11 to 6.22)* | 4.64 (2.10 to 7.19)‡ | −0.98 (−3.49 to 1.54) |
| 4 months | 33.5 (8.7) | 35.4 (7.9) | 33.8 (8.9) | 0.22 (−2.34 to 2.77) | 2.04 (−0.51 to 4.59) | −1.82 (−4.33 to 0.70) |
| 8 months | 36.0 (8.6) | 36.0 (8.9) | 37.2 (7.8) | −0.66 (−3.22 to 1.91) | −0.70 (−3.25 to 1.85) | 0.04 (−2.48 to 2.56) |
| 12 months | 38.2 (8.2) | 36.4 (9.5) | 38.6 (7.8) | −0.04 (−2.61 to 2.54) | −1.80 (−4.36 to 0.77) | 1.76 (−0.77 to 4.29) |
| 24 months | 40.9 (6.7) | 36.9 (9.0) | 39.4 (8.5) | 2.02 (−0.55 to 4.58) | −2.10 (−4.64 to 0.48) | 4.10 (1.58 to 6.62)† |
| QuickDASH | | | | | | |
| Baseline | 36.1 (18.0) | 36.5 (18.4) | 33.8 (16.5) | - | - | - |
| 2 weeks | 24.2 (20.1) | 22.5 (18.6) | 28.8 (17.8) | 5.96 (0.64 to 11.28) | 7.90 (2.59 to 13.21)* | −1.94 (−7.19 to 3.31) |
| 6 weeks | 17.6 (18.0) | 19.3 (18.4) | 28.2 (20.4) | 11.77 (6.43 to 17.11)‡ | 10.34 (5.02 to 15.66)‡ | 1.44 (−3.81 to 6.68) |
| 4 months | 26.6 (21.2) | 22.2 (18.1) | 25.4 (20.9) | 0.04 (−5.30 to 5.38) | 4.60 (−0.73 to 9.91) | −4.55 (−9.80 to 0.70) |
| 8 months | 22.1 (19.6) | 24.2 (21.1) | 19.6 (16.6) | −1.23 (−6.58 to 4.13) | −3.17 (−8.50 to 2.15) | 1.95 (−3.32 to 7.21) |
| 12 months | 17.4 (16.8) | 22.0 (20.7) | 17.3 (17.0) | 0.85 (−4.52 to 6.23) | −3.64 (−8.99 to 1.72) | 4.49 (−0.79 to 9.77) |
| 24 months | 10.0 (13.4) | 19.6 (21.3) | 14.7 (15.6) | 5.97 (0.61 to 11.32) | −3.57 (−8.93 to 1.78) | 9.54 (4.28 to 14.8)‡ |
| VAS pain at night | | | | | | |
| Baseline | 51.6 (26.6) | 57.1 (25.7) | 52.0 (24.2) | - | - | - |
| 2 weeks | 30.0 (27.9) | 29.1 (27.9) | 41.0 (24.9) | 11.24 (2.52 to 19.95)* | 14.38 (5.68 to 23.07)† | −3.14 (−11.75 to 5.47) |
| 6 weeks | 23.3 (26.4) | 28.7 (29.9) | 43.7 (26.2) | 20.36 (11.62 to 29.11)‡ | 17.28 (8.55 to 26.00)‡ | 3.09 (−5.52 to 11.69) |
| 4 months | 39.2 (31.8) | 33.1 (31.8) | 35.1 (30.2) | −4.16 (−12.91 to 4.58) | 4.26 (−4.46 to 12.99) | −8.43 (−17.03 to 0.18) |
| 8 months | 29.9 (29.1) | 40.0 (31.2) | 29.1 (27.3) | −0.72 (−9.49 to 8.05) | −8.57 (−17.30 to 0.15) | 7.86 (−0.78 to 16.49) |
| 12 months | 22.5 (24.5) | 32.9 (34.9) | 23.4 (23.3) | 0.40 (−8.40 to 9.20) | −7.64 (−14.72 to 4.67) | 8.04 (−0.62 to 16.70) |
| 24 months | 17.9 (28.1) | 30.6 (31.6) | 22.5 (26.6) | 4.36 (−4.41 to 13.14) | −6.15 (−14.93 to 2.62) | 10.52 (1.89 to 19.15) |
| VAS pain at rest | | | | | | |
| Baseline | 38.3 (23.0) | 45.0 (24.7) | 36.0 (23.5) | - | - | - |
| 2 weeks | 23.9 (23.5) | 25.0 (25.2) | 32.5 (23.8) | 9.83 (2.31 to 17.35)* | 11.67 (4.14 to 19.20)† | −1.84 (−9.28 to 5.59) |
| 6 weeks | 16.1 (22.4) | 23.4 (26.9) | 30.0 (24.5) | 14.76 (7.21 to 22.30)‡ | 10.38 (2.84 to 17.94)* | 4.37 (−3.07 to 11.81) |
| 4 months | 28.1 (29.3) | 27.0 (27.7) | 26.4 (26.6) | −0.81 (−8.35 to 6.74) | 3.29 (−4.27 to 10.84) | −4.09 (−11.53 to 3.35) |
| 8 months | 22.4 (27.3) | 30.7 (30.4) | 21.8 (21.8) | 0.46 (−7.11 to 8.03) | −5.07 (−12.62 to 2.48) | 5.53 (−1.93 to 12.98) |
| 12 months | 15.5 (21.1) | 28.8 (29.6) | 18.1 (21.1) | 3.24 (−4.35 to 10.84) | −7.18 (−14.77 to 0.42) | 10.42 (2.94 to 17.90)* |
| 24 months | 10.6 (19.6) | 22.7 (26.8) | 16.8 (22.3) | 7.27 (−0.30 to 14.84) | −2.00 (−9.60 to 5.59) | 9.27 (1.82 to 16.73)* |
| VAS pain at activity | | | | | | |
| Baseline | 66.4 (20.7) | 70.5 (20.2) | 65.0 (23.2) | - | - | - |
| 2 weeks | 40.6 (28.6) | 42.1 (29.8) | 56.8 (24.6) | 17.32 (8.06 to 26.58)‡ | 17.81 (8.56 to 27.06)‡ | −0.49 (−9.64 to 8.65) |
| 6 weeks | 31.6 (28.6) | 36.9 (30.7) | 56.1 (26.9) | 25.39 (16.10 to 34.69)‡ | 22.04 (12.76 to 31.32)‡ | 3.36 (−5.78 to 12.50) |
| 4 months | 45.6 (33.1) | 44.4 (31.9) | 48.1 (30.9) | 3.37 (−5.92 to 12.66) | 6.61 (−2.67 to 15.89) | −3.24 (−12.38 to 5.90) |
| 8 months | 37.3 (34.0) | 48.2 (32.6) | 38.0 (28.4) | 1.59 (−7.73 to 10.91) | −7.29 (−16.57 to 1.99) | 8.89 (−0.28 to 18.06) |
| 12 months | 31.1 (27.8) | 43.2 (35.0) | 32.7 (26.5) | 2.48 (−6.87 to 11.83) | −7.79 (−17.13 to 1.54) | 10.28 (1.08 to 19.47) |
| 24 months | 21.3 (28.0) | 38.4 (35.2) | 29.8 (28.7) | 9.41 (0.09 to 18.73) | −5.88 (−15.21 to 3.45) | 15.29 (6.12 to 24.46)† |
| EQ-5D-5L | | | | | | |
| Baseline | 0.76 (0.14) | 0.72 (0.20) | 0.73 (0.16) | - | - | - |
| 2 weeks | 0.84 (0.11) | 0.84 (0.12) | 0.79 (0.16) | 0.05 (0.00 to 0.09) | 0.06 (0.01 to 0.10) | −0.01 (−0.05 to 0.04) |
| 6 weeks | 0.87 (0.15) | 0.84 (0.15) | 0.77 (0.20) | 0.09 (0.04 to 0.13)‡ | 0.08 (0.03 to 0.12)† | 0.01 (−0.03 to 0.06) |
| 4 months | 0.80 (0.19) | 0.82 (0.15) | 0.81 (0.18) | −0.02 (−0.07 to 0.02) | 0.01 (−0.03 to 0.06) | −0.04 (−0.08 to 0.01) |
| 8 months | 0.85 (0.15) | 0.79 (0.20) | 0.84 (0.15) | 0.00 (−0.04 to 0.05) | −0.05 (−0.09 to −0.01) | 0.05 (0.00 to 0.09) |

(*Continued*)

**Table 2 | Continued**

| Outcome measures | Lavage+steroid¶** (n=73/73/73/73/72/73) | Sham lavage+steroid¶** (n=74/74/74/74/74/73/73) | Sham¶** (n=71/70/69/69/69/68/68) | Between group difference (95% CI)§ | | |
|---|---|---|---|---|---|---|
| | | | | Lavage+steroid v sham | Sham lavage+steroid v sham | Lavage+steroid v sham lavage+steroid |
| 12 months | 0.87 (0.12) | 0.81 (0.18) | 0.85 (0.14) | 0.00 (−0.05 to 0.05) | −0.04 (−0.08 to 0.01) | 0.04 (−0.01 to 0.08) |
| 24 months | 0.92 (0.08) | 0.84 (0.18) | 0.91 (0.11) | 0.00 (−0.04 to 0.05) | −0.06 (−0.11 to −0.01)* | 0.06 (0.02 to 0.11)* |

CI=confidence interval; EQ-5D-5L=general health index (1.00=status of full health); n=number of patients at seven time points; OSS=Oxford Shoulder Score (score range 0-48; lower results indicate greater degree of disability); QuickDASH=shortened version of Disabilities of the Arm, Shoulder, and Hand questionnaire (score range 0-100; higher scores indicate greater degree of disability); SD=standard deviation; VAS=visual analogue scale for pain (scales are labelled 0 for no pain at left and 100 for worst imaginable pain at right).
*P=0.01 to <0.05.
†P=0.001 to <0.01.
‡P<0.001.
§Values are adjusted for baseline measurements of variable. Positive values indicate better result for first group in comparison. P values for pairwise comparisons are corrected according to Bonferroni.
¶Values are raw measurement data.
**Protocol violations related to treatment (supplementary treatment was given during follow-up) were noted. Between baseline and 2 weeks: 1 for lavage+steroid, 0 for sham lavage+steroid, 1 for sham; between 2 and 6 weeks: 1 for lavage+steroid, 1 for sham lavage+steroid, 2 for sham; between 6 weeks and 4 months: 2 for lavage+steroid, 2 for sham lavage+steroid, 4 for sham; between 4 and 8 months: 38 for lavage+steroid, 43 for sham lavage+steroid, 34 for sham; between 8 and 12 months: 2 for lavage+steroid, 5 for sham lavage+steroid, 2 for sham; between 12 and 24 months: 2 for lavage+steroid, 2 for sham lavage+steroid, 1 for sham. Patients who received multiple supplementary treatments are registered only once.

primary outcome and the change in the appearance of the deposit on radiographs from baseline to follow-up (whether unchanged, changed but still visible, or disappeared), the volume of extracted calcium in the lavage group (whether ≤0.1 mL or >0.1 mL), the size of the calcification on sonography at baseline (whether ≤12.5 mm or >12.5 mm in the longitudinal or horizontal plane), the adherence to the programme of home exercises, and the patients' positive or negative treatment expectations as given by the SETS.[25] The appearance of deposits on radiographs was examined after the last follow-up had been done. We collected radiographs from the study hospitals in one database, and two of the authors (SM, OME) assessed them independently, blinded for the patient's treatment group. They compared the deposits with baseline and registered them as "unchanged," "changed but still visible," or "disappeared." In a following consensus meeting, results were compared between the examiners and all differing opinions were resolved with a consensus discussion.

### Sample size

Sample size was calculated for an analysis of variance of our primary outcome, the result on the OSS after four months. We found that 60 patients were needed in each treatment group to detect a minimally important difference of 4 (SD 7) points,[27] with a power of 90% and a two sided significance level of 0.05. To compensate for an expected 15% dropout rate, we predefined our required sample size as 210 participants. A supplementary analysis showed that this sample size also allowed for pairwise post hoc t test comparisons between the three treatment groups, still with a significance level after Bonferroni correction of 0.017 but with a power of approximately 80%.

### Statistical analysis

We present categorical baseline data as number of cases with percentages and continuous data as means with standard deviations. We used a linear mixed model for repeated measurements for analysis. Analyses of the primary and secondary continuous outcomes (OSS; QuickDASH; VAS for pain at rest, at night, and during activity; EQ-5D-5L) were adjusted for baseline differences and were performed according to intention to treat. We estimated the linear mixed model by using linear maximum likelihood and included a random intercept, measure of the baseline value as a covariate, and observation time after intervention and type of intervention with their interaction term as factors. We used mean differences (95% confidence intervals) between groups at all follow-ups from the linear mixed model to assess differences between interventions. We considered a two sided P value ≤0.05 to be significant. We did post hoc pairwise comparisons for the primary outcome with P value adjustments according to Bonferroni. We handled missing values by using mixed model analysis. We did supplementary per protocol analyses on the four month and 24 month results of the OSS based on the patients who had adhered to

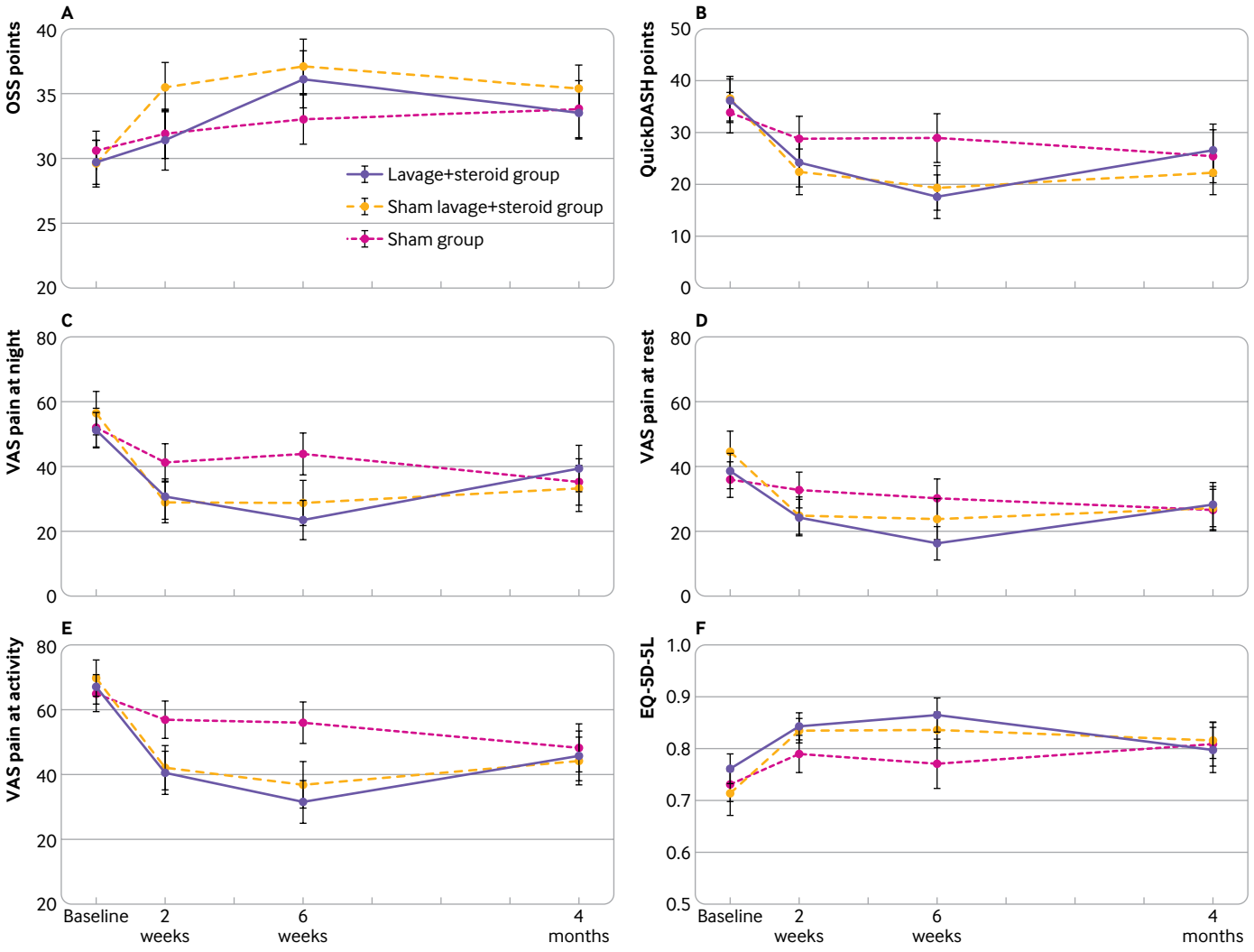


**Fig 2 | Results by treatment group. Whiskers represent 95% confidence intervals. X axes are not proportionally displayed. (A) Oxford Shoulder Score (OSS). Y axis shows interval only from 20 to 40 points. Higher score indicates better shoulder function. (B) Shortened version of Disabilities of the Arm, Shoulder, and Hand questionnaire (QuickDASH). Y axis shows interval only from 0 to 50 points. Lower score indicates better upper extremity function. (C) Visual analogue scale (VAS) for pain at night by treatment group. Y axis shows interval only from 0 to 80 mm. Lower result indicates less pain. (D) VAS for pain at rest. Y axis shows interval only from 0 to 80 mm. Lower result indicates less pain. (E) VAS for pain at activity. Y axis shows interval only from 20 to 80 mm. Lower result indicates less pain. (F) EQ-5D-5L general health score. Y axis shows only interval from 0.50 to 1.0 index points. Higher index value indicates better health related quality of life**

the allocated treatment regimen. For patients who had received supplementary treatment, we present the number of cases in each supplementary treatment group and mean values on the OSS at baseline and at four and 24 months.

We did several exploratory analyses for the impact of prespecified categorical factors on the OSS at the four month follow-up. We used two way between groups analysis of variance to explore the effect of treatment group and deposit size at baseline, of treatment group and deposit appearance at follow-up, and of treatment group and adherence to the exercise programme. We used supplementary one way analysis of variance to compare the effect of treatment group on the primary outcome separately for the two groups of deposit sizes. We used an independent t test to assess the effect of the volume of retrieved calcium during lavage on the result. We used one way analysis of variance to investigate the influence of appearance of deposit on the OSS at 24 months. We investigated the relation between the patients' positive and negative treatment expectations and the outcome on the OSS at four months by using the Pearson correlation coefficient. We assessed the success of blinding by calculating the blinding index according to James at three time points.[29] We investigated clinical safety by assessing procedure related complications and adverse events in a descriptive manner. We used Stata/SE 17.0 and SPSS version 28 for statistical analyses.

### Patient and public involvement

Patients were not involved in setting the research question and the outcome measures, or in the design and implementation of the study, primarily because patient and public involvement was not common in the study countries when the study was initiated. Advisory


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Table 3 | Results according to as-treated principle. Values are mean (SD) score

| Primary treatment | Supplementary treatment measures during follow-up* (No of patients) | OSS | | |
|---|---|---|---|---|
| | | Baseline | 4 months | 24 months |
| Lavage+steroid | No supplementary treatment (27/27/27) | 29.6 (8.1) | 38.4 (8.2) | 40.0 (6.9) |
| | Physiotherapy (17/17/17) | 27.8 (8.0) | 30.5 (9.2) | 41.6 (6.0) |
| | Steroid injection with or without physiotherapy (18/18/18) | 32.3 (12.3) | 31.0 (7.6) | 40.7 (7.7) |
| | Re-lavage (5/5/5) | 28.8 (2.7) | 28.0 (2.7) | 41.2 (7.4) |
| | Surgery (5/5/5) | 34.0 (4.3) | 31.0 (5.7) | 42.8 (3.8) |
| Sham lavage+steroid | No supplementary treatment (21/21/20) | 31.2 (7.5) | 37.7 (8.4) | 38.6 (8.2) |
| | Physiotherapy (12/12/12) | 27.8 (6.5) | 34.5 (5.4) | 35.7 (8.6) |
| | Steroid injection with or without physiotherapy (13/13/13) | 35.7 (7.9) | 36.5 (6.3) | 33.7 (11.1) |
| | Lavage (22/22/22) | 29.3 (7.5) | 32.8 (9.6) | 37.5 (8.4) |
| | Surgery (4/4/4) | 28.3 (13.6) | 37.8 (5.9) | 35.8 (12.6) |
| Sham | No supplementary treatment (27/26/26) | 32.0 (6.0) | 35.7 (9.2) | 42.6 (7.3) |
| | Physiotherapy (12/12/11) | 28.5 (4.9) | 36.4 (5.0) | 35.2 (9.0) |
| | Steroid injection with or without physiotherapy (15/15/15) | 30.8 (7.6) | 32.8 (10.2) | 37.7 (9.3) |
| | Lavage (11/11/11) | 32.8 (8.3) | 31.6 (10.0) | 41.5 (5.9) |
| | Surgery (5/5/4) | 23.8 (4.0) | 28.4 (6.9) | 35.0 (12.8) |

OSS=Oxford Shoulder Score; SD=standard deviation.
*For patients who received multiple supplementary treatments, last treatment given is listed. One patient in lavage+steroid group, two patients in sham lavage+steroid group, and one patient in sham group received other supplementary treatments such as extracorporal shock wave therapy, acupuncture, or synovectomy, which are not listed in table.

panels of patients and public members had not yet been established and necessary experience how to best conduct this process was lacking in our research team.

## Results

Between 24 April 2015 and 3 March 2020, 517 consecutive patients with a radiographic finding of a calcification in the rotator cuff were assessed for eligibility. Of these, 220 patients who fulfilled the study's inclusion and exclusion criteria were included in the trial and were randomly assigned to the three treatment groups (fig 1). Three patients randomised to the sham group did not receive treatment, two because they no longer wanted to participate after randomisation and one because of an overlooked exclusion criterion that was discovered before treatment was given. Collection of data was not possible for two of these patients, and 218 patients were included in the intention-to-treat analyses. Baseline characteristics were balanced between groups (table 1). Data completeness was 98.2% at four months and 97.3% at 24 months. Fourteen patients received supplementary treatment before the four month follow-up (four in the lavage plus steroid group, three in the sham lavage plus steroid group, seven in the sham group) and 129 between the four and 24 month follow-ups. After the four month follow-up, 28 patients insisted on being unblinded and were informed about the treatment they had received.

### Results up to the four month follow-up

#### *Primary outcome*

At four months, mean improvement from baseline on the 48 point scale of the OSS was 3.9 (95% confidence interval 1.9 to 5.9) for lavage plus steroid, 5.7 (3.8 to 7.6) for sham lavage plus steroid, and 3.2 (1.3 to 5.2) for sham. Linear mixed model estimated differences between groups were not significant, with 0.22 (95% confidence interval −2.34 to 2.77; P=1.0) between lavage plus steroid and sham, 2.04 (−0.51 to 4.59; P=0.35) between sham lavage plus steroid and sham, and −1.82 (−4.33 to 0.70; P=0.47) between lavage plus steroid and sham lavage plus steroid (table 2; fig 2, A). Results from a supplementary per protocol analysis (with exclusion of the participants who switched treatment before four months) were not different from those from the intention-to-treat analysis (supplementary table B).

#### *Secondary outcomes*

Lavage plus steroid was superior to sham on all outcome scores at six weeks and, in addition, on the three pain scores at two weeks. Sham lavage plus steroid was superior to sham at two and six weeks on all outcome scores with exception of the EQ-5D-5L at two weeks. Sham lavage plus steroid was superior to lavage plus steroid only on the OSS after two weeks. At four months, however, differences were no longer significant on any of the outcome measures (table 2; fig 2).

### Results after four month follow-up

From baseline to 24 months, 143 patients (46 in the lavage plus steroid group, 53 in the sham lavage plus steroid group, 44 in the sham group) received a total of 193 secondary treatment measures, including guided physiotherapy, steroid injections, first time or repeated lavage, or acromioplasty with or without deposit removal (supplementary table C). Analysis by intention to treat at 24 months showed that neither lavage plus steroid nor sham lavage plus steroid was superior to sham on any of the study's outcome scores (table 2). Likewise, neither a per protocol analysis (with the treatment switchers excluded) nor an as-treated analysis (with the treatment switchers analysed according to the actual treatment they had received) showed an advantage of the active study treatments over sham on any of the study scales (supplementary table B; table 3).

We found differences by intention to treat at 24 months only for the comparison between lavage plus steroid and sham lavage plus steroid, with better results

for lavage plus steroid on the OSS with 4.10 (1.58 to 6.62; P=0.003), on the QuickDASH with 9.54 (4.28 to 14.8; P<0.001), on the VAS for pain at rest with 9.27 (1.82 to 16.73; P=0.003), on the VAS for pain during activity with 15.29 (6.12 to 24.46; P=0.003), and on the EQ-5D-5L with 0.06 (0.02 to 0.11; P=0.02) (table 2).

### Prespecified subgroup analyses

#### *Deposit size at baseline*

Deposit size at baseline on sonography was <12.5 mm in 92 cases and ≥12.5 mm in 124 cases. Analysis of the patients with a deposit ≥12.5 mm showed no differences between treatment groups on the OSS at four months. However, in patients with a deposit diameter of <12.5 mm, sham lavage plus steroid was superior to lavage plus steroid (difference 5.7, 95% confidence interval 0.76 to 10.61; P=0.02) (supplementary table D).

#### *Radiographic changes in appearance of deposit*

After four months, the rate of disappearance of deposit was higher in the lavage plus steroid group (33/72) than for sham lavage plus steroid (6/70) and sham (15/66) (P<0.001). Results on the OSS did not differ between patients with an unchanged or a disappeared deposit but were superior compared with changed but still visible deposits for the former with 3.78 (0.22 to 7.33; P=0.03) and for the latter with 4.06 (0.02 to 8.11; P=0.05) (supplementary table E).

After 24 months, the deposit had disappeared on 146 (73%) of 199 radiographs, was unchanged on 28, and was changed but still visible on 25. Of the 146 disappeared deposits, 94 had disappeared in patients treated with lavage or surgery and 52 had disappeared spontaneously. Difference on the OSS between disappeared and unchanged deposits was 3.68 (−0.37 to 7.73) and was below significance. Compared with the changed but still visible deposits, the disappeared deposits were better with 5.08 (0.90 to 9.27; P=0.01).

#### *Volume of extracted calcium*

In 42 of the 73 primary lavage procedures, the volume of the extracted calcium exceeded 0.1 mL (mean 0.52 (SD 0.41) mL), whereas no calcium or only a small amount of not more than 0.1 mL was extracted in 31 patients. The difference between the two groups on the OSS after four months was not significant.

#### *Adherence to exercises*

Of 160 patients who returned the exercise daybook, 120 had done at least 80% of the planned exercises whereas 97 had done less than 80% of the programme (40 patients) or had not returned the daybook (57 patients). Comparison between the two groups showed no difference on the OSS after four months (supplementary table F).

#### *Stanford expectation of treatment scale*

Weak correlations were found for the relation between positive and negative treatment expectations on the SET and the four month outcome on the OSS, with a Pearson correlation coefficient of −0.08 and −0.10, respectively.

### Supplementary analyses

#### *Adverse events*

Adverse events were few and mild and included temporary dizziness, nausea, headache, haematoma at the injection site, increasing pain, a vasovagal reaction, and capsulitis. They did not differ between the treatment groups (supplementary table G).

#### *Use of post-intervention analgesics*

Only a few patients reported regular use of prescription analgesics at the four month and 24 month follow-ups, and the usage did not differ between the treatment groups (supplementary table H).

#### *Blinding*

Control of the effect of blinding directly after the treatment session showed that only 10 (5%) of 217 patients believed that they had received sham treatment, four of them correctly, six of them incorrectly, whereas 143 (66%) believed that they were treated by one of the two active treatments and 64 (29%) answered that they did not know (supplementary table I). At two and six weeks, the number of patients who believed that they had been treated by sham rose to 46 (21%) and 45 (21%), respectively (supplementary table I). The blinding index of James exceeded the threshold value for successful blinding of 0.5 at all measurement points. The exact index values were 0.63 directly after treatment, 0.55 after two weeks, and 0.52 after six weeks.

## Discussion

The principal finding of the study is that neither lavage plus steroid nor sham lavage plus steroid was superior to sham treatment in the treatment of calcific tendinopathy at four month and 24 month follow-ups. The lack of benefit from both active treatments is further supported by the large number of patients who needed supplementary treatment between four and 24 months of follow-up.

The results from this study are in contrast with the existing literature and question the use of ultrasound guided lavage as a treatment measure for calcific tendinopathy.[30-36] Current treatment recommendations are mainly based on the results from case studies, which are more likely than randomised controlled trials to be influenced by confounding.[11 12 30 35] Results from these studies may also be biased due to small and selected study samples and large percentages, 24-45% of patients, who were excluded from analyses because of additional treatment during follow-up.[8-10 37] None of the few previous randomised studies had a sham control group, and these studies also did not have blinded physiotherapists, patients, and outcome assessors.[31 36 38] The results of existing studies may exaggerate the effectiveness of ultrasound guided lavage, and our trial may represent a more realistic estimate of the true effectiveness of this commonly used intervention.


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The statistically significant improvements on the primary outcome score at four months, which were found in all three study groups, are most likely explained by the placebo response, which includes the natural course of the condition, regression to the mean, and the doctor-patient interaction, and also by the study's programme of home exercises. A treatment benefit exceeding sham occurred only at early follow-ups after two and six weeks and was found in both groups receiving steroids (fig 2). We assume that this early effect was caused by the corticosteroid injection and not by the lavage of the deposit.[39] An early effect from steroids up to six weeks has been reported from studies of subacromial steroid injections in patients with rotator cuff tendinopathy and calcific tendinopathy.[37 40-43] After four months and up to the 24 month follow-up, further improvement was found in both active treatment groups but did not exceed that from sham, neither when analysed with the treatment switchers included nor when analysed separately for the patients who had followed the protocol (table 2 and table 3). The absence of improvement exceeding that with sham, also after switching the treatment, is not surprising, because secondary treatment measures mainly consisted of the same interventions (lavage, steroid injection, physiotherapy alone or combined) that were found to be ineffective at four months in this study. The natural course of the condition may have played a more important role for the further development of the results up to two years.

The findings of this study, in which treatment benefit did not differ between patients with radiographic deposit disappearance after four and 24 months compared with patients in whom the deposit was unchanged (supplementary table E), question current beliefs that successful removal of the calcification results in symptomatic relief.[44] Inferior results were found only in patients whose deposit had changed in size and/or density but was still visible on the follow-up radiography, which may reflect ongoing resorption and pain related to this process. The role of the deposit itself as a cause of pain may further be questioned because removal of a large volume of calcific material during lavage was not associated with better results than removal of a small amount or no removal at all. These findings may suggest that other underlying cellular and molecular mechanisms of tendon pathology than the deposit itself contribute to the symptoms in calcific tendinopathy. A better understanding of physical and psychological pain mechanisms is needed to develop more effective treatment programmes for the condition.

An interesting secondary finding is the superiority of the sham lavage plus steroid group on the OSS over sham at two and six weeks and over lavage plus steroid at two weeks. This indicates that a steroid injection should be preferred when temporary symptomatic improvement is the treatment goal. Whether this short term benefit is outweighed by higher recurrence rates and lower rates of recovery, as reported in previous trials, can, however, be discussed.[45 46] The hypothesis of a rebound effect after a steroid injection may be supported by the results from the sham lavage plus steroid group at 24 months, which were inferior to sham and significantly inferior to lavage plus steroid on all outcome scores (table 2).

### Strengths of study

Firstly, this study had a double blind, three arm design with inclusion of a sham group. Without a sham group, assessing the true clinical effect of active treatment in a condition with a natural course that often ends with spontaneous recovery is not possible. Secondly, the pragmatic, multicentre, and multidisciplinary design contributes to the generalisability of the results. Thirdly, because of the successful blinding of the study patients, we presume that a placebo response occurred in our study groups.

### Limitations of study

Firstly, without a no-treatment group the role of the true placebo effect cannot be separated from the placebo response including all non-specific and contextual effects. Exploring the specific influence from the natural history and from concomitant physiotherapy would have been of particular interest. However, with all factors equal except the specific part of the treatments in question, we conclude that the observation of comparable outcomes in all three groups excludes a specific effect of deposit lavage or corticosteroid injection at four months in this study.

Secondly, the large number of treatment switchers after the four month follow-up makes estimating the true effectiveness of the experimental treatments at the later follow-ups difficult. The point of primary interest for the determination of treatment effectiveness in this study, however, was the four month result, which we selected because earlier studies with repeated measurements over the first six months have shown that the main effect from lavage can be expected early.[9-12 47 48] The frequent occurrence of treatment switching is by itself an important finding, as it reflects an insufficient effectiveness of the study treatments.

Thirdly, the lower limit for inclusion was a 5 mm deposit, and one may argue that lavage is more effective in larger calcifications. Separate analysis of 124 patients with a large deposit (≥12.5 mm), however, showed comparable results between treatment groups (supplementary table D). Although the study was not powered for this analysis, the differences between the groups were small and we think it unlikely that analysis of a larger group would have changed this result.

Fourthly, selection bias may have influenced the study results. The study was done in secondary public health services, and we cannot exclude the possibility that patients treated in primary or private settings differ from our study population. Patients who consent to participate in a study that includes sham treatment might also have a more positive and optimistic attitude and thus differ from the general population.

### Possible implications for clinicians and policy makers

The results of this study should lead to a critical reconsideration of current treatment algorithms. With a result not exceeding sham, the use of deposit lavage and of a steroid injection cannot be recommended. Future studies should investigate alternative treatment methods such as defined physiotherapy programmes and should include a no-treatment group to assess the influence of the natural course of calcific tendinopathy on the results. The absence of outcome differences between deposits that were unchanged and those that had disappeared at follow-up suggests that an exaggerated focus on the radiographic finding of a calcific deposit and its removal may be present in current treatment algorithms. A better understanding of the underlying pathophysiological pain inducing process in and around the tendon may allow development of treatment regimens with reliable and long lasting effects.

## Conclusions

In a multicentre, randomised, sham controlled setting, we found that the results from ultrasound guided lavage with a steroid injection and from sham lavage with a steroid injection for calcific tendinopathy were not superior to those from sham treatment. Our results challenge existing recommendations for the treatment of calcific tendinopathy and may necessitate a critical reconsideration of established treatment concepts for these patients.


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**Contributors:** SM and OME contributed equally to this paper. SM, OME, and JIB developed the concept and designed the study. SM, OME, HBH, IH, SK, NGJ, and JB implemented the trial at the respective hospitals in Norway and Sweden and contributed to patient treatment and data collection. AHP developed the study's analysis plan and did the statistical analysis of the data. SM, OME, JIB, and HBH drafted the manuscript. All authors approved the manuscript after revising it critically for important intellectual content and gave final approval of the version to be published. SM is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Ethical approval:** Approvals from the ethical committee and from the medical products agency have been received in Norway (Regional Committees for Medical and Health Research ethics, Ref. 2014/1183; Norwegian Medicines Agency, Ref. 15/08624-6) and Sweden (Regional ethical review board Linköping, Ref. 2015/7931; Medical Products Agency, Sweden, Ref. 5.1-2015-93735). Written informed consent was obtained from all participants before inclusion.

**Data sharing:** Anonymised patient level data are available on reasonable request from the corresponding author after approval by the medical and health research ethics committees in Norway and Sweden. The full trial protocol is available on request from the corresponding author. The protocol has been published.[13]

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** A link to the publication will be sent to the research participants. The main findings of the trial will be presented to patients and the public on social networking sites. The results will be presented at future information meetings for shoulder patients at our hospital and on the website of our hospital and will be included in our hospital's informational material for patients with shoulder pain.

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**Web appendix:** Supplementary tables
**Web appendix:** Appendix 1