Concise Report

A pilot study of acetic acid iontophoresis and ultrasound in the treatment of systemic sclerosis-related calcinosis

S. Shetty, T. L. Moore, S. Jackson¹, D. Brettle² and A. L. Herrick

Objectives. Our aim was to perform a pilot study to investigate whether iontophoresis of acetic acid, followed by ultrasound, might be a safe and effective treatment for systemic sclerosis (SSc)-related calcinosis. This combination treatment has been used in other calcifying disorders.

Methods. Three female patients (ages 51, 62 and 59 yr) were studied. Each underwent treatment nine times over a 3-week period. Iontophoresis was with 2–5% acetic acid at 100 µA for 20 min, followed by ultrasound at 1.5 W/cm² for 8 min at each visit. The primary endpoint was the degree of radiographic calcinosis as quantified by image analysis after adjusting for soft tissue change.

Results. There were no side-effects from treatment. Mean radiographic intensity fell in all patients (by 18.0, 8.9 and 8.5%), although the maximum density and the area of calcinosis fell in only one patient. However, none of the patients reported any benefits from the treatment.

Conclusions. In this small pilot study none of the patients experienced clinical improvement, despite an intensive treatment schedule over 3 weeks. However, there may have been some radiographic improvement. Given that there is currently no effective treatment for SSc-related calcinosis a larger study incorporating higher ‘doses’ of iontophoresis is indicated.

KEY WORDS: Calcinosis, Iontophoresis, Acetic acid, Ultrasound, Systemic sclerosis.

Subcutaneous or intracutaneous calcinosis occurs in approximately 40% of patients with limited cutaneous systemic sclerosis (SSc) [1] and can be a major cause of morbidity giving rise to pain, ulceration, infection and functional disability. Calcinotic deposits are usually seen over pressure points, most commonly in the hands, where they can be extremely debilitating. Although many different treatments have been suggested, including low-dose warfarin [2], minocycline [3], colchicine [4], diltiazem [5] and carbon dioxide laser therapy [6], the search for an effective treatment continues. At present, surgical debulking remains the mainstay of treatment. However, this is not without risk (especially in fingers where the blood supply is often severely compromised), and after surgery the calcinosis frequently recurs.

The use of acetic acid iontophoresis (with and without ultrasound therapy) has been investigated in other calcific conditions including calcifying shoulder tendonitis [7, 8]. A case report published in 1992 described an almost complete resolution of traumatic myositis ossificans with acetic acid iontophoresis followed by ultrasound [9]. Iontophoresis involves using a small electric current to drive physiologically active ions (in this case the acetate ion) into the skin. The rationale behind using acetic acid iontophoresis in the treatment of calcific lesions is that it is thought that the acetate ion replaces the carbonate ion in the insoluble calcium carbonate deposit, forming a more soluble compound, calcium acetate. The ultrasound possibly disperses the acetic acid, though there have been studies using ultrasound therapy on its own for treatment of calcific deposits [10].

In the absence of other effective treatments, we conducted a small open pilot study in patients with SSc-related calcinosis, using a similar protocol to that of Weider [9]. Our aim was to investigate whether acetic acid iontophoresis followed by ultrasound reduced the calcinosis without adverse effects.

Patients and methods

Patients

Three female patients (ages 51, 62 and 59 yr) with limited cutaneous SSc as defined by LeRoy et al. [11] were recruited from the rheumatology clinic. All had multiple areas of troublesome calcinosis, including their hands. Two of the patients had undergone surgical excision of the calcium deposits. However, both had recurrence of their calcinosis and one had had a post-operative infection.

Two of the patients had very severe Raynaud’s phenomenon with recurrent fingertip ulcerations, and in the past had had intravenous prostanoid infusions. All three patients had tried various oral vasodilators. All were anticentromere antibody positive.

Methods

The study was approved by the Salford and Trafford Local Research Ethics Committee, and written consent was obtained from all participants.

Treatment protocol. For each patient, the most troublesome area of calcinosis in the hand was selected for treatment. Each patient attended three times a week for 3 weeks (nine visits).
At each visit, after a thorough cleansing with alcohol wipes, the active (negative) electrode was attached over the area of calcinosis and the positive electrode over the wrist. Patient 1 was iontophoresed for 20 min with a 2% acetic acid solution at 50 μA for the first two sessions. This was well tolerated and was changed to a 5% acetic acid solution at 100 μA for the next seven sessions and for all nine sessions in Patients 2 and 3. After each iontophoresis, the patients received pulsed ultrasound for 8 min at 1.5 W/cm² at a 50% duty cycle.

**Outcome measures/image acquisition.** The primary outcome measure was the degree of radiographic calcinosis. Secondary endpoints were patient and physician opinion. All patients had hand radiographs taken at baseline and at 3 weeks (after the ninth treatment session). Dorsalpalmar and lateral views were acquired of the area of calcinosis. Reproducibility of the radiographic assessment pre- and post-treatment was maximized by using the same film exposure and by keeping the fingers in the same position using a plastic 90° splint taped to the finger/thumb of interest. A step wedge was included in all images to allow for density correction. The step wedge had five equal steps of 4 mm Al. Mammography film (Kodak MinR 2000) was used to increase contrast sensitivity and resolution. Fixed radiographic parameters were used for all patients (50 kVp, 36 mA s, 100 cm focus to film distance).

**Image analysis.** All images were digitized on a Vidar VXR-12 diagnostic quality film digitizer at 300 dots/inch (dpi), 12 bits of grey level. All image processing/analysis was conducted using the Matlab (The Mathworks Inc., Natick, USA) analysis environment and purpose-written software. Analysis was conducted on the lateral view for all patients as this afforded the best option for successful segmentation. To compensate for any variation in radiographic density caused by variation in exposure and processing, the post-treatment image was normalized to the gamma curve from the pre-treatment image using the step wedge and background level. Successful correction was verified using the step wedge and bone intensities. The images were then cropped to the required region of interest (Fig. 1). Soft tissue intensity was found to vary between the two films, particularly for Patient 1. To correct for this the mean soft tissue intensity, immediately adjacent to the area of calcinosis, was subtracted from the gamma-matched images. Regions of interest (ROI) were manually drawn around the thresholded area of calcinosis on both pre- and post-treatment images. The range and mean of the intensities of calcinosis were recorded. Each measurement was repeated five times to indicate the error in the thresholding due to variation in ROI position.

**Results**

The areas chosen for iontophoresis/ultrasound treatment were the palmar aspect of the interphalangeal joint of the right thumb (Patient 1), the palmar aspect of the proximal phalanx of the left index finger (Patient 2) and the palmar aspect of the metacarpophalangeal joint of the right thumb (Patient 3). None of the patients experienced any side-effects except for a mild burning sensation in the iontophoresed area.

**Radiographic calcinosis**

The intensity of the calcinosis (mean of the five repeat measurements for each visit) fell in all three patients after treatment. The mean (standard deviation) grey-scale intensity values for Patients 1, 2 and 3 were 9.3 (±0.6), 27.3 (±0.8) and 85.6 (±2.6) respectively pre-treatment and 7.6 (±0.3), 24.9 (±0.8) and 78.3 (±0.4) respectively post-treatment. Table 1 shows the percentage changes: the reduction in the mean intensity was between 18 and 8%. However, only in Patient 2 did the maximum intensity of the calcinosis and the area of the calcinosis fall after treatment (Table 1).

**Patient and physician opinion**

None of the patients reported any benefits from the treatment: nor did the rheumatologist reviewing them feel there had been any improvement.

**Discussion**

The intensive treatment schedule was well tolerated by our three patients, all of whom had troublesome and painful calcinosis.
None of the patients experienced significant adverse effects. While it was disappointing that there was no clinically apparent benefit from treatment, image analysis did suggest some radiographic improvement in that the mean intensity on image analysis fell in all three patients. However, it is possible that the reductions in mean intensity are due to persistent intensity variation between the two images, not corrected in the analysis process, perhaps due to variations in projection or non-linear soft tissue variation. Importantly the maximum values did not reduce in line with the calcinosis change, nor did the area, except for Patient 2. It could be argued the area and maximum should change as well; however, this is dependent on the mechanism by which the calcinosis is reduced. The observer was not blinded to the sequence of the radiographs and this would be advantageous in future studies because there is some human intervention in drawing the ROIs.

The key issue is whether our results justify a larger-scale study, given that this form of therapy is time-consuming and labour-intensive. However, it is non-invasive and our conclusion is that before abandoning a potentially safe treatment for an extremely distressing problem, a larger study is required. In a future study we shall use higher ‘doses’ of iontophoresis, given that the protocol used in our pilot study was well tolerated and the probabilities are that higher doses could be used without adverse effect.

### Table 1. Percentage changes in mean and maximum densities and area of calcinosis

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<tr>
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<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Change in mean calcinosis intensity</td>
<td>−18%</td>
<td>−8.90%</td>
<td>−8.50%</td>
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<tr>
<td>Change in maximum intensity</td>
<td>0.63%</td>
<td>−8.80%</td>
<td>−0.70%</td>
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<tr>
<td>Change in calcinosis area</td>
<td>1%</td>
<td>−4.40%</td>
<td>4%</td>
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## Acknowledgement

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The authors have declared no conflicts of interest.

## References