Safety and efficacy of extracorporeal shock wave therapy (ESWT) in calcinosis cutis associated with systemic sclerosis

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ABSTRACT

Objective. *Calcinosis cutis is a frequent, difficult to treat manifestation of systemic sclerosis (SSc) associated with high morbidity. The aim of this prospective, controlled, monocentric study was to assess safety and efficacy of extracorporeal shock wave therapy (ESWT) for calcinosis cutis of the finger in SSc patients.*

Methods. *A 12-week proof of concept study in which 4 SSc patients with calcinosis cutis were treated at one painful finger with high-energy, focused ESWT, in 3 sessions with one-week interval between each session. A second, untreated finger, served as control. The outcome parameters were: change in pain, change in size of calcification measured by ultrasound (US) and computed tomography (CT) and of the force by pressing the finger against a Dolorimeter.*

Results. *Pain was reduced (by 91% and 60%) in the treated finger in two out of four patients. There was no change in the control fingers. The size of the calcinosis in the treated finger was reduced in three (US) and four patients (CT). Inter-assessor agreement was acceptable for US volume measures (ICC=0.863).*

Conclusion. *We could show promising evidence for safety and efficacy of ESWT for chronic, treatment resistant calcinosis cutis in SSc patients, thus justifying the initiation of larger multicentre controlled trials.*

Introduction

Calcinosis cutis is characterised by insoluble calcium deposits in the skin and subcutaneous tissue (1). It occurs in approximately 22% of patients with systemic sclerosis (SSc) (2), particularly in the fingers (3). Calcinosis in SSc is associated with longer disease duration, increased morbidity due to recurrent ulceration and local inflammation. Despite the high disease burden, there is no approved therapy available for calcinosis in SSc (4). There is limited evidence from uncontrolled trials with several agents (5) and, in advanced cases, surgical removal of the calcium deposits may be required despite the risks for delayed wound healing and reoccurrence.

Extracorporeal shock wave therapy (ESWT) has been widely used for kidney stones (6). In rheumatology, it is successfully used to treat calcinosis of the shoulder tendons (7-9). Our aim was to investigate whether ESWT applied to calcinosis cutis in the fingers of SSc patients would safely reduce pain and calcinosis.

Materials and methods

A prospective, controlled study, conducted in the Division of Rheumatology of the University Hospital Zurich. The trial was approved by the local ethic committee and Swissmedic. Written informed consent was obtained from all patients before entering the study.

Inclusion criteria: consecutive SSc patients, male or female, aged >18 years, with painful calcinosis cutis of the finger due to SSc. SSc was defined according to the ACR/EULAR classification criteria (10). Exclusion criteria: coagulopathy or pregnancy.

Patients received high-energy focused ESWT with the device Modulith SLK® (Storz Medical, Switzerland). The most painful finger with calcinosis was selected for treatment. The second most painful finger served as control and was not treated. Treatment was applied in 3 sessions, one-week interval between each. At each session 2000 impulses were given on the calcinosis which was localised fluoroscopically by a coupled mobile x-ray and an inline ultrasound. The energy level applied was as high as tolerated by the patient without local anesthesia. Assessments were made before first treatment (base-

line) and at weeks 6 and 12: level of pain over the past week, using a visual analogue scale (VAS) on a scale of 0-100, with 100 = maximum pain; size of the calcification, calculated by ultrasound (US), which was independently performed by two rheumatologists (SB and MT), with the same machine (Philips HD 15). MT was unaware of the treatment allocation. The longitudinal (A1) and transverse (A2) area of the calcification was calculated after circumnavigation of the calcinosis with the cursor.

The volume of the calcification was also assessed by computed tomography (CT) at baseline and week 12, using a dual-source CT scanner (Somatom Definition Flash, Siemens Healthcare, Germany), with following parameters: detector collimation, 2x32x0.6mm; slice acquisition, 2x64x0.6mm by means of a z-flying spot; gantry rotation time, 0.33 s; tube current-time product, 100 mA s/rotation; and tube potential, 120 kV. Image reconstruction was performed with a slice thickness of 0.6mm (increment 0.4mm) using a medium-soft-tissue convolution kernel (B35f). Images were transferred to an external workstation (Multi-Modality Workplace, Siemens) for semi-automatic quantification of the volume using scoring software (Syngo CaScore, Siemens) by a blinded, experienced CT investigator.

Moreover, a Dolorimeter (Müller, DM 100N, AC Engineering Basel, Switzerland) was applied to the finger, and the maximally tolerated force was measured in Newton (11).

The primary endpoint was change in pain (VAS) at week 12 *versus* baseline (12). Secondary endpoints were change in pain at week 6, change in size of the calcification and change in the maximally tolerated force after 6 and 12 weeks, appearance of new or change in existing ulcers and change in pain medication.

The inter-assessment reliability of volume measurements was assessed with the intraclass-correlation coefficient (ICC) and corresponding 95% confidence interval (CI) for the two assessors. Bland-Altman plots were used for visualisation of the agreement of US measurements by the two assessors.

Table I. Clinical characteristics of patients with localisation of calcinosis.

	Patient 1	Patient 2	Patient 3	Patient 4
SSc Subset	limited	diffuse	limited	limited
Disease duration from first Raynaud in years	38	13	0.5	23
Antibodies	ANA, ACA	ANA, RNA-Polym III	ANA, RNA-Polym III	ANA, PM/Scl
mRSS	12	13	2	2
Acetylsalicylic acid	yes	no	no	yes
Ca-block	no	yes	yes	yes
ACE/AT II	Losartan	Losartan	Lisinopril	no
Major organ involvement	lung, oes, heart	lung, oes, heart	no	lung
Treated finger	II L	II L	IV R	I R
Control-finger	no	III L	no	IV L
Calcification on other fingers	no	I-V L+R	no	I+II L; II+IV R

ANA: anti-nuclear antibodies; ACA: anti-centromere antibodies; RNA-Polym III: anti-RNA polymerase III antibodies; PM/Scl: anti-PM/Scl antibodies; mRSS: modified Rodnan Skin Score; Ca-block: calcium channel blocker; ACE: Angiotensin converting enzyme inhibitor; AT II: Angiotensin II receptor blocker; oes: oesophagus; L: left side; R: right side

Table II. Pain level, tolerated force and size of the calcinosis before and after ESWT.

	Patient 1	Patient 2	Patient 3	Patient 4
Pain VAS, treated finger				
W 0	34	55	70	76
W 6	8	57	67	76
W 12	3	55	42	67
Pain VAS, control-finger				
W 0	NA	52	NA	52
W 6	NA	56	NA	53
W 12	NA	52	NA	53
Force (in Newton), treated finger				
W 0	1.33	0.68	1.97	1.52
W 6	2.27	1.12	3.02	0.90
W 12	2.50	0.90	2.52	1.30
Force (in Newton), control-finger				
W 0	NA	1.23	NA	2.93
W 6	NA	1.56	NA	2.80
W 12	NA	1.03	NA	2.70
US, treated finger in mm^3 (SB)				
W 0	79	124	354	540
W 6	30	68	513	110
W 12	37	97	435	135
US, treated finger in mm^3 (MT)				
W 0	85	163	286	321
W 6	29	81	741	165
W 12	21	92	292	160
US, control-finger in mm^3 (SB)				
W 0	NA	108	NA	433
W 6	NA	41	NA	308
W 12	NA	66	NA	282
US, control-finger in mm^3 (MT)				
W 0	NA	94	NA	431
W 6	NA	112	NA	470
W 12	NA	55	NA	261
CT, treated finger				
W 0	70	160	1370	1800
W 12	60	150	920	1720
CT, control-finger				
W 0	NA	60	NA	3100
W 12	NA	40	NA	3000

W: weeks after first treatment; NA: not applicable (no control-finger available); Force: maximally tolerated force; US: calcinosis size measured by ultrasound; SB and MT: the ultrasound was done by two different rheumatologists; CT: calcinosis size measured by computed tomography.

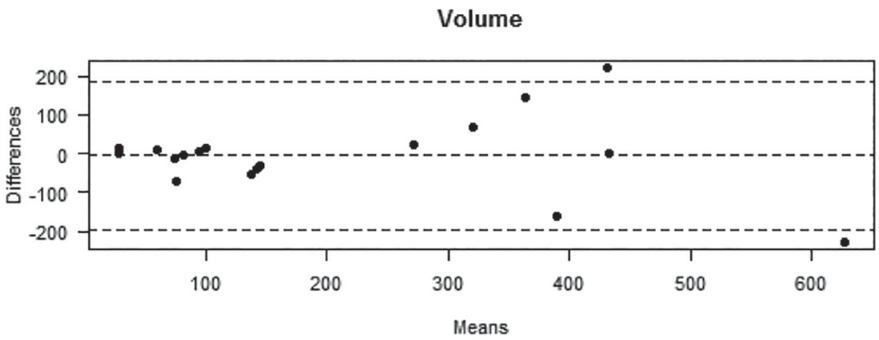

Fig. 1. Bland-Altman plots of inter-assessor agreement of calcinosis measured by ultrasound (mean of measurements x differences).

As this was a proof of concept study, power calculation and formal statistics were not done.

Results

Four patients were included, all women (47 to 72 years) and none took pain medications or had digital ulcers at baseline. All completed the 12-week study. In two patients a control-finger was not available as they only had calcinosis-related pain in the treated finger. Clinical features are summarised in Table I. The ESWT energy levels applied ranged from 0.08-0.75mJ/mm^2. The results of the primary and secondary endpoints are presented in Table II. While there was no change in the pain level of the control-fingers, there was a clinically meaningful reduction of pain (VAS >12mm) in the treated fingers of 2/4 patients (by 91% in patient 1 and 60% in patient 3) (12). Pain increased in patient 4 due to newly occurring digital tip ulcer secondary to calcinosis. The maximally tolerated pressure on the fingertip increased in patients 1-3 by 187%, 132%, and 127% respectively. As expected, it decreased in the patient with the new onset digital ulcer. The size of the calcinosis was reduced in 3 out of 4 patients as measured by US and in 4/4 patients by CT.

Inter-assessor agreement was acceptable for the US volume measures (ICC= 0.863 (95% CI = 0.677-0.946)). The Bland-Altman plots show the level of agreement between the two assessors, with no indication of bias (Fig. 1).

None of the patients required pain medication at any time during the study and there were no serious adverse events. One patient had an upper respiratory tract infection that resolved spontaneously. Patient 4 had an ulcer with extrusion of small calcified debris six days after the last ESWT at the treatment finger.

Discussion

ESWT was shown to have a clinically meaningful effect on pain (primary endpoint) in 2/4 SSc patients with calcinosis cutis. The patients in this study had been suffering from calcinosis cutis for several years and had not responded to previous treatments, such as calcium channel blockers (patients 2-4). The secondary endpoints supported the primary results. Maximally tolerated pressure by the Dolorimeter improved in 3/4 patients and worsened only in the patient with newly occurring digital ulcer. Calcinosis volume was reduced in 3/4 (US) and 4/4 patients (CT).

There were no serious adverse events. Although a causal relationship cannot be excluded for the newly occurring ulcer in patient 4, this was rather not an effect of ESWT, as the patient had experienced multiple episodes of ulcerations before entering this study. Moreover, in SSc patients with calcinosis related ulcers, reduction in wound area has been observed under ESWT. Nevertheless, ESWT might lead to increased friability of calcium deposits leading to extrusion via ulcers (13, 14). Published studies of ESWT in SSc-related calcinosis cutis are limited to a case report and an observational study (13, 14), both showing reduction in pain and size of calcinosis. However, these studies included either a different patient population at baseline (*e.g.* only one patient had calcinosis of the fingers) and/or used different outcome measures compared to the present. Very recently, a phase 2 pilot study showed that ESWT may be effectively added to standard treatments for digital ulcers of SSc (15).

In spite of the positive results shown in the present study, there are some issues to consider. First, fully validated outcome measures for the assessment of the severity of SSc-related calcinosis cutis do not exist (2). However, our primary endpoint was a patient reported measure, and pain VAS assesses a clinically important feature of calcinosis. Both pain VAS as well as the secondary endpoint maximally tolerated pressure were sensitive to change over treatment and appeared to be reliable, as indicated by stable values in the untreated control-fingers. Another limitation is the small number of patients. However, this was designed as a proof of concept study and is the first controlled study with ESWT for calcinosis cutis of the fingers in SSc patients.

Overall, we could show promising evidence for the safety and efficacy of ESWT for chronic, treatment resistant calcinosis cutis in SSc patients, justifying the initiation of a larger multicentre controlled trial.

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