

RESEARCH ARTICLE

Dystrophic calcification in Systemic Sclerosis – Intralesional Injections of Sodium Thiosulfate may have significant Positive Effects on your patients

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Abstract

Purpose: To describe our three year experience with intralesional injection of sodium thiosulfate (STS) as treatment for dystrophic calcification (DC) in patients suffering from systemic sclerosis (SSc), overlap syndrome, or dermatomyositis.

Methods: Between September 2016 and October 2019, selected SSc, overlap syndrome, and dermatomyositis patients with problematic DC were systematically and prospectively recruited to treatment once a week for four weeks and follow up after 12-16 weeks. During each visit, data concerning DC size, ulceration, inflammation, and both patient and physician global score (1-10) (PtGA and PhGA) were collected on customized data sheets. The DC lesions were injected with STS 150mg/ml on top or in the upper part of the lesion by the same clinician. After treatment, the lesion was covered up with a pressure distributing plaster for at least 24 hours.

Results: Among 43 patients offered treatment, 38 patients, 33 women and 5 men, had one or more problematic DC treated with intralesional STS. The total number of treatments was 463. The patients had between 1 and >200 DC lesions and at each session between 1 and 22 lesions were treated.

A total of 36 series consisting of 4 treatments were performed in 29 patients, 26 women and 3 men. Among these patients, 18 had systemic sclerosis of limited cutaneous type (lcSSc), 8, 2, and 1 patient had systemic sclerosis of diffuse cutaneous type (dcSSc), overlap syndrome, and dermatomyositis respectively.

The average PtGA and PhGA before treatment was 6.4 and 6.1 respectively. A significantly decrease of the average PtGA and PhGA score was observed week by week and after the third treatment the average decrease in PtGA and PhGA was 2.7 and 2.5 respectively ($p < 0.001$). Almost all patients experienced intense pain during and after injection (up to several minutes), but otherwise side effects were few and not serious.

Conclusions: We find that intralesional STS injections have positive effect with limited side effects on selected SSc patients with problematic DC. We recognize the limitations of the study design leaving plenty of questions to be addressed. It is our clinical impression that patient, lesion, and clinician related factors may influence the outcome of the treatment. We hope that our treatment regimen may inspire physicians to consider STS injections as a possible treatment for troublesome DC before referring to surgical interventions.

Keywords: Dystrophic calcification, Sodium Thiosulfate, Intralesional injections, Systemic sclerosis, non-surgical treatment

Introduction

Dystrophic calcinosis (DC) is a subtype of cutaneous calcinosis associated with autoimmune connective tissue disorders. DC is characterized by deposition of insoluble calcium salts in skin and subcutaneous tissues and can present as everything from small localized nodules to larger plaques or confluent debilitating lesions involving larger areas of the body. DC is most often associated with systemic sclerosis (SSc) and dermatomyositis (including juvenile dermatomyositis), but may also occur in systemic lupus erythematosus, lupus panniculitis, and overlap syndromes among others.¹ DC can often be very painful, especially when joints are involved or if lesions ulcerate. As such, it may cause considerable morbidity, functional impairment, and, especially with ulcerated lesions, risk of secondary infections, which can be refractory to treatment with antibiotics.² DC has a substantial negative impact on quality of life in patients with SSc. In SSc, the nodules or plaques typically develop on the fingers, feet, extremities adjacent to joints or areas of recurrent trauma.³

The pathophysiology of DC is incompletely understood. It may occur as a result of chronic tissue damage of defective collagen synthesis notably in the setting of normal serum calcium and phosphate levels. Approximately 25% of patients with limited cutaneous SSc (lcSSc) will develop DC during the course of their disease, but DC also occurs in diffuse cutaneous SSc (dcSSc).¹ Most often DC occurs several years after diagnosis of SSc, but time of onset can vary widely and DC has been reported to precede the diagnosis of SSc.²⁻⁴

DC remains a great therapeutic challenge. There is no approved treatment and management is largely based on expert opinions and case series. Surgical interventions may help some patients, but it may also induce even more debilitating new DC lesions and the extent of a single DC lesion or the number of lesions can make surgical intervention obsolete. Alongside

general measures, including improvement of blood flow to the extremities, standard wound care, antibiotics when a secondary infection is suspected, and pain management, several medications have been described with varying results. Among others these include calcium channel blockers, bisphosphonates, warfarin, colchicine, minocycline, biologic agents, and both intravenous, topical, and intralesional sodium thiosulfate (STS).²

The exact mode of action of STS is unclear, but it involves chelation of calcium into calcium thiosulfate salts, which increases the solubility of calcium up to 100,000 times.⁵ STS has been used intravenously in the treatment of calciphylaxis cutis/calcific uremic arteriolopathy and nephrogenic systemic fibrosis, but also cyanide toxicity, and arsenic and other heavy metal poisonings. Generally, intravenous STS is well tolerated, but side effects include nausea, vomiting, diarrhea, stomach ache, and, long term, decreased bone mineral density.⁵⁻⁷ Several studies have reported that topical treatment with STS may have significant effect on DC lesions. In line with several case reports, a case series from the Mayo Clinic reported that 68% of patients with autoimmune connective tissue diseases had improvement of calcinosis cutis when applying 25% STS in zinc oxide ointment to their lesions.⁸⁻¹⁰ Dissolution of calcinosis cutis in connective tissue disease with intradermal STS was first reported in 2013 by Dr. GP Smith.¹¹ In 2014, we treated 5 SSc patients with DC with intralesional STS and observed marked effect on pain scores within 4 weeks, significant reduction in lesion size, and healing of ulcers within 4-12 weeks. Further, we observed very few side effects; ie often transient pain in the injected area and one patient developed an infection in the area of the injected skin.¹² STS is known to be toxic or irritating to the skin, which may be the reason for or contributing to the pain during and after injection. Recently, intralesional STS has also been reported to be effective and with no side effects in the treatment of calcific tendinitis and facial

nodules from calcium hydroxyapatite (used as a cosmetic filler).¹³⁻¹⁴

Our aim in this study is to further investigate the effects and side effects of intralesional STS injections among selected patients with problematic DC.

Methods

Between September 2016 and October 2019, selected SSc, overlap, and dermatomyositis patients with problematic DC were treated with intralesional injections of STS. Patients with problematic DC's in our clinic were invited to participate and patients were also referred from The Department of Rheumatology of Aarhus University Hospital, from other hospitals and from outpatient clinics in Denmark. Patients \geq 18 years old were included if they had one or more problematic DC, was willing and able to comply with the treatment plan, and understood that the treatment is experimental. The only exclusion criteria were known hypersensitivity to STS and pregnancy. Withdrawal from the study was possible at any time and for any reason.

At the primary visit, patients were informed that the treatment of DC with intralesional STS is considered experimental and informed of our prior experience with the treatment including the side effects observed in our pilot study. The patients themselves designated their most problematic DC's for treatment. A DC was defined as problematic if the patient had severe pain (VAS pain score \geq 4 (1-10) on average) and/or dysfunction or changed activity of daily life caused by the lesion. All types of DC was considered eligible to treatment; ie. plaques, nodules, and lesions with ulcer and/or inflammation.

During each visit, data concerning the DC (size, ulcer, and inflammation), patient- and physician global score (PtGA and PhGA), prior treatments of the DC, and side effects were collected prospectively on customized data sheets. PtGA (1-10) was registered by the patient before each treatment; the patient was

asked to indicate how overall problematic the selected DC had been within the last week prior to the visit. After the visit, the clinician made a PhGA (1-10) concerning both symptoms and clinical findings including size, location, subtype, and presence of inflammation and/or ulcer. Complete remission is defined as the DC lesion being gone. Partial remission is defined as decrease in PtGA and either an ulcer has healed and/or the DC lesion is reduced in size.

Treatment was offered once a week for four weeks and a follow up was offered after 12-16 weeks. At follow up, the patients were offered a new series of four treatments once a week and follow up after 12 to 16 weeks if the DC still was problematic.

After alcohol cleaning of the surrounding skin, DC was injected with STS 150 mg/ml on top or in the upper part of the lesion. Injections were performed by the same clinician (Anne Braae Olesen). Any wound was covered with a plastic film and the rim was injected irradiated from the outer rim of the DC to the rim of the ulcer. After treatment, DC was covered with a pressure distributing plaster for at least 24 hours. Four patients were treated with STS 250 mg/ml after individual application to and acceptance from the Danish Medical Agency. The reason for using a higher concentration was the specific location of DC, ie. small DC on the palmar side of the feet, or very big DC close to joints were only very small amounts of STS could be injected. 1 ml lure-lock syringe was used with BD MicrolanceTM 0,3 x 13 mm.

Calculations were made with simple averages. However, if a patient had completed multiple series with treatment of different DC for each series and if the treatment series was separated in time by a least one month, the same patient may be represented more than once in the calculations. P-values were calculated using the assumption of normal distribution statistics.

Results

Among a total of 43 patients offered treatment, 38 patients, 33 women and 5 men, were treated with intralesional STS to one or more DC lesions 463 times. The patients had between 1 and >200 DC lesions. Between 1 and 22 lesions were treated in one clinical session and the size of the DC lesions were between 1 and 500 x 650 mm (longest and widest measures, not a square). Two patients only received one treatment and were subsequently lost to follow up, and thus, data from these patients are not included in the following analyses.

A total of 36 series consisting of 4 treatments of one or more DC with intralesional STS and sufficient registration were performed in 29 patients. 18 patients with lcSSc, 8 with dcSSc, 2 with overlap syndromes, and 1 with dermatomyositis. 3 patients were men and 26 were women. The time between treatments varied from most often one week to about one month. Most series were completed with all 4 treatments, but a few were interrupted due to complete or partial remission of the DC. 13 patients had complete remission of one or more DC, 13 patients had partial remission, and 3 patients reported no response to treatment. 11 patients had one or more DC with ulceration and all ulcerations healed during the treatment series. Average PtGA and PhGA before the first treatment in each series was 6.4 and 6.1 respectively (Fig. 1). Average decrease in PtGA and PhGA before the first treatment and before the fourth (or last treatment in case of complete

or sufficient partial remission) treatment was 2.7 and 2.5 respectively. Likewise, average decrease in PtGA and PhGA after one treatment (before the second treatment) was 2.3 and 1.4 respectively. All were statistically significant ($p \ll 0.001$). Time to follow up after the fourth treatment was too inconsistent and this data is thus not included in the calculations.

Many patients have subsequently been treated with more intralesional injections of STS in the same or other DC lesions, but the results from these subsequent treatments is not included. An example of a treatment course of a patient with lcSSc is shown in the photograph series (Fig. 2). The patient developed a problematic DC on the knee and was first seen in our scleroderma clinic in autumn 2015. The PtGA was 4 and the patient had no interest in receiving treatment with intralesional STS. In autumn 2016, the patient was readmitted since the DC had become more problematic. The PtGA had increased to 10 and the patient had difficulties walking. After 4 series of 4 treatments the PtGA was 1 and the ulcer healed.

Almost all patients experienced short transient intense pain in connection with the injections, and a few patients developed brownish discoloration of the overlying skin 2-4 days after injection. Two patients had infections at the site of injections during the treatment series, and one patient had blistering of the skin 4-7 days after switching from injection with STS 150mg/ml to injection with 250 mg/ml.

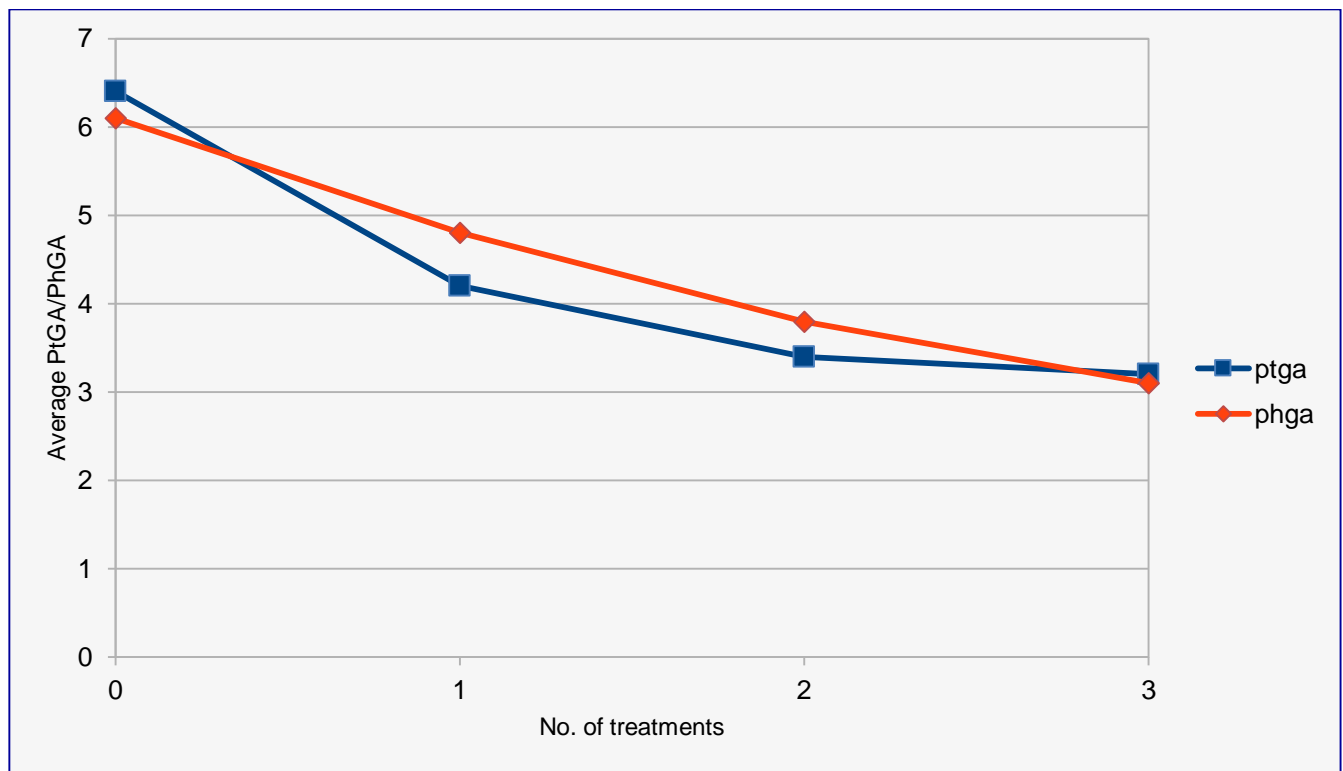


Figure 1: PtGA and PhGA before the first treatment with sodium thiosulfate and after the first, second and third treatment.



Figure 2: A treatment course from November 2016 to the latest follow up after 4 treatment series of 4 treatments in May 2018. The first picture is one year before treatment. At that time the patient global score was 4 and she was not interested in trying the offered treatment.

Discussion

In this prospectively case-series study on consecutively selected patients with SSc, overlap syndrom, and dermatomyositis, we observed a significant improvement of the problematic DC lesions treated with intralesional STS. For most patients, we observed a partial remission and for 50% of the patients, we observed a complete remission of one or more DC lesions. For most patients, a significant improvement of pain and activity of daily life was experienced. A few side effects were noticed – especially severe pain during and after the injection for up to several minutes. However, most of the patients chose to stick to the treatment program because they experienced improvement during the treatment series and especially during the follow up time. None of the side effects described using STS intravenously was observed. This is, in our opinion, good news, since a systemic sclerosis case report published in *Nature*, October 2019, stated that, 'when all ordinary trials of multiple medications do not improve the pain, numbness, and difficulty of handling objects, the only next step is referral for surgical evaluation'.¹⁵ However, our present study is the first larger case series study regarding intralesional treatment of DC with STS and knowledge about efficacy and side effects is thus still only documented to a limited extent.

Recently, Fernández-Codina A et al. have reported of failure of injecting STS in a giant calcinosis of a patient with dermatomyositis/scleroderma overlap syndrome.¹⁶ In our case series, 5 patients had overlap syndromes, among whom 2 patients had overlap to dermatomyositis, and these 2 patients had no other effect of the treatment than improvement of the PtGA (data not shown). Furthermore, it is our clinical impression that new, not previously treated DC lesions, responded better to treatment with intralesional STS compared to older lesion (lesions > 1 year) (data not shown).

The nature of the case series design does not allow for risk factor analyses, but our clinical observations suggest that patient, lesion, and clinician related factors may influence the outcomes of the treatment. Here we report a positive effect on highly selected cases, which previously have had no effect of any other DC treatments, surgical intervention not attempted, but neither risk factor analysis nor comparison of effect can be made, which of course limits the level of conclusions which can be made from this study. Our study, although a case series, also have strengths. Hence, all cases with problematic DC was recruited to the study systematically and prospectively since September 2016 and data have been prospectively recorded on customized data sheets for all cases providing a standardized assessment of clinical response.

The many questions left in this type of study design calls on randomized controlled trials, and according to Cochrane Library a study is on its way comparing the efficacy of intralesional STS versus intralesional normal saline injections for the treatment of DC and idiopathic calcinosis cutis.¹⁷ We look forward to learn more from their results.

Conclusions

We find that intralesional STS injections have positive effect with limited side effects in selected patients with problematic DC lesions. It is our clinical experience that some patients may have better response to the treatment than others. Patient, lesion and clinician related factors may influence the outcome of the treatment. The treatment efficacy needs to be addressed in comparative study designs. We hope that our treatment regimen may inspire physicians to consider STS injections as a possible treatment for troublesome DC lesions before referring to surgical interventions.

References

1. Gutierrez A Jr, Wetter DA. Calcinosis cutis in autoimmune connective tissue diseases. *Dermatol Ther*. 2012; 25(2):195-206.
2. Valenzuela A, Song P, Chung L. Calcinosis in scleroderma. *Curr Opin Rheumatol*. 2018; 30(6):554-561.
3. Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol*. 1995;33(5 Pt 1):693–706.
4. Balin SJ, Wetter DA, Andersen LK. Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996–2009. *Arch Dermatol*. 2012; 148: 455– 462.
5. Cicone JS, Petronis JB, Embert CD. Successful Treatment of Calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis*. 2004;43:1104-1108
6. Hayden MR, Goldsmith DJ. Sodium thiosulfate: a new hope for the treatment of calciphylaxis. *Semin Dial*, 2010. 23(3): p. 258-62.
7. Huilaja L, Turpeinen M, Tokola H. Warfarin-induced calciphylaxis in patients with normal renal function. *J Clin Pharm Ther*. 2016 Aug;41(4):449-452.
8. Tajalli M, Qureshi AA. Successful treatment of calcinosis cutis of fingertip in the setting of CREST syndrome with topical 20% sodium thiosulfate. *JAAD Case Reports*. 2019;5:988-90.
9. Karthik S, Bhatt A, Babu T. Sodium thiosulfate dressings facilitate healing of refractory cutaneous ulcers of calcinosis cutis. *J Postgrad Med*. 2019; 65(2):123-24.
10. Ma JE, Ernste FC, Davis MDP. Topical sodium thiosulfate for calcinosis cutis associated with autoimmune connective tissue diseases: The Mayo Clinic experience, 2012-2017. *Clin Exp Derm* . 2019; 44: 189-192.
11. Smith GP. Intradermal sodium thiosulphate for exophytic calcinosis cutis of connective tissue disease. *J Am Acad Dermatol*. 2013; 69(3): e146-47.
12. Baumgartner-Nielsen J, Olesen AB. Treatment of Skin Calcifications with Intralesional Injection of Sodium Thiosulphate: A Case Series. *Acta Derm Venereol*. 2016;96(2):257-8.
13. Rullan PP, Olson R, Lee KC. The Use of Intralesional Sodium Thiosulfate to Dissolve Facial Nodules From Calcium Hydroxylapatite. *Dermatol Surg*. 2019 Nov 1.
14. Darrieurtort-Laffite C, Bertrand-Vasseur A, Garraud T. Tolerance and effect of sodium thiosulfate in calcific tendinitis of the rotator cuff. *Clin Rheumatol*. 2020 Feb;39(2):561-569.
15. Valido A, Cordeiro I. Calcinosis in Systemic Sclerosis. *N Engl J Med*. 2019; 381;17.:1663.
16. Fernández-Codina A, Camprodon-Gómez M, Pope JE. Giant calcinosis in dermatomyositis/scleroderma overlap. *Arthritis Rheumatol*. 2020;17. doi:10.1002/ART.41262.
17. Weinstein D. A comparative study of the efficacy of intralesional sodium thiosulfate versus intralesional normal saline for the treatment of dystrophic and ideopathic calcinosis cutis. *Cochrane Central Register of Controlled Trials*. <https://clinicaltrials.gov/show/NCT03639779> (accessed 21-MAR-2020)