Concise report

CED
Clinical and Experimental Dermatology

Topical sodium thiosulfate for calcinosis cutis associated with autoimmune connective tissue diseases: the Mayo Clinic experience, 2012–2017

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doi:10.1111/ced.13782

Summary

In this case series, we retrospectively identified all patients treated with topical sodium thiosulfate (TST) for calcinosis cutis (CC) associated with underlying autoimmune connective tissue diseases at Mayo Clinic (Rochester, MN, USA) during the period 1 January 2012 to 27 June 2017. Of 28 patients identified (mean age 57.0 years; 96% female), 19 (68%) had clinical improvement of their CC with TST, 7 (25%) had no response and 2 (7%) had unknown response. There were adverse events in three patients: two had skin irritation and the third, who had a zinc allergy, experienced pain with application. Overall, our findings support those of previous case reports that TST appears to be a relatively well-tolerated adjuvant treatment for CC, although future studies with a control group are warranted to assess the true efficacy of TST for the indication of CC.

Calcinosis cutis (CC) is a chronic calcium-deposition disorder involving the cutaneous and subcutaneous tissues. Dystrophic calcification is the most common subtype in patients with normal serum calcium and phosphorous levels; it most commonly affects those with underlying autoimmune connective tissue diseases (ACTDs).[1] Unfortunately, responses to treatment have been variable.[2] Physiological treatments have included calcium-channel blockers, colchicine, minocycline, intravenous immunoglobulin, bisphosphonates and warfarin.[2] Procedural therapies have included surgical excision, extracorporeal shock wave lithotripsy and carbon dioxide laser.[1]

Intralesional sodium thiosulfate has been successfully used in the treatment of CC associated with ACTD.[3–5] The efficacy of this inorganic salt for calcium-mediated disorders may be multifactorial, possibly including its anti-inflammatory and antioxidant properties, and its ability to chelate calcium into calcium thiosulfate salts, thereby increasing the solubility of calcium.[4,5] However, in one report, three patients with extensive and longstanding CC associated with ACTD who were treated with intravenous sodium thiosulfate had no improvement.[6]

Isolated case reports have documented clinical response of CC with the use of topical sodium thiosulfate (TST).[7–9] A case series from Chile highlighted complete resolution of CC ulcers in four patients with a different topical preparation, 25% topical sodium metabisulfite.[10]

To date, no larger case series have been published on the use of TST for treatment of CC associated with ACTD. The pharmacy at Mayo Clinic (Rochester, MN, USA), has been compounding a TST formulation since 2012, which has been prescribed by providers in dermatology, rheumatology and wound care. In the current study, we aimed to review our institutional experience with the use of TST for CC and its treatment responses over the past 5 years.

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Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 17 June 2018

Report

We used our institutional biomedical text retrieval system to retrospectively identify patients of all ages who received a diagnosis of CC (by *International Classification of Diseases* code: 9th edition, 709.3; 10th edition, L94.2) and were treated with TST during the period 1 January 2012 to 27 June 2017. We also used prescription data from our compounding pharmacy to ensure that all patients who received a prescription for TST were considered.

In total, 28 patients, diagnosed with CC and an underlying autoimmune connective tissue disease, who were prescribed topical TST with follow-up visit assessing treatment response, were included in the study. We reviewed the charts of the patients and extracted patient characteristics (date of birth, sex, race), disease characteristics (duration and symptoms of CC), comorbid conditions, anatomical site(s) of involvement, date(s) of follow-up, recurrence(s), treatment(s), outcomes (clinical changes in skin lesions and self-reported pain as documented by clinician) and number of TST refills (Table 1). Treatment responses were categorized as complete response (CR), partial response (PR), no response (NR) or unknown response (UR). CR indicated total resolution of the lesion and lack of recurrence, while PR indicated that the lesion had regressed or recurred after prior regression and NR indicated the persistence or worsening of treated lesions.

The medication was compounded as 25% sodium thiosulfate in zinc oxide ointment for all patients, except for one patient with an allergy to zinc, for whom sodium thiosulfate was compounded in a gel-based formulation. For another patient, the 25% formulation was increased to 50% after 1 year of treatment on the lower concentration as per the patient's request and clinician's judgement.

Table 1 Characteristics of 28 patients with underlying autoimmune connective tissue disease who used topical sodium thiosulfate for calcinosis cutis during the period January 2012 to June 2017.

Parameter	Mean (range)
Age, years	
At diagnosis of ACTD	47.8 (2–82)
At initiation of TST	57.0 (18–82)
Duration of treatment at initial follow-up, months*	3.9 (0.3–24)
Number of TST prescriptions†	2.2 (1–6)
Amount of TST per prescription, g	180 (60–480)

TST, topical sodium thiosulfate. *Mean time to positive response among patients who experienced clinical improvement with TST therapy was 4.0 months (median time 2.5 months, range 0.5–11 months); †number of prescriptions was not available for nine patients.

Table 2 describes the clinical characteristics of the patients with an underlying ACTD who used TST for their CC. Of the 28 patients, 27 (96%) were female. Table 3 summarizes the prevalence of underlying ACTDs among the 28 patients.

Of the 28 patients, 19 (68%) experienced clinical improvement of their CC with TST (Fig. 1), 7 had NR to TST (25%) and 2 (7%) had UR. Of the 19 patients who had clinical improvement, 2 (11%) had complete resolution of at least one lesion, while the other patients had PR. Of the 19 patients, the 11 patients (58%) with clinical improvement of CC were on TST only, with no concurrent use of wound care therapy or oral medications reported to improve CC. Of the 7 patients who experienced no clinical improvement with TST use, 4 (57%) discontinued the medication within $\leq$ 1 month of treatment initiation. There were adverse events (AEs) in three patients, who experienced irritation or pain with TST and subsequently discontinued usage. No other AEs were reported.

In our cohort of 28 patients who used TST for CC associated with ACTDs, two-thirds (68%) responded to TST. To our knowledge, this is the first large case series to date to report a substantial treatment effect. Nearly 80% of patients who responded to TST had no change in their ACTD treatment immediately prior to or during TST treatment (Table 1), supporting a possible direct benefit of TST in CC improvement. By contrast, TST nonresponders had more changes to their ACTD treatment and had unsuccessfully used more previous CC treatments than TST responders (Table 1), suggesting that patients who did not respond to TST may have had more severe underlying ACTD and CC.

We recognize the study's limitations, including its retrospective design. In addition, lack of a control group with CC not treated with TST diminishes the ability to attribute treatment response directly to TST. We also lacked a standardized method to assess the clinical response of CC to TST therapy and were unable to quantify the percentage change from baseline. Only some patients (39%) had documented objective measurements of the ulcers, extent of calcinosis and pain levels. In addition, many patients of our tertiary referral institution live outside the region and follow-up is mainly with their local providers, which results in less frequent follow-up at our institution. It is possible that some patients did not use TST for a sufficient duration of time, given that more than half the patients who had no response to treatment discontinued TST within 1 month of initiation.

Overall, our study supports previous case reports of sodium thiosulfate as a well-tolerated adjuvant

Table 2 Characteristics of 28 patients with underlying autoimmune connective tissue disease who used topical sodium thiosulfate for calcinosis cutis during the period January 2012 to June 2017.

Parameter	CR, *n*	PR, *n*	NR, *n*	UR, *n*	Total, *n* (%)
Overall[a]	2	17	7	2	28[b]
Race					
White	2	15	6	1	24 (86)
African American	0	0	0	1	1 (3.5)
Middle Eastern	0	1	1	0	2 (7)
American Indian	0	1	0	0	1 (3.5)
Frequency of application					
Twice daily	1	14	6	2	23 (82)
Three times daily	1	3	1	0	5 (18)
Anatomical sites of involvement					
Hands/feet	0	7	3	1	11 (39)
Extremity	1	8	3[c]	1	13 (46)
Trunk	1	0	0	0	1 (4)
Multiple sites[d]	0	2	1	0	3 (11)
Ulceration of CC					
Yes	2	10	4	1	17 (61)
No	0	7	3	1	11 (39)
Initial provider(s) who diagnosed CC					
Dermatologist	0	4	2	0	6 (21)
Other specialist[e]	2	12	4	1	19 (68)
Both	0	1	1	1	3 (11)
Provider who evaluated patient response to TST					
Dermatologist	0	5	1	0	6 (21)
Other specialist[e]	2	12	6	2	22 (79)
Method of CC diagnosis					
Biopsy	0	4	1	0	5 (18)
Imaging	2	9	5	1	17 (61)
Biopsy and imaging	0	4	1	1	6 (21)
Clinical response determined by:					
Patient report	0	9	6	0	15 (54)
Both patient report and provider assessment[f]	2	8	1	0	11 (39)
NA	0	0	0	2	2 (7)
Change in ACTD regimen within $\leq$ 3 months of TST initiation or during TST treatment	1[g]	3[h]	4	2	10 (36)
Concurrent use of other treatments during TST treatment[i]					
Medication(s) reported to improve CC	0	5[j]	2	2	9 (32)
Wound care dressings	0	6	2	0	8 (29)
None	2	9	2	0	13 (46)
Treatments for calcinosis cutis prior to initiation of TST[k]					
Prior surgical resection	0	5	2	0	7 (25)
Prior intralesional or IV sodium thiosulfate	0	2	0	0	2 (7)
Prior medications	1	0	4	0	5 (18)

ACTD, autoimmune connective tissue disease; CC, calcinosis cutis; CR, complete response; CTD, connective tissue disease; IV, intravenous; NA, not available; NR, no response; PR, partial response; TST, topical sodium thiosulfate; UR, unknown response. [a]Patients who did not authorize research participation were excluded by the initial search. Of the 87 patients identified on the initial search, we also excluded those: (i) without a diagnosis of an underlying ACTD (n = 3), (ii) treated with intravenous sodium thiosulfate rather than the topical formulation (n = 43), (iii) who did not have follow-up on their TST treatment (n = 12) and (iv) who did not apply the medication as prescribed to affected areas (n = 1). The three patients that were prescribed TST without underlying autoimmune disease had lower extremity ulcers and dystrophic calcification in the setting of leg oedema, diabetes and peripheral artery disease. Two of the three patients had PR at 1.5 and 2 months, respectively, while the the third patient had UR. [b]Of the 28 patients, 27 (96%) were female and 1 (4%) was male. The male patient experienced PR with TST treatment. [c]Of three patients who experienced no response when TST was applied to lower extremity CC lesions, two had underlying ulcerated lesions documented to be multifactorial in aetiology including severe vascular insufficiency. [d]One patient had CC involvement of the hands or feet and extremities; this patient experienced PR to TST treatment. Two patients had CC involvement of the extremities and trunk; one experienced PR and the other experienced NR. [e]Providers other than dermatologists included wound care providers, rheumatologists and internists. [f]Provider assessment indicates that objective measurements were used to determine clinical response. [g]Azathioprine was initiated 2.5 months prior to start of TST. [h]One patient discontinued methotrexate 1 month prior to start of TST. The second patient switched from chloroquine to mycophenolate mofetil 2.5 months prior to start of TST. The third patient was initiated on azathioprine 2 months into TST therapy but it was discontinued immediately due to a significant drug reaction. [i]Several patients in our cohort used both wound dressings and oral medications concurrently. Specifically, of the 19 patients who had clinical improvement at time of TST therapy, 3 were using both wound dressings and oral medications reported to improve CC, 2 were using wound dressings but not oral medications, 3 were using oral medications but not wound dressings, and 11 were not using either treatment in conjunction with TST. [j]Medications included amlodipine, colchicine, minocycline, nifedipine and warfarin. [k]No patients in our cohort had both prior surgical resection and intralesional or intravenous sodium thiosulfate treatment of their CC prior to initiation of TST.

treatment for CC. Future studies should include a control group (age, sex, ACTD-matched) not treated with TST and compare treatment response rates with those of patients treated with TST.

Acknowledgements

We thank R. Warndahl, compounding pharmacist at the Mayo Clinic Pharmacy, for compounding the TST medication and for identifying patients who completed this prescription.

Table 3 Underlying autoimmune connective tissue disease in 28 patients treated with topical sodium thiosulfate.

ACTD	*n* (%)
Dermatomyositis, juvenile	1 (4)
SS with cutaneous scleroderma	15 (54)
Diffuse	3 (11)
Limited	12 (43)
Overlap CTD	4 (14)*
Undifferentiated CTD	4 (14)†
Lupus erythematosus	2 (7)
Systemic	1 (4)
Cutaneous	1 (4)‡
Rheumatoid arthritis	2 (7)
Classic	1 (4)
Juvenile	1 (4)

ACTD, autoimmune connective tissue disease; CTD, connective tissue disease; SS, systemic sclerosis. *These four patients had overlap connective tissue disease of the following types: systemic sclerosis plus systemic lupus erythematosus, systemic sclerosis plus myositis, systemic sclerosis plus rheumatoid arthritis, and systemic sclerosis plus Sjögren syndrome. †These four patients had features of the following ACTDs: systemic sclerosis ($n = 2$), Sjögren syndrome ($n = 1$) and rheumatoid arthritis ($n = 1$). ‡This patient had the discoid lupus erythematosus and lupus panniculitis subtypes of cutaneous lupus erythematosus.

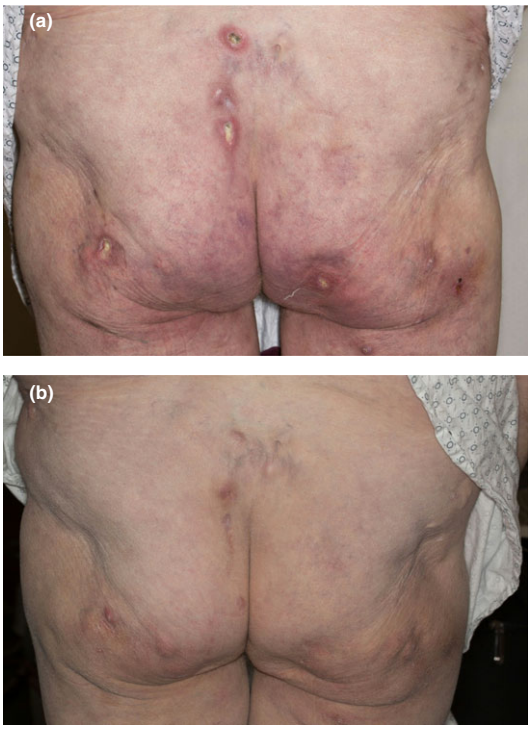

Figure 1 Clinical improvement of calcinosis cutis (CC) with topical sodium thiosulfate (TST). CC on the sacrum and buttocks in a female patient with overlap connective tissue disease (systemic sclerosis with limited cutaneous scleroderma, rheumatoid arthritis) (a) before and (b) after 1 year of applying 25% TST 3 times daily.

Learning points

- In this case series of 28 patients, the majority (68%) of patients experienced clinical improvement of their CC with TST.
- TST may represent a relatively effective and safe adjuvant therapy for CC, although further studies are needed to assess its true efficacy.

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