Efficacy of intralesional sodium thiosulfate for the treatment of dystrophic calcinosis cutis: A double-blind, placebo-controlled pilot study

Amelia R. Winter, BA,[a] Skylar Klager, SM,[a] Rachel Truong, BA,[a] Adam Foley, BS,[a] Naveed Sami, MD,[b] and David Weinstein, MD[b]
Orlando, Florida

Background: Intralesional injection of sodium thiosulfate has emerged as a promising therapy for calcinosis cutis, but to our knowledge there are no randomized controlled trials evaluating its efficacy as a treatment.

Objective: Conduct a prospective, double-blinded investigation of intralesional sodium thiosulfate versus normal saline in the treatment of dystrophic calcinosis cutis.

Methods: This prospective pilot study injected normal saline or sodium thiosulfate at 0.1 mL/cm^2 into lesions at baseline and at 1- and 2-month follow-up. Subjects were followed for a total of 12 weeks. An in-person Physician Global Assessment score was assigned by the injecting physician at each visit and was repeated by an independent observer.

Results: Of 4 subjects who completed the study, only 1 experienced improvement in the size and Physician Global Assessment score of the lesion. By 3-month follow-up, there was no difference between the average size of the treatment and control lesions (P = .39).

Limitations: This was a small single-center study with limited demographic diversity and a short follow-up period. Only dystrophic calcinosis cutis subjects were included, and subjects received only 3 monthly injections of sodium thiosulfate.

Conclusions: With only 1 positive response, our results highlight the need for further study of sodium thiosulfate treatment for dystrophic calcinosis. (JAAD Int 2020;1:114-20.)

Key words: calcinosis; double-blind method; pilot projects; saline solution; sodium thiosulfate; thiosulfates.

INTRODUCTION

Calcinosis cutis is a dermatologic condition characterized by the accumulation of insoluble calcium salts under the skin and subcutaneous tissues, resulting in a range of presentations from firm plaques or nodules to large ulcerations. Dystrophic calcinosis cutis is the most common of the 5 subtypes of calcinosis and occurs because of local tissue damage or abnormalities in collagenous, elastic, or subcutaneous fat tissue.[1] Patients with dystrophic

From the Department of Internal Medicine,[b] University of Central Florida College of Medicine,[a] Orlando.
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Correspondence to: David Weinstein, MD, Department of Internal Medicine, University of Central Florida College of Medicine, 9975 Tavistock Lakes Blvd, Ste 360, Orlando, FL 32817. E-mail: david.weinstein@ucf.edu.
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calcinosis cutis often present with a calcific mass composed of hydroxyapatite and amorphous calcium phosphate in the setting of normal serum calcium and phosphate levels.[1] This subtype is associated with chronic underlying disorders such as autoimmune connective tissue diseases, including systemic sclerosis, dermatomyositis, or systemic lupus erythematous.[1]

Although rare in the general population, calcinosis cutis may occur in up to 49% of patients with systemic sclerosis.[2-4] Affected patients often have increased morbidity because of disease-associated pain, ulceration, and secondary infections that may severely decrease quality of life.[5,6] To alleviate these symptoms, several treatments have emerged aimed at the dissolution or surgical removal of calcium deposits to encourage normal epithelial growth.[7,8] However, many of these treatments are based on single case reports, expert opinion, or small case series.[7] As a result, no standard of treatment exists because of the lack of randomized, controlled trials to evaluate therapeutic efficacy.

Sodium thiosulfate was first introduced as a possible treatment for calcinosis cutis in 2004.[9] It has since been used successfully in several cases via intravenous, topical, and intralesional routes, with increased resolution of lesions and decreased associated pain.[10-17] However, treatment may be complicated by route-dependent limitations and adverse effects. Intravenous administration of sodium thiosulfate may subject patients to potential adverse effects, including fatigue, hypotension, gastrointestinal upset, and anion gap metabolic acidosis.[10,11,18,19] Although it may have fewer associated systemic adverse effects, topical sodium thiosulfate may not penetrate the skin adequately enough to dissolve deep calcifications, and patients must strictly adhere to the application directions.[13,20]

Intralesional injection of sodium thiosulfate has the advantages of localized administration and reduction of unwanted systemic adverse effects while maintaining accessibility to deep lesions. Although several reports have shown positive responses to intralesional sodium thiosulfate for calcinosis cutis, only 1 study was prospective and obtained partial response.[15-17,21] To address the gap in controlled trials, our study sought to create a prospective, double-blinded investigation of the efficacy of intralesional sodium thiosulfate versus normal saline in dystrophic calcinosis cutis.

CAPSULE SUMMARY

- Previous cases studies have used intralesional sodium thiosulfate as a treatment for dystrophic calcinosis cutis.
- Our study was underpowered to detect all but a major difference in Physician Global Assessment score, and it is possible that sodium thiosulfate provides some benefit even in the context of our findings. Further research is warranted.

METHODS

Study design

This was a single-location, double-blind, single-arm, 3-month trial. Subjects attended 4 visits: a baseline visit followed by visits at 1, 2, and 3 months.

Subjects were given identification numbers (1 through 5) and had 2 lesions selected. One lesion was placed into the control group and the other was placed into the treatment group. Before the study began, a control group was randomized via coin flip. The identity of which lesion was the control group was accessible only to designated study personnel responsible for labeling study treatments. Investigators were blinded by restricting their access to the study treatments before they were labeled. Treatment was given in order of subject identification number at baseline and 1- and 2-month follow-up.

Study participants

Subjects were recruited from the University of Central Florida Health Clinic, the Central Florida Society for Dermatology, and the Lupus Foundation of Florida in the United States. Eligible subjects were aged 18 to 80 years, had a diagnosis of idiopathic or dystrophic calcinosis cutis, and had at least 2 lesions 2 mm or larger. Subjects were excluded if they were allergic to sodium thiosulfate or its components, pregnant or breast feeding, unable to consent, unable to read English, or a prisoner. All subjects provided written consent.

Treatment

At the baseline visit, the investigator measured both lesions, and their size was recorded. The investigator then assigned a Physician Global Assessment (PGA) score based on the severity of the lesion (Table I). To achieve as isotonic a solution as possible, the out-of-the-bottle sodium thiosulfate was diluted in a ratio of 1 part sodium thiosulfate 250 mg/mL to 5.25 parts sterile water to yield a solution of sodium thiosulfate at 40 mg/mL. A volume of normal saline or sodium thiosulfate at 0.1 mL/cm^2 was injected into each lesion. A maximum of 0.4 mL of sodium thiosulfate at 40 mg/mL, or 16 mg of sodium thiosulfate (given

Abbreviation used:

PGA: Physician Global Assessment

maximum lesion size of 2 × 2 cm), was used per subject per visit. Subjects were provided with a 0- to 10-point visual analog scale and asked to rate their level of pain from the injection for each lesion, with 0 being no pain at all and 10 being extreme pain. After the visit, a second investigator assigned an independent observer PGA score, using photos of the lesions to ensure the integrity of the PGA. Our second investigator was blinded about which lesions received which treatment and at which visit in the study the lesions were photographed. Subjects were asked to return in 1 month. A total of 3 treatments were performed during the 3-month trial, 1 each at baseline and 1- and 2-month follow-up. Adverse effects, if any, were recorded at each visit.

Study end points

The primary end point of the study was the percentage change in lesion size at the month 3 visit, absolute and percentage change in PGA scores, and average pain experienced by each subject throughout the course of the study. Secondary end points included adverse events during the study.

Statistical analysis

Sample size for the purposes of statistical analysis was established as n = 4 based on the number of participants who completed the study with 2 lesions each. With a β of .2 (power of 0.8) and α of .05, an effect size of 2.4 in PGA would be needed to detect a difference between groups, assuming a standard deviation of 1 in the PGA, although for small exploratory studies such as this, post hoc power calculations may be of little value. All variables were analyzed for percentage change from baseline and averaged across all participants. The primary end point was analyzed with a paired 2-sample-for-means *t* test, with the exception of average pain experienced by each subject throughout the study.

RESULTS

Subject characteristics

A total of 4 subjects were included in our study (Table II), each contributing a control and treatment lesion (n = 4). Underlying diagnoses included morphea, systemic sclerosis, and dermatomyositis. There was no significant difference between the size of the lesions for control and treatment groups at baseline (P = .41). All participants were white and 2 identified as Hispanic or Latino. The average age was 50.6 years (range 23-78 years). At baseline, there were 4 female subjects and 1 male subject. The male subject was lost to follow-up after the 1-month treatment point and was excluded from the analysis (Fig 1). The trial was stopped earlier than planned because of shifting clinical responsibilities of the principal investigator and lack of funding and support.

Table I. Physician's Global Assessment score for calcinosis cutis assigned at baseline and each follow-up visit before injection

Score	Category	Description
0	Clear	No lesion present
1	Almost clear	Minimal signs of lesion
2	Mild	Easily recognizable lesion
3	Moderate	Moderate signs of lesion
4	Severe	Very marked lesion

Response to treatment

Lesion location, percentage change in size, and PGA assessments at baseline and 3-month follow-up are reported in Table III. Of the 4 subjects who completed the study, 1 subject (subject 1) experienced a change in PGA score during the duration of treatment (Fig 2). Treatment with sodium thiosulfate in this subject resulted in a decrease of PGA score of 4 at baseline to a PGA score of zero at 3 months (Fig 2, *A* and *D*). This subject also experienced a reduction of PGA score for the control lesion treated with normal saline, decreasing from a PGA score of 4 at baseline to a score of 1 at 3 months. The remaining 3 subjects had PGA scores of 4 at baseline and 4 at completion of the study for both the treatment and control lesions (Fig 2). The independent observer PGA scores tended to be lower at baseline and assessed an improvement of PGA score in 3 of the 4 sodium thiosulfate—treated lesions and 3 of the 4 control lesions at 3 months.

The average pain score for the sodium thiosulfate and placebo-control injection was 3.5 and 2.6 of 10, respectively. Lesions treated with normal saline ranged from 0.16 to 4 cm^2 at baseline, and those treated with sodium thiosulfate ranged from 0.09 to 4 cm^2. One subject (subject 2) experienced an increase in control lesion size from baseline, from 2 to 4 cm^2 at 3-month follow-up. The subject who experienced improvement in PGA scores (subject 1) also experienced a reduction in lesion size (Fig 2, *A* and *D*). The sodium thiosulfate treatment lesion completely resolved, decreasing from 0.09 cm^2 at

Table II. Subject demographics and underlying medical conditions

Subject	Age, years	Sex	Race	Hispanic or Latino	Medical history	Medications	Underlying disease status	Duration of lesions treated
1	23	Woman	White	Yes	Generalized morphea, gastroesophageal reflux disease	Tocilizumab, hydroxychloroquine, prednisone, tramadol, acetaminophen, pantoprazole	Slowly progressive	8 mo
2	72	Woman	White	No	Dermatomyositis, calcinosis cutis, hypertension, hyperlipidemia, hypothyroidism	Gabapentin, potassium chloride, atorvastatin, losartan, hydrochlorothiazide, amlodipine, primidone, levothyroxine, naproxen, cetirizine, alendronate, prednisone	Stable	20 y
3	51	Woman	White	No	Systemic sclerosis, calcinosis cutis, Raynaud phenomenon, osteoporosis; history of nephrolithiasis	Allopurinol, potassium citrate, alendronate, calcium, vitamin D3	Slowly progressive	>10 y
4	78	Woman	White	No	Systemic sclerosis, calcinosis cutis, Barrett esophagitis	None	Stable	>10 y
5	29	Man	White	Yes	Dermatomyositis, calcinosis cutis; history of gastrointestinal bleeding, transfusion	Methotrexate, prednisone, folic acid, oxycodone, morphine sulfate, hydroxychloroquine, oxandrolone, pantoprazole*	Progressive	>2 y

*New medication for subject 5 added at 1-month follow-up. This subject was lost to follow-up after the 1-month follow-up visit.

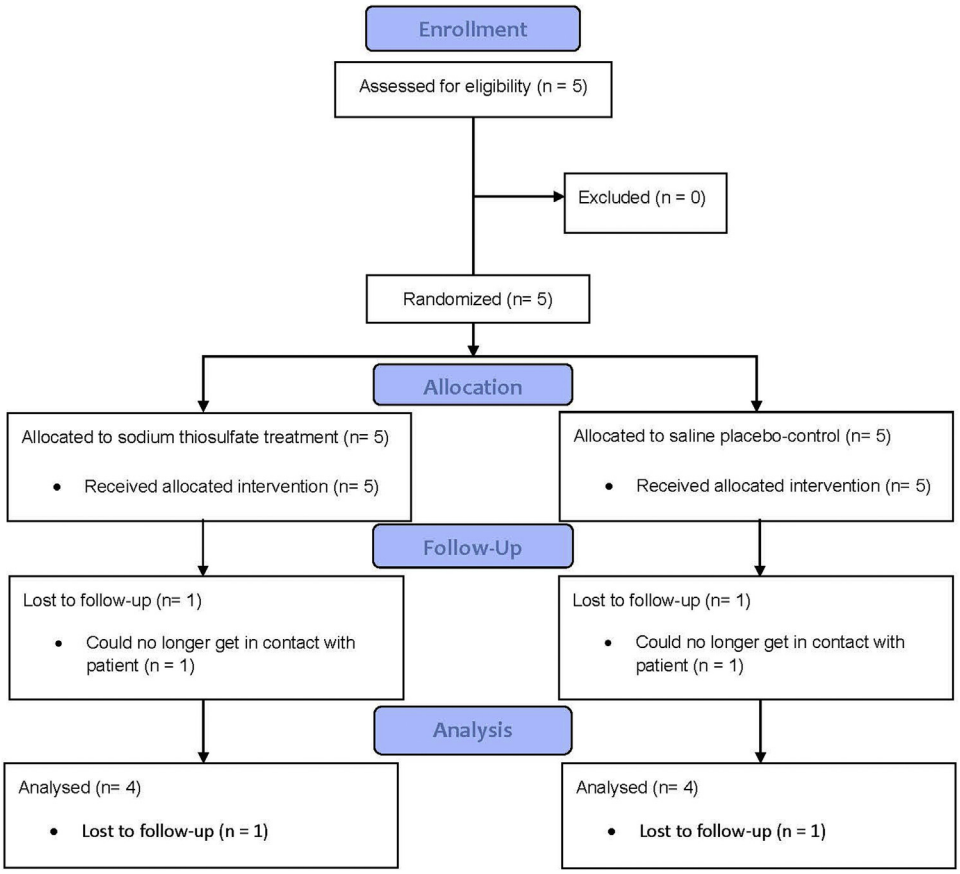

Fig 1. CONSORT flow diagram of subjects through each stage of the pilot study.

baseline to 0 cm^2 at the end of the study. The same subject's control lesion experienced a 44% reduction, from 0.16 to 0.09 cm^2. By 3-month follow-up, there was no statistical significance between the average size of the treatment and control lesions (P = .39). There were no adverse events reported.

DISCUSSION

Calcinosis cutis lesions can be a debilitating condition for patients. According to lesion size and subtype of calcinosis cutis, treatment with warfarin, calcium-channel blockers (diltiazem), bisphosphonates, intralesional corticosteroids, intravenous immunoglobulin, curettage, and surgical excision have all been reported to improve outcomes.[7] Yet because of a paucity of large-scale, controlled trials, no standard of treatment exists for patients with the disease. Intralesional injection of sodium thiosulfate is a promising treatment with a low adverse-effect profile.[15-17,21] The mechanism of action of sodium thiosulfate in calcinosis cutis is hypothesized to result from the solution's high solubility of calcium thiosulfate salts that inhibit precipitation of calcium salt and promote dissolution of calcium deposits.[9] In comparison with the success of previous reports, our pilot study of 4 subjects treated with intralesional sodium thiosulfate showed improvement in 1 subject, as evidenced by decreased PGA scores and percentage change in lesion size, with no statistical significance between sodium thiosulfate– and placebo-treated lesions at baseline or by completion of the study.

In a prospective case series by Baumgartner and Olesen,[21] 6 patients with dystrophic calcinosis cutis were treated with intralesional sodium thiosulfate, and all 6 reported at least some improvement. This study provided injections at a higher concentration of sodium thiosulfate (150 mg/mL) than ours (40 mg/mL). However, sodium thiosulfate is extremely hypertonic and painful if injected out of the bottle. According to verbal communication with Hope Pharmaceuticals (August 31st, 2018), sodium thiosulfate at 250 mg/mL has an osmolarity of approximately 2000 mOsm/kg, and thus we opted to dilute it to obtain an osmolarity close to isotonic to avoid excessive pain and decrease the likelihood of adverse

Table III. Lesion characteristics and response to treatment (sodium thiosulfate) or control (normal saline) injection

	Treatment lesion						Control lesion					
		PGA score		Independent observer score		Change in size,		PGA score		Independent observer score		Change in size,
Subject	Location	Baseline	3 Month	Baseline	3 Month	%	Location	Baseline	3 Month	Baseline	3 Month	%
1	Inferior aspect of left elbow	4	0	2	0	−100	Superior aspect of left elbow	4	1	3	1	−44
2	Right arm	4	4	3	2	0	Left arm	4	4	3	1	100
3	Left arm	4	4	4	3	0	Right arm	4	4	4	2	0
4	Left hand, fifth digit	4	4	3	3	0	Right hand, fifth digit	4	4	4	4	0

Size reported as overall percentage change from baseline to study's end at the 3-month follow-up.
PGA, Physician Global Assessment.

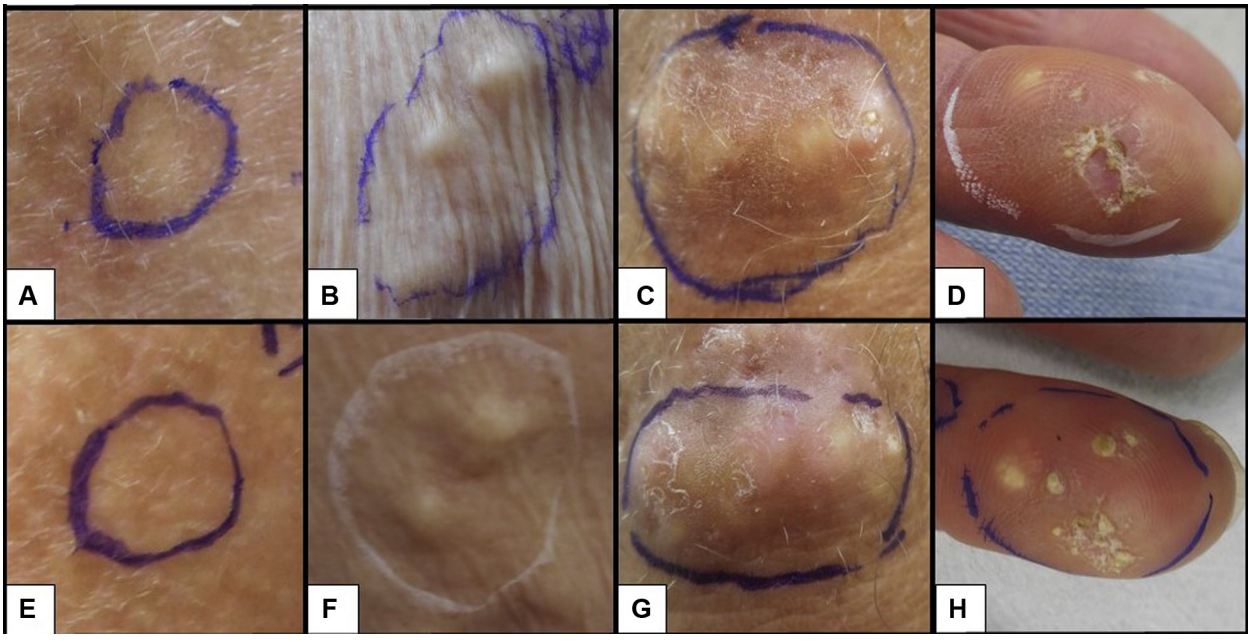

Fig 2. Sodium thiosulfate treatment lesions for subject 1 (**A**, **E**), subject 2 (**B**, **F**), subject 3 (**C**, **G**), and subject 4 (**D**, **H**) at baseline (**A** to **D**) and 3-month follow-up (**E** to **H**).

effects, such as ulceration. This is a concentration similar to that used to treat mechlorethamine extravasation.[22] Unlike those of previous studies, our intralesional sodium thiosulfate treatments at a low concentration of 40 mg/mL failed to lead to improvement in 75% of patients.

Frequency of injection may also affect the success of intralesional sodium thiosulfate treatment. Baumgartner and Olesen[21] performed injections at a maximum frequency of once weekly for 4 weeks and continued to follow for a total of 12 weeks. Patients who received a total of 4 injections experienced percentage reduction in lesion size ranging from 67% to 93%. Other reports of intralesional sodium thiosulfate injected at similarly frequent intervals showed comparable results.[16,17] Our study administered injections monthly during 12 weeks, for a total of 3 sodium thiosulfate injections. Thus, it may be that more frequent injections at a higher concentration of sodium thiosulfate are necessary to achieve significant results with intralesional sodium thiosulfate.

There may be a relationship between lesion size and efficacy of intralesional sodium thiosulfate injection. A case report of a 3 × 4-mm calcinosis cutis of the fingertip described complete resolution of the lesion,[17] as did Baumgartner and Olesen[21] for the smallest calcinosis lesions of 3 to 4 mm. Likewise, the

subject with the most significant response to sodium thiosulfate injection in our study was also the one with the smallest lesion, measuring 0.09 cm^2 at baseline. However, this subject had calcinosis cutis for the shortest duration of all the subjects in our study. It may be that lesions of calcinosis cutis are responsive to treatment with sodium thiosulfate when treated earlier rather than later.

As discussed, our conservative treatment protocol of monthly injections of sodium thiosulfate at 40 mg/mL during the course of 3 months may have limited the success of our results in comparison with those of previous studies. However, some more recent studies also have revealed that sodium thiosulfate might not be as effective as once thought.[18,23] Further investigations are needed that include not just similar placebo-controlled treatments, as in our study, but also ranges of concentrations of sodium thiosulfate that will maximize treatment response. Our single-center pilot study included a limited sample population both in size and demographic diversity, as well as a short follow-up period of 3 months. Additionally, our subjects represented only dystrophic calcinosis cutis, and therefore our results may not be generalizable to all subtypes of calcinosis cutis. Our pilot study was underpowered to detect anything but a significant effect (PGA score improvement of 2.4 points) from sodium thiosulfate treatment; therefore, our inability to reject the null hypothesis should not be interpreted as evidence that sodium thiosulfate is ineffective. Future studies should look at a larger, more diverse sample to analyze the discrepancy in response to treatment and to confirm the validity of previous case reports and series. Despite the limited success in our study, we believe the use of intralesional sodium thiosulfate for the treatment of calcinosis cutis should be explored in larger-scale studies.

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