Clinical Letter

Topical sodium thiosulfate: a reliable treatment for digital calcinosis cutis – a case series with six patients

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Calcinosis cutis (CC) develops in about 25 % of patients with limited cutaneous systemic sclerosis (lcSSc) and also occurs in other autoimmune connective tissue diseases such as dermatomyositis [1]. Patients suffer from severe pain and a reduced ability to perform precision mechanical work [2, 3]. Calcinosis cutis is also a risk factor in development of digital ulceration (55 % respectively) [4].

Topical application of sodium thiosulfate has been reported to result in reduction of calcinosis in several patients [5–8] and to be one of the few treatments to do so with moderately reproducible efficacy in CC [9]. However, these case reports and case series differ in the underlying diseases, their presented outcomes, the method of assessment and their prescription formulas. As each of these parameters can influence the outcome, general appreciation and application of this treatment may have been hampered.

We present a case series of six lcSSc patients with dystrophic calcifications who were treated with topical sodium thiosulfate 10 % incorporated in a formulation, the stability of which warrants home use for at least four weeks. From September 2015 to March 2017 we offered off-label treatment with this compound to six patients who suffered from calcinosis cutis lesions of ≤ 2 mm diameter on their hands; the six patients had been diagnosed with lcSSc [10], one of them by VEDOSS criteria for early SSc [11]. We only included lesions at the fingertips for better comparability.

We applied a compounded prescription according to the following formula: Hydrophilic sodium thiosulfate cream 10 % 20 g, combined with sodium thiosulfate pentahydrate 2.0 g, purified water 2.0 g, propylene glycol 0.4 g; all ingredients dissolved in base cream DAC ad 20.0 g. This prescription was organoleptically stable for at least four weeks, and we confirmed reliable production by having it manufactured by three different and independent pharmacists.

Patients were advised to apply a thin layer of the cream once daily and were seen every four weeks for follow-up visits during which the diameter of lesions in millimeters was measured with a measuring tape. These measurements were taken by the same physician on all consecutive visits. Lesions were photo-documented, and patients were asked about irritations and pain. Patients were usually recommended to continue treatment for at least eight weeks.

All patients experienced a substantial reduction in the number and/or diameter of lesions as outlined in Table 1 (Figure 1a–d). In 5 of 6 cases we had observed a reduction both in number and lesion size, while case #4 showed a reduction in number, but enlargement of one of the lesions. No additional lesion appeared during treatment. Of the cumulative total of 28 lesions in the six patients prior to treatment, only eight lesions remained after treatment. Thus, a reduction of 71 % was achieved in the cohort. An example of one patient with reduction in number and size of lesions is presented in Figure 1a–d. All patients reported a concomitant reduction in discomfort. No ulceration occurred, and no side effects such as erythema, pain or burning sensations after application of the ointment were reported.

Our case series demonstrates that 10 % topical sodium thiosulfate in the formulation prescribed here is an efficacious therapy for small (≤ 2 mm diameter) calcified lesions in patients with lcSSc. Our results help to more accurately define the appropriate indication for this topical therapy. Though its positive effects have been noted before, outcomes have varied [5–8]. In the largest case series so far by Ma et al. [12], clinical improvement was reported in only 19 of 28 patients (68 %),

### Table 1. Number and size of lesions of all patients.

| ID | Age | Duration of treatment in months | Number of lesions | Diameter of largest lesion |
|----|-----|-------------------------------|-------------------|---------------------------|
|    |     |                               | Before treatment | After treatment | Before treatment | After treatment |
| 1  | 52  | 13                            | 5                 | 2              | 3.5 × 2.5 mm     | 1 × 1 mm         |
| 2  | 64  | 9                             | 1                 | 0              | 2 × 2 mm         | 0                |
| 3  | 62  | 2                             | 1                 | 0              | 3 × 2 mm         | 2 × 1 mm         |
| 4  | 52  | 8                             | 4                 | 3              | 2 × 2 mm         | 3 × 3 mm         |
| 5  | 14  | 8                             | 14                | 2              | 3 × 2 mm         | 1 × 1 mm         |
| 6  | 82  | 3                             | 3                 | 0              | 1 × 1 mm         | 0                |

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with a complete response in two patients. However, the authors had also included patients with other underlying connective tissue diseases and in their retrospective analysis treatment regimens differed (twice or thrice daily) and were not restricted to small lesions on fingers. In the only other case series with more than three patients only one of four patients was reported to have complete response and three to have a partial response (photographs, but no quantitative data were provided) and 25 % sodium metabisulfite, applied twice daily, was used [13].

Our case series of six patients, representing the second largest series so far, provides data on exact size, location and number of lesions over time, all assessed according to a standardized method allowing quantification of the percentage change from baseline. Hence, we could demonstrate, in each of our patients, a reduction in number or size of lesions. We also restricted therapy to small and superficial lesions at the fingertips (≤ 2 mm diameter) and exclusively to patients with SSc in order to provide the best comparability possible and to avoid unrealistic expectations in patients with larger lesions.

Although our patients were also on other medications which theoretically could have had an effect on CC (four of our six patients were treated regularly with intravenous iloprost for their Raynaud’s phenomenon and one (#2) also took a calcium channel blocker (nifedipine)), they had been on these drugs for at least twelve months without any effects on calcinosis – indirectly verifying previous reports which, taken together, showed inconsistent effects of these drugs against CC [4, 9].

Previous articles describe different compositions and concentrations of sodium thiosulfate which besides efficacy may also influence side effects. While in the large case series [12] some patients experienced skin irritations likely due to the higher concentration of sodium thiosulfate, none of our six patients reported any local side effects to 10 % topical sodium thiosulfate.

In keeping with two case reports describing well-tolerated topical treatment with sodium thiosulfate in children [5, 7], the youngest patient in our case series, a 14-year-old, experienced no pain or other adverse effects.

Our galenic formulation provided organoleptic stability for at least four weeks, and we observed efficacy without clinically toxic effects on the skin. Given its intended use on an outpatient basis, we verified that the prescription could be manufactured without any difficulties by three independent pharmacies. The mechanism of action of sodium thiosulfate is mainly its capacity to increase solubility of calcium by forming calcium thiosulfate [14, 15].

In conclusion: Our case series (the 2nd largest retrospective series) demonstrates that the given formulation of topical sodium thiosulfate 10 % has a response rate of approximately 100 % when restricting its use to lesions of ≤ 2 mm diameter. It can be manufactured reliably for outpatient use. For larger or more deeply located lesions, subcutaneous or intravenous administration of sodium thiosulfate may be promising [16, 17] but cannot be self-administered.

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Conflict of interest

None.

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