Case Report

Combination of Intravenous and Intralesional Sodium Thiosulfate for the Treatment of Calciphylaxis

Kazuki Ueno, MD, Yoshitaka Wada, MD, PhD, Yoshifumi Iwahashi, MD, Shinichi Murata, MD, PhD, and Shinichi Asamura, MD, PhD

1 Department of Plastic Surgery, Wakayama Medical University, Japan
2 Department of Diagnostic Pathology, Wakayama Medical University, Japan

ABSTRACT

Calciphylaxis is a rare and life-threatening disorder characterized by painful skin ulceration. Treatment is not yet standardized; however, a case of calciphylaxis successfully treated by intravenous sodium thiosulfate was reported in 2004. Since then, several reports have supported the use of sodium thiosulfate in the treatment of calciphylaxis. However, intravenous administration of sodium thiosulfate may be limited owing to its systemic side effects. We report the successful treatment of a female patient with intractable right-leg calciphylaxis who was administered both intravenous and intralesional sodium thiosulfate combination therapy without side effects.

Key words: calciphylaxis, intralesional, intravenous, sodium thiosulfate

Introduction

Calciphylaxis is a rare, highly fatal disorder that presents as painful skin ulceration and necrosis. It is histologically characterized by calcification of the medial layer of small cutaneous arteries and arterioles, leading to microthrombosis and fibrointimal hyperplasia. It is associated with a high morbidity and mortality, with a reported survival rate of approximately 60% to 80%. The ulcers are intractable, and infection leading to sepsis is a common cause of death in patients with calciphylaxis. Although some recurrent cases have been reported, the recurrence rate remains unclear. The interdisciplinary management of calciphylaxis includes histological diagnosis, wound care, analgesia induction, nutritional support, correction of mineral parameters, intensive hemodialysis, administration of sodium thiosulfate and calcimimetic bisphosphonate, hyperbaric oxygen therapy, and withdrawal of iatrogenic factors such as warfarin, calcium-based binders, and vitamin D. Despite the poor survival rate of the disease, the treatment is not standardized.

A case of calciphylaxis was successfully treated by intravenous (IV) sodium thiosulfate (STS) by Ciccone et al. in 2004. Since then, several reports have supported the off-label use of STS in the treatment of calciphylaxis. However, systemic side effects may be a limitation of IV STS administration. As an alternative to IV administration of STS with potentially reduced dosage and frequency, there have been reports of successful treatments by single use of intralesional (IL) STS; however, it is restrictively painful. Therefore, for utilization of the benefits of both methods of administration, we applied IL STS in combination with IV dose in the present case of a female patient with right-leg calciphylaxis.

Case report and methods

A 64-year-old woman had a history of stage V chronic kidney disease (CKD) (estimated glomerular filtration rate of 3.7 mL/min/1.73 m²) owing to Immunoglobulin A nephropathy and hypertension. She was diagnosed with obesity (body mass index, 37.8); however, was non-diabetic. Laboratory values included elevated parathyroid hormone and phosphorus levels, at 744.4 pg/mL and 6.5 mg/dL, respectively.

The patient developed a painful skin ulcer in her right-leg that gradually increased in size and necrotized over a clinical course of 3 months at another hospital before referral to us for treatment (Fig. 1a). Skin biopsy histology revealed ulceration reaching subcutaneous tissue, substantial intramural vascular...
calcium deposition, and septal panniculitis with fibrosis (Fig. 2a, b).

She was diagnosed with calciphylaxis by her clinical features and histopathological findings according to the Japanese criteria, as reported by Hayashi.

The ulcer was initially treated by chemical and surgical debridement according to our standard procedures. After debridement of almost all necrotizing tissue, negative pressure wound therapy (NPWT) was initiated with -25 to -50 mmHg negative pressure intermittently for enhanced granulation tissue formation. After 3 days of NPWT, however, the granulation tissue was observed to be of an unhealthy pale color. (Fig. 1b, c) We immediately discontinued NPWT and switched to conservative therapy with sulfadiazine silver ointment. Despite daily dressing, necrosis progressed to the deep fascia layer. (Fig. 1d)

For recovering from this severe situation, after special ethical approval from the unapproved drug evaluation committee of Wakayama Medical University, we administrated IV-IL STS combination therapy. IL STS in prepared vials of STS 1 g/10 mL, summing up to 0.3 g (3 mL) were injected in a sterile manner as small boluses at the wound edge and wound bed once weekly. Meanwhile, IV STS was initiated at a dose of 10 g after every dialysis and gradually increased by 2 g/week to 18 g. Slight metabolic acidosis was recognized at 18 g dose; however, no other symptoms were noted (Fig. 3). After 6 weeks of STS administration, granulation tissue was well formed, and skin grafting was successfully performed for the remaining skin defects (Fig. 1e, f).

Discussion

STS is a versatile inorganic compound that has historically been used intravenously in the treatment of cyanide poisoning,
and more recently been effective in the treatment of calcium-mediated disorders\cite{12, 15, 16}. The mechanism of STS in the treatment of calcium-related disorders is multifactorial. It is an anti-calcification agent with vasodilatory and antioxidant properties, and it promotes the solubility and mobilization of calcium crystals from soft tissue calcifications\cite{9, 11}. Furthermore, STS acts as a powerful antioxidant agent, which may improve vascular endothelial function and promote vasodilation, reduce proliferation of vascular smooth muscle cells, and restore proper hepatic synthesis of albumin and fetuin-A\cite{9}. These factors may simultaneously contribute to the reduction of vascular calcification and could also explain the rapid improvement of pain after initiation of STS infusion\cite{9}.

Various treatments for calciphylaxis have been proposed. No blinded randomized clinical studies have been conducted for any of these proposed treatments for this potentially fatal disorder. Nonetheless, application of IV STS has emerged as one of the most common modes of treatment. However, STS is used as an off-label for calciphylaxis, and it was utilized in this study with special ethical approval. IV administration of STS was the most common method (70.3\%) for calciphylactic patients with CKD, with its treatment efficiency reported in a systematic review as approximately 65.9\%\cite{17}. It may cause systemic side effects, such as nausea, hypocalemia, metabolic acidosis, QT-interval prolongation, and volume overload\cite{11}.

Thus, for avoiding these adverse effects, single use of IL STS has been proposed, with successful results and fewer side effects\cite{12, 13}. The main drawback of IL STS, is the pain during
injection, which may be reduced by local anesthesia; however, application is difficult for widespread or intensely painful lesions.

IL administration may be effective for the treatment of localized ulcers, such as in the current case. To date, however, there are still far more successfully treated cases of IV administration than those of simple IL administration. In the current case, the initiation of NPWT caused rapid wound necrosis with intense pain; therefore, a relatively common treatment using IV administration was simultaneously applied with the IL administration for ceasing the necrosis promptly.

The most commonly used dose of IV STS is 25 g mixed with 100 mL of isotonic saline administered over the last 30–60 min of dialysis, thrice weekly as an infusion[17]. The dose of IL STS is between 0.1 g and 3.75 g depending on the size of the ulcer[12, 13, 18]. In the current case, by using IL STS, healing could be achieved with a smaller-than-typical amount of IV STS, between 10 g and 18 g. The reason for the absence of systemic side effects in the current case was the dose of IV STS gradually increased by concurrently using IL STS.

The duration of treatment by IV STS ranged from 6 weeks to 34 months[14], and that of treatment by IL STS ranged from 18 weeks to 11 months[12, 13, 18]. The duration of treatment in this case (10 weeks) was relatively short, which indicates that this IV-IL combination may be an effective treatment.

NPWT is a widely used therapeutic technique where wound healing is promoted by delivering negative pressure to the wound using suction pump, tubing, and dressing. Although NPWT generally accelerates the granulation phase of cutaneous wound healing[20], the wound can be immediately worsened by the course of NPWT. Karinos et al. showed that perfusion beneath negative pressure wound dressings decreased with increasing suction pressure. As the tissue pressure rises, the pressure gradient across the capillary wall causes a decrease in the vessel cross-sectional area, resulting in occlusion of the capillary vessels and potential necrosis at the ischemic wound edge[20, 21]. We suggest that infection or inadequate pressure may have been the cause of necrosis in the current case. While there are reports of calciphylaxis ulceration specifically being worsened by infection after using NPWT[22], further analysis is warranted to confirm the benefits of its application for calciphylaxis.

Our case of calciphylaxis was successfully treated with IV-IL STS combination therapy without any systemic side effects. A longer follow-up and randomized controlled study are indicated. Nevertheless, we believe that IV-IL STS combination therapy may be one of the safest methods of administration of STS, which contributes to the rapid formation of granulation tissue.

Conclusion

STS IV-IL combination therapy is the potential first-choice modality for patients with calciphylaxis with relatively small injectable lesions.

Acknowledgments

We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center, Wakayama Medical University.

Sources of funding

This study received no particular funding.

Conflicts of interest

The authors all declare that there are no conflicts of interest.

References

1) Cicone JS, Petronis JB, Embert CD, Spector DA: Successful treatment of calciphylaxis with intravenous sodium thiosulfate. Am J Kidney Dis 2004; 43: 1104-8.
2) Zuhaili B, Al-Talib K: Successful treatment of single infected calciphylaxis lesion with intralesoinal injection of sodium thiosulfate at high concentration. Wounds 2019; 31: ES4-7.
3) Magro CM, Simman R, Jackson S: Calciphylaxis: a review. J Am Col Certif Wound Spec 2010; 2: 66-72.
4) Seethapathy H, Brandenburg VM, Sinha S, El-Azhary RA, Nigwekar SU: Review: update on the management of calciphylaxis. QJM 2018; 112: 29-34.
5) Harris C, Kiai M, Lau W, Farah M: Multi-intervention management of calcific uremic arteriolopathy in 24 patients. Clin Kidney J 2018; 11: 704-9.
6) Subramaniam K, Wallace H, Sinniah R, Saker B: Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfate. Australas J Dermatol 2008; 49: 30-4.
7) Galassi A, Perna F, De Nicola E, Moneghini L, Sganzaroli AB, Cozzolino M: Calciphylaxis in a dialysis patient treated by intralesoinal and systemic sodium thiosulfate on top of multifactorial intervention. Clin Kidney J 2019; 12: 546-9.
8) Brucueler M, Cheigh J, Bauer G, Serur D: Long-term intravenous sodium thiosulfate in the treatment of a patient with calciphylaxis. Semin Dial 2005; 18: 431-4.
9) Hayden MR, Goldsmith DJA: Sodium thiosulfate: new hope for the treatment of calciphylaxis. Semin Dial 2010; 23: 258-62.
10) Hayden MR, Goldsmith D, Sowers JR, Khanna R: Calciphylaxis: calcific uremic arteriolopathy and the emerging role of sodium thiosulfate. Int Urol Nephrol 2008; 40: 443-51.
11) Nigwekar SU, Thadhani R, Brandenburg VM: Calciphylaxis. N Engl J Med 2018; 378: 1704-14.
12) Strazzula L, Nigwekar SU, Steele D, et al: Intralesoinal sodium thiosulfate for the treatment of calciphylaxis. JAMA Dermatol
2013; 14: 946-9.
13) Isoherranen K, Bouchard L, Kluger N: Benefits of intralesional injections of sodium thiosulfate in the treatment of calciphylaxis. Int Wound J 2017; 14: 955-9.
14) Hayashi M: Calciphylaxis: diagnosis and clinical features. Clin Exp Nephrol 2013; 17: 498-503.
15) Bair B, Fivenson D: A novel treatment for ulcerative calcinosis cutis. J Drugs Dermatol 2011; 10: 1042-4.
16) Yatzidis H: Successful sodium thiosulphate treatment for recurrent calcium urolithiasis. Clin Nephrol 1985; 23: 63-7.
17) Peng T, Zhao L, Wang Y, et al: Systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. Nephrology (Carlton) 2018; 23: 669-75.
18) Ossorio-Garcia L, Jimenez-Gallo D, Arjona-Aguilera C, Linares-Barrios M: Intralesional sodium thiosulfate to treat calciphylaxis. Actas Dermosifiliogr 2016; 107: 359-62.
19) Huang C, Leavitt T, Bayer LR, Orgill DP: Effect of negative pressure wound therapy on wound healing. Curr Probl Surg 2014; 51: 301-31.
20) Kairinos N, Voogd AM, Botha PH, et al: Negative-pressure wound therapy II: negative-pressure wound therapy and increased perfusion. Just an illusion? Plast Reconstr Surg 2009; 123: 601-12.
21) Kasai Y, Nemoto H, Kimura N, Ito Y, Sumiya N: Application of low-pressure negative pressure wound therapy to ischaemic wounds. J Plast Reconstr Aesthet Surg 2012; 65: 395-8.
22) Emohare O, Kowal-Vern A, Wiley D, Latenser BA: Vacuum-assisted closure use in calciphylaxis. J Burn Care Rehabil 2004; 25: 161-4.