CASE REPORT

# Potential effect of sodium thiosulfate in calciphylaxis: remission of intractable pain

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## Abstract

Calciphylaxis, a rare disease mainly seen in patients with chronic kidney disease, is characterised by ischaemic skin damages and excruciating pain. Calciphylaxis has poor prognosis which often results in amputation and high mortality. Although guidelines for the management of calciphylaxis are not available, sodium thiosulfate has shown efficacy in many clinical reports. We report the case of a 64-year-old advanced calciphylaxis male patient who had two amputations due to intolerable pain manifested as deteriorating ulcer. After he was treated with intravenous sodium thiosulfate (STS), his pain was significantly relieved with a healing trend of the big wound. One more amputation for the remission of intractable pain was avoided. The treatment experience indicates that sodium thiosulfate is of great value in quick pain relief and reducing suffering of calciphylaxis patients.

**Keywords:** Calciphylaxis, Calcific uremic arteriolopathy, Painful skin ulcer, Maintenance haemodialysis, Sodium thiosulfate.

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## Introduction

Calciphylaxis, also known as calcific uraemic arteriolopathy, is a rare but fatal vascular calcific disease characterised by occlusion of subcutaneous adipose tissue and microvascular in the dermis, which causes severe pain and ischaemic skin damage.[1] Calciphylaxis is typically reported in end-stage renal disease patients with poor prognosis, which has amputation rate of 66.7% and the patient feels incurable pain even with basic treatments such as antisepsis, analgesia and dressing change.[2] The major risk factors are chronic kidney disease, hypercalcaemia, hyperphosphataemia, high serum intact parathyroid hormone (iPTH) level, long-term use of Warfarin and calcium supplement.[3,4] Treatment options including medication, wound care and hyperbaric oxygen are still at an exploratory stage. Sodium thiosulfate (STS) was the first to be reported effective in calciphylaxis[5] and is still most frequently used. STS, a calcium chelator, can inhibit adipocyte-induced vascular calcification with antioxidative and vasodilatory properties.[6] Comprehensive treatment based on intravenous STS is recommended and is routinely used off-label in calciphylaxis.

We report the case of an advanced calciphylaxis patient who had recurrent acral skin necrosis and a third amputation seemed to be inescapable. However, STS administration significantly relieved the sharp pain and delayed deterioration of skin ulcer so that the third amputation was avoided.

## Case Report

A 64-year-old Chinese, non-diabetic male patient with a 23-year history of haemodialysis presented with calciphylaxis. He had been diagnosed with secondary hyperparathyroidism (SHPT) with high iPTH level ( >600 ng/L) and had been on oral calcium supplement for about five years. Since 2015, there were recurrent and progressively worsening skin ulcers along with severe pain in the first and third fingers of his left hand. His condition was such that he could not sleep, which had seriously affected his quality of life. Hence, his two fingers had been amputated, while three toes of the right foot met the same fate one year later. Although he accepted amputation of the right lower limb again, there was also an evolving ulcer on his left heel (Figure-1a) which caused sharp pain. At the same time, the previous operated site of amputation showed poor healing. The pain was difficult to control even with two or more painkillers. He had already received treatment for ulcers and wounds in other hospitals with wound care, debridement and repetitive intravenous antibiotics. He was admitted to our hospital (Department of Nephrology, Zhong Da Hospital) on March 12, 2018 for the dusky discoloured foot ulcer accompanied by growing pain and had agreed to undergo amputation.

Physical examination showed a dark purple necrotic lesion on his left heel without exudates (Figure-1a). Tenderness on the left dorsum pedis was significant, instep skin temperature was lower than proximal part and

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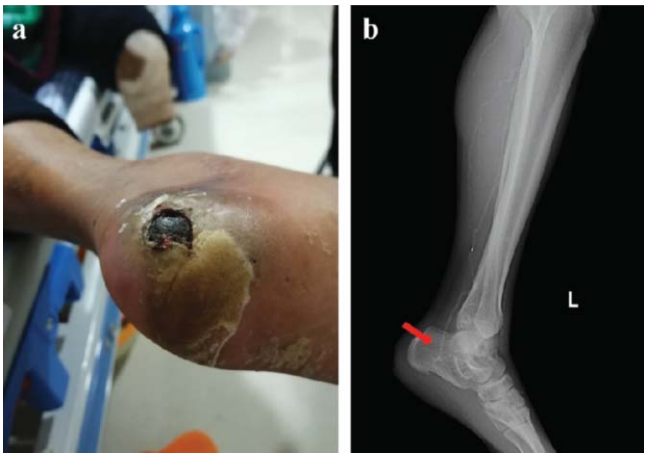


**Figure-1:** (a) Ulcer on the left heel with black- sunken necrosis surrounded with dark purple colour skin (Photographed in March 2018); (b) X-ray of the left lower extremity. The red arrows indicate the calcified vascular which suspected of supplying blood at the necrotic site.

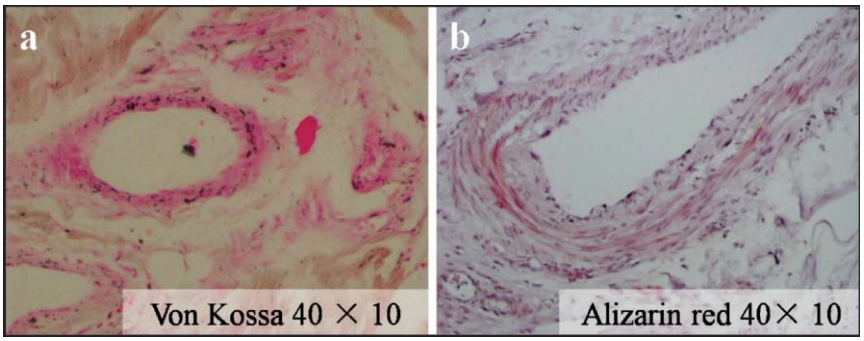


**Figure-2:** Skin Pathological Examination: (a) Von Kossa: positive with black stained calcium deposition in soft tissue, arterioles and middle artery wall of dermal tissue; (b) Alizarin red: positive with orange stained calcium in the vessel wall.

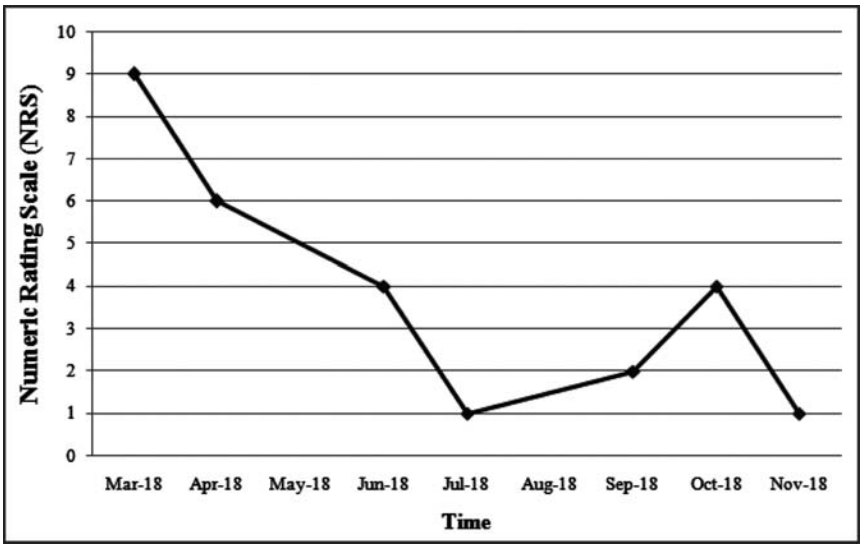


**Figure-3:** Highest pain scores measured in numeric pain rating scale during admission period.

left dorsalis pedis arteries pulsation was weak. The left thumb, middle finger and right extremity were missing. The right thigh amputated wound was poorly healed with obvious redness and swelling. Laboratory evaluation revealed an elevated iPTH of 474.3pg/mL (12~88 pg/mL), serum phosphorus of 1.83mmol/L (0.85~1.51mmol/L) and a normal serum calcium of 2.23mmol/L (2.11~2.52mmol/L). His highest pain score of numeric pain rating scale (NRS) was 9. Radiography (Figure-1b) of left lower extremities showed successive vascular calcification in tibial and dorsalis pedis arteries.

A skin biopsy was performed, which confirmed calcium deposition in the vessel walls with von Kossa and Alizarin red staining (Figure-2). Combined with the risk factors, clinical manifestations, imaging performance and pathological examination, the patient was diagnosed with calciphylaxis. Besides low calcium dialysis, oral calcitriol and wound care, he was given daily intravenous infusion of STS (starting dose: 5g and maintenance dose: 10g i.v. each day) for six months. In the initial week of medication, there was an increase in the dusky area on the left heel but the patient felt the pain was relieved as he did not wake up with pain at night. Within three months, ulcer progression had halted and the amputated wounds in his right lower extremity began to slowly heal. Six months later, serum calcium and phosphorus level were 2.35mmol/L and 1.21mmol/L, respectively. His NRS pain score gradually decreased within the initial five months and fluctuated between 1~4 since the onset of medication (Figure-3). On account of the above treatment, there was no indication for amputation, and the patient received STS treatment periodically.

## Discussion

Calciphylaxis is gradually gaining clinicians' attention with more literature published while the mechanism remains unclear. It's reported that the one-year mortality is 45~80%[3,4] and calciphylaxis in chronic haemodialysis patients has nearly three times higher mortality.[7] Approximately 50% of survivors are bedridden or wheelchair-bound, and more than 70% require hospitalisation because of severe ulcers.[8] Sustained pain

and insomnia could further affect their quality of life.[9] It's important to relive pain and reduce disability rate in calciphylaxis patients.

Our patient was diagnosed with severe calciphylaxis who was characterised by recurrent peripheral gangrene of fingers, toes and heel. His risk factors included chronic haemodialysis, SHPT, high serum levels of phosphate and long-term oral calcium treatment. The patient had a history of two amputations due to unbearable pain. However, the acral-skin necrosis deteriorated continuously and seriously affected his life.

STS (Na2S2O3) has certain efficacy on calciphylaxis owing to its calcium chelating property.[6] The calcium deposited in vascular wall can be dissolved by sodium ions, which synthesise highly soluble calcium thiosulfate. The latter can be further removed by haemodialysis. STS also functions as an anti-oxidation and vasodilatation agent.[6,10]

Nigwekar SU. et al[11] proposed a STS medication regimen in 2015, for an average 70kg person on thrice haemodialysis therapy, they recommended administering 25g STS (Na2S2O3·5H2O) intravenously in 100mL of normal saline during the last half-hour of each haemodialysis session. The same regimen was applied to our patients and obvious adverse reactions including nausea and vomiting were reported. This may stem from racial differences. After repeated attempts, a dosage regimen for Chinese calciphylaxis patients was developed which worked well with fewer side effects. The starting dose of STS (Na2S2O3·5H2O) is 5g with an increase of 1g daily and maintenance dose is 10g. STS is delivered by intravenous drip in 250mL normal saline solution every day. It shows that reduction of phosphorus and NRS are significantly correlated with STS treatment courses. Although incidence of adverse events is up to 40% (nausea/vomiting 10%, hypotension 10%, infection 20%), no one's treatment was interrupted by mild discomfort.

## Conclusion

The case of an advanced calciphylaxis with typical acral-gangrene and history of amputations is presented. The patient responded well to treatment with STS. It's suggested that STS also has a certain therapeutic effect among calciphylaxis patients in advanced stage, which mainly reflects in relieving pain and delaying the progression of skin ulcers. We are applying STS medication regimen in more calciphylaxis patients and hope to see more authoritative treatment guidelines.

**Informed Consent Form:** The patient signed an informed consent and authorised the publication of data and photographs of the case.

**Disclaimer:** None to declare.

**Conflict of Interest:** None to declare.

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