Sodium Thiosulfate as a Treatment for Calciphylaxis

by NATSINEE TANGKIJNGAMVONG, MD; PAWEENA SUSANTITAPHONG, MD; NUMPHUNG NUMKARUNARUNROTE, MD; ONANONG JEARNSUJITWIMOL, MD; PRAVIT ASAWANONDA, MD, DSc; and PAWINEE RERKNIMITR, MD, MSc

Tangkijngamvong, Asawanonda, and Dr. Rerknimitr are with the Division of Dermatology, Department of Medicine, Faculty of Medicine, Skin and Allergy Research Unit, Chulalongkorn University in Bangkok, Thailand. Susantitaphong is with the Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University in Bangkok, Thailand. Numkarunarunrote is with the Department of Radiology, Faculty of Medicine, Chulalongkorn University in Bangkok, Thailand. Jearnsujitwimol is with the Division of Nephrology, Department of Medicine, Prapokklao Hospital in Chantaburi, Thailand.

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ABSTRACT

The use of sodium thiosulfate has emerged as a promising treatment for calciphylaxis, albeit inconclusively in terms of efficacy and variable outcomes. Research in this field has been limited by a paucity of samples due to the rarity of the disease. We herein discuss eight calciphylaxis patients' responses to STS, the potential predictive factors affecting outcomes and compare our results with previously published literature. We are able to show that lesion severity, concomitant drugs, and dialysis duration may be predictive factors of outcomes. Further, improvement of the wound site may be a clinically relevant prognostic determinant.

KEY WORDS: Calciphylaxis, sodium thiosulfate, outcome

Calciphylaxis is a rare but catastrophic condition chiefly observed in dialysis patients.[1] In current practice, a gold standard and recommended approach are still to be established. Despite a multi-interventional approach, the mortality rate remains high. In a search for a cure, sodium thiosulfate (STS) has been in the spotlight. A proposed action is through reversing calcium phosphate deposition.[2] However, because of limited case reports and small case series, the clinical outcome of STS is still inconclusive. In this report, we discuss our patients' responses to STS and the potential predictive factors affecting outcomes and compare our results with those in the previously published literature.

Medical records of patients who received STS between January 2013 and December 2018 at King Chulalongkorn Memorial Hospital in Bangkok, Thailand were reviewed retrospectively. Patients who received STS for indications other than calciphylaxis were excluded. The diagnosis of calciphylaxis was confirmed by histology and/or radiography reports. A total of eight patients were included for analysis and were categorized as responders and non-responders, respectively, where responders were those whose wound sites showed improvement.

Demographics, clinical features, treatment modalities, and outcomes are listed in Table 1. All patients received STS at a dosage of 12.5g to 25g three times weekly. Of the eight patients, four (50%) were classified as responders. The responder and non-responder groups differed in terms of the cumulative dose (1611.3±560.8 g vs. 456.3±280.9 g) and duration of STS (22.3±6.1 weeks vs. 6.0±3.5 weeks), with both being higher/longer in the responder group. Thus, we believe that STS may influence positive outcomes, although determining the optimal dosage and duration is challenging. The earliest positive response that we observed was as late as eight weeks after the treatment was initiated.

Compared to other published reports, fewer positive outcomes were achieved in this series (Table 2). All of the patients in this study presented with ulcer and necrosis, which were moderate to highly severe, according to the previously defined staging system.[3] Two of the non-responders were unable to discontinue warfarin and corticosteroid treatment because of comorbidities. Further, the mean dialysis vintage in this series was longer than that of the others. It is important to note that the non-responders also showed longer dialysis vintage than the responders did (6.3 ± 2.2 years vs. 5.8 ± 6.0 years). It is also possible that these long-standing processes may be associated with poorer wound healing and survival.

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CORRESPONDENCE: Pawinee Rerknimitr, MD, MSc; Email: pawinee.r@chula.ac.th

TABLE 1. Demographics, clinical features, treatment modalities, and outcomes

PATIENT CHARACTERISTICS	RESPONDERS				MEAN ± SD	NON-RESPONDERS				MEAN ± SD
	1	2	3	4		5	6	7	8	
Age, years	47	51	66	69	58.3 ± 10.9	52	60	43	53	52.0 ± 7.0
Sex	F	F	F	F		M	F	F	F	
Dialysis modalities	HD	HD	HD	HD		HD	PD	HD	HD	
Vintage, years	14	0	6	3	5.8 ± 6.0	9	7	5	4	6.3 ± 2.2
Comorbidities	DM, HTN, PAD, tertiary hyperparathyroidism	AKI, hypercalcemia (PTH independent)	DM, HTN	CA rectum, CA corpus, tertiary hyperparathyroidism		DM, CAD, AF, ITP	HTN, CA bladder, gastritis, tertiary hyperparathyroidism	SLE with LN class IV, AIHA, IE	DM, HTN, secondary hyperparathyroidism	
Concomitant agents	VDA	-	-	-		Warfarin, CS, VDA	C-P binder, VDA	Warfarin, CS	VDA	
Serum calcium, mg/dL	11.1	18	n/a	7.6	12.2 ± 5.3	10.5	11.3	9.5	9.6	10.2 ± 0.8
Serum phosphorus, mg/dL	1.7	5.3	n/a	4.4	3.8 ± 1.9	8.7	8	5	5.5	6.8 ± 1.8
Serum iPTH, pg/mL	853.4	12.8	n/a	4629	853.4 (433.1–2741.2) [b]	293.1	2738	73.5	1711	1203.9 (238.2–1967.8) [b]
Location of skin lesions	Distal LE	All extremities, trunk	Proximal and distal LE, trunk	Trunk		Distal LE	Proximal LE	Distal LE	Distal LE	
Lesion characteristics	Gangrene	Ulcer with skin necrosis	n/a	Necrosis		Necrosis	Necrosis	Necrosis	Necrotic eschar	
No. of weeks before STS	18	4	4	8	8.5 ± 6.6	12	3	5	7	6.8 ± 3.9
Time from STS to initial improvement, weeks	30	19	24	8	20.3 ± 9.3	-	-	-	-	-
Total duration of STS, weeks	30	19	24	16	22.3 ± 6.1	5	3	3	11	6.0 ± 3.5
Cumulative dose, g	1,125	2,320	1,800	1,575	1,611.3 ± 560.8	475	150	375	825	456.3 ± 280.9
12-month mortality	No	No	No	No		Yes	No	Yes	Yes	
Time to death[a], weeks	129	-	-	-		5	-	5	11	
Additional treatments	DB, angioplasty with stent	DB, HBO (2 sessions), B	DB	Cinacalcet, parathyroidectomy		DB	Cinacalcet, parathyroidectomy	-	DB, parathyroidectomy	

F, female; M, male; HD, hemodialysis; PD, peritoneal dialysis; DM, diabetes mellitus; HTN, hypertension; PAD, peripheral artery disease; AKI, acute kidney injury; PTH, parathyroid hormone; CAD, coronary artery disease; AF, atrial fibrillation; ITP, idiopathic thrombocytopenic purpura; SLE, systemic lupus erythematosus; LN, lupus nephritis; AIHA, autoimmune hemolytic anemia; VDA, vitamin D analog; CP binder, calcium-based phosphate binder; CS, corticosteroid; iPTH, intact parathyroid hormone; STS, sodium thiosulfate; LE, lower extremities; DB, debridement; B, bisphosphonate; HBO, hyperbaric oxygen therapy.

[a]Time measured from date of STS initiation.

[b]Expressed as median and interquartile range values.

TABLE 2. Comparison among case series reporting the use of sodium thiosulfate in calciphylaxis

	OUR SERIES	NIGWEKAR ET AL[6]	ZITT ET AL[3]	NOUREDDINE ET AL[7]	BALDWIN ET AL[8]	BOURGEOIS ET AL[9]	SOOD ET AL[10]	SALMHOFER ET AL[11]	ROSSO ET AL[12]
Patients (n)	8	172	27	14	7	8	6	5	5
Age (years)	55.1±9.1	55±13	68±12	49.3±11.8	65.1±12.2	72.9±9.6	49.7±12.3	61.2±2.9	60.2±15.3
Female (%)	87.5	73.8	66.7	71.4	85.7	75	83.3	20	80
BMI (kg/m^2)	23.9±6.8	N/A	29.5±9.1	29+9	N/A	N/A	N/A	33.5±9.4	N/A
HD (%)	87.5	100	85	57.1	14.3	37.5	33.3	100	100
PD (%)	12.5	0	15	42.9	71.4	0	66.7	0	0
Vintage (years)	6±4.2	3.1[a] (1.2, 6.2)	1.0[a] (0.3, 6.9)	4.5±4.2	3.0±1.6	N/A	4.5±2.9	2.5±2.5	4.2±2.3
DM (%)	50	55.2	48	35.7	57.1	50	50	40	40
Ulcer/necrosis lesions (%)	100	N/A	88.9	57.1	42.9	≥75	83.3	80	100
Diagnosis	Biopsy (62.5%), radiography (87.5%)	Clinical, biopsy (n=25)	Clinical, biopsy (52%)	Clinical, biopsy (71.4%)	Biopsy (100%)	Biopsy (100%)	Clinical, biopsy (33%), bone scan (83%)	Clinical, biopsy (60%)	Clinical, biopsy (40%)
Trigger agents									
Warfarin (%)	25	N/A	30	21.4	42.9	25	33.3	80	60
C-P binder (%)	12.5	N/A	56	N/A	29	12.5	50	60	60
Vitamin D analogues (%)	50	N/A	63	N/A	57.1	25	66.7	40	100
Laboratory values									
Serum calcium (mg/dl)	11.1±3.3	8.7±0.8	9.6±1.1	8.3±0.6	9.0±1.3	N/A	10.4±0.5	9.2±1.6	10.2±0.6
Serum phosphorus (mg/dl)	5.5±2.3	5.8±1.5	5.1±1.8	5.6±2.8	5.3±1.8	N/A	6.5±1.0	5.6±1.2	4.9±1.0
Serum albumin (g/dl)	3.3±0.5	3.5±0.5	3.3±0.9	N/A	N/A	N/A	2.1±0.5	N/A	N/A
Serum iPTH (pg/ml)	853.4[a] (183.3, 2,224.5)	332[a] (170, 654)	362±298	849±1,647	466±353	N/A	321±430	515±525	1186±296
Treatment modalities									
STS Duration (weeks)	14.8±10.1	13.1[a]	13.7 (7.7, 19)	N/A	8.0±3.7	10.5±9.8	10.8±3.7	80±72.4	82.8
Cumulative dose (g)	1080.6±764.9	950[a]	1268 ±1555	850 ±1648	N/A	862.5±945.2	770.8±253.2	7872±9588	N/A
HBO (%)	12.5	N/A	4	14.3	85.7	0	0	0	0
Parathyroidectomy (%)	37.5	15	4	14.3	14.3	0	33.3	40	0
Cinacalcet (%)	25	57	37	57.1	57.1	25	33.3	100	100
Bisphosphonate (%)	12.5	N/A	N/A	21.4	N/A	25	83.3	20	N/A
Debridement/ wound care (%)	62.5	34	22	N/A	100	100	83.3	N/A	100
Outcome									
Improved (%)	50	73.6 (n=53)	70	71.4	100	75	66.7	100	80
Not improved (%)	50	5.7 (20.8% n/a)	30	21.4 (7.1% n/a)	0	25	33.3	0	20
Death (%) (overall)	50	42	52	71	28.6	50	50	100	0

Unless otherwise noted, values are mean ± SD.; body mass index (BMI); hemodialysis (HD); peritoneal dialysis (PD); diabetes mellitus (DM); calcium-based phosphate binder (C-P binder); intact parathyroid hormone (iPTH); expressed as median and interquartile range ([a]).

predicting poor survival were female sex, higher weight, severe cutaneous lesions, and proximal lesions.[3,4] Interestingly, all non-survivors in our series exhibited distal calciphylaxis. Thus, the proximal type might not necessarily dictate such poor outcomes as previously reported. An additional finding observed in this series was that the improvement of the wound sites might be a clinically relevant prognostic determinant. The mortality rate in the responder group at 12 months was 0%, while that of the non-responders was 75%.

Given the small number of study participants, the fact that not all cases had a histologically confirmed diagnosis, and the difference in clinical evaluation times across the studies, determining the clinical outcome of STS is especially challenging. Further studies are warranted which, in the long run, should be beneficial to those who suffer from this deadly disease.

We propose that lesion severity, concomitant drugs, and dialysis duration might be predictive factors of outcomes. In addition, improvement of the wound site may be a clinically relevant prognostic determinant. Given the proposed action of STS, it may take some time before positive responses are observed. Meanwhile, providing specific treatments such as calcimimetics and parathyroidectomy may lower the rates of wound deterioration and mortality for those with tertiary hyperthyroidism.[5]

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