

Calciophylaxis, sodium thiosulfate and adjunctive treatments : a case series



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Introduction

- Calciophylaxis, a rare arteriolar skin disease affecting up to 4% of end-stage renal disease patients, is associated with painful skin lesions frequently progressing to tissue necrosis. One year mortality can reach 45% to 55% in hemodialysis patients.
- Risk factors include CKD, long term hemodialysis, female gender, obesity, diabetes, Caucasian origin, hypoalbuminemia and elevated serum calcium, phosphorus and alkaline phosphatase. Some medications such as intravenous iron, warfarin, activated vitamin D and calcium-based phosphorus chelators could also be contributory.
- Common treatment approach include bisphosphonates, cinacalcet, activated vitamin D and calcium-based phosphorus chelators cessation, dialysate calcium concentration lowering, dialysis dose intensification, hyperbaric oxygenotherapy and parathyroidectomy but no firm recommendations exist to guide clinicians on the best treatment.
- Sodium thiosulfate (STS), a chemical substance known for its calcium chelating properties has been reported as an effective treatment.

Objectives

- Describe CKD patients diagnosed with calciophylaxis and treated with STS
- Evaluate determinants of a positive STS therapeutic response

Methods

- Design : retrospective study - case series
- All patients aged 18 years old or more, with CKD 4-5D and a diagnosis of calciophylaxis treated with at least one dose of STS between January 1st 2004 and October 1st 2012.
- Data collection : medical charts
- STS positive therapeutic response defined by complete lesion healing
- Statistics

Univariate analysis compared means (Welch's t-test) and proportions (Fisher's exact test). Software : R^{md} . R Core Team (2013) (A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria).

Results

- 12 CKD 4-5D patients with 9 CKD 5D on hemodialysis.
- Lesion location
 - Inferior limbs (10) - 3/10 with abdominal lesion.
 - Abdomen (1) and breasts (1).
- Calciophylaxis risk related patients characteristics
 - diabetes (11)
 - calcium-based phosphorus chelators use (10)
 - warfarin use (9)
 - IV iron use (8)
 - female gender (8)
 - obesity (7)
- STS treatment
 - Median duration : 105 d
 - Complete lesion healing : 5 (42 %)**
 - Lesion improvement : 6 (50 %)
 - Pain relief : 12 (100 %)
 - One year mortality : 3 (25%)**
 - Adjunctive treatments /adjustments
 - Pamidronate (7)
 - Calcium chelators (10/10) – active Vit D (3/6) cessation
 - Dialysis intensification (5) - Dialysate [Ca⁺⁺] lowering (6)
 - Side effects : 6 nausea episodes (50%)**
 - severe or intractable → STS cessation (2)
- Univariate analysis for STS positive therapeutic response
 - no significant factors identified

Table 1. Patients characteristics

Pt	Age Gender	Lesion (s) site (s)	Comorbidities	BMI (Kg/m ²)	Dialysis vintage (years)	Warfarin	IV iron	Baseline lesion	Complete lesion healing	Dx to STS delay (d)	Pain relief delay (d)	Complete lesion healing delay (d)	Total dose to response (mg)	Side effects	Adjunctive treatments and adjustments
1	72F	Abdomen	DBII, HTA, CAD, AVD, CI, AF, DLP, gout	38	1	+	+	+	+	27	9	ND	450	No, Vo, dyspnea, pulmonary overload, diastolic CI	Sevelamer, HD frequency and duration intensification
2	70M	Abdomen, inferior limb (right)	DBII + neuropathy, HTA, CAD, THR, primary hyperPTH	45	5	-	+	+	+	123	1	115	1700	No, Vo, anorexia, hypoalbuminemia, hypoglycemia, weight loss (4 kg)	Pamidronate, Cinacalcet, HD frequency intensification
3	64F	Inferior limbs (2)	DB II, heart transplant, DVT, episodic hyperCa ⁺⁺ , HypoT4, gout	20	NA	+	-	+	+	47	30	225	1650	ND	None
3	70F	Breasts (2)	DBII, AF, HTA, AVD, HTA, depression	37	1	+	+	-	-	107	23	NA	NA	Anasarc	Pamidronate, HD frequency and duration intensification, ↓ dialysate [Ca ⁺⁺]
5	48M	Inferior limb (right calf)	DBII, kidney transplant/MGUS-sarcoidosis, AF + PE, HTA, DLP, inferior limb varicose veins and lesions	26	13	+	+	+	+	13	ND	105	750	None	Pamidronate
6	48F	Abdomen, inferior limb (thighs -2)	DBII, CAD, AVD, HTA, Stevens-Johnson syndrome, gout	29	7	-	-	+	-	273	4	NA	NA	No, Vo	Pamidronate, cinacalcet, HD frequency intensification, ↓ dialysate [Ca ⁺⁺]
7	68F	Inferior limb (left thigh)	DBII, HTA, kidney transplant, CAD, DLP, ICS	45	NA	-	-	-	NA	1	1	NA	NA	No, Vo, headache, hypernatremia (Na + 150)	None
8	76F	Inferior limb (calfs -2)	DBII, HTA, CAD, AF, DLP, DISH, varicose veins - Inf limb	28	4	+	+	-	NA	8	ND	NA	NA	No, Vo	Pamidronate, Al ⁺⁺ carbonate, ↓ dialysate [Ca ⁺⁺]
9	57M	Inferior limb (thighs -2)	DBII, HTA, CAD, DLP, hypoT4, stasis dermatitis + repeat cellulitis, osteoporosis	37	3	+	+	-	+	14	3	133	1095	Volume overload, metabolic acidosis	Pamidronate, sevelamer, HD frequency and duration intensification, ↓ dialysate [Ca ⁺⁺]
10	59M	Inferior limb (right calf)	DBII, HTA, CAD, DLP, AVD	36	3	+	+	-	NA	40	ND	NA	NA	ND	↓ dialysate [Ca ⁺⁺]
11	82F	Inferior limbs (2)	HTA, CAD, AF, DLP, COPD	20	NA	+	-	-	-	13	0	NA	NA	None	Pamidronate, cinacalcet
12	64F	Abdomen, Inferior limb (thighs - 2)	DBII, HTA, CAD, DLP, PVT, kidney transplant, hypoT4, gout	39	7	+	+	+	-	4	7	NA	NA	No	Pamidronate, sevelamer, ↓ dialysate [Ca ⁺⁺]

Légende: + = présence, - = absence, M= Male, F= Female, DBII= type 2 diabetes, DISH = Diffuse Idiopathic Skeletal Hyperostosis; Dx = diagnosis, DLP= dyslipidemia, PE = pulmonary embolism, FAF = atrial fibrillation, HD = hemodialysis, HTA = hypertension, hypoT4 = hypothyroidism, CI = cardiac insufficiency, BMI = body mass index, IV = intravenous, CAD = coronary artery disease, MGUS = monoclonal gammopathy of undetermined signification, COPD = chronic obstructive pulmonary disease, NA = non applicable, ND = no data, * correction. No = nausea, THR = total hip replacement, ICS= irritable colon syndrome DVT = deep vein thrombosis, TSS = thiosulfate de sodium, Vo = vomiting.

Discussion

- Case series reflects literature data in terms of lesions location and risk factors at diagnosis except more than 50% of patients were using warfarin.
- STS positive therapeutic response alone : 42%
 - Adding lesion improvement : 66%.
- One year mortality rate of 25% is lower than those reported in other published series (Sood 2011 50%; Nouredine 2011 70,2 %; Zitt 2013 52%).
- STS causes frequent nausea which is usually not intractable.
- No STS therapeutic factors for success or failure were identified.

Table 2. STS therapeutic response factors

Characteristics	Failure (n=4)	Success (n=5)	P value
Female	4	2	0,17
Obesity	2	3	1
Pamidronate addition	4	2	0,17
Dialysate[Ca ⁺⁺] lowering	3	1	0,15
Dialysis frequency intensification	2	3	1
Dialysis time intensification	1	2	1
Biopsy	3	4	1
Age (mean)	66,0	62,2	0,67
BMI (mean)	31,4	33,1	0,78
STS delay post Dx (mean)	99,25	44,80	0,46
STS duration (mean)	89,75	102,20	0,65

Conclusion

- Calciophylaxis is a serious complication and a highly morbid condition associated with CKD.
- STS seems to be helpful when added to other adjunctive treatments.
- STS severe adverse effects rarely cause STS cessation.
- Participation in national registries should be promoted in order to better define optimal calciophylaxis treatment.

