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CASE REPORT

Oxalate Nephropathy After Continuous Infusion of High-Dose Vitamin C as an Adjunct to Burn Resuscitation

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Fluid resuscitation is the foundation of management in burn patients and is the topic of considerable research. One adjunct in burn resuscitation is continuous, high-dose vitamin C (ascorbic acid) infusion, which may reduce fluid requirements and thus decrease the risk for over resuscitation. Research in preclinical studies and clinical trials has shown continuous infusions of high-dose vitamin C to be beneficial with decrease in resuscitative volumes and limited adverse effects. However, high-dose and low-dose vitamin C supplementation has been shown to cause secondary calcium oxalate nephropathy, worsen acute kidney injury, and delay renal recovery in non-burn patients. To the best of our knowledge, the authors present the first case series in burn patients in whom calcium oxalate nephropathy has been identified after high-dose vitamin C therapy. (J Burn Care Res 2016;37:e374–e379)

Successful early management of the severely burned patient is contingent on effective fluid resuscitation. Burned skin causes a substantial loss of plasma proteins and fluid from the intravascular space. As a result, there can be marked edema, hypotension, and multiple organ dysfunction.[1–4] Free radicals also play an important role during the post-burn hypermetabolic response.[5,6] Oxygen free radicals, such as superoxide, peroxide, and hydroxyl, may cause or exacerbate vascular permeability.[7] Crystalloid solutions are aggressively given to correct hypovolemia and to restore tissue perfusion, and cellular respiration.[1,8,9] High-volume crystalloid resuscitation may, however, worsen outcomes.[9–12]

Administration of vitamin C, a free radical scavenger, may improve microvascular permeability and negative interstitial pressure and reduce the overall volume of fluid necessary during burn resuscitation.[3,4,13,14] These benefits seem to be supported by recent animal studies and a randomized controlled trial, and because of this, many patients in the burn community have started using more high-dose vitamin C during complicated burn resuscitations.[3,6,8,15,16] Here, we present 2 patients with complicated burn resuscitations during which high-dose vitamin C was utilized as rescue therapy. Both patients ultimately died after developing acute kidney injury (AKI) and were found to have calcium oxalate crystals within their renal tubules at autopsy.

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The first patient was a 31-year-old Caucasian woman admitted to our facility after sustaining 65% TBSA thermal injuries in a residential fire. Admission

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bronchoscopy showed grade I inhalation injury. The patient received Lactated Ringers during initial resuscitation titrated to a combined endpoint of urine output and tissue perfusion according to clinical judgment supported by a computer-based clinical decision support system.[17] Her resuscitation was complicated by vasopressor dependent hypotension and increasing crystalloid requirements. Given circumferential burns and decreased pulses, escharotomies were performed on her right upper extremity and bilateral lower extremities. Albumin was started at 8 hours post-burn at 0.4 ml/kg/%TBSA/24 hours when she was transiently hypotensive (mean arterial pressure [MAP] 40–50 for 30 minutes). Vitamin C at 66 mg/kg/hr was initiated 11 hours post-burn as a rescue therapy to reduce oxidative stress and overall fluid requirements. She received a total of 101 g of ascorbic acid in 18 hours (Table 1). She developed AKI with lactic acidosis, and continuous venovenous hemofiltration was planned. Before it could be initiated, she became progressively hypotensive and developed heart block leading to pulseless electrical activity. Despite cardiopulmonary resuscitative efforts, the patient died on hospital day 2. At autopsy, there was mild cerebral edema, and birefringent calcium oxalate crystals were identified in her intratubular spaces in both kidneys.

The second patient was a 20-year-old man with 67% TBSA thermal injuries sustained from a reported industrial accident at a steel plant. On arrival, he was awake with a Glasgow coma scale of 15. He was intubated given the extent of his burns. Admission bronchoscopy was negative for inhalation injury. He required aggressive fluid resuscitation and 4 vasopressors to maintain MAPs of 50 seconds. Vitamin C infusion at 66 mg/kg/hr was initiated at 8 hours post-burn to help reduce oxidative stress and total resuscitative volume. Ultimately, he received 224 g during 20 hours (Table 1). In addition, he received an additional 200 mg of ascorbic acid in his total parenteral nutrition. His hospital course was complicated by bilateral lower extremity and right upper extremity escharotomies for circumferential burns. He then developed primary metabolic acidosis, refractory shock, and AKI requiring continuous venovenous hemofiltration. He ultimately required a left above-the-knee amputation for progressively necrotic tissue. With worsening lactic acidosis and fever despite broad spectrum antibiotics (started 24 hours post-burn), an exploratory laparotomy was performed to identify necrotic bowel, and none was identified. On hospital day 3, his pupils were fixed and dilated with brain imaging showing cerebral edema and tonsillar herniation. Autopsy showed evidence of early cerebellar herniation with ischemic necrosis of the brainstem, cerebellum, and upper cervical spinal cord. Calcium oxalate crystals were identified in the intratubular space in both kidneys (Figure 1).

DISCUSSION

Preclinical studies have demonstrated the role of free radicals in the development of edema and increased vascular permeability after thermal injury.[3,18,19] Other mediators of vascular permeability in burn patients include histamine, prostaglandins, catecholamines, and thromboxane.[3,7] These factors are responsible for both the local and the systemic inflammatory response.[2,7,18,20] Histamine released from mast cells in injured tissue results in upregulation of xanthine oxidase activity and free radical formation.[6,18,21] Local antioxidant activity is altered in the injured tissue and damaged neutrophils contribute to the formation of more free radicals.[5,18] For this reason, antioxidants, such as ascorbic acid, were investigated to decrease the amount of resuscitative volumes and secondary injury caused by free radicals.[3,9] Ascorbic acid was shown to have free radical scavenging effects,[14,22,23] an antihistamine effect,[24] and helped to regulate collagen denaturation.[25] More recent studies have shown high-dose vitamin C infusions to reduce post-burn lipid peroxidation,[6,8,26] vascular permeability, edema, and fluid resuscitative volumes.[3,6,8,13,20]

Animal studies were performed to analyze the effect of high-dose vitamin C on resuscitative volume and edema formation. The water content of the burned skin in the vitamin C group was markedly decreased, suggesting reduced post-burn capillary permeability.[3] Another animal study was performed to test the hypothesis that there is evidence of increased negative interstitial hydrostatic pressure in burn injured tissue.[4] This is suggested as a major pathophysiological mechanism necessary to cause such a rapid and massive edema formation after thermal injury.[4] Tanaka et al[4] investigated high-dose vitamin C and its effect on counteracting the increased negativity of interstitial pressure in rats. They showed a marked attenuation of post-burn interstitial pressure by high-dose vitamin C with moderate decrease in the total body weight.[4] In sheep, there was a significant decrease in the resuscitative volume in those sustaining a 40% TBSA after infusion of high-dose vitamin C.[8] Even in delayed initiation of high-dose vitamin C (2 and 6 hours post-burn), there was still a decrease in the fluid volume required in thermally injury guinea pigs.[16,27] Despite the delayed initiation of high-dose vitamin C and decrease in resuscitation volume, they found that the 24-hour fluid requirement to be reduced to 32.5% of the Parkland formula.[26]

Table 1. Patient demographics and vitamin C dosages

Hours Post-Burn	Crystalloid Total (ml)	Colloid (ml)	Vitamin C (ml)	Other (ml)	Total Fluid (ml)	UOP (ml)	Cr (mg/dl)	CVVH	HCT	ScvO2	Lactate (mmol/l)
Pt 1: TBSA, 65.5%; Wt, 85 kg											
0	620	0	0	20	640	0	0.9	–	36.6	–	–
6	3720	0	0	120	3840	306	0.81	–	46.9	79.5	6.88
12	8340	450	448	630	9841	663	0.86	–	34.4	81.6	6.89
18	9730	990	1792	1073	13,585	1164	1.4	–	34	64	5.62
24 (total)	11,330	1530	3136	1637	17,633	1596	0.98	–	26.3	-	14.43
	2.04 ml/kg/ TBSA	0.4 ml/kg/ TBSA/24 hours	101 g		**3.17 ml/kg/TBSA**	0.78 ml/kg/hr					
Pt 2: TBSA, 67%; Wt, 170 kg											
0	900	0	0	0	900	10	Hemolyzed	–	53	–	5.97
6	7000	100	0	450	7550	64	1.65	–	57.5	–	7.51
12	12,970	700	2040	1086	16,796	821	1.87	–	54	56.4	10.22
18	15,440	1300	4499	1875	23,114	2102	2.29	–	49.9	79.1	11.89
24 (total)	19,640	1900	6953	2480	30,973	3881	2.37	Started	–	90	9.94
	1.72 ml/kg/ TBSA	0.4 ml/kg/ TBSA/24 hours	224 g		**2.72 ml/kg/TBSA**	0.95 ml/kg/hr					

Pt, patient; Cr, creatinine; Wt, weight; UOP, urine output; HCT, hematocrit; ScvO2, central venous oxygen saturation; CVVH, continuous venovenous hemofiltration.

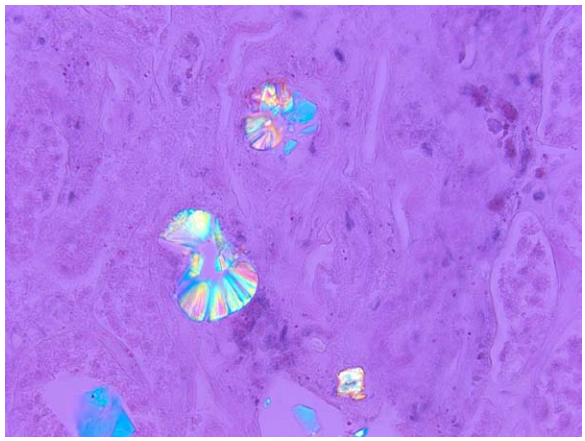

Figure 1. High power (×40) view of birefringent calcium oxalate crystals with "fan-shaped" morphology.

A randomized, prospective study was performed utilizing a continuous ascorbic acid (66 mg/kg/hr) infusion on burn patients with 30% TBSA for 24 hours. They found a 45% decrease in the volume required for resuscitation in the high-dose vitamin C treatment group (5.5 vs 2.1 ml/kg for control $P < 0.01$). There was a 3-fold weight gain in the control group compared with the ascorbic acid group. Ultimately, the vitamin C treatment group required fewer days on mechanical ventilation ($p < 0.05$). Of note, there were no lab abnormalities noted in either group after 7 days.[6] In the retrospective review by Kahn et al,[13] their institute did not give the high-dose vitamin C if there was a delay in transfer or if there was baseline renal impairment. Careful attention was also paid to the patients' volume status as ascorbic acid is hyperosmolar and can cause osmotic diuresis.[13] They carefully followed hematocrit, decreased central venous pressure, decreased urine output, or MAPs. Ultimately, they found infusion of high-dose vitamin C safe and efficacious.[13]

In the above-mentioned studies, toxicity in both animal and human studies did not seem to be a problem. Vitamin C supplementation is recommended in burn patients with typical doses from 500 to 1500 mg/d. This is for increased requirements because of stress and need for wound healing.[28,29] In the average person, the dietary reference intake is 75 mg/d.[30] One review of the literature reports that ingestion of up to 10 g/d of ascorbic acid orally does not pose a health risk to humans[29] and another stated up to 2 g/d can be tolerated.[30] Given the positive effects of high-dose vitamin C infusions in animal and human studies, literature proposes a continuous ascorbic acid infusion at 66 mg/kg/hr for the initial 24 hours of burn resuscitation.[6,13,31]

Vitamin C supplementation, both high and low doses, contributing to renal failure secondary to calcium oxalate deposits has been reported in the literature. In addition to being part of a daily multivitamin, vitamin C is also being used as an alternative medicine in cancer, amyloidosis, and nephropathy.[32,33] Ascorbic acid can induce oxalate nephropathy, worsen renal injury, and delay kidney recovery.[34] Oxalate nephropathy, or AKI as a result of calcium oxalate accumulation, can occur in both primary and secondary hyperoxaluria.[32] Primary hyperoxaluria is because of a group of autosomal recessive inheritance, whereas secondary hyperoxaluria is because of increased oxalate intake, increased absorption of oxalate, or increased production of oxalate.[32,34] Increased production of oxalate is typically because of increased ingestion of oxalate precursors, such as ethylene glycol, and more rarely, vitamin C.[32,34]

Two patients identified in the literature were given 45 and 60 g intravenously of ascorbic acid as an alternative therapy in amyloidosis and cancer, respectively.[33,35] Both patients subsequently developed acute renal failure and showed birefringent crystals on polarized light microscopy consistent with calcium oxalate nephropathy. These patients had normal native renal function before the administration of vitamin C.[32,33,35]

Oxalate nephropathy has been described in non-burn patients even at low doses. Of note, these patients received anywhere from 500 mg to 6.5 g orally. All of the patients reported taking the dosages of vitamin C for months and had normal renal function prior.[32,36,37] Review of the literature identified one other case report of vitamin C-associated nephropathy in a burn patient.[34] The patient sustained 40% TBSA and was given vitamin C supplementation of 1 g/d intravenously. He developed AKI requiring dialysis. He remained anuric and dialysis-dependent for more than 2 months. Renal biopsy showed extensive calcium oxalate deposits within his tubules. Only after decreasing the vitamin C dosage to 0.2 g/day and increasing the dialyzate flow, he has renal improvement. The author proposed that the AKI was initially caused by volume loss from his burn injury and potentially exacerbated by amikacin. He argues that the vitamin C supplementation either potentiated his renal injury or delayed its resolution.[34] Overall, this shows oxalate nephropathy, and calcium oxalate crystals can form in the presence of normal renal function and by taking low doses.[32,34,36]

The finding of calcium oxalate crystals in renal tubules of burn patients has not been previously reported. This has been described in other patient populations receiving vitamin C therapy. Others have

reported patients developing AKI following vitamin C infusion for adjuvant treatment of amyloidosis and cancer and subsequently found calcium oxalate nephropathy on renal biopsy.[32–35,37] All of these patients had normal renal function before the start of vitamin C. In these patients, calcium oxalate nephropathy was described as a clinically significant morbidity.

Our patients differ from those described in the literature. First, our patients had a delay of high-dose vitamin C infusion. Second, our patients had significant burns and were at risk for renal failure. In regard to its delayed initiation, both Tanaka et al[27] and Sakurai et al[16] described a beneficial effect of high-dose vitamin C in guinea pigs, even after its infusion was postponed by 6 hours. In addition, in these studies, no lab abnormalities were noted despite their high-dose vitamin C infusion delay. For this reason, we used high-dose vitamin C as a rescue therapy to help attenuate the total volume of resuscitation and possible reduce the systemic inflammatory response.[38] Of note, the initial studies in utilizing vitamin C were in accordance with the Parkland formula. However, in 1991, Matsuda et al[3] showed that with high-dose vitamin C the total 24-hour resuscitation was able to be reduced from 4 to 1 ml/kg/%TBSA. In the article by Sakurai et al,[16] they resuscitated with lactated Ringer's solution according to the Parkland formula for only the first 6 hours, and then reduced the volume by 25% of the Parkland formula once the high-dose vitamin C was initiated. Tanaka et al initiated resuscitation with the Parkland formula for 0.5 to 2 hours post-injury and then reduced the volume to 25% of the Parkland formula. Despite the delayed initiation of high-dose vitamin C and decrease in resuscitation volume, they found the 24-hour fluid requirement to be reduced to 32.5% of the Parkland formula. However, a known complication of vitamin C is osmotic diuresis. Although our patients did receive a lower volume of resuscitation compared to the Parkland formula (Table 1), they did not have profound diuresis, and their laboratory findings did not show evidence of hemoconcentration after the initiation of vitamin C (Table 1). Our resuscitation practices are guided by a computerized clinical decision support system with initial crystalloid rate determined by the ISR Rule of 10s formula.[17,39] As expected, the initiation of vitamin C resulted in increased urine output (Table 1). Lactate was also monitored serially and rose in both patients consistent with worsening tissue perfusion, despite apparent adequacy of volume resuscitation and oxygen delivery evidence by elevated ScvO2 (Table 1).

The first patient had normal renal function (Cr 0.8 mg/dl) at the time of high-dose vitamin C infusion. Ten hours after high-dose vitamin C was started, her Cr increased to 1.40 mg/dl and was associated with an increase in urine output. Our second patient had renal impairment before high-dose vitamin C infusion, and it only worsened during his hospital course. It is difficult to ascertain the exact cause for the renal impairment in our patients. Both are likely secondary to the extent of burns; however, given the presence of calcium oxalate crystals in their renal tubules, oxalate nephropathy cannot be ruled out. It is expected that the AKI in thermally injured patients is related to hypotension and shock leading to acute tubular necrosis. However, at autopsy, microscopic evaluation of acute tubular necrosis was hindered by diffuse postmortem autolysis of renal tubules. Therefore, with the presence of calcium oxalate crystals on postmortem analysis, the crystals either caused the AKI or were a possible contributor. Knowing oxalate nephropathy can occur when high-dose vitamin C is used as an adjunct to burn resuscitation should be a cause for legitimate concern. It is not our intent to put a moratorium on high-dose vitamin C therapy as burn centers with lots of experience using this resuscitative adjunct have reported overall success without any reports of this particular complication.[6,13] It may be that the benefits of high-dose Vitamin C outweigh potential complications. Only a well-designed prospective clinical trial could answer this question while keeping in mind to deliberately monitor for this complication given our findings.

CONCLUSION

This report identifies a known complication of vitamin C therapy in 2 patients receiving high-dose vitamin C as a rescue therapy in complicated burn resuscitations. Currently, there is much enthusiasm in the burn community about high-dose vitamin C infusions, and there are data supporting its use as an adjunct to complicated burn resuscitations. In other patient populations, ascorbic acid can cause calcium oxalate nephropathy and contribute to clinical AKI. Before high-dose vitamin C becomes a standard of care in burn units, further prospective research is necessary to determine the prevalence of adverse-effects, the optimal dose, timing, and the appropriate patient population for this therapy.

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