Cohort Study

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High-dose intravenous versus low-dose oral vitamin C in burn care: potential protective effects in the severely burned: a retrospective cohort study

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Background: Antioxidant therapies, such as ascorbic acid may have an important role during the acute phase of burn management. However, there are mixed results on the most effective dose and method of administration of ascorbic acid in burn patients. In this study, we compared the efficacy of intravenously and orally administered ascorbic acid in second-degree burns greater than 20% total-body-surface-area.

Materials and methods: The hospital burn database was used to obtain data on all patients with second-degree or deeper burns of 20% total-body-surface-area or greater. Fourteen patients were selected at random to receive a scheduled dose of 1250 mg intravenous ascorbic acid every 6 h for 72 h. This was considered the high-dose group. During same period, 40 patients received scheduled 500 mg oral ascorbic acid every 6 h for 72 h and this was considered the low-dose group. We gathered sociodemographic and clinical variables associated with ascorbic acid dosing.

Results: In our study, statistically significant variables were fluid requirements ($p < 0.001$), hospital stay ($p = 0.011$), length of time intubated on ventilator ($p < 0.001$), colloids used ($p = 0.002$), and total procedures required ($p = 0.014$). Despite higher modified Baux predicted mortality in the high-dose group (10 patients vs. 24 patients, $p = 0.026$) there was no noted significant association in days until the first infection and mortality rate ($p = 0.451$ and 0.326, respectively).

Conclusions: The calculated modified Baux predicted a higher mortality rate with the higher dosing group, yet this study did not find a mortality difference between the groups. We speculate that high-dose intravenous ascorbic acid may have protective effects in burn resuscitation. This finding may support some previous studies that found that high-dose ascorbic acid may improve clinical outcomes.

Keywords: ascorbic acid, Baux score, fluid requirements, total-burn-surface-area

Introduction

Burn injury is marked by a large release of inflammatory mediators which disrupt the normal capillary barrier and cause a rapid shift of intravascular fluid and protein into interstitial spaces, ultimately leading to shock and death. As such, adequate fluid management and resuscitation are critical for burn patients to prevent further cellular injury. Effective management of the systemic inflammatory response syndrome response and metabolic derangement is crucial for the survival of burn patients[1–3].

HIGHLIGHTS

- The accurate dose of vitamin C in burn resuscitation is an ongoing area of research.
- No significant difference in mortality rate was noted between low-dose oral (p.o.) and high-dose intravenous (i.v.) ascorbic acid despite higher modified Baux predicted mortality in the high-dose group.
- Patients with higher total-burn-surface-area (TBSA) receiving greater amounts of fluid given in the first 72 h from the initial injury, may have a positive impact in burn resuscitation and mortality with high-dose i.v. ascorbic acid.

Inexpensive and widely available, ascorbic acid has been shown to have mixed results. Wang *et al.*[4] found no effect and increased incidence of acute kidney injury with the use of ascorbic acid during resuscitation of burn patients and Kahn *et al.*[5] and Nagal *et al.*[6] noted differences in fluid requirements but no further differences in clinical outcomes[4–6]. Although ascorbic acid is a regular part of burn care, there is no consensus on the most effective dose for a reduction in mortality, fluid resuscitation requirement, and other various clinical outcomes[4,7]. A study by Tanaka and colleagues utilized 66 mg/kg/h of ascorbic acid with a reduction in fluid requirements[5,8]. While this dose has shown to be well-tolerated in these studies, there are proposed potential effects of worsening acute kidney injury, osmotic diuresis, and oxalate nephropathy with excess ascorbic acid[9,10]. Although

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ascorbic acid is highly water-soluble and readily excreted by the kidneys, patients with preexisting kidney injury may be overwhelmed by the excess need for excretion. Ascorbic acid is hyperosmolar which can lead to hypovolemia and acute kidney injury. Furthermore, oxalate nephropathy has been noted postmortem after continuous infusion of 66 mg/kg/h of ascorbic acid as an adjunct to burn resuscitation[11]. Mechanistically, absorbed ascorbic acid is metabolized to oxalic acid which is insoluble and deposits in renal tubules. Because of these inadequately defined possibilities of ascorbic acid dose-dependent increases in renal toxicity or kidney injury, defining a clinically efficacious minimal dosage of ascorbic acid is important overall, decreasing morbidity for patients requiring burn resuscitation.

In this study, we aim to evaluate the effects of high-dose i.v. and low-dose p.o. ascorbic acid in second-degree burns greater than 20% TBSA.

Materials and methods

This is a retrospectively analyzed 3-year historical cohort study. A review on 54 burn-injured inpatients at an institution from 1 January 2018, through 1 January 2021, with second-degree greater than or equal to 20% TBSA burns. TBSA reassessment after 24 h was felt to be the most accurate and is used in this study to identify patients. This institution serves as a level I trauma center, primary stroke center, and regional burn center, and has more than 130 000 emergency department visits each year.

Initial burn admission orders provide burn patients with a wide array of standard burn vitamins and supplements. Patients at our institution have historically received 500 mg p.o. ascorbic acid and few have received i.v. ascorbic acid. Due to protocol changes and noted benefits from clinical research higher ascorbic acid administration high-dose i.v. ascorbic acid was administered to newly admitted patients. Patients that were a part of the high-dose group received a scheduled dose of 1250 mg i.v. ascorbic acid every 6 h for 72 h. The low-dose group received a scheduled 500 mg of p.o. ascorbic acid every 6 h for 72 h. This allowed us to separate our patients into two comparison groups: low-dose p.o. ascorbic acid and high-dose i.v. ascorbic acid. During this 3-year period, there were 40 patients in the low-dose p.o. group and 14 patients in the high-dose i.v. group.

The extracted data included demographics, admission date, discharge date, TBSA on reassessment, recreational drug use, ventilator days, infections, and mortality. Additional data include ascorbic acid dosing for the first 72 h; fluid requirements for the first 72 h; and total surgeries required along with the description. On admission to the hospital and during the intubation of patients, there was documentation to the extent of inhalation injury. Patients with inhalation injury had swollen vocal cords, as shown by direct laryngoscopy, soot in the nostrils with stinged nasal hairs, and soot in the airway when suctioned after initial intubation. Exclusion criteria included patients whose TBSA was under 20%. Consent, ethics approval, data gathering, and analysis was obtained from the Institutional Review Board (IRB #20-49). The work was reported in line with the STROCSS criteria[12]. This project has also been registered with clinicaltrials.gov/ct2/show/NCT05612867.

Data was compiled into an Excel spreadsheet and statistical analysis was then performed using the Statistical Package for the Social Sciences (SPSS), version 27.0 (SPSS Inc.; IBM Corp.). A p-value less than 0.05 was considered statistically significant. All data groups were assessed for normal distribution and non-normally distributed variables were assessed with nonparametric tests. Chi-square analyses were conducted where appropriate.

Results

Between the low-dose and high-dose groups, there was good separation noted by the statistically significant difference in the degree of burn (32 vs. 57%, $p < 0.001$). Overall fluid requirements for the first 3 days (9 vs. 25 l, $p < 0.001$) were also significantly higher in the group given the higher i.v. ascorbic acid dose. In addition, percent colloid used, and units of fresh frozen plasma given was also significantly larger in the high ascorbic acid dose group (37.5 vs. 85.7%, $p = 0.002$; 0 vs. 2 U, $p = 0.011$). The outcomes of length of stay (13 vs. 38 days, $p = 0.011$), length on a ventilator (2 vs. 13 days, $p < 0.001$), and total procedures required (1 procedure vs. 5 procedures, $p = 0.014$) were also significantly higher in the group given the i.v. dose. The use of illegal drugs was not significantly different between the two dosing groups (69 vs. 71%, $p = 0.543$). However, time to first infection and the mortality rate was not significantly different between the low-dose ascorbic acid and high-dose ascorbic acid group (4 vs. 8 days, $p = 0.326$; 8 vs. 14%, $p = 0.451$, respectively). This contrasts with the mortality predicted by the modified Baux between the two groups (10 patients vs. 24 patients, $p = 0.026$). The results are summarized in Table 1.

Discussion

A challenge in burn resuscitation is the effective management of disrupted capillary barriers and a massive shift of intravascular fluid into extravascular space. As shown in previous studies, ascorbic acid has been a key component in treatment to improve outcomes in burn resuscitation. In particular, ascorbic acid administration has shown to significantly decrease early postburn lipid peroxidation, reduce microvascular leak of fluid by preventing endothelial dysfunction, and decrease edema formation in burned tissue[13–15]. Mechanistically, absorbed vitamin C is metabolized to oxalic acid which is insoluble and hyperosmolar which can lead to hypovolemia and acute kidney injury. Furthermore, oxalate nephropathy has been noted postmortem after continuous infusion of 66 mg/kg/h of vitamin C as an adjunct to burn resuscitation[11]. However, Wang and colleagues' meta-analysis on ascorbic acid and the clinical outcomes of critically ill patients determined patients developing acute kidney injury were not associated by vitamin C administration. There was a noted reduction of vasopressor support, mechanical ventilation, and mortality in patients receiving intravenous vitamin C doses of 3–10 g/day[4]. Due to the possibility of acute kidney injury defining a clinically efficacious minimal dosage of vitamin C is important for critically ill burn patients. While the benefits of initiating ascorbic acid administration at the start of burn resuscitation are evident, a clear effective dose for a reduction in fluid resuscitation requirement and mortality have yet to be defined.

In this study, the significant difference in the extent of burn injury between the low-dose p.o. ascorbic acid and high-dose i.v. ascorbic acid group was expected. From Table 1, we can see that patients with higher TBSA burns and higher ascorbic acid dosing were given more fluids, colloid, and fresh frozen plasma during

Table 1

Sociodemographic and clinical variables for patients given oral and intravenous ascorbic acid

Characteristics	Oral ascorbic acid (N = 40)	Intravenous ascorbic acid (N = 14)	P[a]
Demographics			
Age[a]	43 (25, 55)	39 (26, 47)	0.92
Male	31 (78)	10 (71)	0.65
Total burn surface area (%)[a]	32 (23, 49)	57 (40, 67)	**< 0.001**
Inhalation injury	19 (48)	11 (79)	**0.04**
Health and burn status			
Fluid requirements: first 24 h[a]	6000 (4000, 10 000)	12 500 (9000, 16 000)	**< 0.001**
Fluid requirement: second 24 h[a]	3000 (1000, 5750)	8500 (5150, 12 000)	**< 0.001**
Fluid requirements third 24 h[a]	0 (0, 3000)	4000 (1750, 7000)	**0.001**
Ascorbic acid dose: first 24 h[a]	500 (375, 1000)	4500 (2625, 6000)	**< 0.001**
Ascorbic acid dose: second 24 h[a]	1000 (500, 1000)	6000 (4125, 6000)	**< 0.001**
Ascorbic acid dose: third 24 h[a]	1000 (500, 1000)	4500 (3625, 6000)	**< 0.001**
Length of stay[a]	13 (4, 29)	38 (14, 63)	**0.01**
Length on ventilator[a]	2 (0, 6)	13 (5, 64)	**< 0.001**
Colloid use	15 (37.5)	12 (85.7)	**0.002**
Fresh frozen plasma units	0 (0, 2)	2 (1, 4)	**0.01**
Total procedures required[a]	1 (0, 3)	5 (2, 7)	**0.01**
Days until first infection[a]	4 (3, 9)	8 (3, 10)	0.33
Mortality	3 (8)	2 (14)	0.45
Modified Baux predicted mortality (%)[a]	10 (2, 30)	24 (14, 43)	**0.03**
Drug use	27 (68)	10 (71)	0.54
Opiates	8	1	–
Methamphetamine	13	5	–
Marijuana	6	4	–

Categorical variables are shown as the *n* (%); continuous variables are articulated as median (interquartile range).

[a]Analyzed with Mann–Whitney *U*-test. All other comparisons with chi-square test.

burn resuscitation. Of the outcomes analyzed in Table 1, we can see the length of stay, length on a ventilator, and total procedures required were also significantly higher in the group given the higher i.v. ascorbic acid dose, all consistent with a more critically ill group due to worse burn injury. This was expected as higher TBSA burns usually require a longer length of stay, length on a ventilator, and more total procedures required over their hospital course. However, the two outcomes of time to first infection and mortality rate were not significantly different between the low and high-dose ascorbic acid despite higher mortality in the high-dose group predicted by the modified Baux Score.

Moreover, the two dosing groups also had significantly different fluid requirements in the first 3 days. Despite the significantly greater amount of fluids given to the higher TBSA burn, high ascorbic acid dosing group, the days until first infection and mortality rate had no significant difference compared with the group with the smaller TBSA burn. This could suggest that the high-dose i.v. ascorbic acid given to the high TBSA burns may have played a protective role in burn resuscitation. This supports other studies that high-dose ascorbic acid may improve outcomes from a reduction in capillary leak[7].

Limitations to this study need to be addressed. As a retrospective chart review of 3 years of data, the accuracy of the data is inferior to a prospective study. As such, this study is subject to confounding biases due to other risk factors that may be present but were not documented. As noted above, the changes in the guidelines for ascorbic acid dosing in sepsis in 2018 set an inherent bias in using the higher i.v. dose in the more severely burned patients. However, this emphasizes the possibility that the higher dose group did do better than expected with similar mortalities when the modified Baux Score predicted higher mortality in this group with greater TBSA. Similar mortality can be due to the small number of patients reducing the statistical power to show a difference. However, a statistical significance was found comparing the modified Baux Score between the groups. Another possibility for similar mortality could be better care of the critically ill from better management of lung injury to better wound care products that is not accounted for by the modified Baux Score.

All these factors limit how our study's conclusion should be interpreted and used for future research studies. This study cannot determine causation and only suggest an association between high-dose ascorbic acid and improved burn resuscitation outcomes. While our study shows a significantly improved outcome of days to infection and mortality with the use of high-dose ascorbic acid in burn resuscitation, an adequately powered randomized prospective research study is needed to better define dosing parameters and see the specific benefits of high-dose ascorbic acid administration as well as clarify side effects. Future studies could consider if higher doses of vitamin C influence the time until first burn debridement and skin grafting and the possible percentage of skin graft take.

Conclusions

Ascorbic acid has been a key component in treatment to improve outcomes in burn care. While the benefits of initiating ascorbic acid administration at the start of burn resuscitation are accepted, thus far a clear effective dose has yet to be defined. Our clinical retrospective study looking at the differences between low and high-dose ascorbic acid administration with various outcomes showed that a high ascorbic acid dose of 15 000 mg over the first 72 h had a potential protective effect on time to first infection and mortality rate, showing that even with a higher TBSA burn and greater amounts of fluid given in the first days, a high dose of i.v. ascorbic acid may have a positive impact in burn resuscitation and mortality.

Ethical approval

Ethics approval granted from Institutional Review Board (IRB #20-49).

Consent

All data were anonymized and confidential.

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Author contribution

A.M. performed the literature review, writing, and editing of the manuscript. S.J. performed the initial manuscript write-up, data collection, literature review, and editing of the manuscript. K.F. assisted with the writing and editing of the manuscript. D.T.W. attended on the case and contributed to decision-making, management of the patients, literature review, as well as editing of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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