ORIGINAL ARTICLE

Reduction of Resuscitation Fluid Volumes in Severely Burned Patients Using Ascorbic Acid Administration

A Randomized, Prospective Study

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Hypothesis: High-dose ascorbic acid (vitamin C) therapy (66 mg/kg per hour) attenuates postburn lipid peroxidation, resuscitation fluid volume requirements, and edema generation in severely burned patients.

Study Design and Setting: A prospective, randomized study at a university trauma and critical care center in Japan.

Subjects and Methods: Thirty-seven patients with burns over more than 30% of their total body surface area (TBSA) hospitalized within 2 hours after injury were randomly divided into ascorbic acid and control groups. Fluid resuscitation was performed using Ringer lactate solution to maintain stable hemodynamic measurements and adequate urine output (0.5-1.0 mL/kg per hour). In the ascorbic acid group (n = 19; mean burn size, 63% ± 26% TBSA; mean burn index, 57 ± 26; inhalation injury, 15/19), ascorbic acid was infused during the initial 24-hour study period. In the control group (n = 18; mean burn size, 53% ± 17% TBSA; mean burn index, 47 ± 13; inhalation injury, 12/18), no ascorbic acid was infused. We compared hemodynamic and respiratory measurements, lipid peroxidation, and fluid balance for 96 hours after injury. Two-way analysis of variance and Tukey test were used to analyze the data.

Results: Heart rate, mean arterial pressure, central venous pressure, arterial pH, base deficit, and urine outputs were equivalent in both groups. The 24-hour total fluid infusion volumes in the control and ascorbic acid groups were 5.5 ± 3.1 and 3.0 ± 1.7 mL/kg per percentage of burn area, respectively ($P<.01$). In the first 24 hours, the ascorbic acid group gained 9.2% ± 8.2% of pretreatment weight; controls, 17.8% ± 6.9%. Burned tissue water content was 6.1 ± 1.8 vs 2.6 ± 1.7 mL/g of dry weight in the control and ascorbic acid groups, respectively ($P<.01$). Fluid retention in the second 24 hours was also significantly reduced in the ascorbic acid group. In the control group, the ratio of Pa_{O_2} to fraction of inspired oxygen at 18, 24, 36, 48, and 72 hours after injury was less than that of the ascorbic acid group ($P<.01$). The length of mechanical ventilation in the control and ascorbic acid groups was 21.3 ± 15.6 and 12.1 ± 8.8 days, respectively ($P<.05$). Serum malondialdehyde levels were lower in the ascorbic acid group at 18, 24, and 36 hours after injury ($P<.05$).

Conclusions: Adjuvant administration of high-dose ascorbic acid during the first 24 hours after thermal injury significantly reduces resuscitation fluid volume requirements, body weight gain, and wound edema. A reduction in the severity of respiratory dysfunction was also apparent in these patients.

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FREE RADICALS generated as a result of burn injury[1] are thought to play an important role in tissue injury. Friedl and associates[2] demonstrated that histamine released from mast cells after burn injury increases xanthine oxidase activity, in turn producing oxygen free radicals. It has been reported previously that antioxidant therapy with continuous administration of high-dose ascorbic acid (vitamin C) reduces postburn lipid peroxidation,[3] the vascular permeability increase,[4] and burn and nonburn tissue edema,[5] thereby reducing the resuscitation fluid volume requirement in animals.[6,7]

In our study, we investigated whether adjuvant intravenous administration of high-dose ascorbic acid during the first 24 hours after injury also produces these beneficial effects in severely burned patients, especially the reduction of the resuscitation fluid volume requirement.

RESULTS

The mean arterial pressure, heart rate, hematocrit concentration, base deficit, and central venous pressure were all equivalent between groups during the first 24-hour study period and thereafter (**Figure 1**).

SUBJECTS AND METHODS

We studied 37 consecutive patients with burns over more than 30% of their total body surface area (TBSA) who were admitted within 2 hours after injury to the Trauma and Critical Care Center, Kyorin University Hospital, Tokyo, Japan, from December 1, 1992, to December 31, 1997.

The study inclusion criteria are as follows: older than 16 years; thermal injury within 2 hours before admission; burn covering greater than 30% of TBSA; no preexisting hepatic, respiratory, cardiac, or renal dysfunction; and no preexisting coagulopathy. Informed consent was obtained from each patient, and all aspects of the study were performed in accordance with the regulations of the Institutional Review Board. Patients were randomized prospectively into a control or an ascorbic acid group. Randomization was performed according to the month of admission. The profiles of both groups were similar regarding age, sex, body weight, type of thermal injury, percentage of TBSA, percentage of full-thickness burn, and the presence of smoke inhalation (**Table 1**).

Inhalation injury, as diagnosed using fiberoptic bronchoscopy, was found in 12 of 18 controls and 15 of 19 patients in the ascorbic acid group ($P = .96$).

FLUID RESUSCITATION

Fluid resuscitation during the first 24 hours was started immediately after admission using Ringer lactated solution (RL) according to the Parkland formula. The hourly infusion volume of RL was adjusted to maintain stable hemodynamic measurements and a urine output of 0.5 to 1.0 mL/kg per hour. On subsequent days, fluid infusion volumes were adjusted individually. Intravenous 5% albumin was given in the amount of 0.5 mL/kg per percentage of burn during the second and third 24 hours after injury.

PREPARATION AND ADMINISTRATION OF ASCORBIC ACID SOLUTION

An injectable ascorbic acid solution (Vitacimin; Takeda Pharmaceutical Co, Osaka, Japan) was diluted 10-fold with distilled water. Final concentrations of sodium, ascorbate, and osmolality were 130 mmol/L, 25 mg/mL, and 272 mOsm, respectively, in the RL solution. The ascorbic acid solution, which was covered with black paper to prevent auto-oxidation by sunlight, was administered as a continuous intravenous infusion by pump only during the initial 24-hour study period at a dose of 66 mg/kg per hour, beginning as soon as possible after admission. The control group did not receive the ascorbic acid infusion. The administered volume of ascorbic acid was included in the 24-hour fluid intake calculations.

STUDY VARIABLES

Body weight was measured on admission and 24, 48, and 96 hours and 7 days later. Intake of all fluids and output (urine volume, gastric drainage volume, and stool weight) were determined hourly and recorded for the 96-hour study period. The first 24-hour insensible loss was calculated by subtracting the 24-hour body weight gain and all outputs from the total fluid intake.

Heart rate, mean arterial pressure, and central venous pressure were measured hourly with a multichannel hemodynamic monitor (HP-M1094B and HP-M166S; Hewlett-Packard, Saronno, Italy). The following factors were measured within 2 hours after burn injury (designated as 0 hours) and 6, 12, 18, 24, 36, 48, 72, and 96 hours later. Arterial blood P_{O_2}, P_{CO_2}, pH, and base deficit were measured using a blood gas analyzer (288 Blood Gas System; Ciba-Corning Diagnostics Corp, Medfield, Mass); the ratios of Pa_{O_2} to fraction of inspired oxygen (F_{IO_2}) were calculated; and the positive end-expiratory pressure (PEEP) levels were recorded. Concentrations of hematocrit, serum total protein, serum albumin, and serum and urine sodium were determined using an automated analyzer (Hitachi 7150; Hitachi Medical, Ibaragi, Japan). Serum and urine osmolality were measured using a micro-osmometer (model 13MO; Advance Instruments Inc, Needham Heights, Mass).

The serum vitamin C concentration was measured using high-performance liquid chromatography with the precolumn derivatization method described by Speek et al.[8] Serum malondialdehyde (MDA) level was measured using the thiobarbituric acid method described by Ohkawa et al.[9]

The definition by Goris et al[10] of multiple organ failure (MOF) was used. The number of patients with MOF was recorded at 7 days.

For the determination of wound water content, a 4-mm punch biopsy specimen of the burned skin was obtained at 24 hours after injury, weighed, and dried at 65°C to constant weight (2-3 weeks). Tissue water content was taken as the difference between wet and dry weights (milliliters per gram of dry weight).

STATISTICAL ANALYSIS

Group values are expressed as the mean ± SD. Two-way analysis of variance with repeated measures was used to analyze the interactions between the group and time factors. Tukey test was used to compare values between the groups at individual times. The *t* test and χ^2 test (Yates correction) were used to compare nonrepeated measures. *P* values of less than .05 were accepted as significant.

Fluid balance during the first 24 hours in both groups is shown in **Figure 2**. The 24-hour resuscitation fluid volume requirement in the control group was 5.5 ± 3.1 mL/kg per percentage of burn, whereas the ascorbic acid group required only 3.0 ± 1.7 mL/kg per percentage of burn, representing a 45.5% reduction ($P<.004$). The corresponding urine outputs were 1.1 ± 0.3 and 1.3 ± 0.6 mL/kg per hour, respectively. Sensible losses in the control and ascorbic acid groups were 26.2 ± 10.3 and 32.4 ± 13.0 mL/kg ($P = .12$), and the insensible losses were 43.8 ± 12.5 and 52.9 ± 15.8 mL/kg ($P = .06$), respectively. During the first 24-hour period, fluid retention was 162 ± 87 mL/kg in the controls and 89 ± 92 mL/kg in the ascorbic acid group ($P = .02$); after indexing by burn size, 24-hour fluid retention was 3.8 ± 2.7 and 1.2 ± 1.2 mL/kg per percentage of burn in the control vs ascorbic acid group, representing a 68.5% reduction ($P<.01$). During the second 24-hour period, the values were 48 ± 26 vs

Table 1. Patient Demographics*

	Ascorbic Acid Group (n = 19)	Control Group (n = 18)	*P*
Age, mean ± SD, y	40 ± 20	49 ± 22	.67
Sex, No.			
Male	13	12	.91
Female	6	6	
Body weight, mean ± SD, kg	57.0 ± 9.5	58.0 ± 7.6	.73
No. of flame/scald burn	15/4	15/3	.73
TBSA, mean ± SD, %	63 ± 26	53 ± 17	.17
Full-thickness burn, mean ± SD, %	51 ± 26	40 ± 13	.11
No. of inhalation injuries†	15	12	.32

**TBSA indicates total body surface area.*
†Determined using results of bronchoscopy.

32 ± 18 mL/kg per percentage of burn (P = .04). Importantly, fluid volume requirements, urine outputs, and net fluid retention on the third and fourth days were the same in both groups (**Table 2**). Similarly, the percentage of weight gain in the first 24 hours after injury was 9.2% ± 8.2% in the ascorbic acid group vs 17.8% ± 6.9% in the control group (P<.01). The difference of body weight gain increased subsequently and was more than 3-fold at 7 days (Table 2). Changes in the wound water contents in the control and ascorbic acid groups were 6.1 ± 1.8 vs 2.6 ± 1.7 mL/g dry weight, respectively, representing a 57.4% reduction (P<.01). Four patients underwent fasciotomy in the ascorbic acid group, compared with 8 in the control group (P = .45).

Although the positive end-expiratory pressure, F_{IO_2}, and P_{CO_2} levels of both groups were similar throughout the study period, the control group had a lower P_{O_2}/F_{IO_2} ratio at 18, 24, 36, 48, and 72 hours after injury (**Figure 3**). The length of mechanical ventilation in the control and ascorbic acid groups was 21.3 ± 15.6 and 12.1 ± 8.8 days, respectively (P = .03).

The sodium concentration in serum and urine and the serum and urine osmolality of both groups was similar.

The serum levels of vitamin C, MDA, total protein, and serum albumin are shown in **Figure 4**.

Serum vitamin C levels in the ascorbic acid group progressively increased for 12 hours, remained elevated for 36 hours, and disappeared quickly. Serum MDA levels in both groups were above normal on admission, then gradually decreased. Levels of MDA in the ascorbic acid group were lower than those in the control group at 12, 18, 24, 36, and 48 hours, however (P = .03).

During the 96-hour study period, no deaths occurred in either group. Two patients had died in the ascorbic acid group and 3 in the control group by 7 days after injury. Overall mortality was 9 in the ascorbic acid group and 7 in the control group (**Table 3**). The hospital stay, incidence of pneumonia, and number of surgeries were equivalent in both groups. No abnormalities in hematologic, hepatic, or renal function were evident 7 days after ascorbic acid administration. The incidence of MOF was equivalent in both groups.

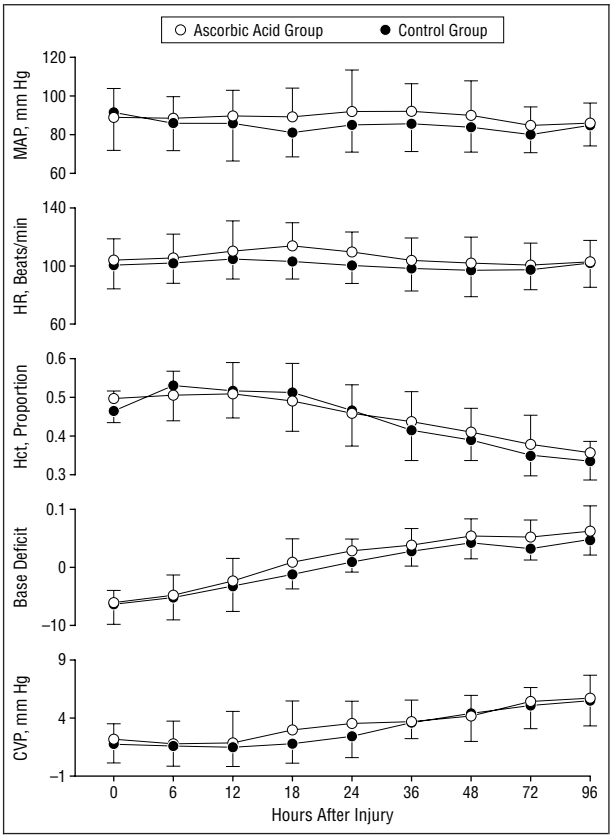

Figure 1. *Heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), and hematocrit concentration (Hct) of both groups were all equivalent during the 24-hour study period.*

COMMENT

In our study, adjuvant administration of high-dose ascorbic acid produced a significant reduction in postburn lipid peroxidation and resuscitation fluid volume requirements in patients with severe burns. This fluid reduction was associated with fewer days receiving mechanical ventilation and improved early respiratory function.

Previously, high-dose ascorbic acid was reported to reduce burn wound edema[5] and resuscitation fluid volume requirements by up to 75% in experimental animals.[7,11] Similarly, our study demonstrates a 45.5% reduction in the initial resuscitation fluid volume requirement in burned patients. Despite the reduced fluid intake in the ascorbic acid group, the hemodynamic measurements and hourly urine output values were equivalent to those in the control group, indicating that neither group appeared to have been overresuscitated or underresuscitated. In addition, the final ascorbic acid solution had an identical osmolality and sodium concentration to that of RL, and none of the measured biochemical factors indicated an osmotic diuretic effect. Moreover, fluid retention on days 2, 3, and 4 was identical in both groups.

The difference in the resuscitation fluid volume requirement was not due to differences in urine output or insensible loss, but solely to the difference in retained fluid. Edema in burned skin was reduced significantly

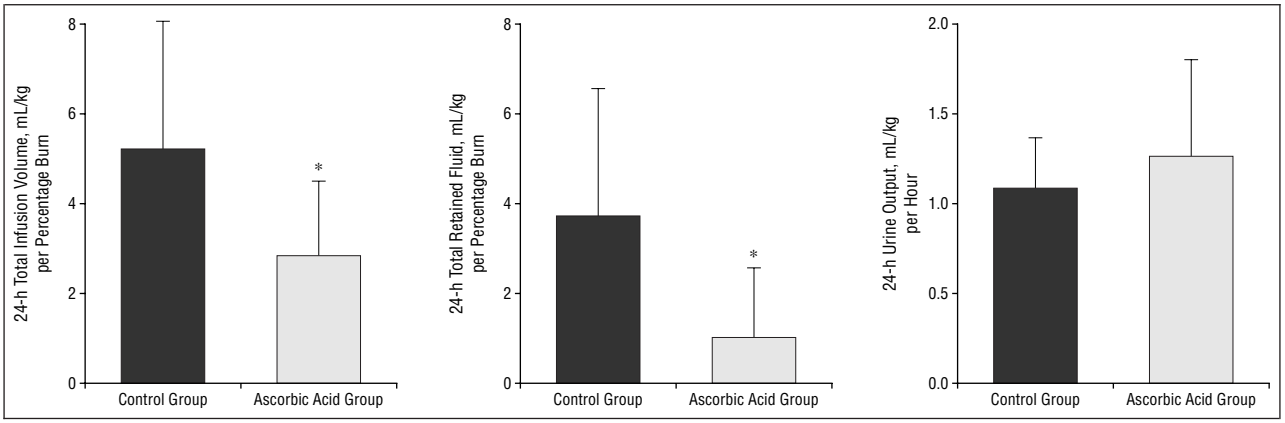

Figure 2. *The 24-hour resuscitation fluid volume requirement and urine output in both groups. Data are given as mean ± SD. Fluid volume requirement in the control group was 5.5 ± 3.1 mL/kg per percentage of total body surface area (TBSA) burn, whereas the ascorbic acid group required only 3.0 ± 1.7 mL/kg per percentage of TBSA burn, representing a 45.5% reduction. Asterisk indicates* P<.05 *compared with the ascorbic acid group.*

Table 2. Percentage of Body Weight Gain and Net Fluid Retention During First 4 Days*

Postburn Interval, h	Body Weight Gain, %		Net Fluid Retention, mL/kg	
	Ascorbic Acid Group	Control Group	Ascorbic Acid Group	Control Group
24	9.2 ± 8.2	17.8 ± 6.9†	89 ± 92	62 ± 87†
48	8.7 ± 7.4	23.2 ± 7.1†	32 ± 18	48 ± 26†
72	7.0 ± 5.8	19.6 ± 4.5†	23 ± 12	31 ± 15
96	5.3 ± 5.5	17.7 ± 5.5†	21 ± 16	19 ± 12
168	3.1 ± 1.4	9.9 ± 6.2†	16 ± 11	15 ± 13

**Data are given as mean ± SD.*
†P<.05, compared with the ascorbic acid group.

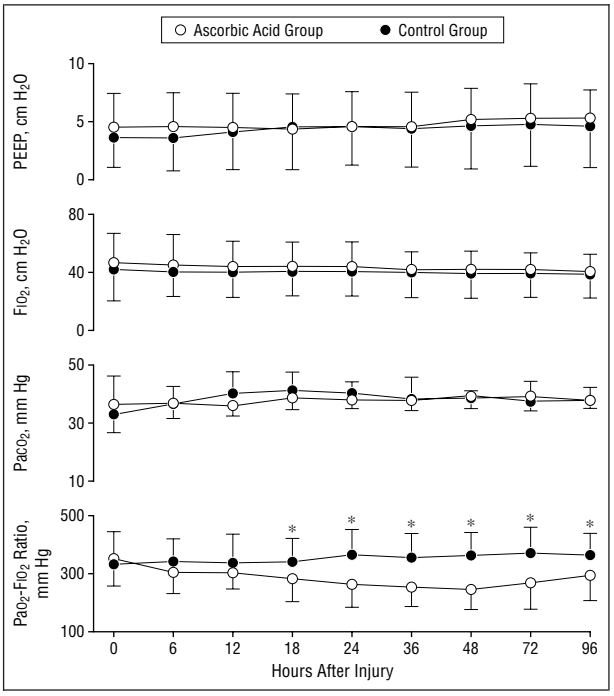

Figure 3. *Fraction of inspired oxygen (F_{IO_2}), positive end-expiratory pressure (PEEP), P_{aO_2}/F_{IO_2} ratio, and P_{aCO_2}, of both groups. The control group had a lower P_{aO_2}/F_{IO_2} ratio at 18, 24, 36, 48, and 72 hours after injury. Asterisk indicates* P<.05 *compared with the ascorbic acid group.*

in the ascorbic acid group, paralleling the decreased fluid retention.

The median lethal dose of ascorbic acid is unknown[12]; however a dose of 5 g/kg per day is considered safe.[13] In a previous study, no abnormalities in hematologic, hepatic, and renal function during 7 days after ascorbic acid (33 mg/kg per hour) administration were found.[14] The dose of ascorbic acid used in our study is 4-fold higher than that used in guinea pigs.[15] The optimum dose of ascorbic acid in humans has not been determined, but in a canine model of 50% TBSA burn, similar benefits were observed using 66 mg/kg per hour. Large mammals may need larger doses because of their more complex oxygen free-radical–generating systems.[16]

Oxygen radicals are considered to play an important role in increased vascular permeability,[1] lipid peroxidation of the cell membrane,[17] and initiation of local and systemic inflammation[18] after burn injury. In particular, increased xanthine oxidase concentrations have been well described in an animal model.[19] Burn edema has been reported to be attenuated significantly in several burn models by preinjury administration of antioxidants such as catalase, superoxide dismutase, deferoxamine hydrochloride, allopurinol, and lodoxamine tromethamine. However, no clinically applicable drug has been reported.

The potential clinical benefit of modifying postburn edema formation and lipid peroxidation using systemically administered antioxidants has been explored previously. Thomson et al[20] reported that postburn increases of lipid peroxidation in humans can be reduced by administration of superoxide dismutase, a free-radical scavenger. Recently, Knox and associates[21] have advocated the use of a mixture of antioxidants and anti-inflammatory drug (ascorbic acid, vitamin E, L-glutamine, and ibuprofen) in the early treatment of patients with severe burns, but the effectiveness of such treatment has not been confirmed.

Ascorbic acid is a potent water-soluble natural antioxidant capable of scavenging oxygen radicals,[22,23] ter-

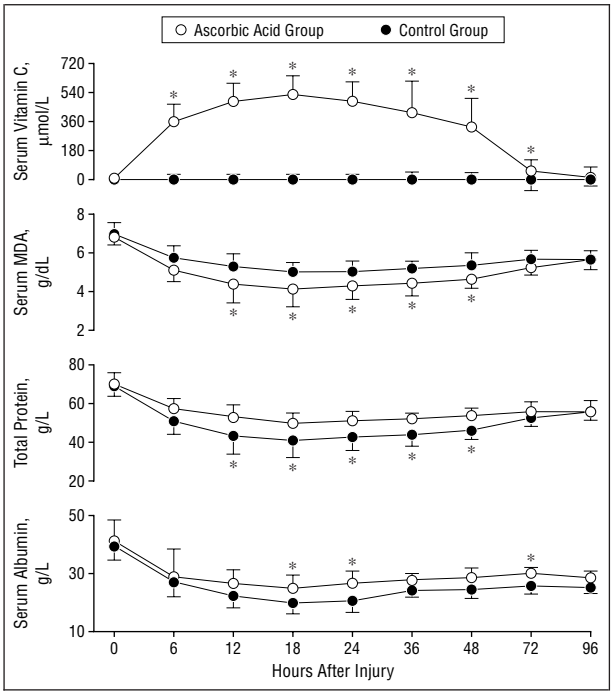

Figure 4. *Serum levels of vitamin C, malondialdehyde (MDA), total protein, and albumin. Asterisk indicates* P<*.05 compared with the ascorbic acid group.*

Table 3. Outcomes

	Ascorbic Acid Group (n = 19)	Control Group (n = 18)	*P*
Hospital stay, mean ± SD, d	40 ± 28	49 ± 44	.46
Length of mechanical ventilation, mean ± SD, d	12.1 ± 8.8	21.3 ± 15.6	.03
No. of patients with pneumonia (within 2 wk)	7	6	.86
Day of first surgery, mean ± SD	5.8 ± 2.5	7.1 ± 2.5	.12
No. of surgeries, mean ± SD	2.3 ± 1.3	2.4 ± 1.4	.82
No. of fasciotomies	4	8	.45
Mortality, No. of patients	9	7	.97

minating lipid peroxidation,[3] regenerating vitamin E,[24,25] and exerting various different effects.[26-29]

Antioxidant therapy with adjuvant administration of high-dose ascorbic acid has been previously reported to reduce postburn lipid peroxidation,[3] early postburn microvascular fluid and protein leakage,[4] postburn wound edema,[5] and increased microvascular permeability[30] and to decrease resuscitation fluid volume requirements in a guinea pig model.[6]

Lipid peroxides increase immediately after burn injury, indicating oxygen free-radical injury. Conjugated dienes and the more stable MDA are often used as markers of lipid peroxidation.[14,20,31-33]

We confirmed herein that high-dose ascorbic acid reduces postburn serum MDA levels in burned patients. We did not measure cardiac output and cardiac contractility, and so cannot exclude the possibility of a direct cardiotonic action of ascorbic acid.

The Parkland formula is the most popular resuscitation formula in the United States.[34] The original experimental studies by Baxter[35] reported that 4 mL/kg per percentage of TBSA burn are needed on average in the first 24 hours. However, patients with large burns and with inhalation injury need more fluid than those with lesser burns.[34,36] Our control group required 5.5 mL/kg per percentage of TBSA burn.

The clinical benefits of the reduced fluid resuscitation volume with stable hemodynamic values that we observed using ascorbic acid led to a clear reduction in edema and body weight gain and were associated with reduced respiratory impairment and a reduced requirement for mechanical ventilation. We did not reach a significant reduction of mortality rate in this study, because most deaths in modern burn centers occur during the septic shock phase. Only in elderly patients or those with fatal thermal injury (at least 70% TBSA) with inhalation injury does resuscitation failure occur during the early phase of injury. However, in our small series, there were numerically fewer deaths in the ascorbic acid group at 7 days after injury and fewer fasciotomies as well, which we find encouraging. We believe that this new therapy is also effective in much more serious cases.

Our study involved a small number of patients and therefore must be viewed as preliminary. Questions remaining unanswered at this time include the metabolic and immunologic responses and wound healing in patients subsequent to the initial period described herein. Our results show, however, that high-dose ascorbic acid therapy as an adjunct to resuscitation in severely burned patients is well tolerated, and that further investigation is clearly warranted.

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