Reduced Fluid Volume Requirement for Resuscitation of Third-Degree Burns with High-Dose Vitamin C

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The effects of high-dose vitamin C therapy (170 mg, 340 mg, and 680 mg/kg/day) were evaluated in 70% body surface area third-degree burns in guinea pigs that were resuscitated with 1 ml/kg/%burn Ringer's lactate solution. The water content measurements of the burned skin at 24 hours after burn injury in the vitamin C-treated groups were significantly lower than those of the control group (1 ml/kg/%burn) and those of the standard resuscitation group (4 ml/kg/%burn). The cardiac outputs in the group that received 340 mg vitamin C were significantly higher than those of the control group but not significantly different than those of the standard therapy group at 2 hours after burn injury and thereafter. In comparison with the regimen of 340 mg vitamin C, the regimen of 680 mg vitamin C was no more beneficial, and the regimen of 170 mg was less effective. With administration of adjuvant high-dose vitamin C, we were able to reduce the total 24-hour resuscitation volume from 4 ml/kg/%burn to 1 ml/kg/%burn, while a comparable cardiac output was maintained. (J BURN CARE REHABIL 1991;12:525-32)

Burn injury is characterized by increased microvascular permeability, which requires massive fluid volume resuscitation during the first 24 hours after the burn. Many inflammatory mediators including histamine,[1] serotonin,[1] bradykinin,[2] complement activation,[3] and prostaglandins[4,5] have been studied. Recently, free oxygen radicals have been reported as a possible cause for the increase in postburn vascular permeability.[6-8]

Boykin, Crute, and Haynes[9] have reported a 70% reduction in resuscitation fluid volume in guinea pigs as a result of early administration of the histamine H_2 blocker, cimetidine. More recently, however, Boykin and Manoon[10] have postulated that the beneficial effects of cimetidine may be due to its free radical scavenging capability rather than to its H_2 receptor blocking activity, since ranitidine does not show the same beneficial results as cimetidine. In effect, it has been shown by Friedl et al.[11] that cimetidine has free-radical scavenging capability.

Vitamin C is another free-radical scavenger.[12] We have studied the effects of antioxidant therapy with high-dose vitamin C on the reduction of the resuscitation fluid volume.

MATERIAL AND METHODS

The experiments were performed in accord with the standards in "The Guide for the Care and Use of Laboratory Animals" (National Institutes of Health Publication no. 86-23, 1985, Department of Health and Human Services). The experimental protocol was approved by the Animal Care Committee of the Cook County Hospital.

Detailed experimental procedures were previously reported elsewhere.[13] In brief, 18 adult guinea pigs, which weighed 500 to 700 gm were anesthetized intraperitoneally with 25 mg/kg pentobarbital sodium. They were shaved over the anterior neck and from the mid-chest level caudally. A polyethylene catheter was inserted into the right jugular vein and advanced to the entrance of the right atrium for fluid infusion. Another catheter was placed into the right

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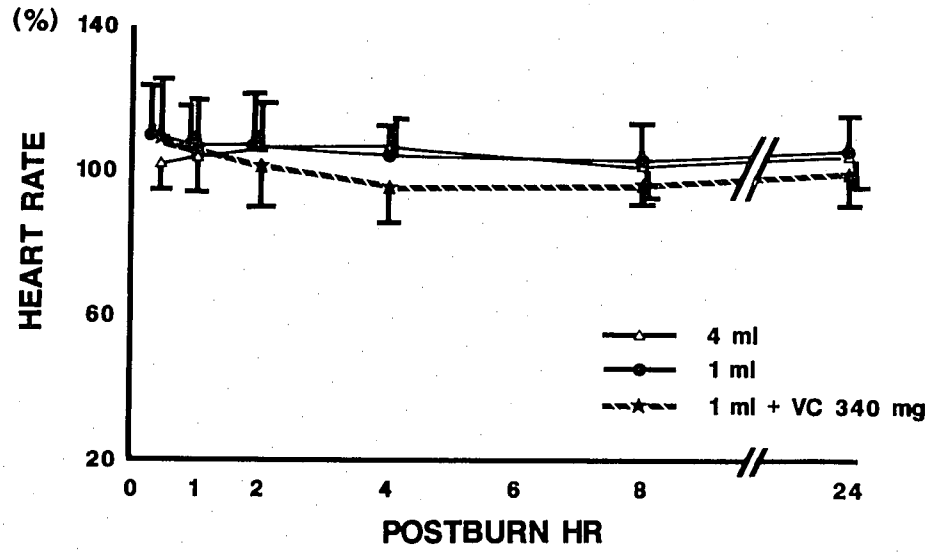

Figure 1. Heart rates (percent preburn value, mean ± SD) of 340 mg vitamin C group, control group (1 ml), and standard therapy group (4 ml). There are no significant differences among the groups.

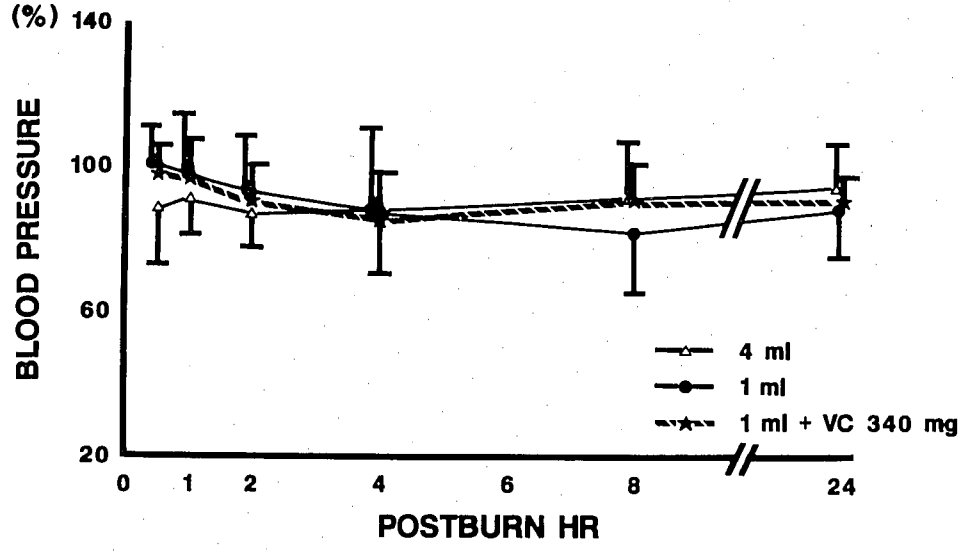

Figure 2. Mean arterial blood pressures (percent preburn value, mean ± SD) of 340 mg vitamin C group, control group (1 ml), and standard therapy group (4 ml). There are no significant differences among the groups.

axillary artery for heart rate and blood pressure measurements. A thermistor-tip catheter was inserted into the left carotid artery and advanced to the aortic arch for determinations of cardiac output (CO).

After baseline measurements were obtained, each animal underwent subxiphoid immersion into water at a temperature of 100° C for 6 seconds. This produced a 70% body surface area (BSA) third-degree burn. The animals were dried immediately and returned to temperature-controlled cages for the duration of the study.

Vitamin C (Cenolate, Abbott Laboratories Hos-

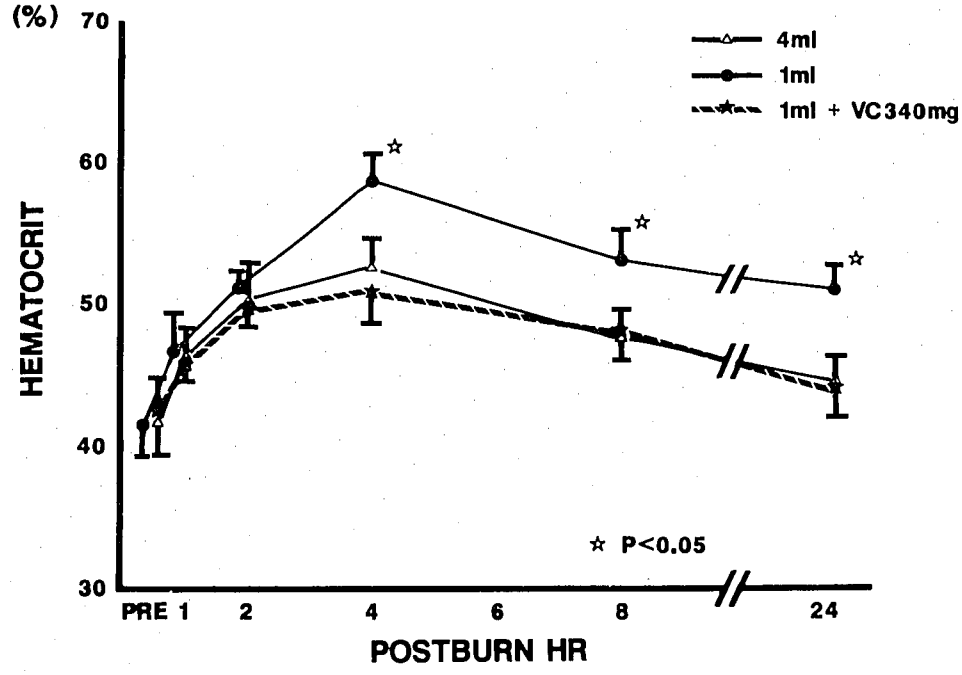

Figure 3. Hematocrits (mean ± SD) of 340 mg vitamin C group, control group (1 ml), and standard therapy group (4 ml). The 1 ml control group shows significantly higher hematocrit values at 4 hours after burn injury and thereafter, which indicates decreased plasma volume and hemoconcentration. $*p < 0.05$ compared with 340 mg vitamin C group.

pital Products Div., Abbott Park, Ill.) solution was mixed into a 250 ml bag of Ringer's lactate solution after its sodium concentration was adjusted to that of Ringer's lactate solution with distilled water. All of the animals were resuscitated with Ringer's lactate solution that contained vitamin C, beginning at 0.5 hour after burn injury. The resuscitation fluid volume that was administered was 1 ml/kg/%BSA burn during the first 24 hours after injury (50% was administered during the first 8 hours and the remaining amount was given during the next 16 hours). The animals were divided into three groups of six animals each. Group 1 received 680 mg/kg/day vitamin C; group 2, 340 mg/kg/day; and group 3, 170 mg/kg/day. Microinfusion pumps (model 8500, Baxter Healthcare Corp., Parenterals Div, Deerfield, Ill.) were used to infuse the resuscitation fluid that contained vitamin C.

Cardiac output was determined in triplicate by the thermal dilution method with the R-option of Cardio-Max (Columbus Instruments International Corp., Columbus, Ohio). A micro-injector (model 400, Columbus Instruments International Corp.) was used to inject 0.25 ml of Ringer's lactate solution at room temperature. The amount of fluid that was injected was reduced from the resuscitation fluid volume accordingly.

Approximately 1 cm^2 of skin was excised, weighed immediately, minced, and dried. The water content of the skin was determined as the difference between the wet and dry tissue weights and expressed as the percentage of wet tissue.

Data from the three study groups were compared with data from the two groups from our ongoing investigations of resuscitation fluid volume reduction in third-degree burns. Identical experimental procedures were performed on these two groups (six animals each) by the same investigator. The only exception was that these two groups were resuscitated with Ringer's lactate solution without vitamin C, the volume of which was 1 ml/kg/%BSA burn in one group (control group) and 4 ml/kg/%BSA burn in the other group (standard therapy group).

Group values were expressed as the mean plus or minus one standard deviation. Two-way analysis of variance for split-plot design with repeated measures[14] was used to determine the statistically significant differences. When the two-factor interaction was significant, simple main effects tests were performed at timed intervals. When the latter were sig-

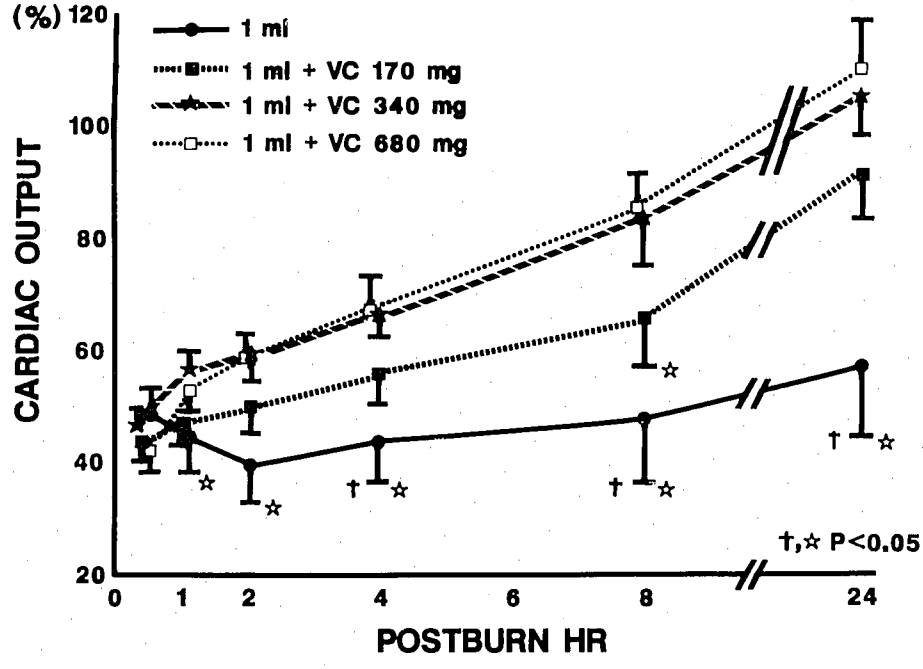

Figure 4. Cardiac outputs (percent preburn value, mean ± SD) of the 1 ml control group and of groups 1, 2, and 3. There are no significant differences in cardiac output between the 680 mg vitamin C and the 340 mg vitamin C groups. The 170 mg vitamin C group shows consistently lower cardiac outputs compared with the 340 mg vitamin C group, which suggests a dose-dependent phenomenon, although the differences are only significant at 8 hours after burn injury. Also, the 170 mg vitamin C group shows significantly higher cardiac output values compared with the 1 ml control group at 4 hours after burn injury and thereafter. $*p < 0.05$ compared with 340 mg vitamin C group. $\dagger p < 0.05$ compared with 170 mg vitamin C group.

nificant, Tukey's test was used to determine significant differences between the groups. A p value of less than 0.05 was accepted as significant.

RESULTS

The heart rates of groups 1, 2, and 3 at 0.5, 1, 2, 4, 8, and 24 hours after burn injury are shown in Table 1. There were no significant differences between the groups at any time during the 24-hour study period. The heart rates of group 2 are compared with those of the control group and those of the standard therapy group in Figure 1.

The blood pressures of groups 1, 2, and 3 at 0.5, 1, 2, 4, 8, and 24 hours after burn injury are shown in Table 2. There were no significant differences between these groups at any time during the study period. The blood pressures of group 2 are compared with those of the control group and those of the standard therapy group in Figure 2.

The hematocrits of groups 1, 2, and 3 at 0.5, 1, 2, 4, 8, and 24 hours after burn injury are shown in Table 3. The hematocrits of group 2 are compared with those of the control group and those of the standard therapy group in Figure 3.

The cardiac outputs of groups 1, 2, and 3 are compared with those of the 1 ml control group in Figure 4. There are no significant differences in cardiac outputs between the 680 mg vitamin C and the 340 mg vitamin C groups. Although the differences are only significant at 8 hours after burn injury, the 170 mg vitamin C group shows consistently lower cardiac outputs compared with the 340 mg vitamin C group. However, the 170 mg vitamin C group shows significantly higher cardiac output values compared with those of the 1 ml control group at 4 hours after burn injury and thereafter. Thus it appears that this is a dose-dependent phenomenon.

The cardiac outputs of the 4 ml group are significantly higher than those of the 340 mg vitamin C

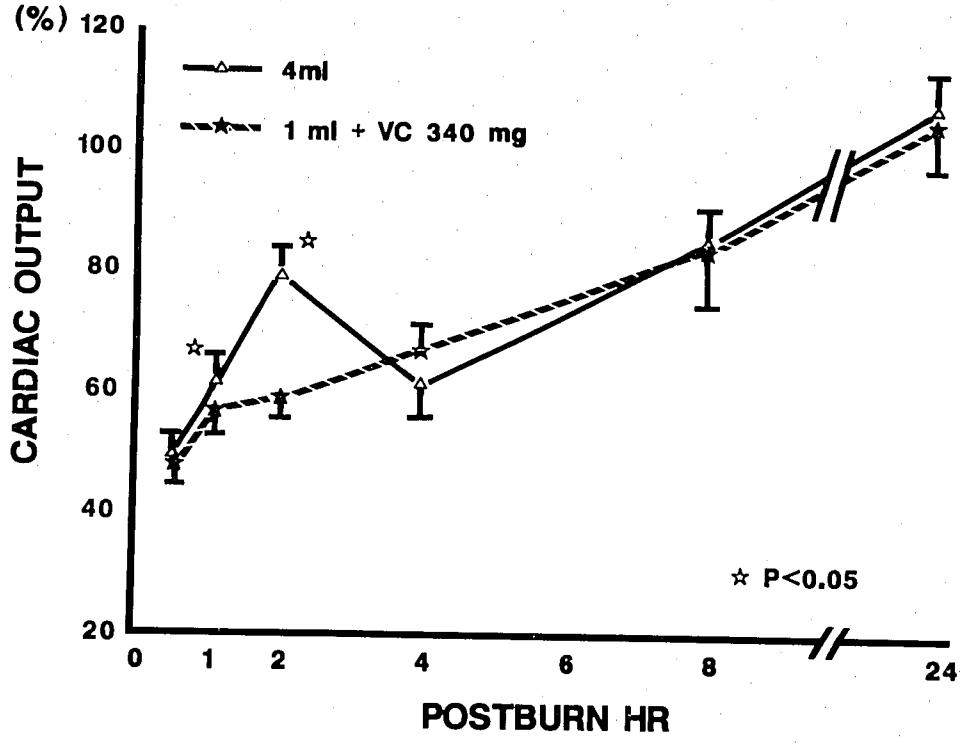

Figure 5. Cardiac outputs (percent preburn value, mean ± SD) of the 4 ml group and the 340 mg vitamin C group. The cardiac outputs of the 4 ml group are significantly higher than those of the 340 mg vitamin C group at 1 and 2 hours after injury; the differences, however, are no longer significant at 4 hours after burn injury and thereafter. $*p < 0.05$ compared with the 340 mg vitamin C group.

group at 1 and 2 hours after burn injury (Figure 5). However, there are no significant differences at 4 hours after burn injury and thereafter.

The water content of the skin before burn injury in groups 1, 2, and 3 comprises 66.5% to 67.7% of the wet tissue weight; there are no significant differences between these groups (Table 4). Similarly, there are no significant differences in the water content of the burned skin at 24 hours after burn for groups 1, 2, and 3; nor are there any differences in the water content of the unburned skin at 24 hours after burn injury for the same groups (Table 4).

Comparisons of the water content of the skin before burn injury in the 340 mg vitamin C group with those of the 1 ml (67.6% ± 1.1%) and the 4 ml (67.1% ± 0.8%) groups show no significant differences. However, in group 2 at 24 hours after burn injury, the burned skin had a significantly lower water content than did burned skin in the 1 ml (74.1% ± 1.3%) and 4 ml (78.0% ± 2.1%) groups, which indicates less burn-wound edema in the 340 mg vitamin C group. The water content of the unburned skin in group 2 at 24 hours after burn injury was not significantly different from that of the 1 ml group (68.4% ± 1.4%) but was significantly less than that of the 4 ml group (72.7% ± 1.0%).

DISCUSSION

Boykin, Crute, and Haynes[9] reported that adjuvant therapy with the histamine H_2 blocker, cimetidine, reduced the resuscitation fluid volume requirement by 70% in 75% BSA burns. Boykin and Manoon[10] later postulated that the beneficial effects of cimetidine were not due to H_2-receptor blocking activity but rather to its free-radical scavenging capability because ranitidine did not produce the same beneficial effects as cimetidine.

Vitamin C is another proven antioxidant.[12] Reports of Vitamin C therapy for the treatment of burn

Table 1. Heart rates (percent preburn value) of groups 1, 2, and 3

Group	0.5 hr	1 hr	2 hr	4 hr	8 hr	24 hr
1	106.2 ± 10.7	110.3 ± 7.7	110.5 ± 20.1	101.3 ± 14.9	95.3 ± 5.2	97.3 ± 4.3
2	109.0 ± 16.5	106.3 ± 13.2	101.2 ± 10.3	96.3 ± 7.1	96.5 ± 4.2	99.7 ± 8.5
3	109.0 ± 3.3	107.3 ± 4.3	102.5 ± 8.0	100.2 ± 6.5	100.3 ± 6.5	100.0 ± 6.2

Values are expressed as means ± SD.
Group 1 (n = 6): vitamin C 680 mg/kg/day; group 2 (n = 6): vitamin C 340 mg/kg/day; group 3 (n = 6): vitamin C 170 mg/kg/day.
There were no significant differences among the groups.

Table 2. Mean arterial blood pressures (percent preburn value) of groups 1, 2, and 3

Group	0.5 hr	1 hr	2 hr	4 hr	8 hr	24 hr
1	92.5 ± 18.3	93.8 ± 16.4	91.5 ± 17.8	87.8 ± 13.5	91.5 ± 11.5	94.0 ± 17.0
2	97.2 ± 5.2	96.0 ± 10.0	90.7 ± 10.2	84.8 ± 15.1	90.8 ± 11.0	90.3 ± 7.7
3	88.0 ± 8.6	84.5 ± 14.2	90.7 ± 12.4	93.8 ± 12.3	94.3 ± 11.7	92.5 ± 6.8

Values are expressed as means ± SD.
Group 1 (n = 6): vitamin C 680 mg/kg/day; group 2 (n = 6): vitamin C 340 mg/kg/day; group 3 (n = 6): vitamin C 170 mg/kg/day.
There were no significant differences among the groups.

Table 3. Hematocrits of groups 1, 2, and 3

Group	Preburn	1 hr	2 hr	4 hr	8 hr	24 hr
1	44.5 ± 1.4	48.2 ± 1.3	51.2 ± 1.3	51.3 ± 1.8	49.3 ± 1.8	46.7 ± 1.2
2	42.3 ± 2.3	46.2 ± 0.8	50.0 ± 1.3	51.0 ± 2.1	48.8 ± 2.1	44.2 ± 2.6
3	43.0 ± 2.4	47.5 ± 1.5	52.3 ± 1.5	54.5 ± 2.0	50.7 ± 2.2	48.0 ± 1.3*

Values are expressed as means ± SD.
Group 1 (n = 6): vitamin C 680 mg/kg/day; group 2 (n = 6): vitamin C 340 mg/kg/day; group 3 (n = 6): vitamin C 170 mg/kg/day.
*Indicates a significant difference ($p < 0.05$) compared with group 2.

Table 4. The water content of the skin (percent wet tissue weight) of groups 1, 2, and 3

		24 Hours after burn injury	
Group	Preburn	Burned skin	Nonburned skin
1	66.7 ± 0.8	68.5 ± 1.9	67.4 ± 2.3
2	67.7 ± 1.1	69.3 ± 3.0	67.6 ± 2.6
3	66.5 ± 1.8	72.4 ± 2.0	68.0 ± 1.5

Values are expressed as means ± SD.
Group 1 (n = 6): vitamin C 680 mg/kg/day; group 2 (n = 6): vitamin C 340 mg/kg/day; group 3 (n = 6): vitamin C 170 mg/kg/day.
There were no significant differences among the groups.

injury are scarce in the literature. Nirankari et al.[15] reported that both superoxide dismutase and ascorbic acid were effective in preventing corneal perforations when daily subconjunctival injection was given after occular alkali burns. Hollinshead, Spillert, and Lazaro[16] reported that intraperitoneal vitamin C (1 to 2 gm/kg), administered shortly after thermal injury, significantly retarded tissue necrosis in the murine burn wound for 72 hours. We evaluated the effects of continuous intravenous infusion of vitamin C on the hemodynamic response of burned guinea pigs that received only 25% of the standard resuscitation fluid volume.

In the immediate postburn period, hypovolemia is the main cause for decreased cardiac outputs, although a myocardial depressant factor has been reported by Baxter and Shires.[17] The vitamin C-treated group in our study demonstrated significantly lower hematocrit values and higher cardiac output values compared with those of the control group that received the same amount of resuscitation fluid. This indicates that the improvement in cardiac outputs in the vitamin C group was due to a reduction in plasma volume loss. We did not take wedge pressure measurements or blood volume determinations in this

study, so we cannot exclude the possibility of a direct cardiotonic action of vitamin C.

Plasma vitamin C levels were not measured; therefore, the minimum therapeutic plasma level of vitamin C could not be assessed. Nonetheless, a continuous infusion of 340 mg/kg/day of vitamin C appears to be the minimum therapeutic dose needed to reduce the resuscitation fluid volume requirements by 75%. The 170 mg/kg dose was less beneficial than the 340 mg/kg dose of vitamin C, although it was still more effective compared with the control group, which received no vitamin C. The 680 mg/kg dose did not appear to show any additional benefits to those of the 340 mg/kg dose of vitamin C.

The water content of the burned skin at 24 hours after burn injury in the vitamin C group was lower than that of the control group, which suggests that increased postburn capillary permeability was effectively suppressed. The water content of the unburned skin at 24 hours after injury in the vitamin C group was significantly less than that of the 4 ml resuscitation group but not different from that of the 1 ml control group. Historically, Baxter[18] suggested that the postburn capillary leak seals at 24 to 36 hours. More recent animal studies, however, have suggested that this may occur as early as 6 to 12 hours after the burn injury.[19,20] In the presence of normal vascular permeability, however, a continued increase in net transvascular fluid flux occurs in unburned tissues. Because of the increased capillary permeability, protein as well as fluid leaks into the burned tissue, especially during the first 8 hours after burn injury. The crystalloid resuscitation fluid, when given in large quantities, will dilute the plasma proteins. The hypoproteinemia and resulting low colloid oncotic pressure will, in turn, require greater crystalloid volume infusion to maintain the plasma volume. Other investigators have demonstrated the same degree of edema in soft tissues with hypoproteinemia alone as seen after burn injury with a comparable protein deficit.[21-23] They also showed that about one half of the 24-hour fluid requirement after a 50% BSA burn resulted in edema in the unburned tissue when no colloid was used.[24]

The 1 ml control group in our study did not receive a large amount of crystalloid infusion; thus, it is reasonable to assume that the guinea pigs did not have dilutional hypoproteinemia. As a result of this inadequate crystalloid infusion, the plasma volume remained contracted, which caused higher hematocrit and lower cardiac output values. The 340 mg vitamin C group had reduced volume of fluid and protein leakage into the burned skin and received only 1 ml/kg/%burn crystalloid resuscitation. This combination of a small leak and a small resuscitation volume presumably prevented dilutional hypoproteinemia, which subsequently required a smaller volume of crystalloid infusion to maintain the necessary blood volume for adequate cardiac output. We did not measure serum protein levels, so we can not quantify the correlation between the plasma oncotic pressure and the edema formation in the unburned skin.

The vitamin C dose of 340 mg/kg during the first 24 hours after burn injury translates to approximately 1 gm/hr or 24 gm/day for a 70 kg man. The possible toxicities and side effects should be clarified, and its mechanism of action should be studied before high dose vitamin C therapy should be tried in the clinical setting.

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