

# Administration of Vitamin C and Vitamin E in Severe Head Injury: A Randomized Double-blind Controlled Trial

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Free radicals are highly reactive molecules generated predominantly during cellular respiration and normal metabolism. Increased production of free radicals and reactive oxygen species leading to oxidative stress appears to play an important role in the pathogenesis of ischemic, hemorrhagic, and traumatic brain injury.<sup>1,2</sup> Oxidative stress has been implicated as a potential contributor to the pathogenesis of acute central nervous system (CNS) injury. Radicals can cause damage to cardinal cellular components such as lipids, proteins, and nucleic acids, leading to subsequent cell death by modes of necrosis or apoptosis.<sup>1</sup>

Therefore, treatment with antioxidants may theoretically act to prevent propagation of tissue damage and to improve both survival and neurological outcome. Several such agents of widely varying chemical structures have been investigated as therapeutic agents for acute CNS injury.<sup>2</sup>

The main bodily defense system against lipid peroxidation includes compounds such as vitamin C, vitamin E, and glutathione, which work fairly effectively in the absence of a major oxidative stress.<sup>3</sup> However, numerous studies have shown that each of these is rapidly consumed during the early minutes and hours after traumatic brain injury.<sup>4,5</sup> This fact has shifted the direction of antioxidant therapeutic research toward newer drugs other than these compounds. Another way to compensate for this rather rapid consumption is to provide higher doses of these compounds to patients with a major stress. This practice constitutes the main idea behind this study.

Vitamin C (ascorbic acid) appears to be particularly important in limiting oxidative lipid damage in biological systems. Numerous studies have demonstrated that under many different types of oxidizing conditions, ascorbic acid forms the first line of antioxidant defense and effectively protects the lipids in plasma and lipoproteins against detectable peroxidative damage, even in the presence of free, redox-active iron.<sup>4,6</sup>

Many studies have shown early depletion of vitamin C in brain injury, which may be promising for the effectiveness of vitamin C supplementation in patients with brain injury. In a study by Huang et al<sup>6</sup> on an experimental model of stroke, dehydroascorbic acid, a blood-brain barrier-transportable form of vitamin C, caused dose-dependent increases in postreperfusion cerebral blood flow, with reductions in infarct volume, neurological deficit, and mortality. In studies by Gey et al,<sup>7</sup> Keli et al,<sup>8</sup> and Daviglius et al,<sup>9</sup> increased antioxidant vitamin C intake resulted in a decreased risk of stroke.

Vitamin E ( $\alpha$ -tocopherol) has also shown promise in modifying oxidative stress pathways and improving neurological outcome in many animal studies. In an animal head-injury study, administration of vitamin E caused a neuroprotective effect by decreasing the rate of lipid peroxidation.<sup>10</sup>

Although effectively proven in experimental animal studies, no controlled randomized clinical trials have ever evaluated the effectiveness of such available antioxidants as vitamin C and vitamin E compounds on outcome of brain injury. In this study, we attempted to evaluate the effect of these compounds on mortality, patient outcome, and evolution of perilesional edema in severely head-injured patients.

## METHODS

The study protocol was approved by the ethics committee of the university as a randomized, double-blind, placebo-controlled trial. All adult patients (age  $\geq 16$  years) with severe head injury, as defined by a Glasgow Coma Scale score of  $\leq 8$ , with the radiologic diagnosis of diffuse axonal injury were evaluated for randomization. These patients were admitted within the first 8 hours after trauma to 1 of 2 university-affiliated hospitals caring for head trauma in Shiraz in Southern Iran. Patients with significant liver or renal disease, or glucose-6-phosphate dehydrogenase deficiency were excluded. Patients with previous significant CNS pathology (eg, stroke, head injury, or previous craniotomy) affecting measurements on imaging were also excluded. Patients with space-occupying lesions necessitating emergency evacuation and those with preresuscitation shock and

hypoxic ischemic encephalopathy also were not included in the study.

All patients were randomized into 4 groups receiving any of the following protocols: group A, low-dose vitamin C (500 mg/d IV) for 7 days; group B, high-dose vitamin C (10 g IV on the first [admission] day and repeated on the fourth day, followed by vitamin C 4 g/d IV for the remaining 3 days); group C, vitamin E (400 IU/d IM) for 7 days; and group D, placebo. To ensure a double-blind protocol, the drugs were administered in packages by one of the residents who did not take part in any of the other parts of the study, including data collection, interpretation of brain computed tomography (CT), or patient evaluation.

All patients were admitted to the neurotrauma intensive care unit and were managed on the basis of an intracranial pressure-targeted strategy. Glasgow Coma Scale score was recorded every hour. Brain CT was performed on admission, 6 to 8 hours later, and on the third, fifth, and the seventh days after admission, if not indicated more frequently. All brain CT findings, including the presence and location of hematoma, appearance of basal (ambient) cistern, midline shift, diameter of intracerebral hematoma or contusion, and specifically the diameter of the perilesional hypodense area, were recorded. In cases of multiple lesions or contusions, the largest one located supratentorially was taken into account.

Outcome was assessed with Glasgow Outcome Scale (GOS) scores measured at the time of discharge and on follow-up at 2 months and 6 months after discharge. All data were analyzed with SPSS software using the  $\chi^2$  test, 1-way ANOVA, and repeated measurements. Any value of  $P < .05$  was considered to be significant.

## RESULTS

Of the 290 patients assessed for eligibility, 100 patients (34.5%), including 83 male and 17 female patients, were randomized. Ninety-one percent attended the follow-up session at 2 and 6 months. Mean age of patients was 31.6 years (SD = 8.7 years). The study groups turned out to be highly comparable with respect to baseline characteristics such

as age, sex, Glasgow Coma Scale score on presentation (range, 4-8), diffuse axonal injury grade (Marshal grading range, 1-4), and brain CT findings. (Table 1).

Mean length of hospitalization was 15.2 days (SD = 4.3 days). Length of hospitalization was nonsignificantly more prolonged in the placebo group compared with the other groups, which experienced a shorter (although not significantly) hospitalization ( $P = .08$ ).

Twenty-six patients died during the hospital course, which increased to 28 and 30 patients after 2 and 6 months; respectively. The vitamin E group showed a significantly lower rate of mortality than the control and other treatment groups ( $P = .04$ , Table 2). The GOS scores at discharge and follow-up were also significantly better for the vitamin E group patients ( $P = .04$ ; Figure 1).

The effect of drug administration on halting or decelerating the progression of perilesional edema (hypodense region in brain CT) was most pronounced in the high-dose vitamin C group. High-dose vitamin C stabilized or reduced the diameter of perilesional hypodense region in subsequent days in 68% of patients ( $P = .01$ ). This trend did not show significance in any other groups (Figure 2).

No other significant trend could be extracted from serial measurements of brain CT scan such as size of hematoma ( $P = .1$ ), appearance of basal cisterns ( $P = .82$ ), and midline shift ( $P = .36$ ). No adverse effects related to the vitamin dosing and administration occurred.

## DISCUSSION

The newest investigational treatment strategies in the field of hemorrhagic, ischemic, and traumatic brain injury have focused on the modification of oxidative stress in vivo. Several agents of wildly varying chemical structures have been studied in animal studies as antioxidants for treatment of acute CNS injury.<sup>2</sup> Although appearing rather simple and ordinary for such a serious disease, many animal studies have proven benefits on administration of vitamin C and vitamin E compounds as antioxidants in brain injury models. However,

**TABLE 1.** Baseline Characteristics of the Patients in the Trial

Treatment Groups	Group A (Low-Dose Vitamin C)	Group B (High-Dose Vitamin C)	Group C (Vitamin E)	Group D (Placebo)	Total	<i>P</i> value
Number	26	23	24	27	100	
Age (y; mean, range)	31.1 (16-67)	29.5 (19-75)	36.8 (16-73)	29.4 (16-68)	31.6 (16-83)	0.23
Sex (male/female)	20/6	20/3	20/4	23/4	83/17	0.28
Admission GCSs (mean, range)	5.9 (3-8)	6.1 (3-8)	6.5 (3-8)	6.5 (3-8)	6.3 (3-8)	0.14
DAI grading (mean, range)	3.15 (1-4)	3.27 (1-4)	2.58 (1-4)	3.15 (1-4)	3.04 (1-4)	0.17
Perilesional edema (cm <sup>3</sup> ; mean $\pm$ SD)	4.19 $\pm$ 2.20	5.21 $\pm$ 1.75	4.27 $\pm$ 1.78	4.54 $\pm$ 1.26	4.54 $\pm$ 1.9	0.25

**TABLE 2.** Mortality at Different Time Points

Treatment Groups	Group A (Low-Dose Vitamin C)	Group B (High-Dose Vitamin C)	Group C (Vitamin E)	Group D (Placebo)	Total
Hospital mortality	7 (26.9%)	7 (30.4%)	4 (16.7%)	8 (29.7%)	26
Mortality after 2 mo	8 (30.8%)	7 (30.4%)	5 (20.8%)	8 (29.7%)	28
Mortality after 6 mo	9 (34.6%)	7 (30.4%)	6 (25.0%)	8 (29.7%)	30

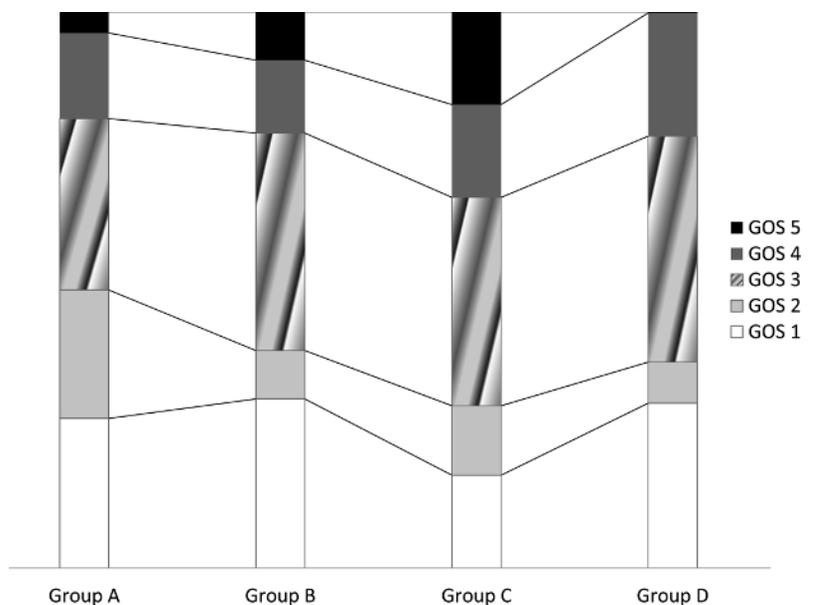
no randomized controlled trials have evaluated these 2 compounds in the setting of severe traumatic brain injury.

As stated earlier, although natural body defense mechanisms against oxidative stress and lipid peroxidation (including glutathione, vitamin C, and vitamin E) act rather effectively in the absence of major stress, their quantity decreases significantly in systemic stresses.<sup>3</sup> In the case of ascorbic acid, some studies have shown that plasma vitamin C levels are decreased in the setting of brain injury,<sup>4</sup> showing early vitamin C depletion and the subsequent need for further supplementation. Two other studies also have shown the inability of the injured brain to elevate levels of ascorbic acid in the setting of oxidative stress.<sup>5,11</sup> Supplementation of vitamin C is now a routine practice for many patients and diseases; however, the sufficiency of routine dosing had never been established. In our trial, routine low-dose (1 500-mg ampoule daily) administration of vitamin C did not cause any recognizable impact on disease course and prognosis. However, high-dose vitamin C blunted the progression of perilesional edema, probably a product of secondary oxidative insults in brain injury. This is in agreement with the fact that

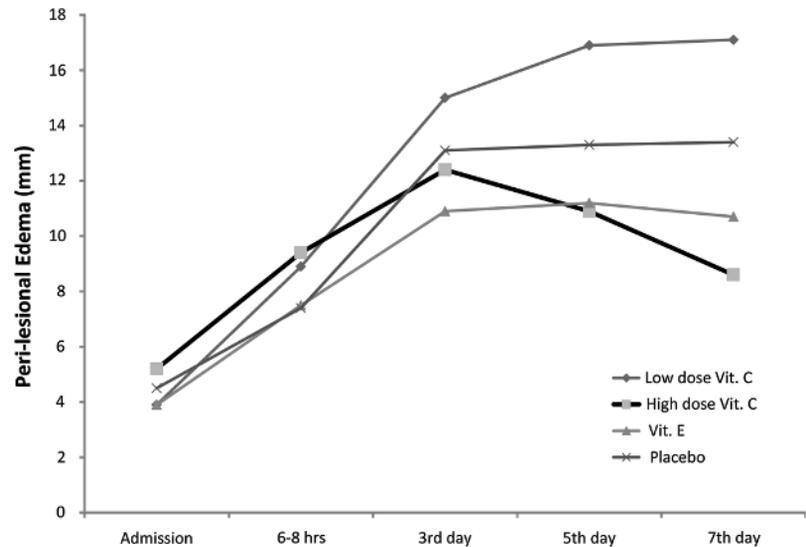
the dosage for supplementation of vitamin C in severe inflammatory diseases, malignancies, and trauma far outweighs the routine dosing in otherwise healthy subjects.<sup>6</sup>

Neither of the 2 dosing strategies for vitamin C administration showed any promise for short- and long-term neurological outcome (as assessed by GOS scores) in severely head-injured patients. Furthermore, our data show a higher rate of unfavorable outcome at discharge (GOS scores 1 and 2) for the low-dose and high-dose vitamin C groups (50% and 40%, respectively) compared with the placebo group (35%). Such a difference (especially in the low-dose group) might have been brought about by random chance or by a statistical bias caused by inadequate numbers in each group. Another explanation is a potential adverse effect of vitamin C, leading to increased mortality and vegetative states in our patients. However, if this explanation were true for low-dose vitamin C, a more severe effect would have occurred for the high-dose group, which was not the case.

Although never tested in an clinical study, some reports have shown the efficacy of vitamin E in exerting an neuroprotective effect by decreasing the rate of lipid



**FIGURE 1.** Glasgow Outcome Scale (GOS) at the time of discharge.



**FIGURE 2.** Evolution of peri-lesional edema during the first 7 days after trauma. Data represent mean edema in centimeters. Standard deviations have been omitted to avoid complexity. Vit., vitamin.

peroxidation.<sup>10,12</sup> Another experimental study showed that vitamin E is depleted in the early period after head trauma.<sup>13</sup> Although not efficacious in affecting the progression of peri-lesional infarct in our study, vitamin E showed a beneficial effect in significantly reducing mortality rate and improving functional outcome at discharge and follow-up. This effect was caused by a borderline dosing of vitamin E (400 IU/d), above which increased rates of death have been reported.<sup>10</sup> Closer examination of the mortality data shows that the significant impact of vitamin E is strongest at discharge and that the difference decreases at 2 months and decreases further at 6 months of follow-up, when only 2 patients contributed to the difference in mortality rates between vitamin E- and placebo-treated patients. The significant *P* value is perhaps related more to the difference at discharge, and the small number of patients in each group might have resulted in such a small difference that at follow-ups that it seems significant. It is therefore more reasonable to report that beneficial effects of vitamin E on survival are prominent only at discharge, and further deduction about follow-up mortality rates must be done on a larger population of patients.

Another important point is that although vitamin E has significantly reduced mortality, especially at discharge, and that favorable outcome scores (GOS scores, 4 and 5) occur more frequently in this group compared with the placebo group, the number of vegetative patients (GOS score, 2) is also higher. The probable reason is that more severe injuries, which must have contributed to death in placebo-treated patients, caused vegetative states because of their severity based on a mortality-reducing effect of vitamin E. This effect has also been experienced with other trials on brain injury in which, for instance, the successful effect of decompressive craniectomy

in reducing mortality rates might contribute to an accumulation of vegetative patients.<sup>14</sup>

We have to admit that we have chosen a rather crude and inexact index of secondary oxidative insults in the brain. The peri-lesional hypodense area may be affected by oxygenation, vascular sufficiency, and many other uncontrollable factors. The absence of sophisticated monitoring techniques (except intraventricular intracranial pressure monitors) in our center best explains why we have chosen such a rather simple index. Nonetheless, the high incidence of head injury in the region helped us apply strict inclusion and exclusion criteria, which may in turn explain the relative success of this study in finding such significant trends.

From the results of the present study and considering the relative safety of the tested compounds, we recommend the administration of vitamin E and high-dose vitamin C in routine critical care of head-injured patients, which will probably cause modifications in pathogenesis and improvements in the outcome of the disease.

## CONCLUSION

We observed a significant stabilization of the peri-lesional edema in severely head-injured patients receiving high-dose vitamin C. Our data also showed a reduction of hospital mortality (at the expense of more patients in a vegetative state) and an improvement in long-term outcome for patients receiving vitamin E.

## Disclosure

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financial or institutional interest in any of the drugs, materials, or devices described in this article.

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