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Original Article

The effect of Vitamins C and E on clinical outcomes of patients with severe traumatic brain injury: A propensity score matching study

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ABSTRACT

Background: The aim of this study was to assess the effect of Vitamins C and E on mortality, intensive care unit (ICU) length of stay, and Glasgow Outcome Scale-Extended (GOS-E) score of traumatic brain injury (TBI) patients.

Methods: Using data from records of patients in a retrospective cohort study, we included 1321 TBI patients, 269 treated and 1052 untreated, aged over 18 years with information on exposure (i.e., Vitamins C and E) and confounders. Age, Glasgow Coma Scale, pupil status, Rotterdam classification, blood sugar, blood pressure, international normalized ratio, and comorbidity of patients were considered as the confounding factors. Endpoints were GOS-E on follow-up, mortality, and ICU length of stay. Propensity score matching was performed to adjust the confounders.

Results: Based on the average treatment effect estimates, the use of Vitamins C and E reduced the risk of mortality (risk difference [RD]: −0.07; 95% confidence interval [CI]: −0.14–−0.003) and reduced the length of ICU stay (RD -1.77 95% CI:-3.71-0.16). Furthermore, our results showed that GOS-E was improved significantly (RD: 0.09, 95% CI : 0.03-0.16).

Conclusion: Our study suggests that using Vitamins C and E could decrease mortality and length of ICU stay and improve the GOS-E score and functions of the patients with severe TBI. As they are safe and inexpensive medications, they can be used in routine practice in ICUs to improve the outcomes of TBI patients.

Keywords: Ascorbic acid, Traumatic brain injury, TBI, Vitamin C, Vitamin E

INTRODUCTION

Traumatic brain injury (TBI) is an acute injury to the skull caused by external sources that can be classified into mild, moderate, and severe according to the patient's condition.[6,15] Every year, TBI leads to 2.8 million emergency room visits, admissions, and deaths, imposing a cost of approximately 80 billion dollars on society.[17,34] Falling, objects, and vehicle accidents are the most common mechanisms of TBI in the USA between 2007 and 2013 (413.2, 142.1, and 121.7 events of TBI and age adjusted, respectively).[46] Computed tomography (CT scan) is the main

modality used to evaluate the severity of injury.[42] Severe TBI carries a 30% mortality risk, and roughly half of the patients with moderate or severe TBI regain their independence.[27,36] Based on the severity of the insult, different surgical and medical treatments may be needed to diminish the burden of the damage to the brain.[36] There have been numerous reports of medical interventions to accelerate the prognostic improvement of patients, including corticosteroids, erythropoietin, and magnesium.[3,40,41] Recently, Vitamins C and E have been administered in patients with TBI to investigate the clinical outcomes of patients.[37] Ascorbic acid (AA) plays a crucial role in reducing oxidative stress besides being a cofactor in many reactions, and its concentration is 80 times higher in brain cells compared to the plasma fluid. This indicates the importance of AA for maintaining the function of the central nervous system.[18,21,25,38] Vitamin E is a fat-soluble agent and a part of the tocopherols and tocotrienols families which are shown to have significant antioxidative effects, inhibitory effects on lipoprotein oxidation, and anti-inflammatory and platelet anti-aggregation features.[2,8,24] Furthermore, evidence shows the neuroprotective effect of this vitamin and its role in nervous system development in addition to the aforementioned effects.[10,19] Given the scarcity of evidence on the effect of Vitamins C and E on the outcomes of patients with TBI and the remarkable primary outcomes of the present studies,[25,37] we aimed to examine the above-mentioned outcomes of severe TBI patients following administration of combined Vitamins C and E in a large-scale cohort.

MATERIALS AND METHODS

This study was a retrospective cohort and was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[47] We collected records of all patients admitted to the emergency room of the tertiary trauma center, affiliated with Shiraz University of Medical Sciences, who suffered a TBI between 2017 and 2021, and followed until the time of discharge from the hospital. The patients with early death, within 2 days after surgery, were excluded from this study. Then, based on the Abbreviated Injury Scale (AIS)-head, we isolated severe TBI patients from others.[16] Severe TBI was defined as AIS-head more than and equal to 3 without AIS more than 3 in other regions. As there was no unique protocol for the prescription of these two vitamins, based on the clinical judgment of physicians, some patients received these supplements and others did not. Furthermore, for some periods of time, the medication shortage was considerable. These issues divided the patients into treated and untreated groups. Propensity score matching (PSM) was performed on the entire cohort to include a sample of matched patients from both treated and untreated patients. Baseline characteristics (including demographic features, Glasgow Coma Scale (GCS), pupil status, Rotterdam classification, blood sugar and systolic blood pressure on arrival, international normalized ratio, and comorbidities) along with measures such as duration of hospital and intensive care unit (ICU) stay and Glasgow Outcome Scale-Extended (GOS-E) and prescription of combined Vitamins C and E extracted from documents. The exposure was receiving Vitamins C and E, and the outcomes were follow-up GOS-E on follow-up, mortality, and ICU length of stay in patients who survived.

We considered the follow-up time for the GOS-E score to be 6 months after discharge from the hospital. Given the availability of these drugs in our hospital and the expert opinion of attending physicians regarding the patients' conditions, Vitamins C and E were prescribed. The prescribed dosage of Vitamins C and E in the ICU setting was 3 days of intravenous administration of both vitamin C (500 mg) and vitamin E (100 units) started within 5 days after TBI.

Statistical analysis

We performed PSM using a logistic regression model to balance the potential confounders, including the admission age, GCS on arrival (motor part), pupil condition, Rotterdam CT classification, blood sugar, systolic blood pressure, international normalized ratio, and preexisting comorbidities condition (i.e., diabetes, hypertension, and other cardiovascular diseases), between treated and untreated patients. We assessed PS matching (one to many matching) between treated and untreated patients using a caliper of 0.05, meaning that the PS could have varied by 5% for the two members of a matched set.[5,14] Furthermore, we used the standardized mean difference (SMD) to evaluate the adequacy of no major imbalance for the measured potential confounders; an SMD of 10% or less, as a general rule, has been indicated as a sufficient balance on the confounders.[20,26]

After PS matching, we estimated the average treatment effect (ATE) using the risk difference (RD) for the outcome of interest, and the 95% confidence intervals (CIs) were derived using robust standard error.

Ethics

The ethics committee of Shiraz University of Medical Sciences approved this study to be conducted with registry number IR sums.med.rec.1400.600.

RESULTS

Among the total of 1321 patients included in the study, we identified 269 (20.36%) patients treated with Vitamins C and E. The baseline characteristics of patients treated and untreated with Vitamins C and E are presented in Table 1.

Table 1: Baseline characteristics of patients treated and untreated with Vitamins C and E.

Characteristic	Entire cohort	Entire cohort	
		Untreated, *n* (%)	Treated, *n* (%)
Total, *n* (%)	1321	1052 (79.64)	269 (20.36)
Demographic			
Age, median (IQR)	32 (23–50)	31 (23–50)	34 (24–50)
Gender, *n* (%)			
Male	1132 (85.76)	902 (85.82)	230 (85.50)
Female	188 (14.24)	149 (14.18)	39 (14.50)
Clinical			
GCS on arrival (motor part), mean (SD)	3.79 (1.49)	3.75 (1.50)	3.96 (1.45)
Pupil condition, *n* (%)			
Anisocoria	98 (7.71)	75 (7.37)	23 (9.06)
Brisk	806 (63.41)	647 (63.62)	159 (62.60)
Fixed	287 (22.58)	233 (22.91)	54 (21.26)
Not checked	80 (6.29)	62 (6.10)	18 (7.09)
RCTC, mean (SD)	2.71 (1.12)	2.65 (1.08)	2.95 (1.26)
First BS, median (IQR)	159 (131–156)	157 (128–196)	162 (138–195)
SBP, mean (SD)	129.33 (24.96)	129.04 (25.37)	130.43 (23.35)
INR (INR), mean (SD)	1.34 (0.67)	1.35 (0.68)	1.31 (0.61)
Comorbidities			
Hypertension, *n* (%)	81 (6.13)	61 (5.80)	20 (7.43)
Diabetics, *n* (%)	69 (5.22)	55 (5.23)	14 (5.20)
Cardiovascular accident/cardiovascular disease, *******n* (%)	24 (1.82)	17 (1.62)	7 (2.60)
ICU length of stay, median (IQR)	12 (6–20)	12 (6.20)	12 (7–21)
Hospital length of stay, median (IQR)	18 (10–31)	18 (10–31)	18 (9–33)
GOS-E on flow-up, mean (SD)	4.92 (3.01)	4.90 (3.04)	5 (2.90)
Mortality	316 (25.61)	260 (25.56)	56 (21.96)

GCS: Glasgow Coma Scale, RCTC: Rotterdam computed tomography classification, BS: Blood sugar, SPB: Systolic blood pressure, INR: International normalized ratio, ICU: Intensive care unit, GOS-E: Glasgow Outcome Scale-Extended, IQR: Interquartile range. *BS has been measured in mg/dl and SBP in mmHg. **Other cardiovascular diseases excluding hypertension such as heart failure and ischemic heart disease

The median (interquartile range [IQR]) age of the patients untreated and treated with C and E at the entry into the study was 31 (IQR: 23–50) and 34 years (IQR: 24–50). Patients who were untreated with Vitamins C and E were more likely to be dead, with a lower rate of cardiovascular diseases (except hypertension such as heart failure and ischemic heart disease) and hypertension, but they had a higher international normalized ratio score [Table 1].

Figure 1 shows the distribution of the estimated propensity score in the patients untreated and treated with Vitamins C and E. Those who were treated with Vitamins C and E had, on average, a greater estimated probability of receiving Vitamins C and E (0.18) than those who did not receive them (0.21). After matching, SMD indicates no major imbalance on confounders in the propensity-matched cohort (Table 2; SMD all ≤0.1, a sufficient balance on the confounders).

Based on ATE estimates, the use of Vitamins C and E reduced the risk of mortality (RD: −0.07; 95% CI: −0.14–−0.003) and reduced the ICU length of stay (RD: −1.77; 95% CI: −3.71–0.16). Furthermore, our results showed that GOS-E was improved significantly (RD: 0.09, 95% CI : 0.03-0.16).

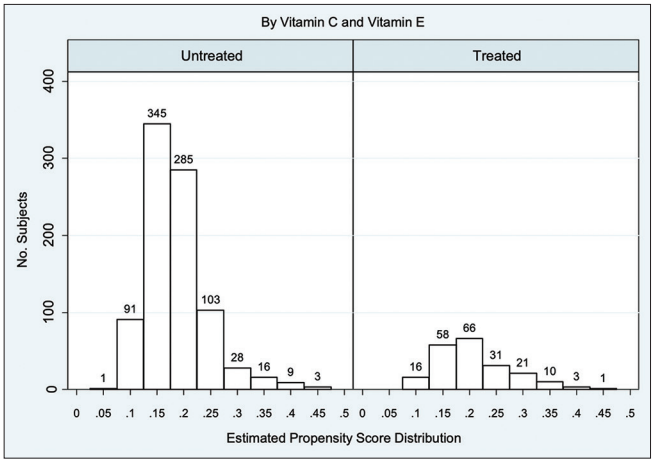

Figure 1: Distribution of the estimated propensity score in patients untreated and treated with Vitamins C and E.

DISCUSSION

To the best of our knowledge, this is the first study with a large number of patients and PSM that investigates the effect of Vitamins C and E on clinical outcomes of TBI patients.

Table 2: Standardized mean difference for the confounders in matched data.

Confounders	Standardized mean differences		
	F-GOS-E	Mortality	ICU length of stay
Age	0.07	0.09	0.05
GCS on arrival (motor part)	0.03	0.07	0.08
Pupil	0.08	0.01	0.10
RCTC	0.02	0.08	0.06
First BS	0.07	0.01	0.001
SBP	0.05	0.04	0.07
INR	0.01	0.07	0.07
Hypertension	0.06	0.06	0.04
Diabetes	0.06	0.07	0
Cardiovascular accident/ cardiovascular disease*	0.03	0.07	0.009

GCS: Glasgow Coma Scale, RCTC: Rotterdam computed tomography classification, BS: Blood sugar, SPB: Systolic blood pressure, INR: International normalized ratio, ICU: Intensive care unit, F-GOS-E: Follow-up-Glasgow Outcome Scale-Extended. *Other cardiovascular diseases excluding hypertension such as heart failure and ischemic heart disease

Our results showed that Vitamins C and E could remarkably reduce the risk of mortality and ICU length of stay and help improve the GOS-E score of patients as a clinical outcome index.

Corticosteroid Randomization after Significant Head Injury and the International Mission for Prognosis and Analysis of Clinical Trials in TBI are two models that were developed in 2008 for the prediction of TBI patients' prognosis.[32,44] These models suggested the country, age, GCS, the status of pupils, extracranial injury, CT findings, hypoxia, hypotension, Marshall CT grade, glucose, and hemoglobin concentration as prognostic factors. Among the mentioned prognostic factors, GCS on admission is regarded as the most important one, in a way that patients with GCS <8 have a 30% risk of mortality.

By taking these factors into account, as we wanted to divide the patients into cases and controls, we considered the above-mentioned baseline characteristic as a cofounder of our study and performed a PSM to eliminate systematic differences. Originally introduced by Rosenbaum and Rubin in 1983, PSM is a technique for ensuring that in observational studies, the distributions of baseline covariates are approximately the same for both treatment and control groups. Based on the similar characteristics of these two groups, a setting that mimics randomized clinical trials is simulated.[4]

Preclinical studies on animal models demonstrated that Vitamin C could decrease the mortality rate in rats with hypoxic brain damage and vasospasm following subarachnoid hemorrhage. Three out of four studies that evaluated the effect of Vitamin C on TBI in rats[25] concluded that AA could significantly improve the functions of rats;[29,30,48] another study showed that survival of rats was increased after a supplementary dose of Vitamin C.[23] Furthermore, Lin *et al*. observed that disruption of the blood–brain barrier (BBB) was decreased following the administration of Vitamin C.[29]

The only clinical study was carried out by Razmkon *et al*. During this double-blinded controlled trial, they administrated low (500 mg/day for 7 days intravenously) and high (10 g/day for the 1st and 4th days and 4 g/day for other 3 days) doses of Vitamin C. Patients with a head injury, GCS under 8, and radiology imaging in favor of diffuse axonal injury were included and significant renal or liver failure, glucose-6-phosphate dehydrogenase deficiency (G6PDD), and previous central nervous system lesions were the exclusion criteria. Duration of hospital stay (29.7% vs. 26.9% and 30.4% in low dose and high dose of Vitamin C, respectively) and mortality rate (29.7% vs. 34.6% and 30.4% in low dose and high dose of Vitamin C, respectively) were not significantly different between the control group and the patients who were administrated Vitamin C. Interestingly, perilesional edema was stable or reduced in 68% of patients receiving a high dose of Vitamin C.[37] These results were in contrast with ours in that we observed decreased mortality of patients receiving combined Vitamins E and C and significantly shorter hospital stay in the treatment group.

There was some difference, regardless of design, between our study and Razmkon's study that is worth mentioning. To begin with, our study had a sample size 13-fold greater than this study. Second, although this study included a control group of patients, the controls were not matched to the treatment arm in terms of confounding factors. Third, the severe patients have been defined by Razmkon *et al*. as patients with a GCS score of less than 8 while our study considered patients with AIS-head more than and equal to 3 without AIS more than 3 in other regions. Last but not least, there was a difference in vitamin dosage. The dose of Vitamins C and E in our study was similar to the low dose of Vitamin C and Vitamin E in the Razmkon *et al*. study, but they prescribed these two drugs separately for 7 days, and we administered them simultaneously for 3 days.

The role of Vitamin E has been described as a booster of cognitive disturbance improvement following TBI.[11,13] Animal studies showed promising outcomes following the administration of Vitamin E. In a study on pigs, Vitamin E led to attenuation of brain tissue damage.[22] Studies on rats revealed more interesting outcomes. Vitamin E improved the survival and neurocognitive and motor functions and decreased brain edema, inflammation, necrosis, and histological damage following induction of TBI.[2,9,49] The study carried out by Razmkon *et al*. was the only clinical

study that administrated 400 IU/day for 7 days in previously discussed patients. Their results revealed a lower mortality rate (16.7% vs. 29.7%) and significantly better GOS score at discharge time compared to the control group.[37] These outcomes were congruent with what we observed ($P = 0.04$). As our center is the focal referral point of TBI in the south of Iran, we have included a large scale of patients with diverse baseline characteristics. This diversity would be helpful in the generalization of the results of this study.

Mechanism and rationale for administration of Vitamins C and E

In traumatic brain injuries and the following secondary insults, oxidative stress and release of free radicals are significantly increased.[28] In such situations, the antioxidative nature of AA and Vitamin E encounters the cascades. The proof for this has been illustrated in Polidori *et al*. and Brau *et al*.'s studies. These two studies showed that after the brain insult, the concentration of AA decreased in both plasma and cerebrospinal fluid.[7,35] Furthermore, after trauma, the integrity of the BBB will be disturbed, leading to the migration of the leukocytes, the release of cytotoxic agents, free radicals, and the expansion of the inflammation to intact areas. Thus, it is important to maintain the integrity of BBB.[43] Vitamin C has been proven to stabilize the integrity of BBB in TBI.[28] Vitamin E is a critical cell membrane unit that acts as an antioxidative agent and peroxidative of lipids. Vitamin C restores the function of oxidized Vitamin E;[12,33,45] this justifies the administration of Vitamin C and coadministration of Vitamin E.

Costs and adverse effects

To speak economically, it has been reported that supplementary administration of AA during pregnancy will cost about 20$, and monthly administration of Vitamin E costs 5$.[39,50] Although the route of administration in our study differed from these two reported studies, it reflects how low the costs are. The most serious adverse effects of Vitamin C are nausea, vomiting, headache, and flushing and it is contraindicated in G6PDD, thalassemia, and hemochromatosis.[1] Except for allergy, no contraindication was reported for Vitamin E, and nausea, vomiting, gastrointestinal upset, increase in serum creatinine, and inhibition of platelet aggregation are the common side effect.[31] Overall, both these vitamins are safe and inexpensive.

Limitation

Our study was limited by the unavailability of these two vitamins in our center. The retrospective nature of our study and being conducted in a single center are the other limitations. Since we estimated the effect of Vitamins C and E from an observational study, instead of a well-defined randomized clinical trial, some unknown confounders might have also distorted our results.

CONCLUSION

Our study suggests that administering Vitamins C and E may decrease the mortality and length of ICU stay and improve the GOS-E score and functions of the patients with severe TBI. This study suggests that these two vitamins may have neuroprotective effects. Besides the fact that they are safe and inexpensive, they can be used in routine practice to decrease the burden of TBI on the patients. For consolidation of our results, further randomized clinical trials with different doses and both separate and combined administration of Vitamins C and E are needed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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