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Research Article

EFFICACY OF ASCORBIC ACID (VITAMIN C), METHYL COBOLAMINE AND TOCOPHEROL (VITAMIN E) IN SEVERE TRAUMATIC BRAIN INJURY: A RANDOMIZED DOUBLE BLIND CONTROLLED TRIAL

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ABSTRACT
Traumatic brain injuries are now more commonly occurring traffic incidents. Early intensive care with vitamin supplementation reduces morbidity & mortality and improve long term outcome.

Keywords: *Traumatic Brain Injury, Ascorbic Acid, Tocopheral, Methylcobalamine, Perileisonaledema, Glascow Outcome Score*

Introduction

Traumatic Brain injuries (TBI) contribute significant morbidity and mortality in young adults and adults, males being more commoner than females. Traumatic brain injuries occur as a result of falls, vehicle accidents, violence. In addition to primary injury that occur at the moment of impact, secondary injuries follow due to variety of events like disturbances in the cerebral blood flow, alterations in the intra cranial pressure, which occur within minutes to days following primary injury.

Free radicals, the highly reactive molecules, are generated predominantly during cellular respiration and normal metabolism. Increased production of free radicals and reactive oxygen species, which cause oxidative stress, seem to play significant role in the pathogenesis of Traumatic Brain Injury. Free radicals can cause damage to major cellular components like lipids, proteins & nucleic acids, leading to subsequent cell death by modes of necrosis or apoptosis.

Therefore, treatment with antioxidants may theoretically act to prevent propagation of tissue damage and to improve both survival and neurological outcome. Though several such agents of varying chemical structures have been under trial as therapeutic agents for TBI, and despite the volume of research, no satisfactory antioxidant has been found to halt the progression of initial brain injury to secondary brain injury. Neuro protective agents, so far tried, to halt or mitigate the secondary brain injury largely have met with failures.

The main bodily defence system against lipid peroxidaitation includes compounds such as vitamin C, vitamin E, glutathione and methyl cobolamine which work fairly effectively in the absence of a major oxidative stress. Numerous studies have shown that vitamin C, E, glutathione are rapidly consumed during the early minutes and hours after Traumatic brain injury. This fact has directed the antioxidant therapeutic research towards developing newer drugs, other than these compounds with antioxidant properties. Rapid consumption of these agents, has led to the administration of higher doses of these compounds to patients with TBI.

Ascorbic acid (vitamin C) seems to be significantly important in limiting oxidative lipid damage in biological systems. A large number of studies have demonstrated that under many different types of oxidising conditions, Ascorbic acid forms the first line of anti-oxidant defence and by significantly donating electrons for important enzymes, ascorbic acid protects the lipids in plasma and lipo proteins against detectable peroxidase damage even in the presence of free redox active iron (Polidori *et al.*, 2001; Huang *et al.*, 2001).

Ascorbic Acid plays significant role in the transport of fatty acids into mitochondria for ATP generation, the mitochondrial energy being the foundation for all human energy. Vitamin C has been consistently

observed to play significant roles in the development of blood vessels, production of norepinephrine from dopamine and in modulation of tyrosin metabolism.

As many studies have shown early depletion of Ascorbic acid in brain injuries, vitamin C supplementation at the earliest in brain injury may prove promising. In a study by Huang *et al.,* (2001), on an experimental stroke, a blood-brain barrier transportable form of vitamin C i.e. dehydroxy ascorbic acid caused dose dependent increase in post tr.perfusion cerebral blood flow, reduced the infarct volume, neurological deficit and mortality.

Gey *et al.,* (1993), Keli *et al.,* (1996), Deviglus *et al.,* (1997) showed increased vitamin C intake resulted in decreased risk of stroke. In normal persons, the daily recommended dietary allowance is 90mg/day in males and 75 mg/day in females. Tolerable upper limit for both sexes is 2000mg/day. Common side effects are indigestion, diarrhoea, fatigue, headache, disturbed sleep, kidney stone formation (oxalate deposits). Lethal dose is approximately 0.84kg in a 70kg man. Up to 300,000mg/day have been administrated without side effects.

Vitamin E has shown promising effects by modifying oxidative stress pathways and improving neurological outcome in many animal studies (Choi *et al.,* 2015; Inci, 1998). Vitamin E caused neuroprotective effect by decreasing the rate of lipid peroxidation in animal head injury models (Moor *et al.,* 2006). Methyl cobalamine (vitamin B12 analog) has also shown promising results, modifying oxidative stress pathways and improving neurological outcome in many animal models. In some animal studies, methyl cobolamine caused neuroprotective effect by decreasing the rate of solubilisation and collapsibility of neurons and myelin sheaths. Methyl cobolamine is shown to counter the lowering of the plasma & cerebral levels of lysophosphotidicacid, a multifunctional phospholipid messenger, which has a growth factor like function.

Methylcobolamine is shown to offer protection against glutamate-aspartate induced neurotoxicity in acute brain injuries. Though experimental animal studies effectively prove the effects of some of the antioxidants, no controlled, randomized clinical trials have ever evaluated the effectiveness of such available anti oxidants as vitamin C, vitamin E, methyl cobalamine on the outcome of brain injury.

In this study, we attempted to evaluate the effect of these compounds on mortality, patient outcome and evaluation of perileisonal edema in severe Traumatic Brain Injury Patients.

MATERIALS AND METHODS

Methods

The study protocol was approved by head of the institution & his committee. All adult patients at (or) above 16 with severe Traumatic Brain Injuries with Glasgow coma scale of 8 (or) less with radiologic diagnosis of diffuse axonal injury were evaluated for randomization. These patients were admitted within 24 hrs after trauma. Patients with intracranial hematomas requiring surgery, those with stroke requiring resuscitation were also excluded. All patients were randomized into 5 groups & each received the following protocols. Group A = High dose vitamin C 10gm/Iv on first day and repeated third and sixth day, followed by vitamin C 2 gm Iv /day for remaining 24 days. Group B = vitamin E 800Iu/day/Po (Rylestube injection forms not available) for 30 days. Group C = Inj. Methylcobolamine 1500 mcg/Iv/day for 30 days. Group D = vitamin C 1gm/iv/day+ vitamin E 800 iu/ po +methyl cobolamine 1500mcg/iv/day for 30 days. To ensure a double blind protocol, the drugs were administrated in packages. All patients were admitted in the neurotrauma critical care unit, and were managed on the basis of Intracranial pressure–targeted strategy. Gloscow coma scale score was recorded every three hours. Brain CT was performed on admission, on 3 rd and 7th and 10th days of admission. All CT findings i.e. presence and location of hematomas, appearance of basal cistern, if any midline shift, diameter of intracerebral hematoma and contusion, specifically the diameter of perileisonal hypodense area were recorded. In case of multiple lesions or contusions, the larger one located supratentorially were taken into account. Glascow outcome scale scores were measured at the time of discharge & follow-ups at two months and six months after discharge. All data's were statistically analysed by Mr. Subramani, Post Graduate in statistics, any value of $P < 0.05$ was considered to be significant.

RESULTS AND DISCUSSION

Results

Of the 200 patients assessed for eligibility, 127 patients (63.5 %) including 97 male and 30 female patients were randomized. Ninety percent attended the follow up sessions at 2nd & 6th month. Mean age of the patient was 32.6 years (SD = 8.9 years). The study group turned out to be highly comparable with respect to base line characteristics such as age, sex, glascow coma scale score on presentation (range 4 – 8) ; Diffuse Axonal injury (Marshal Grading range 1- 4) and brain CT findings (table 1). Mean Length of hospitalization was 30.4 days (SD 4.3 days). The length of hospitalization was more in placebo groups than the other groups, Thirty patients died during hospital course, which increased to 34 & 36 after 2 and 6 months, respectively. The vitamin E group and Group D (combined vitamins) showed significantly lower rate of mortality than the control and other groups (Table 2) (P = 0.04). The effect of drug administration on halting (or) retarding the progression of perileisonaledema (hypondense region in CT Brain) was most pronounced in high dose vitamin C group & combined vitamin groups. Vitamin C stabilized or reduced the diameter of perileisonal hypodense area in the subsequent days in 70% of the patients. In combined vitamins group, reduction of the perileisonaledema was seen in 72% of the patients. No other significant trend could be observed from serial CT scans, such as size of hematoms, appearance of basal cisterns, and midline shifts. No adverse effects related to the vitamins administration and dosing were noted.

Discussion

Several agents of widely varying chemical structures have been studied in animal models in Traumatic Brain Injuries, for reduction of oxidative stress. Animal studies consistently prove the beneficial effects of vitamin C and vitamin E as antioxidents in Brain Injury. However, no randomized controlled trials have evaluated these 2 compounds in the setting of Traumatic Brain Injury. Natural body defence mechanisms (gutathione, vitamin C, vitamin E & mecobalamine) act effectively while there is no major stress, but in systemic stresses, their level significantly go down & hence, their anti oxidant role decrease significantly. Hence, supplementation of the vitamins at the earliest becomes indispensable. Two other studies have shown that injured brain was not able to elevate the levels of vitamin c upon setting up of oxidative stress. Now, it has become a routine practice to supplement vitamins at the earliest of traumatic brain injury.

High dose vitamins C & vitamins E & Combined Vitamins in supplementation have shown to decrease the perileisonaledema. This suggests that dosage supplementation of vitamins in severe brain injuries far outweighs the routine dosing in otherwise healthy subjects. The unfavourable outcome at discharge (mortality 33.3%) inspite of high dosage of vitamin c might be due to statistical bias, due to inadequate numbers in each group. Some reports have shown the efficacy of vitamin E in exerting neuro protective effect by decreasing the rate of lipid peroxidation (Wu *et al.*, 2010; Moor *et al.*, 2006) vitamin E showed beneficial effect in reducing mortality rate & improved outcome on discharge in our study. Closer examination of mortality data shows significant impact by all vitamins combined at discharge & follow up. There was significant difference in mortality between all vitamins group & placebo. It is reasonable to report that beneficial effects of vitamin E & the combination of vitamin C, E, mecobalamine are prominent at discharge & follow ups. And further inferences & deduction about follow up mortality and morbidity have to be done on larger population of patients. Through the vitamin E & combined vitamins significantly reduced the mortality especially at discharge, the number of vegetative patients were higher (GOS score 2) when compared with placebo where they could have died & hence mortality is more with placebo. We admit that we have chosen a rather crude method and inexact index of secondary oxidative insults in the brain. The perilesional hypodense area may be affected by oxygenation, vascular insufficiency and many other uncontrollable factors. The absence of sophisticated monitoring techniques in our centre best explains why we have chosen such a rather simple index. From the result of the present study & considering the relative safety of the tested compounds we recommend the administration of vitamin E, high dose vitamin C, multivitamins combined and mecobalamine in routine critical care of the head injured patients which will probably cause modification in pathogenesis and improvement in the outcome of the disease.

Table 1

Treatment P Value	Group A High Dose Vitamin C	Group B Vitamin E	Group C Methyl Cobalamine	Groups Group D Vitamin C+Vitamin E+Mecobalamine	Placebo	Total	P Value
1.Number	24	25	26	25	27	12.7	
2.Age (Y:mean Range)	32.1(16-68)	29.5(20-74)	36.9(16-75)	29.6(16-70)	29.4(17-67)	31.5(16-81)	0.2
3.Sex (Male/Female)	20/4	20/5	20/6	21/4	22/5	103/24	0.25
4.Admission GCS Score (Mean Range)	6.4(3-8)	6.3(3-8)	5.9(3-8)	6.4(3-8)	6.1(3-8)	6.22(3-8)	0.16
5.DAI Grading (Mean Range)	3.25(1-4)	3.02(1-4)	3.26(1-4)	2.68(1-4)	3.04(1-4)	3.05(1-4)	0.17
6.Peruilaisonal Xsema	4.18±2.20	5.20±1.70	4.20±1.78	4.16±1.26	4.32±1.9	4.41±1.74	0.26

Table 2: Mortality at Different Time Points

Treatment Groups	Group A High Dose Vitamin C	Group B Vitamin E	Group C Methyl Cobalamine	Group D Vitamin C+Vitamin E+ Methyl Cobalamine	Placebo	Total
Hospital Mortality	7 (29.2%)	4 (16.0%)	5 (19.2%)	4 (16.0%)	10 (37.03%)	30
Mortality after 2 Months	8 (33.3%)	5 (20.0%)	6 (23.1%)	4 (16.0%)	11 (40.8%)	34
Mortality after 6 Months	8 (33.3%)	6 (24.0%)	7 (26.9%)	5 (20.0%)	11 (40.8%)	37

We observed significant stabilization of perileisionaledema in severely head injured patients receiving high dose vitamin C & in patients with "vitamins combined" administration. Our data also showed a reduction of hospital mortality (at the expense of more patients turning to be vegetative) and an improvement in long term outcome for patients receiving vitamin E & "Vitamins E, C, mecobalamine combined together".

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