

Research Paper

Neuroprotective Effects of Vitamin D on Patients With Traumatic Brain Injury: A Clinical Trial



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Citation Shafiei S, Sardar Zaheriani M, Sahfizad M, Ehteshami S, Mosazadeh M, Haddadi K. Neuroprotective Effects of Vitamin D on Patients With Traumatic Brain Injury: A Clinical Trial. *Iran J Neurosurg.* 2022; 8:E4. <http://dx.doi.org/10.32598/irjns.8.4>

doi <http://dx.doi.org/10.32598/irjns.8.4>



Article info:

Received: 10 Feb 2022

Accepted: 23 May 2022

Available Online: 07 Jun 2022

Keywords:

Traumatic Brain Injury,
Vitamin D, GCS

ABSTRACT

Background and Aim: Traumatic brain injury (TBI) is a globally-critical socioeconomic and public health problem. Introducing medications and strategies to treat and improve the prognosis of TBI is crucial. Current literature not only supports the key role of vitamin D on normal brain function, but also helps recovering from a myriad of pathologies. The present research was conducted to evaluate the neuroprotective effects of vitamin D on patients with TBI presenting to Imam Khomeini Hospital, Sari, Iran.

Methods and Materials/Patients: This randomized clinical trial assigned patients with vitamin D levels of over 30 ng/ml to an intervention group (n=42) and a control group (n=42), who respectively received a single dose (150,000 units) of vitamin D and a placebo upon admission. The Glasgow Coma Score (GCS) and mortality were recorded at the beginning of the study and three months after the final prescription.

Results: The mean GCS score upon admission was obtained as 8.64±2.29 in the vitamin D group and 8.42±2.93 in the placebo group. This score was respectively obtained as 13.50±1.85 and 10.97±2.37 upon discharge, suggesting a significant difference as per the t-test (P=0.04). The mean Glasgow Outcome Score (GOS) upon discharge was obtained as 4.24±1.51 in the intervention group and 4.10±1.40 in the controls. The t-test suggested insignificant differences in the GOS between the two groups upon admission (P=0.823). After three months, the GOS respectively reaching desirable levels in 49.7% and 62.8% of cases in the placebo and intervention groups revealed statistically significant differences among the two groups (P=0.03).

Conclusion: The present results showed the improving effects of vitamin D on level of consciousness and outcomes in patients with acute TBI. More studies are suggested to be performed to investigate the effects of other medications, including amantadine and methylphenidate with a larger sample size.

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Highlights

- Given the profound biochemical effects of vitamin D on numerous pathways, this vitamin appeared useful in the acute phase of severe TBI.
- The present findings demonstrated the improving effect of vitamin D on level of consciousness in patients with acute TBI.
- Further studies with larger samples are required for clarifying the effects of other medications such as methylphenidate and amantadine.

Plain Language Summary

Given TBI as a potentially disastrous event with devastating socio-familial consequences, the present and previous research suggested the use of vitamin D and other neuroprotective medicines in patients with diffuse axonal injury and altered consciousness. Given the profound biochemical effects of vitamin D on numerous pathways, this vitamin appeared useful in the acute phase of severe TBI.

1. Introduction

A

s the leading cause of mortality and morbidity at the age of 18-45 years, traumatic brain injury (TBI) occurs as a result of brain dysfunction caused by penetrating head injuries or a blow or bump to the head [1, 2].

Major TBI-induced disabilities may impose a huge socioeconomic burden on the patients and their families. In the US, TBI-associated medical expenses were estimated at \$9.2 billion and lost productivity at \$51 billion in 2000 [3, 4].

The maximum incidence of TBI was reported in three age groups of at most 4, 15-24 and over 65 years. Falls and motor vehicle accidents constitute the two leading causes of TBI. The increased number of TBIs coupled with the decreased mortality due to TBI have grown the population of patients living with significant disabilities [4, 5].

Pathophysiology of brain inflammation in TBI

The multifaceted array of immunological/inflammatory tissue reactions induced by TBI resembles that in ischemic reperfusion injury. Both primary and secondary insults activate the release of cellular mediators, including prostaglandins, pro-inflammatory cytokines, free radicals and complements, induce adhesion molecules and chemokines and mobilize glial and immune cells in a synergistic parallel manner [6, 7].

These inflammatory processes eliminate injured and adjacent tissues based on spreading depression and

cause astrocytosis to produce neutropines and microfilaments and synthesize scar tissues. Pro-inflammatory enzymes, including tumor necrosis factor, interleukin-1 β and interleukin-6, are upregulated within hours of the injury. The development of tissue destruction directly relates to the neurotoxic mediators release and indirectly to the cytokines and nitric oxide release. Further release of vasoconstrictors such as leukotrienes and prostaglandins, obliteration of microvasculature through adhesion of leucocytes and platelets, the blood-brain barrier lesions and edema reduce tissue perfusion and aggravate secondary brain damage [8-12].

Recovery from TBI markedly varies among the patients. Neuroendocrine dysfunction caused by TBI can lead to persistent symptoms such as hypopituitarism reported in 5-20% of patients and growth hormone deficiency [5]. As an effective hormonal factor in recovery from TBI, the fat-soluble seco-steroid vitamin D is predominantly synthesized in the skin upon sun exposure and helps preserve the musculoskeletal health. Rat models of TBI exhibited that vitamin D inhibits the neuro-inflammation which impairs recovery from TBI [6, 13, 14].

Vitamin D and TBI

Given the wide distribution of vitamin D receptors and vitamin D activating enzymes such as 1-alpha-hydroxylase [15] in the brain, vitamin D affects quality of life and recovery from TBI by contributing to the improvement or exacerbation of psychiatric and cognitive problems. Moreover, 25-hydroxycholecalciferol, 25 (OH) D₃ functions as the main circulating form of vitamin D with a half-life as



long as 2-3 weeks [16, 17]. The neuroprotective properties of vitamin D have been demonstrated in the models of acquired traumatic, ischemic, degenerative, excitotoxic and autoimmune brain injuries [18]. Vitamin D contributes to the brain development by affecting cellular proliferation and differentiation, neurotrophism, neuroprotection and calcium signaling. Vitamin D also plays a role in synaptic plasticity and neurotransmission and relates to dopaminergic neurotransmission [19, 20]. The physiological effects of vitamin D on brain functions include preventing neuronal death and promoting neurotransmission, synaptogenesis, neurogenesis and amyloid clearance. Observational studies suggest positive associations between serum levels of vitamin D and cognitive performance [21, 22].

Optimal blood levels of vitamin D are essential for neurological development and protecting the brain in adults given the global pandemic of vitamin D deficiency. The present review aimed at determining relationships between vitamin D and neurological diseases [22, 23].

Serum 25 (OH) D deficiency can merely constitute an independent risk factor for 1-year poor prognosis in patients with ischemic stroke and without hyperglycemia. It is recommended that further studies be conducted to improve the long-term prognosis of ischemic stroke through vitamin D supplementation [23].

Given TBI as a globally-major socioeconomic health problem, finding medicines and adopting strategies to treat and improve the prognosis of these patients are crucial. Research suggests the protective effects of vitamin D on the brain health. The present research investigated the neuroprotective effects of vitamin D on patients with TBI and without vitamin D deficiency presenting to Imam Khomeini Hospital in Sari.

2. Methods and Materials/Patients

Protocol review

This study was approved by the local institutional ethics committee (IR.MAZUMS.IMAMHOSPITAL.REC.1398.117) and recorded in the Iranian Registry of Clinical Trials (IRCT20191026045243N2). The legal guardians of the patients signed an informed consent form before beginning the study and after briefing the participants on the experimental method and its potential risks and benefits.

Participants

The study population comprised patients with moderate-to-severe TBI due to traffic accidents (GCS<13) presenting to the emergency department of Imam Khomeini Hospital over 1.5 years. The current double-blind, randomized, placebo-controlled crossover trial was performed to assess the effect of vitamin D on acute TBI. Out of 200 patients with TBI, 84 with normal serum levels of vitamin D were assigned to Group 1 (D) (n=42) receiving a single dose of vitamin D and Group 2 (P) (n=42) receiving a placebo. (Flow Diagram)

Inclusion criteria

The inclusion criteria comprised having diffuse axonal injury diagnosed based on neurosurgery and clinical and imaging characteristics, an age of 15-75 years, GCS score of below 13 within the first 24 hours of the injury, no history of life-threatening diseases before TBI, ability to receive medication orally or through nasogastric tubes and vitamin D levels of over 30 ng/ml. Subjects with a stable medical disease were also included at the discretion of the researchers. A legal guardian of the participants signed written informed consent forms on their behalf.

Exclusion criteria

The exclusion criteria consisted of unwillingness of the legal guardians or the participants to participate in the study, receiving other investigational medicines within 30 days before the injury, severe ischemic heart disease, congestive heart failure, myocardial infarction, spinal cord injury with ongoing deficits, cancers, other severe diseases or multiple traumas with potential effects on the findings, pregnancy, renal failure, any types of penetrating head injuries, receiving chronic steroids, brain death and a history of severe TBI, brain tumors, cerebral vascular events and other stable brain insults.

Acute neurology

According to the standard neuro-trauma protocol of [Mazandaran University of Medical Sciences](#), all the patients were treated with anticonvulsant medicines upon their admission. The researchers completed questionnaires, including age, gender, mean duration of mechanical ventilation, length of ICU stay, GCS upon admission, discharge or in-hospital death status, GOS and mortality rate. The primary caregivers signed informed consent forms before the vitamin D therapy. According

to the Declaration of Helsinki, the patients were assured of the confidentiality of the information they provide.

Pharmacological agents

This randomized clinical trial assigned the patients with minimum vitamin D level of 30 ng/ml to two groups of 42. The intervention and control groups respectively received an oral single dose (150,000 units) of vitamin D and the placebo upon admission.

Outcomes measures

The primary outcome measures included GCS during the initial hospitalization, a full medical history, and a physical and neurological examination. The researchers completed a questionnaire including demographic characteristics, i.e. age and gender, mean duration of mechanical ventilation, length of ICU stay, GOS and mortality rate in the patients. In addition to a resting electrocardiography, CBC and UA, laboratory tests were performed to measure the serum levels of sodium, potassium, chloride, bicarbonate, glucose, urea nitrogen and creatinine.

The GOS defined as follows was classified as “favorable” (GOS= good recovery (normal or almost normal), moderate disability (disable but independent)) and “unfavorable” (GOS= severe psychophysical disability (dependent) post-coma unresponsiveness, death) [24].

Statistical analyses

The quantitative and qualitative variables were respectively expressed as mean±SD and frequency by percentage. Independent t-test was used for matching the GCS, GOS, mean age, duration of mechanical ventilation and length of stay among the two groups. The Fisher exact test was also used to compare the two groups in terms of the frequency of mortality and gender. The statistical analyses were performed in SPSS v.24 at a statistical significance threshold of $P < 0.05$.

3. Results

Out of 42 patients in the vitamin D group, 30 (71.4%) were male and 12 (28.6%) female. Males accounted for 78.6% ($n=33$) of the subjects in the placebo group and females 21.4% ($n=9$). The Chi-squared test showed insignificant differences in gender between the two groups ($P=0.45$). The mean age of the patients was 36.76 ± 16.12 years in the vitamin D group and 41.92 ± 16.79 in the placebo group, suggesting insignificant differences based on the t-test ($P=0.15$).

The mean GCS upon admission was respectively calculated as 8.64 ± 2.29 and 8.42 ± 2.93 in the vitamin D and placebo groups, suggesting insignificant differences between the two groups as per the t-test ($P=0.71$). The mean GCS upon discharge calculated as 13.50 ± 1.85 in the intervention group was significantly higher than 10.97 ± 2.37 in the controls as per the t-test ($P=0.04$) (Figure 1) (Table 1).

According to the t-test, the duration of mechanical ventilation estimated at 13.62 ± 13.87 days in the intervention group and 16.42 ± 12.33 days in the controls and the mean length of stay respectively obtained as 19.37 ± 13.24 and 22.67 ± 13.39 days suggested insignificant differences between the two groups (Table 2). Out of 42 patients in the intervention group, 36 (86%) were discharged and 6 (14%) died. In the other group, 39 (92.8%) were discharged and 3 (7.2%) died. The Fisher exact test showed insignificant differences between the two groups in terms of the outcome of the patients with TBI ($P=0.5$). The mean length of stay calculated as 29.89 ± 13.19 days in the discharged patients and 31.23 ± 10.43 days in the passed away patients was insignificantly different as per the t-test (Table 2).

Table 1. Comparing the mean GCS and GOS upon admission and discharge between the two groups

Variable	Mean±SD		P
	Intervention Group		
	Vitamin D	Placebo	
Length of stay	19.37 ± 13.24	22.67 ± 13.39	0.49

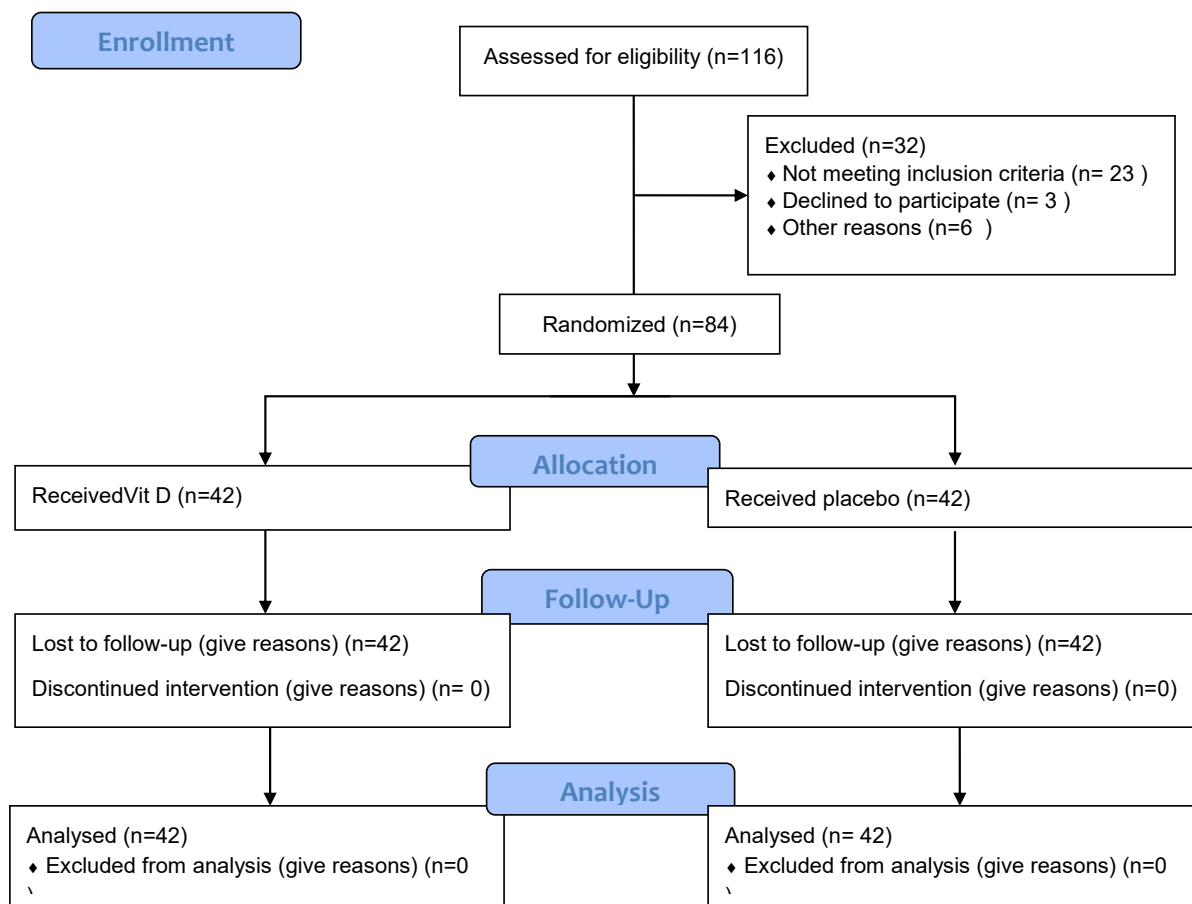


Figure 1. Comparing changes in the GCS between the two groups from admission to discharge



According to the t-test, the two groups were not significantly different in terms of their mean GOS in discharge ($P=0.823$), which was respectively obtained as 4.24 ± 1.51 and 4.10 ± 1.40 in the intervention and control groups. After three months, the GOS respectively reached desirable levels in 49.7% and 62.8% of cases in the placebo and intervention groups and showed statistically-significant differences between the two groups ($P=0.03$) (Figure 2).

4. Discussion

Long-term disabilities caused by TBI include neuropsychiatric and cognitive problems such as memory and executive dysfunction, mood and sleep disorders and lethargy. Recovery from TBI markedly varies among the patients. Neuroendocrine dysfunction caused by TBI can lead to persistent symptoms such as growth hormone deficiency and hypopituitarism, as reported in 5-20% of patients [25].

The fat-soluble seco-steroid vitamin D is an effective hormonal factor in recovery from TBI that is primarily synthesized in the skin upon sun exposure and helps maintain the musculoskeletal health. The prevalence of vitamin D deficiency is increased through decreased sun exposure and as a result of TBI-associated hospitalization, impaired social functioning and leave of absence [25,26]. As a common problem in patients with TBI, vitamin D deficiency impairs cognitive function and exacerbates depressive symptoms. Vitamin D can also function as a modifiable risk factor and precipitate recovery from TBI [26, 27].

A large body of literature suggests the role of vitamin D in the brain function of mammals; nevertheless, its role in the human brain requires further elucidation. A special receptor and enzyme with a layer-specific and regional pattern were observed in glial cells and neurons. The wide distribution of 1,25-dihydroxyvitamin D3 receptors suggests the autocrine/paracrine mechanism of vitamin D in the human brain and its operational similarity with known neuro-steroids [28].

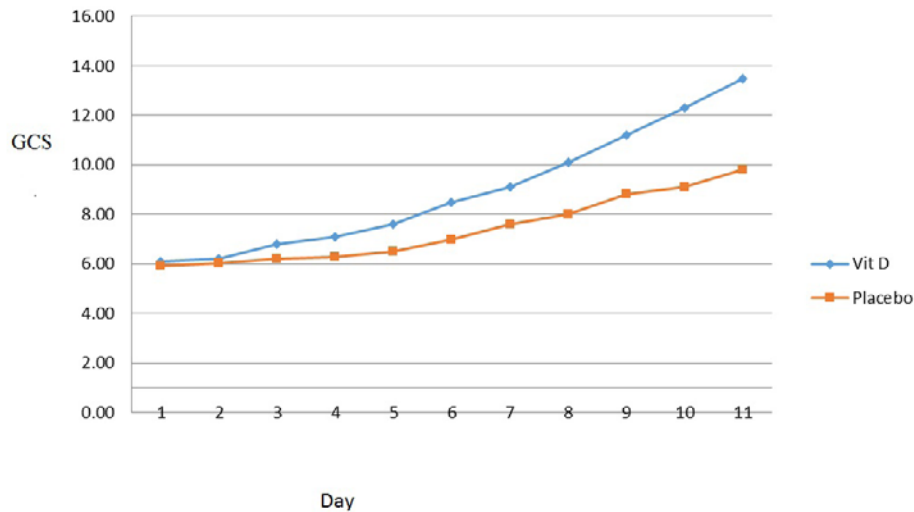


Figure 2. Comparing the GCS between the two groups from admission to discharge



The central nervous system (CNS) levels of vitamin D hormone (VDH) appeared to be a function of the active and passive transport of VDH from plasma across the blood-brain barrier [29, 30]; though, specifying 25-hydroxylase and 1 α -hydroxylase in the human brain questioned this finding and supported the local bio activation of vitamin D in the CNS [31, 32]. Although the CNS levels of VDH are not correlated with the plasma levels of VDH, they depend on the plasma concentration of vitamin D prohormones such as 25OHD after oral supplementation with vitamin D3 [33, 34].

Neuroprotective mechanism of vitamin D

The complex and multidimensional neuroprotective effects of vitamin D are exerted by reducing inflammatory responses and neuro-inflammation in TBI [35, 36],

which helps heal neuronal injuries, decrease neuronal apoptosis and improve functional outcomes [35, 37]. Vitamin D stimulates post-injury apoptosis by minimizing the influx of neuronal calcium and the released excitotoxic glutamate [36, 37]. Vitamin D reduces intracellular Ca²⁺, indiscriminate glutamate release and neurotoxicity by down regulating L-type voltage-sensitive Ca²⁺ channels and up regulating intracellular Ca²⁺ buffering (38, 39). Vitamin D elevated free radical scavenging and declines oxidative stress by raising intracellular glutathione as an antioxidant [40, 41]. It promotes axon genesis and increases axon diameter in traumatic axonal injury by improving microtubule protection and regeneration of axonal and neuronal cytoskeleton [36, 37, 42]. This vitamin upregulates neurotropic growth factors and other markers involved in the neuronal survival, development and function [37, 43].

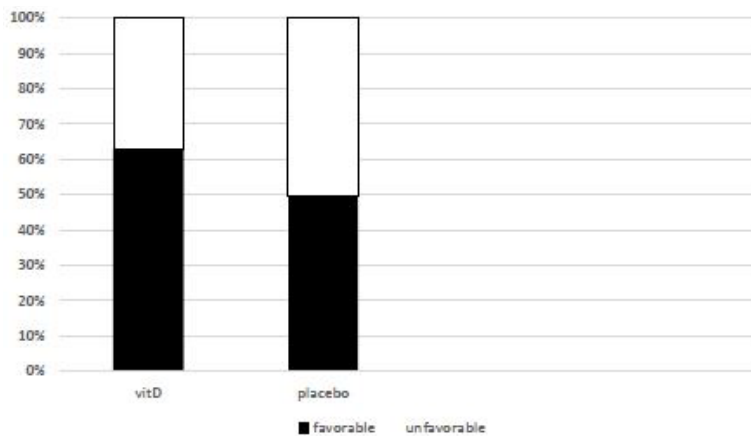


Figure 3. Comparing the dichotomized GOS between the patients receiving the placebo and those vitamin D after 3 months



Table 2. Comparing the mean length of stay between the two groups

Variables	Mean±SD		P
	Intervention Group		
	Vitamin D	Placebo	
Admission GCS	8.64±2.29	8.42±2.93	0.71
Discharge GCS	13.50±1.85	10.97±2.37	0.04
GOS	4.24±1.51	4.10±1.40	0.823



A retrospective study measuring the serum levels of vitamin D within 24 hours of hospitalization and GCS upon admission and discharge in 46 Italian patients with TBI reported vitamin D deficiency in 74% of the patients. A univariate analysis also suggested no relationships between GCS and vitamin D levels, and this study failed to demonstrate the effect of serum levels of vitamin D on neurological recovery [44].

Despite the reported role of vitamin D in predicting prognosis, supplementation with vitamin D neither significantly improved the outcomes nor affected acute clinical recovery in neuro-critical patients [45].

Amin Mansour et al. assigned patients with severe TBI (GCS≤8) to placebo, progesterone and progesterone-vitamin D groups' of 20. The Mean±SD baseline GCS calculated as 6.3±0.88 in the placebo group, 6.31±0.87 in the progesterone group and 6±0.88 in the progesterone-vitamin D group, respectively increased to 9.16±1.11, 10.25±1.34 and 11.27±2.27 three months after the intervention. The three groups were significantly different in terms of the GCS (P=0.001). GOS was categorized as desirable and undesirable recovery, and a desirable GOS was observed in 25% of cases in the placebo group, 45% in the progesterone group and 60% in the progesterone-vitamin D group, which suggested statistically-significant differences among the groups (P=0.03). These groups were ranked by recovery rate as progesterone-vitamin Progesterone and placebo [17].

Analyzing the prevalence of vitamin D deficiency and the relationships of vitamin D with quality of life and severity of TBI in 124 patients with TBI showed significantly lower levels of vitamin D in the patients with severe TBI than in those with mild TBI (n=95, P=0.03, CI=95%, -23.60 to -1.21, mean effect size=12.40 nM). The patients with optimal levels of vitamin D reported improved quality of life compared to those with vita-

min D deficiency, which helped control the severity of the damage (n=81, P=0.05, CI=95% -0.07 to 21.27). This study pioneered the investigation of relationships between severity of head injury and vitamin D levels [46].

In line with the present research, a study investigated the protective effects of D3 administered in vivo on ischemic brain injuries in adult male Sprague-Dawley rats. The animals were injected daily with D3 or saline for 4 or 8 days and received a 90-min right MCA ligation on the 4th or 8th day after their anesthesia with chloral hydrate. D3 was found to reduce the ischemia-induced brain damage through up regulating GDNF mechanisms in cortex [18].

The current study examined the effect of vitamin D on GCS in patients with TBI. The GCS upon discharge significantly increased in both groups. The mean GCS was significantly higher in the intervention group compared to in the controls.

The strength of the present research lies in its exclusion of patients with vitamin D deficiency and analysis of the effect of vitamin D on the prognosis of TBI. No significant differences were detected among the two groups in terms of length of ICU stay, duration of mechanical ventilation and mortality, Vitamin D was found to significantly increase the GCS and recovery rate in the patients. Vitamin D accelerated recovery from acute severe TBI in the patients with consciousness problems. The GCS was higher in the patients with severe brain damage treated with a standard therapy plus vitamin D than in those treated only with the standard therapy, especially three months after discharge. It is recommended that further studies be conducted to investigate the effects of vitamin D on long-term outcomes and recovery at functional levels.

The present study limitations comprised its small sample and impossibility of following up the patients after their discharge. The GOS was accurately recorded just before and three months after discharge given that some of the patients were inaccessible after their discharge. The present study therefore failed to address the effects of prolonged treatments on long-term outcomes.

The present findings demonstrated the improving effect of vitamin D on level of consciousness in patients with acute TBI; nevertheless, the interventions reported in literature focused on individual's outcomes of TBI and the obtained data are unreliable. It is advised that additional trainings with larger samples be conducted to determine the role of pathophysiological traits in response to vitamin D and other neuroprotective medications such as methylphenidate or amantadine in patients with non-traumatic brain injuries. The optimal dose, duration of treatment and administration timing as well as the effectiveness of this administration should be also determined.

5. Conclusion

Given TBI as a potentially-disastrous event with devastating socio-familial consequences, the present and previous research suggested the use of vitamin D and other neuroprotective medicines in patients with diffuse axonal injury and altered consciousness. Given the profound biochemical effects of vitamin D on numerous pathways, this vitamin appeared useful in the acute phase of severe TBI. The present results demonstrated the effect of vitamin D compared to placebo on level of consciousness and outcomes in the patients with acute TBI. Further studies with larger samples are required for clarifying the effects of other medications such as methylphenidate and amantadine.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the local institutional ethics committee (IR.MAZUMS.IMAMHOSPITAL.REC.1398.117) and recorded in the Iranian Registry of Clinical Trials (IRCT20191026045243N2). The legal guardians of the patients signed an informed consent form before beginning the study and after briefing the participants on the experimental method and its potential risks and benefits.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conception and design: Kaveh Haddadi, Sajjad Shafiei, Mohammad Sardar Zaheriani; Data Collection: Mohammad Sardar Zaheriani; Data Analysis and Interpretation: Kaveh Haddadi, Mahmoud Mosazadeh; Drafting the article: Misagh Sahfizad, Saeid Ehteshami; Critically revising the article: Kaveh Haddadi, Sajjad Shafiei; Reviewing submitted version of manuscript: Kaveh Haddadi; Approving the final version of the manuscript: Kaveh Haddadi

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

This study was conducted as a thesis in neurosurgery specialty by Dr. Mohammad Sardar Zaheriani which was financially supported by Mazandaran University of Medical Sciences in north of Iran. The study was approved in the Clinical Research Development Unit of Imam Khomeini Hospital, Mazandaran University of Medical Sciences. The authors would like to thank the volunteers who participated in this study.

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