Trauma Monthly 2022; 27(6): 616-625

10.30491/tm.2022.328724.1445

Trauma Monthly

Original Article

Neuroprotective Effects of Methylphenidate on Diffuse Axonal Injury in Acute Traumatic Brain Injury Patients

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Received 2021-09-29; **Accepted** 2022-12-03; **Online Published** 2022-12-30

Abstract

Background: This study aimed to evaluate the effect of methylphenidate on the level of consciousness and length of hospitalization of patients with moderate to severe acute Traumatic Brain Injury (TBI) categorized as diffuse axonal injury.

Methods: This randomized, double-blind clinical trial comprised 62 patients with moderate to severe traumatic brain injury with a Glasgow Coma Scale (GCS) between 5 and 12 referred to our emergency department. Methylphenidate tablets were administrated from the second day with a dose of 0.3 mg/kg up to a maximum of 20 mg daily. A placebo was administered in the same manner and the patient's level of consciousness, delirium using the Confusion Assessment Method for the intensive care unit (CAM-ICU), agitation using Richmond Agitation Sedation Scale (RASS), and predicting the outcome of patients with GOS, were assessed.

Results: The patients' GOS on the day of discharge was significantly higher in the intervention group (P=0.013). The duration of hospitalization was significantly shorter in the intervention group (P<0.001). The patients' GCS upon discharge was significantly higher in the intervention group (P=0.01).

Conclusion: Our results suggest that methylphenidate has some beneficial effects on the consciousness level and outcomes of patients with acute TBI. The use of methylphenidate also reduces the length of ICU stay and hospitalization and improves the outcome in patients with moderate to severe TBI not requiring surgery.

Keywords: Methylphenidate; Acute Traumatic Brain Injury; Diffuse Axonal Injury.

Introduction

Traumatic Brain Injury (TBI) is the leading cause of death and disability in young people [1, 2]. Despite the advances in research and improvements in neuro-intensive care in recent years, the clinical outcome of patients with severe brain injury is still poor. In the United States, TBI's direct and indirect costs are approximately $60 billion annually [3-6].

A combination of primary and secondary injuries characterizes post-traumatic brain injury. Prior damage is caused by mechanical forces applied to the skull and brain during a collision, which leads to patterns of focal or diffuse brain damage. Unlike primary injury, secondary brain damage develops over time. These damages are characterized by a complex set of molecular and biochemical events that lead to neuro inflammation, cerebral edema, and delayed neuronal death. Primary hypoxia and hypotension cause persistent cerebral ischemia and reperfusion damage and are independent predictors of adverse outcomes after TBI [7].

In the last decade, our understanding of the cellular and molecular changes that occur after TBI has increased significantly. Several potential new therapeutic targets have been identified that may prevent the onset or reduction of secondary brain damage. The Brain Trauma Foundation has recently revised the evidence-based guidelines for treating TBI patients [8].

Interestingly, most recommendations in published guidelines based on Class II or III evidence are due to the persistent need for Class I evidence-based data on treatment strategies 8. There is currently no specific drug treatment for TBI that can prevent secondary brain damage. In a study of patients with moderate to severe TBI (48 hours after injury), methylphenidate treatment significantly reduced the level of ICU care needed [9].

Methylphenidate (Ritalin) is a dopamine reuptake inhibitor tested in treating neurobehavioral disorders following TBI [10]. This drug's exact mechanism of action has yet to be fully understood. Still, its agent is assumed first: to interfere with dopamine reabsorption and second to inhibit norepinephrine transporter [11].

The clinical safety of methylphenidate has been demonstrated, and the drug is safely prescribed to patients after TBI [12, 13]. Preliminary results indicate recovery and improvement of cognitive skills after TBI. A recent review of articles in the Cochrane database found insufficient evidence to support the administration of methylphenidate or other related agents (such as amantadine) in TBI [14]. A phase III clinical trial is currently underway to evaluate the effects of methylphenidate on TBI in children.

Little information is available on using methylphenidate in the acute phase of TBI. In the present study, the therapeutic effect of methylphenidate (Ritalin) on the acute treatment of patients with moderate to severe TBI (diffuse axonal injury), except surgically treated patients, was evaluated as a clinical trial based on the available data and relying on previous studies.

Methods

Protocol review

The study was approved by the local ethics committee of the institution (CODE: IR.MAZUMS.IMAMHOSPITAL.REC.1399.037). The project was also recorded as a clinical trial with the Iranian Registry of Clinical Trials (IRCTID: IRCT20140915019185N3).

Before beginning the experiments and after briefing the participants on the study methods and potential risks and benefits of the procedure, the legally authorized representative of each patient signed an informed consent form. The patients' information as confidential, and the researchers complied with the Declaration of Helsinki.

Participants

The study population consisted of patients enrolled over a 1.5-year period who were directly admitted to the ER of Imam Hospital in Sari, Iran, with only moderate TBI and a GCS score of <13. The trial was a double-blind, randomized, placebo-controlled, crossover study conducted primarily to evaluate the safety of methylphenidate in acute TBI with the secondary goal of obtaining the drug efficacy data in these cases. Finally, out of 92 traumatic patients admitted to the ER, 62 were eligible to enter the study and were assigned to either Group 1 (n=31) to receive a single dose of methylphenidate or Group 2 (n=31) to obtain a placebo (**Chart 1**).

Inclusion criteria

all the patients had to have a diagnosis of diffuse axonal injury based on neurosurgical clinical and imaging characteristics and meet the following requirements:

15-75 years of age, GCS score 5 to 12 within the first 24 hours of injury, and not needing craniotomy surgery at any time after admission. No known life-threatening diseases before the head injury; however, subjects with a stable medical illness might have been allowed to enter the study at the researcher's discretion. The legal representative or guardian of the issue giving written informed consent on the patient's behalf, Ability to receive medications orally or by nasogastric tube.

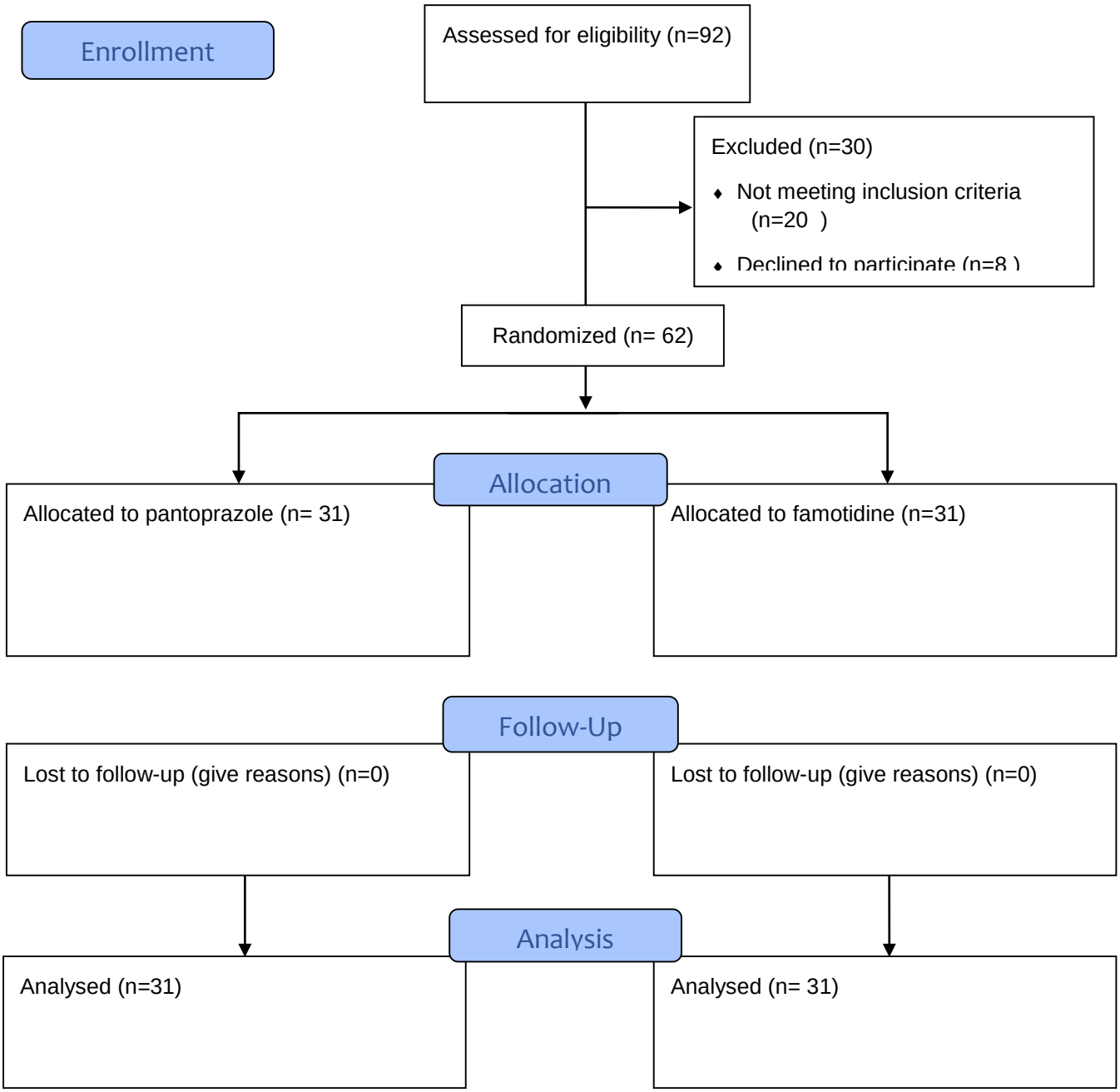

Chart 1: CONSORT 2010 Flow Diagram

Exclusion criteria

The unwillingness of the patients or their guardians or legal representatives to participate in the study; The patients received other experimental drugs within 30 days before the injury. The patients suffering from severe ischemic heart disease or congestive heart failure, myocardial infarction, chronic hypertension, cancer, or any other severe illnesses as determined by the researcher, which would affect the assessment of the therapy, Having multiple traumas (chest, abdomen, etc.) which could jeopardize the evaluation of the treatment as per the researcher's opinion, A penetrating head injury, Death in the first 72 hours after the injury, Prior significant TBI, brain tumor, cerebral vascular event, or another stable brain injury, Acute renal failure

and acute infection (temperature above 39 °C), Pregnancy, and Brain death were excluded.

Acute Neurological Management

During the initial hospital admission, all the patients were treated according to the standard neuro-trauma protocol of Mazandaran University of Medical Sciences, which included anticonvulsant drugs. All the patients were included in the study based on their emergency CT scan results and the surgeon's approval of no need for craniotomy surgery.

Pharmacological agents

Oral medications were administered from the second day of admission as soon as gastric tube feeding was started. Methylphenidate tablets (Stimdate, manufactured by Iranian Mehrdaru Company.) were issued at a dose of 0.3 mg per kg of body weight up to a maximum amount of 20 mg daily, and a placebo was administered in the same form and the same chronological order for the patients.

Outcome variables

during the initial hospital admission, all the patients were treated according to the standard neuro-trauma protocol of Mazandaran University of Medical Sciences, which included anticonvulsant drugs. The researchers filled out a form containing data on the patient's demographic characteristics (age and sex), length of ICU and hospital stay, and frequency of mortality.

GCS and delirium were measured using the Confusion Assessment Method for the ICU (CAM-ICU), and the degree of agitation was measured using the Richmond Agitation Sedation Scale (RASS) score on admission days 2 and 7 and discharge days for all the patients.

The Glasgow Outcome Scale (GOS) was also filled out at discharge and three months after discharge. The GOS criteria were defined as follows:

Five = Good recovery: Normal or near normal recovery

Four = Moderate disability: Disable but independent

Three = severe disability: Dependent with physical/psychological disabilities

Two = Persistent vegetative state

1 = Dead

These criteria were divided into two categories, including "favorable" (good recovery and moderate disability) and "unfavorable" (the other three criteria) [15].

Statistical analysis

The quantitative variables were presented as mean ±SD and the qualitative variables as numbers (percentage). The repeated-measures ANOVA was used to assess the changes in the quantitative outcomes, and Friedman's test and Cochran's Q-test were also used to determine the qualitative results. The t-test was used for the comparative analysis of the independent groups in the standard data distribution and Mann-Whitney's test in case of abnormal allotment. To study the trend of changes after controlling the effect of the other variables, the generalized estimating equation (GEE) was used. Statistical significance was set at 0.05, and all the statistical analyses were performed with IBM SPSS software, version 24.

Results

This study examined 62 people aged 17 to 75 years with a mean (standard deviation) age of 36.5 (15.73) years. The median age was 40 years in the methylphenidate group and 30 years in the placebo group (P). 74.2% of the drug-receiving group were male, 25.8% were female; 90.3% of the placebo group were male, and 9.7% were female.

Also, there was no significant difference between the two groups receiving the drug and the placebo regarding gender. Table 1 presents the subjects' general characteristics based on their drug intake and grouping. As can be observed, the differences between the two groups in terms of age and sex, BMI, GCS, and GOS at baseline were not statistically significant (P>0.05). The ratio of men in the methylphenidate and placebo groups was higher than in women, and the difference was statistically significant (P=0.04); that is, the number of men studied was much higher than women (**Table. 1**).

Table 1: General characteristics of the subjects according to the status of Receiving Methylphenidate.

	Study Group		P Value
	Methylphenidate (number = 31 people)	**Placebo (number = 31 people)**	
Age, year, mean (standard deviation)	40.08 (17.4)	33 (12.71)	0.13
Body mass index, kg / m2, mean (standard deviation)	25.2 ± 1.7	25.4 ± 2.0	0.737
Gender, male / female	8.23	3.28	0.04
GCS Study Start, Middle (First Quarter - Third Quarter)	6 (6-7)	7 (6-8.5)	0.12
GOS Start of Study, Middle (First Quarter - Third Quarter)	6 (5-7)	5 (4-6)	0.013

Implications examined

GCS

The consciousness level of subjects was assessed at the time of arrival and then again on days 2 and 7 (**Table 2** & **Figure 1**). As can be seen, the subject's level of consciousness had an increasing trend regardless of the study group, and this trend was statistically significant (i.e., there was a time effect) (P<0.001). Irrespective of the time, however, the level of consciousness was consistently higher in the methylphenidate group compared to the placebo group, although this difference was not statistically significant (i.e., there was no group effect) (P=0.37). The increasing trend was significantly more evident in the methylphenidate group than in the placebo group (i.e., there was a group-by-time interaction) (P=0.001).

After controlling for the effect of age, BMI, and sex in the GEE, we found that the difference between the two groups was not statistically significant (P=0.44; **Figure 1**).

GOS

As shown in the table above, GOS was 6 in the group receiving methylphenidate and 5 in the group receiving placebo, suggesting a significant intergroup difference (P=0.013). The patients receiving methylphenidate have higher GOS and better outcomes.

Nonetheless, favorable GOS was observed in 48.8% of subjects in the placebo group and 61.3% in the methylphenidate group after three months, suggesting a significant intergroup difference (P=0.03; **Figure 2**).

Table 2: Mean (standard deviation) level of consciousness (GCS) of the subjects at the time of arrival and at 2 and 7 days.

	Study group		
	Placebo (Number = 31 people)	Methylphenidate (Number = 31 people)	
Upon arrival	7.38 (1.56)	6.45 (1.19)	
2 days after arrival	6.81 (2.42)	6.9 (1.77)	
7 days after arrival	8.14 (3.6)	6.85 (2.06)	
Clearance time	9.38 (5.03)	11.25 (3.09)	
effects, F statistics (P value)	Between groups	37.43 (<0.001)	
	Intergroup	0.87 (0.32)	
	On group interaction and time	5.92 (0.001)	

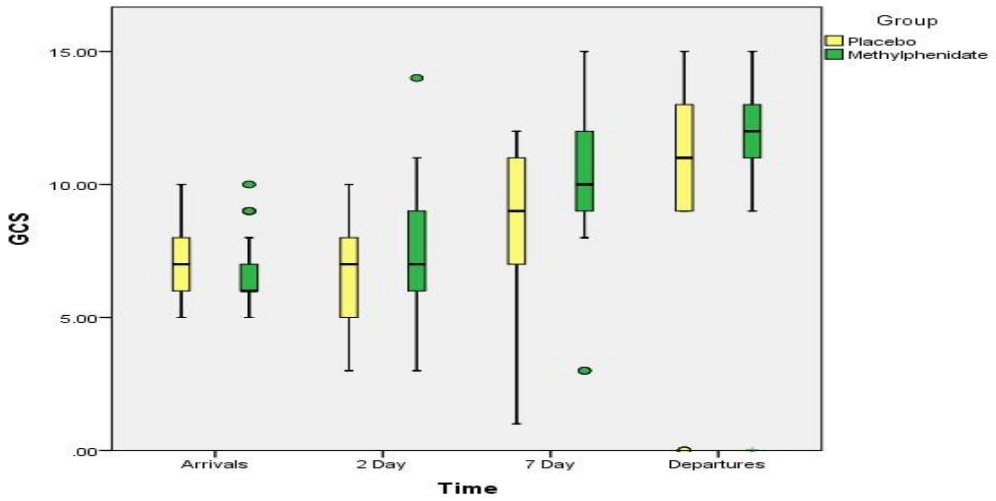

Figure 1: Changes in GCS during hospitalization and discharge in the two groups of study.

Length of ICU and hospital stay

According to the results, the mean days of ICU stay was 8.1±2.3 days in the placebo group and 6.8±1.8 days in the methylphenidate group, suggesting a significant intergroup difference (P=0.014). The mean ICU stay was lower in the methylphenidate group.

The mean hospital stay was 9.2±2.4 days in the methylphenidate group and 12.7±4.2 days in the placebo group, suggesting a significant intergroup difference (P=0.000). The methylphenidate group had a shorter hospital stay than the placebo group (**Table 3**).

Death

Two men from the methylphenidate group (6.4%) died on days 5 and 7 of ICU admission, respectively. Five patients (all male) from the placebo group (16.1%) died around day 6 of ICU admission. The difference between the methylphenidate and placebo groups regarding death was not statistically significant (P>0.05).

Delirium

There was no significant relationship between the two groups regarding CAM-ICU score on the day of discharge (P=0.365). The above table results show the mean RASS on days 2 and 7 of hospitalization and on the day of discharge in the two groups.

These RASS values suggest the lack of a significant difference between the two groups in this regard (P=0.165). To conclude, methylphenidate had no better effect than a placebo on delirium in patients with acute brain trauma (**Tables 4 and 5**).

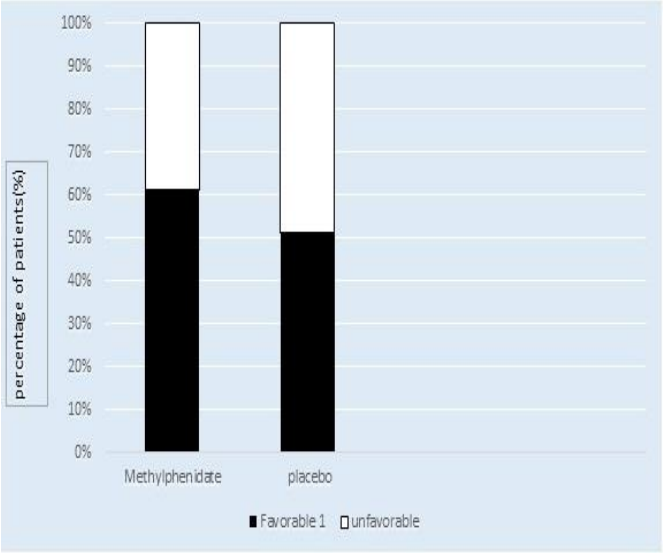

Figure 2: Comparison of dichotomized Glasgow Outcome scale score for patients receiving placebo or methylphenidate after 3 month of discharge.

Table 3: Evaluation of patients in terms of number of hospitalization and ICU stay in the two study.

Variable	Methylphenidate	placebo	Levene's Test		T-Test		
	Mean ± SD	Mean ± SD	F	P-Value	t	df	P-Value
Hospitalization	9.2±2.4	12.7±4.2	6.646	0.012	-3.9	48.4	0.000
Hospitalization in the ICU	1.8 ± 6.8	2.3 ± 8.1	1.304	0.258	0.014	60	-2.539

Table 4: Evaluation of patients in terms of CAM-ICU in two study groups.

CAM-ICU						
Study group						
Time	**Placebo (Number = 31 people)**			**Methylphenidate (Number = 31 people)**		
	Yes	**No**	Incalculable	**Yes**	**No**	Incalculable
Two Days	3 (9.7)	23(74.2)	5(16.1)	2(6.5)	22(71.0)	7(22.6)
7 days	4 (12.9)	21(67.7)	6(19.4)	2(6.5)	26(83.9)	3(9.7)
Clearance time	1(3.2)	25(80.6)	5(16.1)	3(9.7)	26(83.9)	2(6.5)
Intragroup effect	0.47			0.09		
Intergroup effect	0.69					

Table 5: Evaluation of patients in terms of RASS in two groups receiving methylphenidate and placebo.

RASS						
	Study group					
Time	**Placebo (Number = 31 people)**			**Methylphenidate (Number = 31 people)**		
	Deep sleep	Light sleep	Agitation	Deep sleep	Light sleep	Agitation
Two Days	7(22.5)	20(64.5)	4(12.9)	9(29)	18(64.5)	2(6.4)
7 days	8(25.8)	20(64.5)	3(9.6)	5(16.1)	24(77.4)	2(6.4)
Clearance time	8(25.8)	19(61.2)	4(12.9)	4(12.9)	24(77.4)	4(12.9)
Intragroup effect	0.55			0.12		
Intergroup effect	0.67					

Discussion

Brain damage, including ischemic and hemorrhagic stroke and traumatic brain injury (TBI), can lead to many defects, including behavioral changes, sensory loss, physical limitations, and cognitive impairments [16-18]. Stroke and TBI are both among the most common and costly causes of disability in developed countries, imposing both direct costs associated with complex medical strategies and indirect costs related to reduced daily functioning in the affected population. As the population ages, the prevalence of stroke and TBI also increase [19-21].

Managing functional damage depends on the initial acute treatment based on the guideline followed by extensive rehabilitation [16, 17]. The management of patients with post-traumatic stress disorder is complicated and clinically challenging due to their inability to participate in critical neuro-rehabilitation interventions [22-24].

Consciousness disorders may include minimal or vegetative states that may persist for months to years after the primary brain injury [22, 23]. These disorders are associated with high rates of morbidity and mortality [23], 24. Several neurotransmitters may be affected in TBI patients. It is hypothesized that an imbalance in catecholamines, cholinergic tone, and serotonergic system may be associated with complications in these patients [16, 17].

Completing and modifying changes in dopaminergic, noradrenergic, and serotonergic transmission are hypothesized to correct cognitive, and motor impairments and partially improve consciousness partially. Although many studies have examined the use of neuro stimulants during recovery from brain injury, there is little evidence that neuro stimulants improve motor, behavioral, and cognitive function due to small patient samples and conflicting results from ambiguous studies in this era.

In addition, medical associations and institutions have published very few guidelines in this area. Based on the American Academy of Neurology, Recommendations of the 2018 American Rehabilitation Medical Congress on the use of neuro-stimulators, the use of amantadine for patients with unanswered awakening syndrome or traumatic vegetable injury is encouraged to accelerate performance improvement and reduce recovery timing [16, 17]. Other pharmacological agents are not recommended in clinical guidelines. However, they may still be used in practice, including methylphenidate or other stimulants, acetylcholinesterase (AChE) inhibitors such as dopezil, and selective serotonin reuptake inhibitors (SSRIs).

Methylphenidate, mainly used to treat Attention Deficit Hyperactivity Disorder, has been used in clinical trials to improve cognitive and motor function after stroke and TBI [25-29]. In a randomized controlled trial of 21 patients with acute stroke, mood and motor function improvements were reported using methylphenidate during initial rehabilitation. These patients continued methylphenidate for three weeks or until discharge from the rehabilitation unit [28].

In a second randomized trial, more activity was shown on fMRI, but there was no significant improvement in post-stroke depression with methylphenidate [30]. Whyte et al. 27-29 conducted several studies on TBI, which showed that methylphenidate improved mental processing speed. Despite the observed improvements in processing speed, methylphenidate did not lead to improved concentration, distraction, or sustained attention. Nonetheless, the duration of these experiments was limited to six weeks, and the effect of methylphenidate on overall performance was therefore unclear. In addition, safety assessment was limited in short-term studies. The rate of side effects was low. However, some patients were excluded from the study due to abdominal pain and hypertension [29].

Subsequent studies have shown that methylphenidate improves mental fatigue and several aspects of cognitive function, including mental processing speed, attention, and working memory [31, 32]. Methylphenidate was administered for three or six months in the cited studies, but it might take longer than that to achieve clinical benefits. In addition, these trials showed more pronounced side effects, including increased blood pressure and heart rate, as well as restlessness, which led to the discontinuation of the drug in a small number of the participants [33, 34].

Moein et al. found that methylphenidate reduces the length of ICU and hospital stay in surgically treated traumatic brain injury patients [9]. These findings are consistent with the results of the present study. In our study, the length of ICU and hospital stay was significantly shorter in the methylphenidate group. Contrary to the discussed studies, the results of the present study focused only on brain trauma patients who did not require craniotomy surgery.

Also, opposing the comparative study, GCS clearance day was significantly higher in the methylphenidate group in our research, and a considerably higher GOS was observed in this group.

Despite this finding, caution is quite needed, given that these patients are still at risk for acute secondary complications from TBI, and the safety of methylphenidate in these conditions is not unknown. Some limitations that should be considered in these studies are the small sample size and the need for placebo control in some studies, making it difficult to make any definitive inferences from the findings. In addition, the dosing strategies in these studies have been very different, including weight-based strategies and increasing fixed dose titration. These studies have also used various dosage forms (fast versus slow release).

Based on these studies, it seems that methylphenidate can be helpful in people with mild to moderate and moderate to severe TBI, even in the acute phase of hospitalization. Unlike previous studies, methylphenidate apparently affects the length of hospital stay of patients with brain trauma without prospective side effects like delirium. However, more extensive studies are needed to validate further determination of the most effective dose and duration of methylphenidate in this population.

Thus, the long-term following of TBI patients, especially in terms of GOS, should be our priority.

Conclusion

Traumatic brain injury sometimes is a disastrous event with devastating familial and societal consequences. Our results emphasized that methylphenidate has some beneficial effects on the consciousness level and outcomes of patients with acute TBI compared to placebo. The use of methylphenidate also reduces the length of hospital or ICU stay, and the result will be better in patients with moderate to severe TBI who do not require surgery.

Further investigations on this topic should be performed with larger sample sizes and other medications like amantadine.

Acknowledgements

This study was conducted as part of a dissertation in neurosurgery by Dr. Fatemeh Fahiminia and was funded by Mazandaran University of Medical Sciences (MAZUMS) in the north of Iran. The study was approved in the clinical Research Development unit of Imam Khomeini Hospital, MAZUMS. The authors thank the volunteers who participated in this study.

Disclosure statement

None.

Authors' contributions

Conceiving and designing the study: Kaveh Haddadi, Forouzan Elyasi, Abbas Alipour

Data collection and manuscript drafting: Kaveh Haddadi, Misagh Shafizad, Fatemeh Heidari, fatemeh fahiminia

Statistical analysis: Abbas Alipour

Final prepration; Kaveh Haddadi, Abbas Alipour

Funding Sources

None.

Ethical Statement

The study was approved by the local ethics committee of the institution (CODE: IR.MAZUMS.IMAMHOSPITAL.REC.1399.037). The project was also recorded as a clinical trial with the Iranian Registry of Clinical Trials (IRCTID: IRCT20140915019185N3).

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