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ORIGINAL RESEARCH **INTENSIVE CARE**

The effect of methylphenidate on the level of consciousness and weaning from the ventilator in patients with brain injury in the intensive care unit

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Abstract

Introduction: Brain injury is the one of the leading cause of death and disability in the most active sections of society, especially in people under 45 y. The prevalence and severity of traumatic brain injury is rising in the Iranian population. The clinical effects of methylphenidate in improving treatment outcomes and cognitive function in this set of patients have been demonstrated in some studies. We conducted this clinical trial to assess the efficacy of methylphenidate in improving the level of consciousness and weaning from the ventilator in patients with brain injury in the intensive care unit.

Methodology: This clinical trial study was performed on 90 intubated patients admitted to the intensive care unit of Valiasr Hospital in Arak, Iran. The patients were randomly divided into two groups. Patients in the intervention group (Group M) received methylphenidate 0.3 mg/kg twice daily, in addition to the routine drugs that the control group (Group C) received. All patients were compared for ventilator isolation, Glasgow Comma Scale (GCS) and APACHE II. The results were compared and analyzed in the two groups using SPSS software version 22.

Results: The mean age of the patients in methylphenidate and control groups was 34.20 ± 7.87 y and 34.53 ± 8.31 y, respectively. There was no significant difference between the two groups in terms of age and gender ($p > 0.05$). The mean APACHE II score on the first and third day in Group M was 15.98 ± 1.70 and 13.73 ± 1.72, while in the Group C it was 16.02 ± 1.75 and 13.87 ± 1.84, respectively ($p > 0.554$). The GCS in the Group M was significantly and rapidly normalized ($p < 0.0001$). The mean duration of intubation in methylphenidate and Group Cs was 7.18 ± 0.83 and 9.8 ± 1.04 days, respectively. This time was significantly lower in the Group M ($p < 0.0001$).

Conclusion: The use of methylphenidate in patients with traumatic brain injury on mechanical ventilation in the intensive care unit is associated with a reduced duration of intubation and early return of the level of consciousness to normal.

Abbreviations: TB I– traumatic brain injury; GCS – Glasgow Comma Scale; APACHE – Acute Physiology and Chronic Health Evaluation

Key words: Methylphenidate; Brain Injury; Intensive Care unit; Glasgow Comma Scale; .APACHE II score

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1. Introduction

Traumatic brain injury (TBI) is a condition in which an external physical force causes temporary or permanent impairment in functional, social, and physical abilities.[1] Approximately 2 million people in the United States are reported to suffer from TBI annually, and this is one of the leading causes of death and disability in people under 45 y of age.[2] Motor accidents, falls and physical activity are the main causes of these traumatic brain injuries.[3] The prevalence and severity of TBI is increasing in the Iranian population. Typically, a large number of patients with TBI are waiting to be admitted to the intensive care unit (ICU). Over the years, a variety of treatments have been used to improve the short-term and long-term treatment outcomes of TBI.[4] The severity of TBI can be calculated using the Glasgow Coma Scale (GCS). This scale includes visual, verbal and motor responses.[5] Neurobehavioral disorders are one of the most common consequences in patients with TBI. The extent of the disorder depends on the severity of the injury, the part of the brain involved, and the degree of damage. Neurobehavioral disorders are characterized by impaired mood, cognition, or behavior. Cognitive impairment is accompanied with TBI including impaired attention, concentration, and memory.[6] Cognitive impairment may occur immediately after trauma and may be temporary or permanent. Behavioral abnormalities in patients with TBI include agitation, irritability, verbal and physical aggression, anxiety, depression, and impulsive behaviors.[7] These manifestations may be mild, moderate or severe.

Methylphenidate (Ritalin®) has both dopaminergic and slightly noradrenergic effects, stimulating the central nervous system, which can show protective effects on the nerves.[8] The clinical effects of methylphenidate in improving treatment outcomes and cognitive function in patients with TBI have been demonstrated in some studies.[9, 10] However, other studies have denied these beneficial effects of methylphenidate in improving the treatment outcomes of patients with TBI.[11] This drug is used in the treatment of patients with attention-deficit / hyperactivity disorder (ADHD). Methylphenidate can be useful in both groups of patients due to similar behavioral and cognitive problems in both groups of patients.[12] Methylphenidate can have many effects on improving the cognitive status of patients with TBI and can also accelerate the healing of brain processes.

Clinical safety of this drug in these patients has also been confirmed in studies.[13] Since the exact effects of this drug on improving treatment outcomes in patients with TBI admitted to the intensive care unit are not well understood. We investigated the effect of methylphenidate on the level of consciousness and on the weaning of the patients with brain injury in the ICU off the mechanical ventilation.

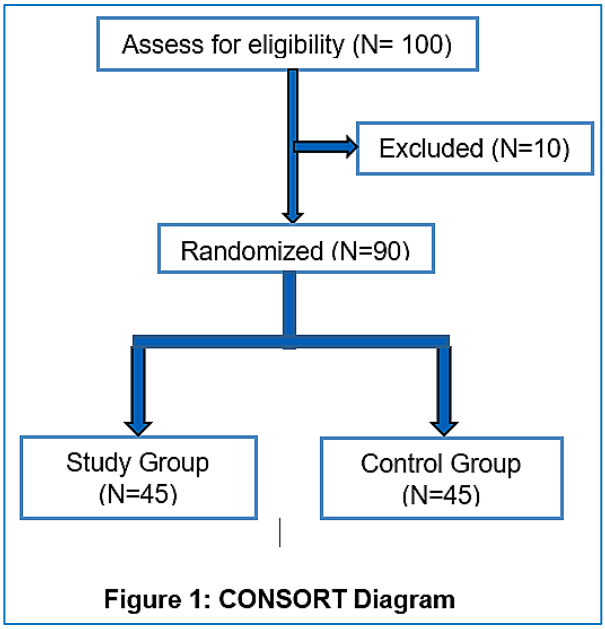

Figure 1: CONSORT Diagram

2. Methodology

2.1. Study population

This clinical trial was performed on 90 intubated patients admitted to the ICU of Valiasr Hospital in Arak. The names and details of patients were recorded confidentially and no additional costs were imposed upon them. Written consent was obtained from all patients to participate in this study. At all stages of the current study including the collection and analysis of data, researchers were required to comply with ethical provisions. This research project with the ethics code IRCT20141209020258: IRCT was approved by the ethics committee of the Research Council of Arak University of Medical Sciences.

2.2. Inclusion criteria

Patients included in the study were aged between 16 to 50 y, with GCS less than 10, intubated, no history of brain injury, seizures, hypertension, ischemic heart disease and diabetes mellitus, no evidence of a space occupying lesion on CT scan, no addiction to psychedelics and drugs, or amphetamine use. Heart rate less than 120 beats per min

2.3. Exclusion criteria

Patients with history of seizures, arrhythmias, and evidence of drug allergies were excluded

2.4. Treatment protocol

Patients who met the inclusion criteria were randomly divided into two groups; Group M and Group C.

Consolidated Standards of Reporting Trials (CONSORT) diagram is presented as Figure 1.

Patients in the intervention group (Group M) received 0.3 mg/kg methylphenidate twice daily (6 AM and 2 PM), in addition to the routine drugs that the Group C received. All patients were compared in terms of ventilator isolation (i.e., extubation and tracheostomy and T-piece tolerance), GCS and APACHE II.

2.5. Data analysis

Data analysis was performed using SPSS software version 22. Chi-square and t-test were used for determining statistical significance.

3. Results

Table 1 shows the demographic information of patients in the two groups. In this study, age and the gender were not significantly different between the groups. GCS changes in the two groups over 8 days are shown in Table 2. The reason for the 8-day study was that the mean intubation period was 7.18 days in the Group M and 9.8 days in the Group C, so there was no comparable data for the ninth and tenth days in the Group M. According to Table 2, between the two groups of Group M and Group C. in terms of mean GCS on different days, no significant difference was seen (p = 0.1).

APACHE II score changes on the first and third days are listed in Table 3. There was no significant difference between the two groups in terms of APACHE II scores on day 1 and 3. The mean intubation time in Group M and Group C was 7.18 ± 0.83 in vs. 9.8 ± 1.04 (p = 0.0001) respectively.

Table 1: Patient demographic information

Variable		Methylphenidate Group (n = 45)	Control Group (n = 45)	P value
Age in y (Mean ± SD)		34.20 ± 7.87	34.53 ± 8.31	**0.846**
Sex	Male	21 (46.7)	24 (53.3)	**0.802**
	Female	24 (53.3)	21 (46.7)	

Data presented as n (%), unless specified.

Table 2: Changes in patients' GCS in two groups (Mean ± SD)

Day	Methylphenidate Group	Control Group	p-value
Day 1	5.87 ± 0.92	6.28 ± 0.65	0.1
Day 2	7.10 ± 0.73	6.23 ± 0.62	
Day 3	7.20 ± 0.56	6.36 ± 0.64	
Day 4	7.80 ± 0.56	7.20 ± 0.63	
Day 5	8.33 ± 0.49	7.42 ± 0.63	
Day 6	8.80 ± 0.41	7.78 ± 0.47	
Day 7	9.40 ± 0.51	8.27 ± 0.58	
Day 8	9.88 ± 0.35	8.71 ± 0.59	

Table 3: APACHE II score changes in patients in both groups (Mean ± SD)

Day	Methylphenidate Group	Control Group	p-value
Day1	15.98 ± 1.70	16.02 ± 1.75	0.4
Day3	13.73 ± 1.72	13.87 ± 1.84	

4. Discussion

The prevalence and severity of TBI is increasing in the Iranian population. Over the years, a variety of treatments have been used to improve the short-term and long-term treatment of traumatic brain injuries.[4] Neurobehavioral disorders are one of the most common consequences in patients with TBI. The extent of the disorder depends on the severity of the injury, the part of the brain involved, and the degree of the damage. Neurobehavioral disorders are characterized by impaired mood, cognition, or behavior. Cognitive impairments are associated with TBI include impaired attention, concentration, and memory.[6] TBI (change in brain function caused by an external factor),[3]) is one of the major health problems in the world that can lead to disease, disability and mortality. It is estimated that TBI is responsible for nearly half of all trauma-related deaths.[14] In the present study the mean age in the two groups did not show a significant difference (p = 0.846). The gender preponderance did not differ significantly (p = 0.527).

In the current study, the mean duration of intubation in the Group M was significantly less than the control group (p < 0.0001). In other words, methylphenidate reduced the intubation time compared to the Group C by about 2.7 days and can be used to reduce the intubation time in these patients, with a reduction in the length of stay in the ICU.

The results of our study are in line with the studies of other researchers, in which methylphenidate (0.3 mg / kg) was given orally twice a day in the intervention group consisting of patients with TBI and the other group received placebo.[15, 16] They found that the mean length of stay in the ICU in the Group M was 6.9 ± 4.44 days and in the placebo group was 9.36 ± 7.04 days, which was significantly lower in the Group M (p

= 0.031). Methylphenidate is a potent inhibitor of dopamine and norepinephrine in the central nervous system. Ritalin has been shown to have a high protective effect against diseases such as Parkinsonism and methamphetamine abuse. [15, 16] In addition, various studies have shown significant effects on brain protection against trauma-induced brain damage. According to our study, the reduction in the duration of intubation by this drug may be due to the same neuroprotective effects of methylphenidate on the brain.

Attention disorders and the information processing speed are among the most common persistent cognitive changes that are evident following brain injury.[17] For example, Willmott et al.[17] in a study evalauted the effects of methylphenidate on attention rehabilitation and brain consciousness activities following brain injury. They found that methylphenidate increased the speed of information processing during the inpatient rehabilitation phase following TBI and could increase brain awareness activities. The effectiveness of methylphenidate in facilitating information processing speed in hospitalized patients with traumatic spinal cord injury has also been demonstrated.

In our study, the Group M significantly increased the patients' GCS level faster than the Group C ($p < 0.0001$). The mean GCS in the Group M increased from 5.87 ± 0.92 on the first day to 9.88 ± 0.35 on the eighth day, while in the Group C it increased from 6.38 ± 0.65 on the first day to 8.71 ± 0.59 on the eighth day.

The findings of our study on increased consciousness and brain abilities of methylphenidate were also in line with previous meta-analysis conducted by Huang et al.[16] By analyzing ten double-blind trials, they indicated significant benefits in the use of methylphenidate for increasing vigilance-associated attention in patients with TBI. However, no positive effect was observed on the facilitation of memory or processing speed.

In our study, the mean APACHE II score for the Group M was 15.98 ± 1.70 and 13.73 ± 1.72 on the first and third days, respectively, while it was 16.02 ± 1.75 and 13.87 ± 1.84 in the Group C on the first and third day respectively. There was no significant difference between the two study groups in this field ($p = 0.554$). The lack of difference in the APACHE II scores in the two groups on the first and third days may be attributed for no differ in survival and mortality in the ICU in the first days. More studies in line with our study were not found in scientific sources to compare this score.

5. Conclusion

The use of methylphenidate in patients with traumatic brain injury admitted to the ICU can reduce the duration of intubation and the restoation of the consciousness to normal level, enabling early weaning from the mechanical ventilation.

6. Conflict of interests

None declared by the authors.

7. Authors' contribution

AK: Design of the study , drafting the manuscript, statistical analysis, final approval

BM: Design of the study, statistical analysis, final approval

SMJ, AK, MD: Analysis,literature search, drafting the manuscript

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