Clinical Trial/Experimental Study

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Efficacy of methylphenidate for the treatment of mental sequelae after traumatic brain injury

Wei-Tao Zhang, MD[a,*], Ya-Fei Wang, MD[b,*]

Abstract

Background: This study aimed to evaluate the effect of methylphenidate for treating mental sequelae after traumatic brain injury (TBI).

Methods: Thirty-six patients with TBI were randomly divided into the intervention group and placebo group. The participants in the intervention group received methylphenidate, while subjects in the placebo group were administered a placebo. This study was conducted from January 2014 to December 2016. The outcome measurements included Mental Fatigue Scale, Choice Reaction Time, Compensatory Tracking Task, Mental Arithmetic Test, Digit Symbol Substitution Test, Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), and Hamilton Rating Scale for Depression. In addition, safety was also recorded and assessed.

Results: A total of 33 subjects completed the study. Methylphenidate showed greater efficacy than placebo, with decreased scores on the Mental Fatigue Scale, Choice Reaction Time, and Compensatory Tracking Task in the intervention group compared to the placebo group ($P < .01$, respectively). Furthermore, increased scores on the Mental Arithmetic Test, Digit Symbol Substitution Test, and MMSE in the intervention group, compared to those in the placebo group ($P < .01$ respectively), were observed. In addition, a significant difference in the scores on the BDI ($P = .04$) and Hamilton Rating Scale for Depression ($P = .005$) was observed between the 2 groups. The safety at the end of the 30 week-treatment was similar between the 2 groups ($P > .05$).

Conclusion: The results of this study demonstrated that methylphenidate could effectively improve mental fatigue and cognitive functions in patients with TBI.

Abbreviations: BDI = Beck Depression Inventory, BP = blood pressure, MMSE = Mini-Mental State Examination, TBI = traumatic brain injury.

Keywords: mental sequelae, methylphenidate, randomized controlled trial, traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) often results from traffic-related and other accidents.[1] Patients with TBI may present various neuropsychiatric and mental sequelae, such as depression, sleep disorders, fatigue, cognitive impairments, headache, emotion instability, and sensitivity to stress.[2–10] Although many studies have been conducted for treating such conditions, no specific studies have focused on the treatment of mental sequelae after TBI.[11,12]

Currently, there are no effective therapies for treating mental sequelae after TBI. Although the guidelines recommend methylphenidate for deficits in attention and processing speed after TBI, there are no guidelines for mental sequelae treatment after TBI.[13]

Methylphenidate, which acts on the dopamine and noradrenergic systems, is known to block the reuptake of norepinephrine and dopamine into presynaptic neurons. It has been used for treating narcolepsy and attention deficit hyperactivity disorder in children.[14] Moreover, it has been reported to have controversial therapeutic potential against TBI-associated neurological sequelae.[15] In addition, it has been shown to have an effect on patients with TBI with cognitive impairment by affecting the speed of mental processing.[16] Furthermore, its pharmacological properties are similar to those of amphetamines. However, its exact mechanism of action for treating TBI mental sequelae is still unknown, although a previous study reported that it might act via activation of the brainstem arousal system, cortex, and subcortical structures.[17]

Currently, no existing randomized controlled trial has tested the effect of methylphenidate in patients with mental sequelae after TBI. In this study, we compared the effect of methylphenidate with that of placebo in patients with TBI in China. We tested the hypothesis that methylphenidate reduces mental fatigue and improves cognitive functions in patients with TBI.

2. Methods

2.1. Study design

This study was designed as a 30-week double-blinded randomized placebo-controlled trial. It was approved by the Medical Ethical Committee of The People's Hospital of Yan'an

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[a] Department of Neurosurgery, The People's Hospital of Yan'an, Yan'an, [b] Department of Neurosurgery, The People's Hospital of Ningxia, Yinchuan, China.

[*] Correspondence: Ya-Fei Wang, Department of Neurosurgery, The People's Hospital of Ningxia, No.301 Zhengyuan North Street, Yinchuan 750001, China (e-mail: wangds1958@163.com); Wei-Tao Zhang, Department of Neurosurgery, The People's Hospital of Yan'an, Yan'an 716000, China (e-mail: weitao20000@outlook.com).

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and The People's Hospital of Ningxia from January 2014 to December 2016. Thirty-six patients with TBI with mental sequelae, including mental fatigue and cognitive impairment, were recruited and randomly assigned to the intervention group or placebo group in a 1:1 allocation ratio. All participants met the inclusion and exclusion criteria. In addition, written informed consent was obtained from all the included patients.

2.2. Participants and recruitment

All subjects with TBI were recruited through the clinic at the department of neurosurgery at The People's Hospital of Yan'an and The People's Hospital of Ningxia from January 2014 to December 2016. All eligible patients were evaluated by clinical evaluation, physical examination, and brain computed tomography. After screening, the subjects were randomized to either the intervention or placebo group. All investigators were trained before this study. All subjects were informed about the research and given an information sheet; then, they were administered either methylphenidate or placebo.

2.3. Inclusion and exclusion criteria

The inclusion criteria included age between 18 and 65 years; diagnosed based on the major depressive episode by Diagnositc and Statistical Manual of Mental Disorders[18]; mild-to-moderate degree of TBI, according to a previously reported definition[19]; Beck Depression Inventory (BDI) score of ≥18[20]; Mini-Mental State Examination (MMSE) score of ≥20[21]; and the period of injury ranging from 2 weeks to 1 year.

Patients were excluded in case of multiple trauma that might affect the examinations; serious diseases, such as cancer; abnormal laboratory examinations; allergy to any drug; have been treated with neuroleptics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and lithium within 4 weeks; involved in other clinical trials in the past 3 months; pregnancy; or if declined to participate.

2.4. Randomization and blinding

The randomization of this study was conducted by a statistician using SAS Software (version 8.3; SAS Institute, Inc., Cary, NC) with a computerized number generator. After the randomization, the allocation assignments of patients were concealed in opaque, sequentially numbered, and sealed envelopes. The patients, investigators, outcome assessor, and data analyst were all blinded to the intervention allocation.

2.5. Intervention

The comparison interventions were methylphenidate and placebo. Patients recruited to the intervention group received methylphenidate (flexibly titrated from 5 mg/d at the beginning, then gradually increased by 2.5 mg/d until reaching 20 mg/d). Patients were administered methylphenidate in equally divided doses at 8 AM and 12 PM. The dose was selected based on a previous study.[22] Participants assigned to the

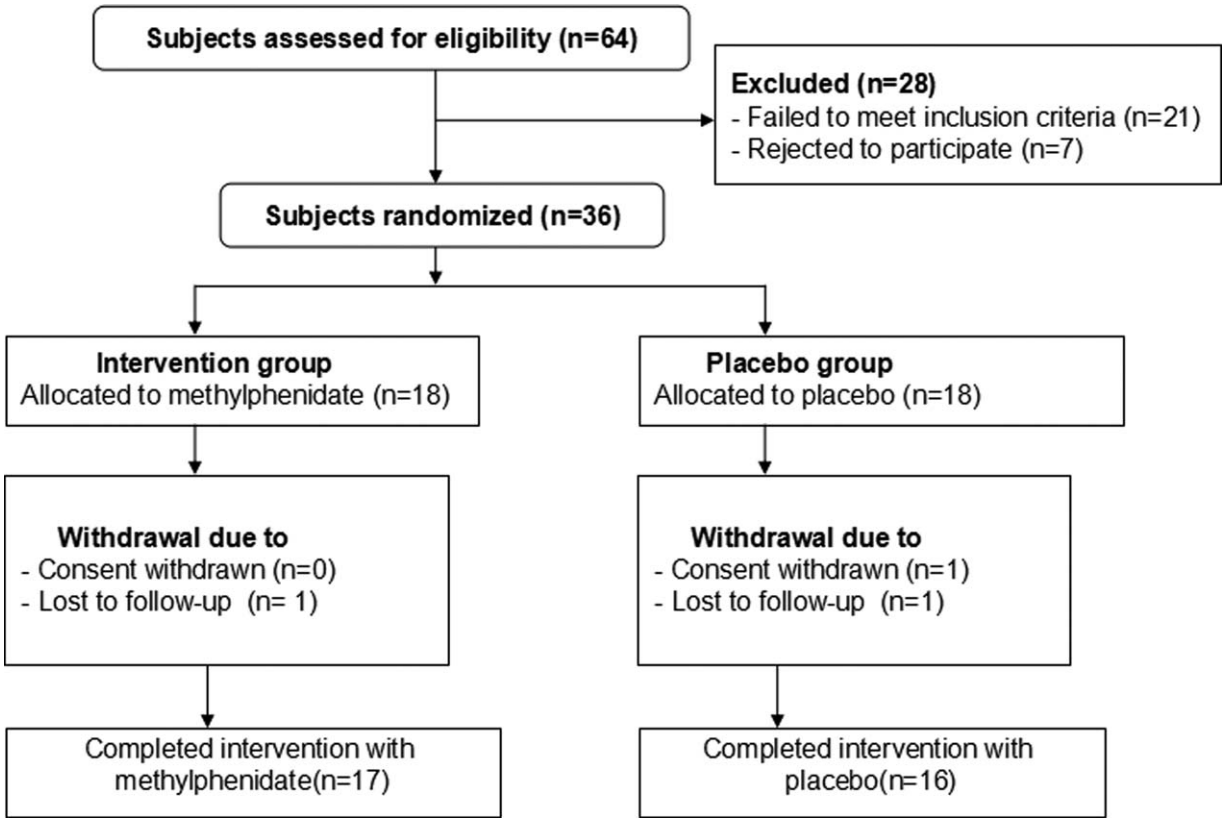

Figure 1. Flowchart of patients selection.

placebo group received placebo at the same dose as the intervention group.

2.6. Outcome measurements

The primary outcomes were fatigue and cognitive functions. Fatigue was measured using the Mental Fatigue Scale.[23,24] The cognitive functions were evaluated by the Choice Reaction Time,[25] Compensatory Tracking Task,[26] Mental Arithmetic Test,[27] Digit Symbol Substitution Test,[28] and MMSE.[21] The secondary outcomes included depression, evaluated by the BDI and Hamilton Rating Scale for Depression.[29] Safety was evaluated based on the heart rate, systolic blood pressure (BP), diastolic BP, and body weight measurements.

2.7. Statistical analysis

The required sample size for this study was estimated to be 15 patients in each group, based on the standard difference, with a statistical power of 80% and a significance level of 0.05. Assuming 20% dropout rate, at least 36 patients (with 18 in each group) were required to be recruited for this study. All outcome data were analyzed using an intention-to-treat approach. In addition, Chi-square tests and *t* tests were used to analyze the categorical and continuous data, respectively, with relative risks and 95% confidence intervals.

3. Results

Sixty-four patients with TBI were initially assessed for the selection (Fig. 1). Of them, 28 subjects were excluded, including 21 patients who failed to meet the inclusion criteria, and 7 patients who rejected to participate in the current study. After this, 36 patients were included and randomly assigned to the intervention group or placebo group, with 18 patients each group. At the end of treatment, 3 subjects withdrew from the study. Thus, 33 patients completed the treatment (Fig. 1).

The basic characteristics of the included patients in both groups are presented in Table 1. Both groups did not show significant differences in terms of age, sex, race, education background, duration since their head injury, levels of fatigue, cognitive functions, and depression as investigated at baseline (Table 1).

At the end of the 30-week treatment, Mental Fatigue Scale score, to evaluate mental fatigue, was 12.1 (±4.9) in the intervention group, which was significantly lower than that in the placebo group (17.9 (±7.3); $P = .005$, Table 2). The results of cognitive functions, measured using Choice Reaction Time, Compensatory Tracking Task, Mental Arithmetic Test, Digit Symbol Substitution Test, and MMSE scores, showed significant differences between 2 groups at the end of 30 weeks ($P < .05$, Table 2). In addition, the depression scores of BDI and Hamilton Rating Scale for Depression were 14.9 (±8.1) and 15.1 (±6.0) respectively in the intervention group, compared to 20.1 (±7.3) ($P = .04$, Table 2) and 20.3 (±5.1) ($P = .005$, Table 2) respectively in the placebo group.

No significant differences in the heart rate, systolic BP, diastolic BP, and body weight were found between the 2 groups regarding safety at the end of 30-week treatment ($P > .05$, Table 3).

4. Discussion

A previous study evaluated the effects of methylphenidate on mental fatigue, cognitive function, and safety for treating patients with TBI. It found that methylphenidate reduces mental fatigue and improves cognitive functions with long-term methylphenidate treatment.[30] Although this study did not involve any type of control intervention,[30] its finding is consistent with the present study in showing that methylphenidate can reduce mental fatigue

Table 1

Patients characteristics at baseline.

Characteristics	Intervention group (n = 18)	Placebo group (n = 18)	*P*
Age, y	36.3 (10.9)	34.9 (12.1)	.72
Sex			
Male	13 (72.2)	14 (77.8)	.70
Female	5 (27.8)	4 (22.2)	.70
Race			
Han ethnicity	12 (66.7)	10 (55.6)	.50
Hui ethnicity	6 (33.3)	8 (44.4)	.50
Education background			
Elementary school	4 (22.2)	6 (33.3)	.46
High school	8 (44.4)	6 (33.3)	.50
College/university	6 (33.3)	6 (33.3)	1.00
Interval since head injury, d	43.5 (6.8)	46.1 (7.2)	.27
Fatigue			
MFS	24.5 (5.1)	25.1 (5.3)	.73
Cognitive function			
CRT	642.5 (84.3)	661.8 (76.1)	.47
CTT	50.9 (22.4)	48.7 (21.6)	.76
MAT	4905.7 (1658.3)	5127.5 (1702.6)	.69
DSST	34.3 (12.5)	32.8 (11.9)	.27
MMSE	26.4 (3.1)	26.7 (2.9)	.71
Depression			
BDI	26.4 (7.1)	25.5 (6.9)	.70
HAMD	25.9 (5.8)	25.1 (5.5)	.67
Safety			
Heart rate	73.1 (10.5)	75.4 (11.1)	.52
Systolic BP	124.5 (14.2)	122.7 (13.8)	.70
Diastolic BP	75.6 (8.0)	76.0 (7.7)	.88
Body weight	77.6 (17.8)	73.3 (17.2)	.46

Data are present as mean ± standard deviation or number (%). BDI = Beck Depression Inventory, BP = blood pressure, CRT = Choice Reaction Time, CTT = Compensatory Tracking Task, DSST = Digit Symbol Substitution Test, HAM-D = Hamilton Rating Scale for Depression, MAT = Mental Arithmetic Test, MFS = Mental Fatigue Scale, MMSE = Mini-Mental State Examination.

Table 2

Primary and secondary outcome measurements after 30 weeks treatment.

Outcomes measurements	Intervention group (n = 18)	Placebo group (n = 18)	*P*
Fatigue			
MFS	12.1 (4.9)	17.9 (7.3)	.005
Cognitive function			
CRT	342.8 (54.3)	526.4 (63.3)	<.001
CTT	19.5 (8.8)	36.7 (16.4)	<.001
MAT	6839.9 (1927.4)	5422.6 (1755.8)	.02
DSST	60.3 (13.1)	45.6 (12.2)	<.001
MMSE	36.7 (2.2)	30.1 (1.8)	<.001
Depression			
BDI	14.9 (8.1)	20.1 (7.3)	.04
HAMD	15.1 (6.0)	20.3 (5.1)	.005

Data are present as mean ± standard deviation or number (%). BDI = Beck Depression Inventory, CRT = Choice Reaction Time, CTT = Compensatory Tracking Task, DSST = Digit Symbol Substitution Test, HAM-D = Hamilton Rating Scale for Depression, MAT = Mental Arithmetic Test, MFS = Mental Fatigue Scale, MMSE = Mini-Mental State Examination.

Table 3

Safety between 2 groups after 30 weeks treatment.

Safety	Intervention group (n = 18)	Placebo group (n = 18)	*P*
Heart rate	79.4 (11.1)	75.3 (10.9)	.26
Systolic BP	123.7 (13.4)	120.2 (13.0)	.43
Diastolic BP	74.9 (7.7)	75.3 (7.5)	.87
Body weight	76.5 (17.1)	72.8 (16.5)	.51

Data are present as mean ± standard deviation. BP = blood pressure.

and improve cognitive outcomes in patients with TBI. Another reported study with a small sample size investigated the effects of methylphenidate and sertraline compared with placebo on various neuropsychiatric sequelae associated with TBI.[31] It found that methylphenidate and sertraline had similar effects on depressive symptoms.[31] However, methylphenidate seemed to be more beneficial in improving cognitive function and maintaining daytime alertness.[31] In addition, methylphenidate also offered better tolerability than sertraline. Two literature reviews also assessed the effect and safety of methylphenidate for treating subjects with TBI.[32,33] Of those, one demonstrated that methylphenidate is likely to improve memory, attention, concentration, and mental processing; however, its effects on behavior have not been determined.[32] The other one reported the positive effects of methylphenidate for enhancing vigilance-associated attention.[33] However, no significant positive impact was noted on the facilitation of memory or processing speed.

In the present study, patients with TBI in the intervention group showed a significant decrease in fatigue and an improvement in cognitive outcome, compared to patients in the placebo group. This suggests that methylphenidate had a positive effect on mental fatigue and cognitive functional outcomes. In addition, this study also demonstrated that methylphenidate could improve depression in patients with TBI.

This study has several limitations. First, although this study was a randomized placebo-controlled trial, its sample size was quite small, which may affect the results. Second, differences in the severity of the clinical symptoms between the 2 groups may have affected the outcomes, such as cognitive functions, though no differences were found at baseline. Third, other factors, such as the area of brain injury, cognitive difficulties, and psychiatric history, that were not investigated might also affect the outcome measurements.

This study showed that methylphenidate treatment in patients with TBI improved not only fatigue and cognitive functions but also depression. Further randomized controlled trials with larger sample sizes are still needed to verify these results.

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