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Methylphenidate on Cognitive Improvement in Patients with Traumatic Brain Injury: A Meta-Analysis

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Abstract: Although methylphenidate has been used as a neurostimulant to treat patients with attention deficit hyperactivity disorder, its therapeutic role in the psychomotor or cognitive recovery of patients with traumatic brain injuries (TBIs) in both intensive care and rehabilitation settings has not been adequately explored. To address this issue, this meta-analysis searched the available electronic databases using the key words "methylphenidate", "brain injuries", "head injuries", and "traumatic brain injury". Analysis of the ten double-blind RCTs demonstrated significant benefit in using methylphenidate for enhancing vigilance-associated attention (i.e., selective, sustained, and divided attention) in patients with TBIs (standardized mean difference: 0.45, 95% CI: 0.10 to 0.79), especially in sustained attention (standardized mean difference: 0.66, 95% CI: 0.22 to 1.10). However, no significant positive impact was noted on the facilitation of memory or processing speed. More studies on the efficacy and safety of methylphenidate for the cognitive improvement of patients with TBIs are warranted.

Keywords: Attention, cognitive function, methylphenidate, traumatic brain injury.

INTRODUCTION

Traumatic brain injuries (TBIs) are health threats that contribute to staggering mortality rates and cause enormous social and economic burdens worldwide. Recent data show that approximately 1.7 million people sustain TBIs annually [1]. Its debilitating neurological sequelae, including cognitive impairments and psychomotor retardation, have been reported to be attributable to alterations in the chemistry and structure of brain cells after a TBI, especially the long-term changes in the levels of neurotransmitters [2]. A reduction in the secretion of serotonin and catecholamine has been demonstrated to be related to TBI-associated neurological morbidities [3]. Although no relevant medication has been approved by the U.S. Food and Drug Administration (FDA), methylphenidate, a psychostimulant known to block the reuptake of norepinephrine and dopamine into the presynaptic neuron for treating narcolepsy and attention deficit hyperactivity disorder (ADHD) in children [4], has been shown to be of controversial therapeutic potential against TBI-associated neurological sequelae [5]. The drug shares pharmacological properties similar to those of the amphetamines. Although its exact mechanism of action is not well known, methylphenidate is thought to activate the brainstem arousal system, cortex, and subcortical structures including the thalamus to produce its stimulant effect [6].

Although a recent study has evaluated the efficacy and safety of dopamine agonists in the treatment of TBI-associated neurological deficits, no statistical pooling has reported the effects of methylphenidate [7]. Therefore, by reviewing all available randomized controlled trials (RCTs) related to the use of methylphenidate in patients with TBIs from the databases of biomedical sciences, the objective of this meta-analysis was to systematically evaluate the treatment outcome of methylphenidate in patients with neurological deficits following TBIs based on the improvement of cognitive and psychomotor functions.

METHODS

Literature Search Strategy

Two of us (CHH and CCH) performed a comprehensive literature search in electronic databases, including MEDLINE, PubMed, the Cochrane Central Register of Controlled Trials, CINAHL, EMBASE, and PsycINFO, for relevant studies from the earliest available articles to those published in Dec 2014. The key words "brain injuries", "head injuries", and "traumatic brain injury" were used and

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searches were exploded with MeSH terms. Methylphenidate, as well as its generic and brand names used worldwide, including Ritalin, Concerta, Daytrana, Metadate, Methylin, Quillivant, Biphentin, were used for searching. Medical subheadings included "craniocerebral trauma", "trauma, nervous system", "head injuries, closed", "cerebrovascular disorders, craniocerebral trauma", "head injuries, penetrating", "brain injuries", "brain injury, chronic", "cerebrovascular trauma, "head injuries, penetrating, hemorrhage", "brain stem hemorrhage, traumatic", "subarachnoid hemorrhage", "cerebral hemorrhage, traumatic", "cerebral hemorrhage", "subarachnoid hemorrhage, traumatic", "brain hemorrhage, traumatic", "putaminal hemorrhage", "choroid hemorrhage", "basal ganglia hemorrhage", "intracranial hemorrhage, traumatic", "intracranial hemorrhages", "hematoma, epidural, cranial", "hematoma, subdural", "hematoma, subdural, chronic", "hematoma, subdural, acute", and "basal ganglia cerebrovascular disease".

As recommended by the Cochrane Handbook, searching was conducted without using filters to maximize the retrieval of studies. No language limits were imposed. Hand searching was performed to screen potentially relevant articles by using specific titles, abstracts, and a full text review from electronic databases. We personally contacted the authors of relevant studies to gain access to published and unpublished data (Nathan J. Blum, MD and John Whyte, MD). The searches were performed independently by two reviewers (CHH and CCH). A consensus was obtained through discussion with the third reviewer (WHH).

Selection Criteria

References acquired from all databases were initially screened according to the titles, followed by the abstracts and full text. Only RCTs on patients sustaining TBIs associated with cognitive deficits and receiving methylphenidate treatment with at least one primary outcome related to cognitive or attention ability were included in this study. Studies involving subjects with cerebrovascular diseases, ADHD, or organic amnesia were excluded. No age, sex, race, or economic social status was restricted.

Data Extraction

Baseline and outcome data were independently extracted by two reviewers (CHH and CCH). Disagreement on specific studies between the two reviewers was settled through discussion with the third reviewer. If the required information was unavailable in the published article, we attempted to obtain additional information from the authors. Study characteristics (authors, published year, country, study design, measurements, and adverse events), the number of randomized patients, patient characteristics (age, Glasgow Coma Scale, severity of TBI), regimens (methylphenidate dosage, administration frequency, intervention durations, and washout period), and quality scores were listed for comparison. Cognitive domains, including attention, memory, processing speed, psychomotor ability, global cognitive function, were considered the primary outcome. Any reported adverse events were considered the secondary outcome.

Data Analysis

Appropriate outcome data were entered into an electronic database by using Cochrane Review Manager Software (version 5.1) for statistical analysis to estimate the treatment effects. Continuous outcomes from individual studies were compared to compute the effect size at a 95% confidence interval in a random-effects model. Heterogeneity was assessed using Cochrane's Q statistic and quantified using the I^2 statistic. The I^2 statistic represents the percentage of total variation attributable to between-study heterogeneity rather than sampling errors. The I^2 values of approximately 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively. Sensitivity analysis was performed by removing one study at a time to assess the effect on study results.

Quality Assessment

Two reviewers (CHH and CCH) assessed the quality of each included study by using the Oxford Quality Scale, a validated scale published by Jadad *et al*. [8]. The studies were evaluated on a 5-point scale, with a maximum of 2 points awarded for the first two questions and 1 point for the third: (a) Was the study described as randomized? (b) Was the study described as double-blind? (c) Was information on description of study withdrawals and dropouts provided?

RESULTS

We identified 683 published studies potentially relevant to the use of methylphenidate for enhancing cognitive improvement following a TBI from electronic literature databases, reference lists of systematic reviews, and identified articles. A selection flowchart of the ten citations retrieved for systematic review is shown in Table **1**.

After excluding three studies without mean (n = 2) or standard deviation (n = 1) values, [9-11] the ten RCTs listed in Table **2** were identified as potentially appropriate for this meta-analysis [12-21]. The articles were scrutinized to identify variables for comparing the outcomes: attention, memory, processing speed, psychomotor ability, and global cognitive function. Although no theory or hierarchical structure could explain all domains of cognition so far, these variables were selected for outcome measurements on the basis of MATRICS developed by the National Institute of Mental Health (US) [22-24]. Sensitivity analysis showed no evidence of bias or heterogeneity on the effectiveness of methylphenidate treatment. The mean Oxford Quality Scale of the acquired literature was 3.2 ± 0.91.

Cognitive Function

According to various tools in different categories, similar outcome measurements were combined in every domain. However, studies focusing on psychomotor ability and global cognitive function were too scarce to lead to a meta-analysis.

Attention

Four RCTs evaluated the parameters of attention, including the time to responses and the percentage of correct

Table 1. Selection flowchart of retrieved literature.

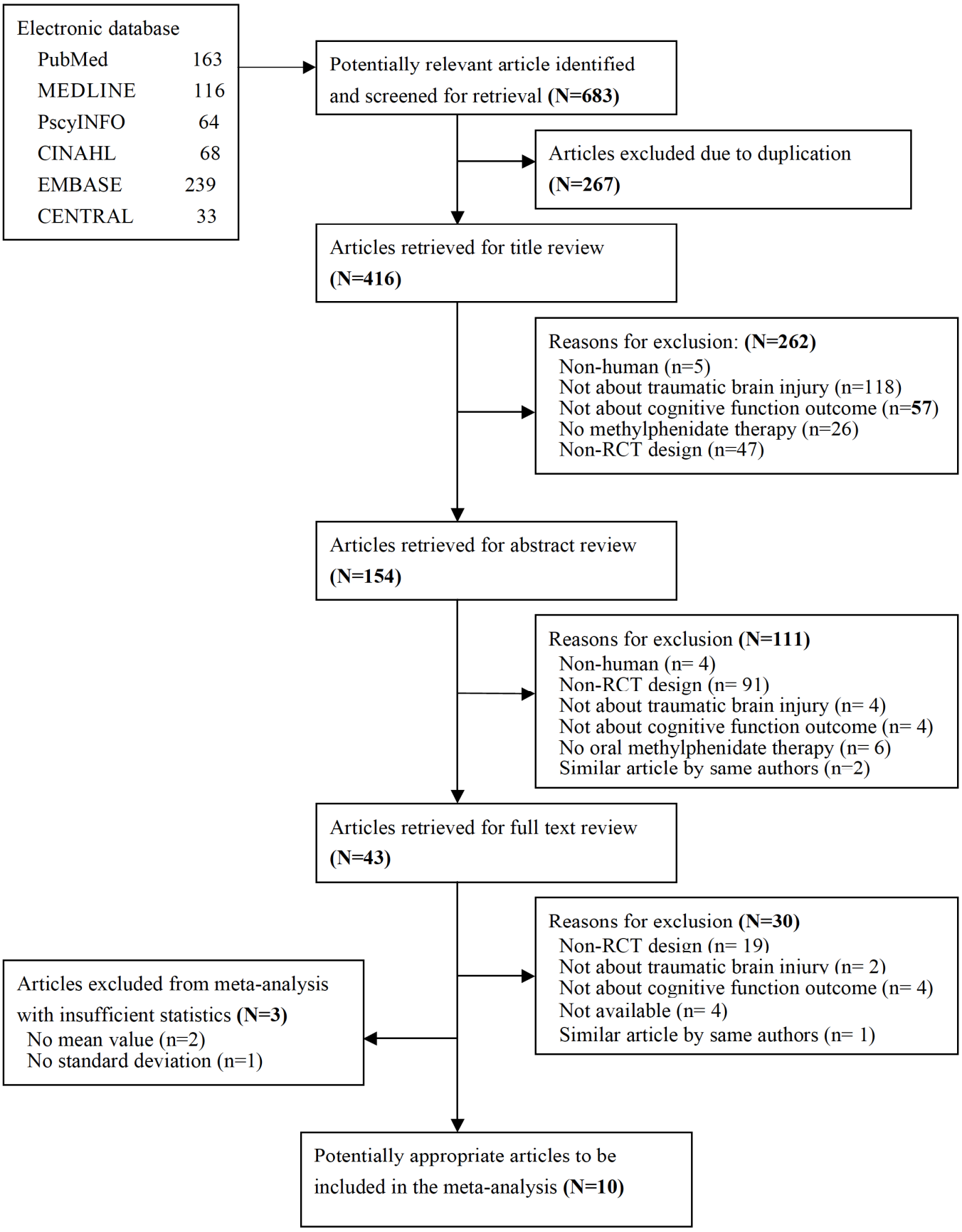

Table 2. Characteristics of 10 randomized, controlled trials included for analysis.

Study Year Country	Participants (Severity and Localization of Lesion)	Age (Year)	Sample Size and Study Design	Dose Regimen	Measurements	GCS	Adverse Events	Jadad Quality Score (Total Score: 5)
Kim 2012 USA [21]	Moderate severity TBI	Mean: 34.2 (11.5)	MP group: 23 Placebo group: 23 crossover	Dose: 0.3mg/kg, qd (nearest 2.5mg) Duration: single dose Sessions: Wash out: *	Attention Visual sustained attention task (VSAT) (go-no-go visual reaction time task) Memory Two back task	less than 12	Not mentioned	4
Willmott 2009 Australia [12]	Mild to severe TBI	Mean: 26.3	40 participants crossover	Dose: 0.3mg/kg, bid Duration: 2 days Sessions: 6 Wash out: not mentioned	Attention 1.Simple Selective Attention Task 2.Rating Scale of Attentional Behavior (RSAB) 3.Sustained Attention to Response Task (SART) Memory 1.Letter Number Sequencing Task Processing speed 1.Four Choice Reaction Time Task (4CRT) 2.Symbol Digit Modalities Test (SDMT) 3.Ruff 2 and 7 Test Global cognition function 1.Wechsler Test of Adult Reading (WTAR)	Mean: 5.3 Range: 3-13	No adverse events	5
Levin 2007 [13]	Severe TBI	Mean: 28.4	MP group: 38 Placebo group: 36 parallel	Dose: 15mg, bid Duration: 28 days Sessions: 1 Wash out: *	Memory 1.A visual N-back working memory task 2.Verbal selective reminding test 3.Consonant trigram distracter memory test Processing speed 1.Symbol Digit Modalities Test (SDMT)	Mean: 6.9 Range: NA	Not mentioned	2
Kim 2006 Korea [14]	Chronic phase of TBI (more than 6 months)	Mean: 34.2	MP group: 9 Placebo group: 9 parallel	Dose: 20mg, qd Duration: single dose Sessions: Wash out: *	Attention 1.Endogenous visual-spatial attention task Memory 1.Two-back working memory task	NA	No adverse events	4
Lee 2005 Korea [15]	Mild to moderate TBI	Mean: 34.8	MP group: 10 Placebo group: 10 parallel	Dose: starting at 5 mg/day and increasing to 20 mg/day in a week Duration: 28 days Sessions: 1 Wash out: *	Memory 1.Sternberg Memory Scanning Task (STM) Processing speed 1.Critical Flicker Fusion Threshold (CFFT) 2.Choice Reaction Time 3.Mental Arithmetic 4.Digit Symbol Substitution Psychomotor ability 1.Compensatory Tracking Task (CTT) Global cognition function 1.Mini-Mental State Examination	NA	Nausea/vomiting, diarrhea, constipation, palpitation, sweating	2
Williams 1998 USA [16]	Open head injury, sustained	Mean: 10.8	10 participants crossover	Dose: <20kg: 5mg; 21~29kg: 7.5mg; >30kg: 10mg bid Duration: 4 days Sessions: 3 Wash out: 72 hrs	Attention 1.Continuous Performance Test Memory 1.Sternberg Memory and Reaction Time Task 2.Sentence Repetition Task (SRT) Processing speed 1.Rapid Automatized Naming Test (RANT) 2.Symbol Digit Modalities Test (SDMT) Psychomotor ability 1.Finger Tapping Test 2.Developmental Test of Visual-Motor Integration 3.Purdue Pegboard	NA	No adverse event	3

Table 2. contd….

Study Year Country	Participants (Severity and Localization of Lesion)	Age (Year)	Sample Size and Study Design	Dose Regimen	Measurements	GCS	Adverse Events	Jadad Quality Score (Total Score: 5)
Mahalick 1998 USA [17]	mild to severe	Mean: 10.7	14 participants crossover	Dose: 0.3mg/kg, bid Duration: 14 days Sessions: 2 Wash out: 12 hrs	Attention 1.The Vigilance Commission and Distractibility Commission indices of the Gordon Diagnostic System Processing speed 1.Woodcock-Johnson Psychoeducational Test Battery-Revised 2.The Ruff 2 and 7 Cancellation Test	mean: 6.9 range: 3-15	NA	3
Whyte 1997 USA [18]	mild to severe	Mean: 30.8	19 participants crossover	Dose: 0.25 mg/kg bid Duration: 2 day Sessions: 3 Wash out: not mentioned	Attention 1.Go/no-go task (sustained arousal task) 2.Phasic arousal task 3.Distraction task 4.Behavioral inattention Processing speed 1. Choice reaction-time task	mean: 5.8 range: 3-14	NA	3
Speech 1993 USA [19]	Moderate to severe	Mean: 27.6	12 participants crossover	Dose: 0.3mg/kg bid Duration: 7days Sessions: 2 Wash out: not mentioned	Attention 1.Gordon Diagnostic System Memory 1.Digit Span Test of WAIS-R 2.Selective Reminding Test 3.Serial Digit Test Processing speed 1.Digit Symbol Test of WAIS-R 2.Stroop Interference Task 3.Sternberg High Speed Scanning Task	NA	No adverse vent	3
Baker 1990 USA [20]	mild to severe	Mean: 11	8 participants crossover	Dose: 15mg qd (< 0.6mg/kg) Duration: 9-14days Sessions: 1 Wash out: not mentioned	Attention 1.Matching Familiar Figures Test (MFFT) 2.Continuous Performance Test (A-X version) (CPT) 3.Seahore Rhythm Test Memory 1.Central-incidental method (not a standardized test) Processing speed 1.The Stroop Color and Word Test 2.Trail-Making Test (part A & B) 3.Progressive Figures Test Global cognition function 1.Wechsler Intelligence Scale for Children-Revised (WISC-R)	mean: 11.3 range: 3-15	shaking, dizziness, decreased appetite, stomachaches, irritability, cold hands, stomachaches, emotional hypersensitivity	3

*: Wash out period is not applicable in parallel study
NA: not available

answers among all responses [17-19, 21]. Gordon Diagnostic System and Sustained Attention Task were selected for analysis. A pooled effect size of 0.45 (95% CI: 0.10 to 0.79), based on the fix-effects model, denoted significant overall improvement of selective attention for the methylphenidate group (Fig. **1**). Only small heterogeneity emerged among all of the included trials [Chi^2= 3.52, df = 3 (p = 0.32); I^2 = 15%]. In the subgroup analysis, Sustained Attention Task also showed significant benefits in the methylphenidate group (standardized mean difference: 0.66, 95% CI: 0.22 to 1.10) (Fig. **1**).

Memory

Six RCTs measured memory impairment by using three tools: the Selective Reminding Test, the Sternberg Memory Task, and Two Back Test [13-16, 19, 21] that showed no significant differences either in total or subgroup analysis among the methylphenidate and placebo groups (standardized mean difference: -0.09, 95% CI: -0.77 to 0.18; Fig. **2**).

Processing Speed

Of all RCTs, four compared Choice Reaction Time, the interval between a correct response and a stimulation hint,

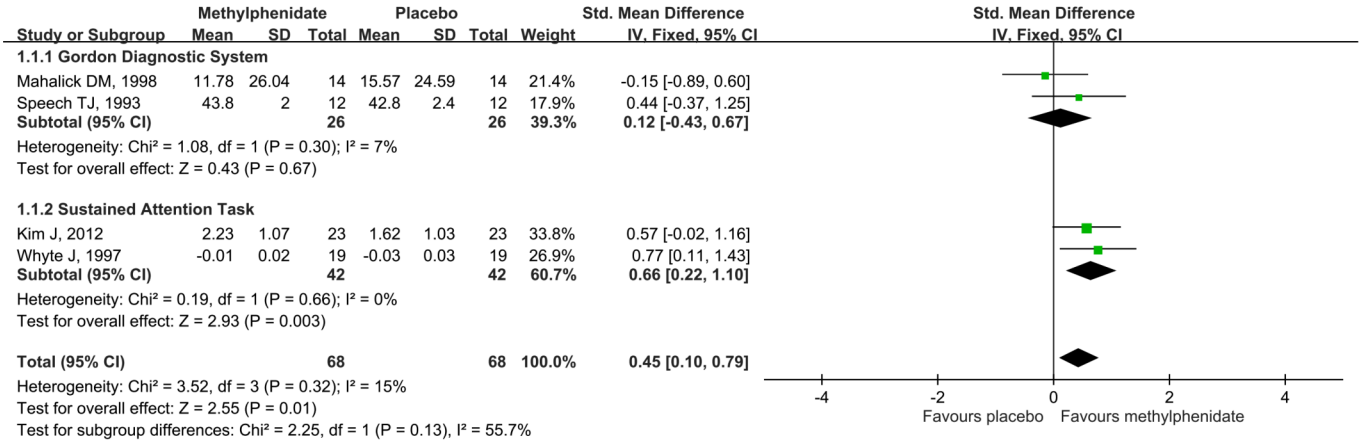

Fig. (1). Comparison of attention after administrating methylphenidate reported in four RCTs.

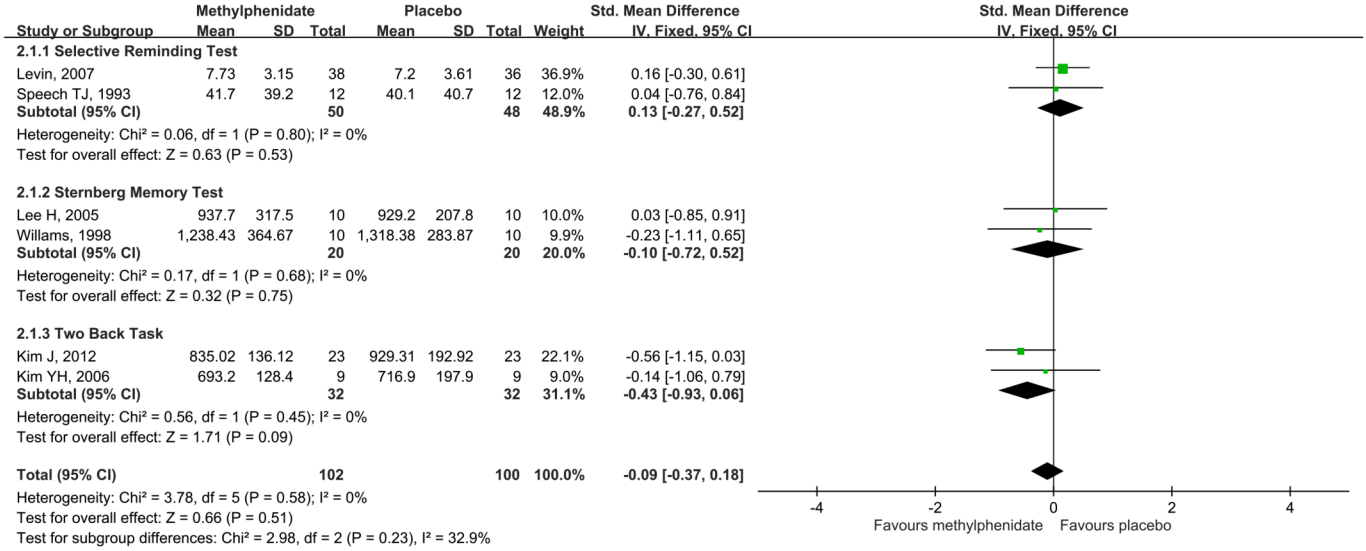

Fig. (2). Comparison of memory improvement after administering methylphenidate, as reported in six RCTs.

after administrating methylphenidate. No statistically significant improvement was observed between the methylphenidate and placebo groups (95% CI: -0.97 to 0.15; Fig. **4**). Processing speed of accuracy, detected by Ruff 2 and 7 Attention Test or Symbol Digit Modalities Test, was enhanced in the methylphenidate group, despite the lack of statistical significance (95% CI: -0.17 to 0.42; Fig. **3**).

ADVERSE EVENTS

Regarding adverse events, which were included as a secondary outcome in this study, the most commonly reported side effects of methylphenidate were gastrointestinal upsets, including decreased appetite, nausea, vomiting, diarrhea, constipation, and stomachache, in two studies [15, 20]. Less common side effects were associated with central nervous system manifestations, including dizziness, insomnia, irritability, and headache [10, 20]. However, no serious morbidities or mortalities were noted in any studies.

DISCUSSION

Cognitive complaints were common, even after mild TBIs, both immediately and in later follow-ups. The prevalence rates of memory and attention complaints after mild TBIs vary, but have been reported to range from 40% to 60% at 1–3 months post-injury [5, 25]. These cognitive impairments are often diffuse with more prominent deficits in information processing, attention, memory, cognitive flexibility, and problem solving [25]. Substantial economic resources are consumed annually, and are estimated to cost as much as $48.3 billion in the United States [26, 27]. However, today, no medication has received approval from the U.S. FDA for treating the neuropsychiatric consequences of TBIs [1]. Psychostimulants, including noradrenaline agonists, dopamine agonists, and acetylcholine agonists, are widely used in an effort to improve arousal, attention, and related neurobehavioral difficulties after a TBI, although evidence-based clinical guidance has been lacking [5, 28].

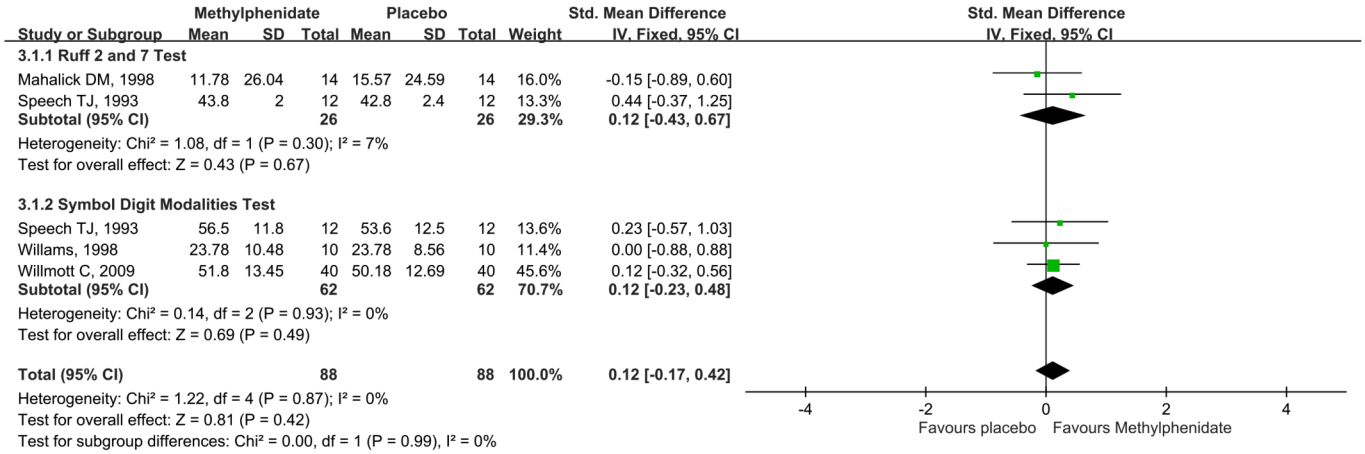

Fig. (3). Comparison of processing speed (accuracy) after administrating methylphenidate reported in four RCTs

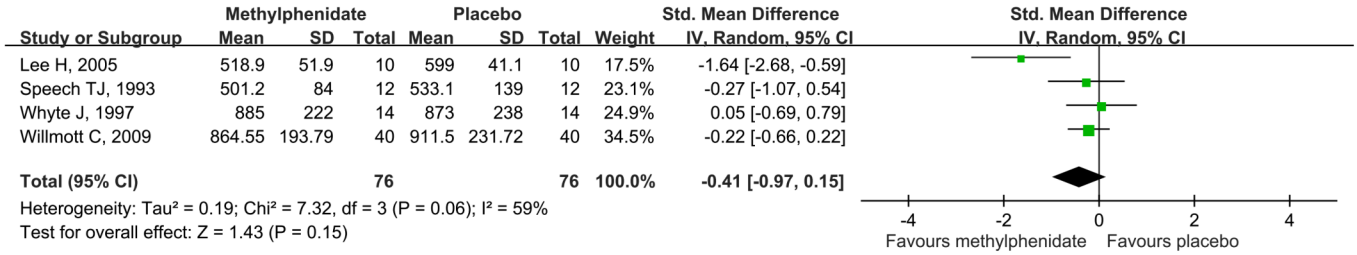

Fig. (4). Comparison of processing speed (time) after administrating methylphenidate reported in four RCTs

Methylphenidate was first synthesized in 1944. It has a short half-life and produces minimal side effects (e.g., abdominal pain and nausea) that often dissipate with continued use. Methylphenidate, a psychostimulant and a dopamine reuptake inhibitor, has been shown to increase the levels of dopamine in the central nervous system, including the frontal cortex [29]. Although it has been indicated for a number of conditions such as chronic fatigue, lethargy, depressive states, disturbed senile behaviors, and narcolepsy [30], the current major therapeutic use of methylphenidate is for the treatment of narcolepsy and ADHD in children [3].

There are several different types of attention including selective attention, sustained attention and the divided attention [31]. Selective attention is a cognitive process of selectively concentrating on one specific stimulus while suppressing unnecessary information, as well as a basic process of executive functioning. This process is also the most frequently documented benefit from methylphenidate treatment. Anatomically, there are three networks to explain the attention system in human brains, namely, an alerting network arising from the brain stem arousal system and right hemisphere system related to sustained vigilance, an orienting network situated on the parietal cortex, and an executive network located on midline frontal/anterior cingulate cortex [32, 33]. Although the detailed mechanism is not well known, methylphenidate elevates the synaptic concentration of dopamine and noradrenalin by blocking their reuptake, resulting in an increase in the extracellular levels of these neurotransmitters in various brain regions [34].

The use of methylphenidate to enhance the processing speed in patients with TBI has also been viewed as an adequate pharmacotherapy [28, 35]. Common clinical experience suggests considerable benefits in appropriately treated individuals after years of therapy [36]. A recent systematic review mentioned the use of methylphenidate in the treatment of attention deficit after non-progressive acquired brain injury, showing an improvement in information processing speed but not all attention aspects in some TBI patients [5]. However, no sufficient or validated systematic review supports its use to promote overall cognitive function, including attention and memory, because of wide variations in the study populations involved. One report, a meta-analysis investigating the effect of the timing of pharmacological treatment on efficacy, demonstrated an improved outcome in patients receiving early treatment (<7 days) after injury [37], but whether treatment administered weeks or months after injury is also beneficial remains unclear. The reliability of the results of another report studying the impact of pharmacological treatment on cognitive and behavioral outcomes in the post-acute stages of adult TBI [38] was hampered because only two electronic databases (PsycINFO and PubMed) were searched, and non-English literature was excluded. Therefore, some relevant studies may have been missed. In contrast, another study demonstrated a greater response to methylphenidate treatment in patients with more severe injuries compared with those with less severe TBI

according to their Glasgow Coma Scale (Mean GCS = 5.33) [12].

Although some previous studies have explored the effectiveness of methylphenidate, no study has presented forest plots to generate more in-depth results. Therefore, we combined similar concepts of cognitive-related outcome measures to obtain valid results and provide a clear conclusion. This meta-analysis, which is the first study to quantitatively address the effectiveness of methylphenidate in the treatment of TBI-associated cognitive deficits, included only studies with double-blind, parallel-group, or crossover designs in which age, sex, and education level were matched. We analyzed the primary outcome of attention, memory, processing speed, psychomotor ability, global cognitive function from the eligible trials and similar assessment tools were chosen for comparison.

Regarding the impact of methylphenidate on attention, four of the RCTs in the current study[17-19, 21] showed significantly increased vigilance-associated attention after methylphenidate treatment consistent with the findings of previous studies[10, 12, 28]. The result is also in concert with that of a review by Frenette *et al.* who reported statistically positive outcomes in 10 out of 15 attention-related studies following methylphenidate use. Accordingly, the finding of subgroup analysis of the present study, which demonstrated a beneficial impact of methylphenidate on sustained attention, is consistent with that of previous studies that reported statistically significant positive results using Sustained Arousal and Attention Task [9, 12, 17]. Although INCOG recommendations previously concluded that no methylphenidate treatment-related improvement was seen in divided attention, sustained attention, or susceptibility to distraction [35], the present study demonstrated positive therapeutic effect of methylphenidate on attention after taking into account the results of more recent studies [18, 21].

In analyzing the outcomes of memory improvement, no evidence of memory improvement after administrating methylphenidate was noted. Compared to Frenette *et al*., we statistically analyzed two additional memory measurement tools (i.e., the Sternberg Memory Task and Two Back Test) in four RCTs, and revealed the trend of the positive effect of methylphenidate that failed to reach statistical significance [14-16, 21, 39].

Moreover, similar assessment tools for processing speed from all included studies, including the Ruff 2 and 7 Attention Test, and Symbol Digit Modalities Test, also did not demonstrate statistically significant improvement after administrating methylphenidate. Frenette *et al*. presented 21 types of tests that have been adopted for measuring the processing speed of attention; however, only one measure (i.e., the Symbol Digit Modalities test) has been utilized in more than three studies [7, 39].

Concordant with the results of the present study, MICROMEDEX® 2.0 (Thomson Micromedex, Greenwood Village, CO, USA) has categorized the use of methylphenidate in the treatment of TBI-related cognitive dysfunction into Class IIb that signifies its usefulness and indications only in selected cases. Methylphenidate is eliminated from the plasma with a mean half-life of 2-4 hours with 80% metabolized through the liver and excreted through urine after 24 hours [40]. An adequate washout period (i.e., at least 24 hours), therefore, was necessary before conducting the measurements in the crossover studies. Among the seven crossover studies, only three completed neuropsychological measurements with an elimination period of which only two reported sufficient time to exclude carryover effects. The remaining three RCTs did not require washout periods because they did not involve a crossover design.

LIMITATIONS

This study has limitations. First, the small number of subjects recruited in most studies from our comprehensive search precluded drawing a powerful conclusion. In addition, the wide age range in the included studies generated potential variations in study outcomes. Moreover, because only two studies focused on pediatric patients [16, 17], the effectiveness of the meta-analysis in examining the effect of methylphenidate on the pediatric population was severely limited. Second, some studies did not report the mean or standard deviation, which prevented the accurate computation of the effect size. Furthermore, although one study mentioned the inter-rater reliability of the neuropsychological measures [9], none reported the statistical issues of minimal clinical important difference (MCID), the reliable change index (RCI) for significant change scores, or the inter-subject variability in parallel group designs. Third, several of the studies provided insufficient clinical details to allow an adequate assessment. For instance, while most trials have recruited patients with moderate to severe TBI within a Glasgow Coma Scale range of 5 to 9, the information on the severity of TBIs was unavailable in two studies [14, 16]. Fourth, only two of the included studies addressed the dropout rate. One of the studies disclosed a high dropout rate (47.82%) on the 30th day after administrating methylphenidate [10], whereas the dropout rate of another study was 12.80% following six sessions of intervention [9]. Because the reported symptoms and signs in all studies were well tolerated, the causes of the dropouts remain unclear. In addition, intention-to-treat analysis was conducted in only one of those studies [12]. Finally, the variations in the dosage and frequency of methylphenidate administration among the studies may contribute to potential difficulty in interpreting the study results. For instance, three studies used fixed doses [13, 15, 20], whereas the other studies adopted body weight-adjusted doses [12, 16-19]. Regarding the administration frequency, one study reported using a single dose (20 mg) [14], whereas another study administered doses at intervals of 28 days [13, 15]. Nevertheless, there were no significant differences in outcome among the studies.

CONCLUSION

The present study showed statistical significance in using methylphenidate for enhancing the attention in patients with TBIs, whereas no notable benefit was observed in the facilitation of memory or processing speed. Well-designed large-scale studies are warranted to determine the optimal

timing, dosage, and duration of treatment, and to identify the long-term effects and suitable candidates to achieve maximal benefits.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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