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Original article

Short-term efficacy and tolerability of methylphenidate in children with traumatic brain injury and attention problems

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Abstract

Purpose: This study aims to investigate the short-term efficacy and tolerability of immediate-release methylphenidate (IR-MPH) in children with a history of traumatic brain injury (TBI).

Methods: Twenty children with TBI (mean age: 12.7 ± 3.1 years) who had clinically significant attention deficit and/or hyperactivity-impulsivity symptoms and twenty children with primary Attention Deficit Hyperactivity Disorder (ADHD) (mean age: 12.3 ± 3.05 years) were included. Study measures, which included the Turgay DSM-IV based ADHD rating Scale (T-DSM-IV-S), Conners' Parent Rating Scale (CPRS), Conners' Teacher Rating Scale (CTRS-R) and Clinical Global Impression-Improvement Scale (CGI-I), were completed at the baseline for both of the groups. For the TBI group, study measures and an adverse effect scale developed by the authors were completed 8 weeks after IR-MPH treatment (10 mg dose t.i.d).

Results: No significant difference was found regarding the baseline scale scores between the study groups. Among children with TBI, most of the scores on T-DSM-IV-S, CPRS and CTRS-R were found to improve significantly after MPH treatment, ($p < 0.05$). 70% ($N = 14$) of the sample were much improved at the endpoint. MPH was generally well-tolerated (95% had either no adverse effect or mild adverse effects).

Conclusion: In this preliminary open-label study, IR-MPH was found as a safe and effective treatment option for ADHD symptoms after TBI. However, future controlled studies are needed to confirm our findings.

Keywords: Traumatic brain injury; Children; Methylphenidate

1. Introduction

Traumatic brain injury (TBI), one of the main causes of morbidity and mortality of childhood, has been shown to result in impaired psycho-social and cognitive functioning [1]. Cognitive deficits may involve problems with attention, memory and executive functions [2–4]. One to four years after injury, more than one-fifth of children with TBI are under the risk of attention problems [5,6]. This is much higher than the 5–12% prevalence of developmental Attention Deficit Hyperactivity Disorder (ADHD) [7]. Although not completely established, a terminology is growing recently to define ADHD symptoms after TBI. Attention deficit, hyperactivity and impulsivity symptoms that occur following brain injury, rather than from the

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neuro-developmental causes, is often referred to as secondary ADHD (S-ADHD) [8]. There is evidence that S-ADHD has some different features from primary ADHD; hyperactivity may be generally less severe, with the inattentive subtype predominating in the first two years post injury [8,9]. Some studies have shown that severe TBI is more likely to be associated with ADHD symptoms [10–12]. The possible relationship between TBI lesion characteristics and S-ADHD has not been clarified. It has been shown that lesions in frontal cortex may be related with S-ADHD in the first 6 months, but not from 6 to 24 months after TBI [5,6]. One study which used susceptibility weighted imaging has found an association between increased lesion number and poorer functioning in neuropsychologic performance including attention and executive functions [4].

Children with TBI and attention problems, frequently having other cognitive deficits including those on perception and memory, usually face academic underachievement [11]. The consequences of attention problems may extend beyond school functioning and can have negative impacts on a child's social relationships, emotional well-being, self esteem and quality of life [9]. Long-term attention problems have also been reported after TBI. Yeates et al. [10] have found that almost half of children with severe TBI displayed significant attention problems on the Child Behavior Checklist (CBCL) on average 4 years post-injury. Despite the high burden of attention problems in children after TBI, only a limited number of controlled studies, all with small sample size and short duration, have focused on the treatment options [1,13–16]. Moreover, all of these studies are from Western countries. While numerous studies have shown that central nervous system (CNS) stimulants are generally a well-accepted treatment for developmental ADHD [17], less is known about their efficacy and tolerability on ADHD after TBI [14–16]. The main aim of this study was to investigate the short-term efficacy and tolerability of immediate-release methylphenidate (IR-MPH) in children with a history of TBI. The possible relationship between TBI-related variables, including TBI severity and location, and treatment response was also examined.

2. Methods

2.1. Sample

The study sample with TBI were recruited from the Pediatric Neurology Clinic of Mersin University School of Medicine Hospital. The inclusion criteria, which was based on the criteria used by Nickles et al. [1], were as follows: (1) Age of 6–18 years. (2) Neurological diagnosis of moderate to severe TBI, with severity based on the initial Glasgow Coma Scale (GCS) Score at presentation to the study hospital. Moderate TBI was defined as the GCS 9 to 12, or the presence of mechanical ventilation for less than 24 h; and severe TBI was defined as the GCS less than 9, or the presence of mechanical ventilation for 24 h or longer. (3) One to four years post injury. (4) Clinically significant attention/concentration problems and/or hyperactivity-impulsivity symptoms at the Schedule for Affective Disorders and Schizophrenia for School-age Children-present and Lifetime version (K-SADS-PL) interview. (5) No other psychiatric diagnosis on K-SADS-PL interview (only comorbid Oppositional Defiant Disorder (ODD) was allowed). (6) Normal intelligence based on (a) clinical interview and (b) either a WISC-R full scale IQ score above 80 or the average/above average academic achievement documented with the last year's final school grades. All of the psychiatric evaluation, including the assessment of intellectual functioning, was made in the presence of a faculty member of child and adolescent psychiatry. The children with developmental delay, motor and visual handicaps, uncontrolled seizure disorder and other chronic diseases were excluded.

The study was conducted during May–July 2015 and the sample included patients who had TBI one to 4 years before the study procedure (between May 2011 and May 2014). From the pediatric intensive care medical records, a total of 112 TBI patients who fulfilled the neurological and post-TBI duration inclusion criteria were detected. Sixty-seven of these patients met the age criteria of 6–18 years of age. These eligible children and adolescents were then called for an evaluation by a child psychiatry faculty member of the same hospital. Appointments were given to fifty-eight patients (parents of nine patients did not want to participate in the study), and fifty-one of them attended to the psychiatric evaluation which included the K-SADS-PL interview. According to the K-SADS-PL, twenty-two children and adolescents with TBI met the psychiatric inclusion criteria and were recruited for the study. The parents of the sample were informed about the study procedure in detail and informed consent was obtained for twenty patients (two parents did not accept the medication treatment). The final sample included 20 patients. The study protocol was approved by the Mersin University School of Medicine Ethics Committee. During the K-SADS-PL interview, the possible history of pre-injury developmental ADHD was briefly questioned. However, most of the parents did not give a conclusive information (60% gave the answers of "I can't remember" or "My child has some behavioral problems and attention problems but not at an impairing level"). None of the patients were reported to have a pre-injury ADHD diagnosis or MPH treatment history.

To compare the baseline ADHD characteristics of children with TBI with primary ADHD, a control group was included. For the control group, the same number