

ORIGINAL ARTICLE

The Effect of Long-Acting Methylphenidate and Modafinil on Attention and Impulsivity of Children with ADHD using a Continuous Performance Test: A Comparative Study

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Abstract

Objectives

Given the importance of having a continuous performance for the academic and social life of children with attention-deficit/hyperactivity disorder (ADHD). in this study, a Continuous Performance Test (CPT) was used to compare the effect of long-acting methylphenidate and modafinil on attention and impulsivity of these children.

Materials & Methods

A randomized clinical trial was conducted on 50 children with ADHD aged 6 to 12 years in the child and adolescent psychiatric departments of Imam Hossein and Mofid hospitals, Tehran, Iran. The children were selected by availability sampling and randomly assigned into two equal groups (n=25 in each). While the first group was treated with long-acting methylphenidate, the second was treated with modafinil for 14 days. The CPT was carried out before and after the treatment. The obtained data were analyzed by F and t tests.

Results

Long-acting methylphenidate and modafinil were both effective in improving attention and impulsivity in children with ADHD. There was no significant difference between the two drugs in terms of effectiveness on attention and impulsivity.

Conclusion

The findings of this study showed that long-acting methylphenidate and modafinil are equally effective in improving attention and impulsivity in children with ADHD aged 6 to 12 years.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental syndrome characterized by a persistent pattern of inattention or impulsivity and hyperactivity at much higher levels of frequency and severity than what can normally be observed in people of the same developmental age and with symptoms appearing and lasting to a degree that is inconsistent with the person's developmental level. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a person is diagnosed with ADHD if six or more of the nine symptoms of inattention or six or more of the nine symptoms of hyperactivity/impulsivity, which cannot be better explained by other disorders, have been present for at least six months, starting before age 12, and is causing poor performance in at least two settings (academic, social, or daily life) (1)

Affecting about 7% of school children and about 5% of adolescents and adults, ADHD is believed to be one of the world's most common chronic developmental disorders (2). However, there is no general consensus on the exact prevalence of this disorder. In the 2014 report of the American Psychiatric Association (APA), the prevalence of ADHD in children aged 4 to 12 years was reported to be between 6 and 11% (3). In a study on elementary schools in Tehran, ADHD was found to be the second most common problem after adjustment disorders (4). A study by Shafaat et al. (2013) estimated the prevalence of this disorder to be 14.2% (5). This disorder is more common

among boys than girls, with a male-to-female ratio ranging from 2:1 to 9:1 (6).

ADHD is identified by its three major symptoms: inattention, hyperactivity, and impulsivity. However, based on the results of factor analyses, in recent years, these three symptoms have been classified into two behavioral dimensions: attention deficit and hyperactivity/impulsivity (disinhibition) (7).

In ADHD, the term 'attention' refers to the ability to focus and remain focused on a specific aspect of information. The most important attention problem of children with ADHD is their inability to maintain 'sustained attention'. There is growing evidence of the relationship between inhibitory control deficiency and sustained attention deficit in children with ADHD, as it has been demonstrated in multiple studies conducted with different tests, including the Stroop task (8), the stop-signal task (9), the go/no-go task (10), and the flanker task (11). Many studies on children with ADHD have shown abnormalities in the structural processes of the brain and the functioning of brain regions related to the response inhibition (12). In Iran, a study by Nazifi et al. showed that children with ADHD performed worse in maintaining sustained attention than normal children (13).

People with ADHD also exhibit impulsivity or impulsive behavior, which is often attributed to a lack of response inhibition. The impulsive behavior of these people can be considered a functional response to avoid situations associated with delay. This dislike of delay is one of the main signs of

ADHD (14).

According to the existing evidence, the problems of children with ADHD in behavioral inhibition can be attributed to several sources. For example, parents and teachers describe the behavior of these children as impulsive and uncontrollable, stating that these children have difficulty dealing with delayed rewards or satisfaction and also delays in gaining what they need or require (15). Also, numerous studies have shown that response inhibition, as measured by the ability to handle multiple neuropsychological tasks, is impaired in these children (16, 17).

Studies conducted with a variety of tests have suggested that defects in response inhibition could be one of the major causes of impairment in the executive functioning of children with ADHD (18, 19). Three of the best-known tests used in this area include the Continuous Performance Tests (CPTs), the Sign-Stop Task, and the Stroop Test (20). In CPTs, the subject needs to maintain attention on performing a continuous task while avoiding impulsive responses. In recent years, CPTs have been widely used not only in the assessments of attention and impulsivity problems for research purposes but also in the rehabilitation of people suffering from these problems, like children with ADHD (21). In this study, a CPT was used to measure attention and impulsivity variables.

Numerous studies have shown that attention deficit and response inhibition problems, which can manifest as impulsive behaviors, are associated with poor academic performance in children with ADHD (22, 23). Compared to their peers, children with ADHD are more likely to perform poorly in school and become academic underachievers (24, 25). These issues highlight the importance of treating the symptoms of ADHD in the affected

children.

In current treatment guidelines, including those issued by the National Institute for Health and Care Excellence (NICE), the first-line drug treatment for ADHD is methylphenidate (26). Indeed, multiple systematic reviews and meta-analyses, including (27, 28), and multiple clinical studies, including (29, 30), have shown that methylphenidate has a clear and significant effect on ADHD, at least in the short term.

However, some patients may need to be treated with non-stimulant drugs for the following reasons: a) poor response to stimulant drugs, b) the child or the family refusing the treatment with stimulant drugs, c) comorbidity of ADHD with medical and mental disorders, anxiety, cardiovascular disorders, and seizures, and d) the child being vulnerable to the side effects of stimulant drugs (31).

Modafinil, which is structurally different from other psychostimulants, is also effective in relieving the symptoms of ADHD. However, children with ADHD may need higher doses of this drug compared to the amounts used in the treatment of narcolepsy (32). Research has shown that modafinil is indeed significantly effective against the symptoms of ADHD in both home and school settings, its prescribed doses are well tolerated by children and adolescents (32, 33), and abrupt discontinuation of the medication will not cause recurrence (33). Multiple studies have shown the efficacy of modafinil in improving attention and reducing the impulsivity of children with ADHD (34, 35, 36, 37, 38, 39).

Accordingly, this study aimed to compare the effect of modafinil and long-acting methylphenidate in children and adolescents with ADHD to gain a better understanding of alternative drugs available for treating the symptoms of this disorder, thus

improving the quality of life of these patients.

Materials & Methods

This randomized clinical trial (pre-test and post-test with two treatment groups) was conducted on children with ADHD aged 6 to 12 years in the child and adolescent psychiatric departments of Imam Hossein and Mofid hospitals in Tehran, Iran. The sample consisted of 50 children with ADHD diagnosed based on the clinical interviews, Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) semi-structured interviews, and confirmation by two psychiatrists. The children were randomly assigned into two equal groups (n=25 in each), one treated with long-acting methylphenidate and the other with modafinil.

Exclusion criteria were: mental disability, neurological diseases such as epilepsy, acute psychotic disorders, autism spectrum disorders, mood disorder (with current episode), anxiety disorder (with current episode), psychiatric illnesses other than oppositional defiant disorder (ODD), and conduct disorder, and use of other medications.

Before interventions (use of long-acting methylphenidate or modafinil), both groups underwent a pre-test, in which a CPT was used to measure attention and impulsivity variables. For 14 days, the methylphenidate group was treated with long-acting methylphenidate (manufactured by Sandoz Inc.) at a dose of 18 mg for the first five days and up to 45 mg if necessary, and the modafinil group was treated with modafinil (manufactured by Sobhan Daroo Co.) at a dose of 50 mg a day and up to 200 mg if necessary. At the end of the two-week period, both groups underwent a post-test identical to the pre-test. None of the patients

was forced to participate, all costs were borne by the researchers, and written consent was obtained from the parents of the patients.

In this study, we used the CPT and the K-SADS tools. The CPT was developed by Rosvold et al. in 1956 and refers to a group of tests that measure sustained attention in children with ADHD (40). One of the CPTs is the Integrated Visual and Auditory test (IVA-2), which measures two factors in the visual-auditory mode: response control and attention. This test has been developed based on the DSM-5 guidelines and can be used to detect different subtypes of ADHD, including inattentive (distractible) type, impulsive (hyperactive) type, combined type, and a fourth type called not otherwise specified (NOS). The Persian version of this test has been validated by Bakhshi (2010), who has reported a validity coefficient of 0.53 to 0.93 for this tool (41). The K-SADS is a form of semi-structured interview designed to diagnose disorders in children and adolescents. This test measures a range of psychiatric disorders based on diagnostic and statistical guidelines for mental disorders. According to Shahrivar et al. (2010), this tool has good to excellent concurrent validity in the diagnosis of major psychiatric disorders and excellent test-retest reliability in the diagnosis of ADHD and ODD (42).

Results

Table 1 shows the mean and standard deviation of attention and impulsivity scores (visual attention, auditory attention, visual response control, and auditory response control) of the groups treated with long-acting methylphenidate and modafinil in pre-test and post-test stages.

Table 1. Mean and standard deviation of attention and impulsivity scores (visual attention, auditory attention, visual response control, and auditory response control)

Variables	Statistical measure	Modafinil		Methylphenidate	
		Pre-test	Post-test	Pre-test	Post-test
Visual attention	Mean	86.52	92.28	77.96	92.84
	Standard deviation	24.07	65/12.65	20.51	19.01
Auditory attention	Mean	82.92	94.68	73.72	91.40
	Standard deviation	20.71	18.99	23.95	1.31
Visual response control	Mean	91.44	105.64	84.92	101.92
	Standard deviation	13.84	14.72	17.49	15.95
Auditory response control	Mean	81.44	99.40	75.88	98.88
	Standard deviation	17.76	17.18	17.77	19.45

Table 2 shows the results of the independent t-test of research variables in the long-acting methylphenidate and modafinil groups in the baseline.

Table 2. Results of the independent t-test of research variables in the methylphenidate and the modafinil groups in the baseline

Group Variable	Methylphenidate	Modafinil	t	Df	P
Visual attention	77.99 (20.51)	86.52 (24.07)	1.353	48	0.928
Auditory attention	73.72 (23.95)	82.92 (20.71)	1.452	48	0.433
Visual response control	84.92 (17.49)	91.44 (13.84)	1.461	48	0.386
Auditory response control	75.88 (17.77)	81.92 (17.76)	1.202	48	0.781

As shown in Table 2, the independent t-test showed no significant difference between the two groups in the pre-test stage (baseline). The dependent t-test was used to examine the changes in attention and impulsivity variables in each group after the treatment with long-acting methylphenidate or modafinil (Table 3).

Table 3. Results of the dependent t-test of attention and impulsivity variables

Variables	Group	Mean in pre-test	Mean in post-test	t statistic	P-value
Visual attention	Methylphenidate	77.96	92.84	-2.85	0.009
	Modafinil	86.52	98.28	-2.88	0.008
Auditory attention	Methylphenidate	73.72	91.40	-2.75	0.011
	Modafinil	82.92	94.68	-2.56	0.014
Visual response control	Methylphenidate	84.92	101.92	-4.35	0.000
	Modafinil	91.44	105.64	-4.14	0.000

Auditory response control	Methylphenidate	75.88	98.88	-5.01	0.000
	Modafinil	81.92	99.40	-4.21	0.000

According to the results presented in Table 3, within each group, there were significant differences between pre-test and post-test scores of the variables visual attention (methylphenidate group: $t=-2.85$ and $P=0.009$; modafinil group: $t=-2.88$ and $P=0.008$), auditory attention (methylphenidate group: $t=-2.75$ and $P=0.011$; modafinil group: $t=-2.56$ and $P=0.014$), visual response control (methylphenidate group: $t=-4.35$ and $P=0.000$; modafinil group: $t=-4.14$ and $P=0.000$), and auditory response control (methylphenidate group: $t=-5.01$ and $P=0.000$; modafinil group: $t=-4.21$ and $P=0.000$).

The analysis of covariance (ANCOVA) was used to compare the effect of long-acting methylphenidate and modafinil on the attention variables (visual attention and auditory attention) and the impulsivity variables (visual response control and auditory response control) (Table 4).

Table 4. Results of the analysis of covariance of post-test scores of attention and impulsivity variables

Efficacy	Variable	Sum of Squares (SS)	Degrees of freedom (df)	Mean Squares (MS)	F	P-value
Intergroup? (long-acting methylphenidate and modafinil)	Visual attention	158.501	1	158.501	0.651	0.424
	Auditory attention	0.315	1	0.315	0.001	0.981
	Visual response control	30.049	1	30.049	0.179	0.675
	Auditory response control	16.019	1	16.019	0.050	0.624

As Table 4 shows, there was no significant difference between the two groups in terms of the variables visual attention ($F=0.651$ and $P=0.424$), auditory attention ($F=0.001$ and $P=0.981$), visual response control ($F=0.179$ and $P=0.675$), and auditory response control ($F=0.050$ and $P=0.624$). Accordingly, it can be concluded that long-acting methylphenidate and modafinil were equally effective in improving attention and impulsivity in children with ADHD.

Discussion

The objective of this study was to compare the efficacy of long-acting methylphenidate and modafinil in improving attention and impulsivity in children with ADHD aged 6-12 years. The results of the dependent t-test (Table 3) showed that two weeks of treatment with long-acting methylphenidate improved the attention and impulsivity scores of children with ADHD. Meanwhile, two weeks of treatment with modafinil had the same effect.

This result is consistent with the findings of Muhiberger et al. (29) and Chidress et al. (30), which showed the positive effect of long-acting methylphenidate on the symptoms of ADHD and cognitive functions (especially sustained attention). One of the main causes of the symptoms of ADHD is the deficiency and impaired functioning of dopamine and norepinephrine neurotransmitters. Since methylphenidate inhibits the reuptake of dopamine and, to a lesser extent norepinephrine through synapses in the prefrontal cortex, it can be effective in improving the symptoms of ADHD by increasing the activity of these two neurotransmitters.

To maintain sustained attention while performing visual and auditory tasks in the CPT, the patient must be able to hold two sets of information simultaneously, switch between them constantly, and prevent interference between responses using cognitive flexibility and executive functions, including working memory. Many studies have shown that these abilities are weaker in children with ADHD than in normal children. It is possible that by integrating the dopaminergic system, methylphenidate might have a direct amplifying effect on executive functions and, consequently, on attention and response control skills.

The findings of the present study are also consistent with the results of Wang et al. (34), Kahbazi et al. (35), and Biederman et al. (36), indicating that modafinil was effective in improving attention and reducing impulsive behaviors in children with ADHD.

While the mechanism of action of modafinil in improving attention and impulsivity is not fully understood yet, it appears that modafinil alters the balance of γ -aminobutyric acid (GABA) and glutamate, resulting in the activation of the hypothalamus (43). Modafinil also increases the metabolic rate in the centrolateral thalamus, central nucleus of the amygdala, and hippocampus. This effect is different from the effect of methylphenidate and amphetamines, which primarily act by restoring dopamine secretion in the striatum (44) and can have positive effects on the symptoms of ADHD in children.

The results of this study showed that the children treated with modafinil experienced a better improvement in the visual attention subscale than those treated with long-acting methylphenidate (mean post-test score of 98.28 in the modafinil group versus 92.84 in the methylphenidate group). The children treated with modafinil also showed better improvement in the auditory attention subscale than those treated with long-acting methylphenidate (mean post-test score of 94.68 in the modafinil group versus 91.40 in the methylphenidate group). In other words, modafinil had a greater impact than long-acting methylphenidate on the performance of children in both of these subscales, but the difference between the two drugs was not statistically significant.

Modafinil was also more effective than methylphenidate in the visual response control and auditory response control subscales, but this

difference was also statistically insignificant. This can be attributed to the small number of subjects and the limited duration of treatment with these drugs (14 days). Considering the lack of significant difference between the mean post-test scores of the modafinil and methylphenidate groups, modafinil can be considered a promising alternative to stimulant drugs for children with ADHD. However, more clinical trials are needed to confirm this issue.

The most important limitation of this study was the use of a computer program to evaluate the attention and impulsivity of children treated with methylphenidate and modafinil. These programs measure the children's attention and response control over a short period of time; however, to improve their academic and social performance, children must be able to maintain sustained attention throughout a longer period, like a day. Thus, it is recommended to be cautious in generalizing the results.

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Author's Contribution

Ghazal zahed contributed to the study conception and design. rozbakhsh contributed in case selection and led monitoring and implementation of the study.all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Conflict of interest

The authors declare no conflict of interest.

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