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A Comparative Study of the Efficacy of Methylphenidate and Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Background and Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood. The aim of this study was to compare the efficacy of methylphenidate (Ritalin) and atomoxetine in improving ADHD symptoms and also their side effects.

Methods: The randomized clinical trial included 60 children aged 6-14 years with ADHD who were referred to the psychiatric clinic of Yahyanejad Hospital. They were randomly divided into two groups, one of which received methylphenidate and the other atomoxetine. The patients were followed up by a psychiatrist after treatment. Improvement in symptoms was measured by examining the ADHD Rating Scale (RS) scores. The results were analyzed using an independent t-test and a value of $p \leq 0.05$ was considered significant.

Findings: The mean ADHD RS score decreased in both groups in the fourth- and eighth-week intervals after the intervention, with a statistically significant difference in the eighth week compared to pre-treatment and the fourth week for both groups (P-value=0.001). However, no statistically significant difference was observed in the mean scale score between the two groups (P-value=0.48). In the fourth week, the mean complication rate was significantly lower with atomoxetine than with methylphenidate (P-value=0.001). Even in the eighth week, no significant difference was found in the side effects of methylphenidate and atomoxetine (P-value=0.553).

Conclusion: The efficacy and tolerability of atomoxetine and methylphenidate were described as similar. However, there was no significant treatment difference between the two drugs. The frequency of side effects was similar for both drugs after eight weeks of treatment.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental disorders in children, usually persisting into adulthood [1]. Children with ADHD often struggle with cognitive and behavioral problems in addition to the "core symptoms" of inattention, impulsivity, and hyperactivity [2-7]. ADHD is a common neurobehavioral problem affecting children aged 6-17 years. In the United States, it is prevalent in 2-18% of 6- to 17-year-olds [3]. In Iran, the prevalence rate is 10-12% among children. The symptoms of ADHD persist into adulthood in the majority of children, reaching up to 60%.

The disorder is associated with life-threatening consequences, such as the disruption and breakdown of relationships with parents, teachers, and peers in childhood, educational problems, delinquency, and substance abuse in adolescence and adulthood [5]. This disorder also leads to learning disabilities at school and can then manifest itself in the form of social disabilities (low self-concept and self-esteem, low motivation and interest, and confrontational behavior) [6]. ADHD is divided into the following types: 1- Combined hyperactive – inattentive form 2- Predominantly inattentive form 3- Predominantly hyperactive/impulsive form [7]. The ratio of boys to girls is 3 to 1 and a maximum of 5 to 1. This disorder is more common in the first sons in the family. Although boys are more likely to be diagnosed with ADHD than girls, the rate of diagnosis in adulthood is the same for women and men [8].

The disorder is important due to its high prevalence. 50% of children with psychiatric disorders and 3-5% of school-age children have ADHD [9]. Studies estimate the prevalence at 1-20%, depending on the diagnostic criteria used, the child population studied, the research methods, and the sources of information [10]. Due to the high prevalence of behavioral disorders like ADHD and the lack of attention to its consequences in children and adolescents, timely diagnosis, intervention, and treatment of ADHD is considered necessary and important. Medication is the most commonly recommended treatment to intervene without complications [11]. Drug treatment and behavioral therapy are the predominant forms of treatment, with the former receiving more attention from physicians [12]. As with other chronic conditions, research on ADHD provides parents and physicians with new data on the diagnosis, causes, treatment, long-term effects, and complications associated with the disorder.

Methylphenidate (Ritalin) is one of the most commonly used stimulants to treat children with ADHD. A study by Khajeh Piri et al. on 71 patients receiving methylphenidate showed that 100% of them had at least one complication. Anorexia, irritability, and sleep disorders are the most common side effects in methylphenidate users, which are dose-dependent and transient [13]. In addition, atomoxetine is effective in the treatment of ADHD in children and adolescents with 1 or 2 doses and in adults with 2 doses per day. A recent study has indicated that atomoxetine would be equally effective if administered twice daily (morning and evening). That is, although the efficacy of atomoxetine is 5 hours, its effects on ADHD symptoms remain greater than the direct pharmacological effects. This is a difference between atomoxetine and stimulants, as the effects of stimulants are related to the plasma level of the drug [14].

In a meta-analysis, Hennison et al. (2017) examined the cardiovascular therapeutic effects of stimulants and non-stimulants in children and adults with ADHD. They reviewed 18 articles and found that atomoxetine and amphetamine both led to a significant increase in systolic and diastolic blood pressure and heart rate, while methylphenidate only led to an increase in systolic blood pressure. About 2% of patients did not continue their medication due to cardiovascular effects and most cardiovascular complications resolved spontaneously. Statistically, no serious cardiovascular complication was observed due to the use of three drugs [15]. However, some studies have shown that this drug can be abused and cause various side effects such as increased heart rate, etc. [16, 17]. In addition, some children do not tolerate or respond well to this medication. Therefore, clinically, the treatment of children with ADHD requires non-stimulants with

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the greatest efficacy and least side effects. Since the table of side effects, the mechanism of action and the duration of action of the two drugs methylphenidate and atomoxetine are different and according to the different results reported in previous studies, a comparison of the effects and side effects of these drugs in patients with ADHD may be useful for specialists in this field of psychiatry. Hence, the present study was designed to compare the therapeutic effect of methylphenidate and atomoxetine in the treatment of children with ADHD and to evaluate the side effects of these drugs.

Methods

Study Design and Participant

It is a clinical trial and a single-blind study. The population included children aged 6-14 years who were referred as outpatients to the psychiatric clinic of Yahyanejad Hospital. The subjects were selected by convenience sampling and random allocation using a table of random numbers from the files of newly admitted and diagnosed patients of Yahyanejad Hospital of Child and Adolescent Psychiatry into two groups. Finally, 60 subjects were selected as a sample based on the DSM-V criteria and an interview by a psychiatrist for the diagnosis of ADHD patients. Patients who had previously been treated with atomoxetine or methylphenidate were not included in the study, and this study was only conducted on children who were being treated with medication for the first time.

Patients were included if they were diagnosed with ADAD based on the DSM-V hyperactivity and inattention criteria, had no liver, kidney, heart, or chronic diseases requiring special care, and had not taken MAOI (monoamine oxidase inhibitor) medications in the past 15 days.

Patients with substance use disorders, eating disorders, psychiatric disorders such as history of tic disorders, mental retardation, autism spectrum disorder, individual history of Tourette syndrome, history of seizure, history of hyperthyroidism, or history of medication use with methylphenidate or atomoxetine were excluded.

Sample Size

Based on previous studies by other researchers, 60 children aged 6-14 years who were referred to the psychiatric clinic of Yahyanejad Hospital with a diagnosis of ADHD were selected for this study.

Procedure

The parents and guardians were informed about the research method and the nature of the intervention. After the parents signed the informed consent form, the children were randomly assigned to two groups, Ritalin or Atomoxetine. Using a table with random numbers, the file numbers of the newly admitted and diagnosed patients of the Yahyanejad Child and Adolescent Psychiatric Clinic were selected.

The children were monitored for parameters such as blood pressure, heart rate, height, and weight before taking the medication and then referred to a cardiologist if necessary. Methylphenidate (Brand name: Ritalin, Company name: Novartis, Country: Switzerland) was initially administered in tablet form at 0.3 mg /kg/day after breakfast and lunch. Atomoxetine (Brand name: Stramox, Company name: Tadbir Kala Jam, Country: Iran) was initially administrated at 0.5 mg/kg/ day as a single daily dose in the morning after breakfast. The maximum dose increase was set at 10-60 mg/day for Ritalin and 10-100 mg/day for Atomoxetine. The patients received the medication for up to 8 weeks. The children's parents completed an ADHD Rating Scale (RS) questionnaire (an 18-item questionnaire with an ADHD symptom measurement scale used as a measure of ADHD recovery) before treatment and at the end of weeks 4 and 8. The sum of the scores for the 18 items gives the total score (ranging from 0 to 54). The validity of the scale was determined on the basis of Cronbach's alpha (0.79-0.84) and the test-retest reliability is 0.78-0.89 [18]. The rate of improvement and therapeutic response was measured by ADHD-RS scores, and a reduction in score of 30% or more was considered a measure of the effectiveness of drug treatment [12]. At the end of the fourth and eighth weeks, a checklist of side effects was completed for each patient. In addition, patients were provided with a telephone number during the

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breaks between visits so that they could inform the study management about the side effects if any occurred, and they were contacted if necessary.

Outcomes

Information collected from each patient and used for the final analysis included the ADHD subtype, the patient's ADHD-RS test score at the 4th and 8th visit, and the patient's ADHD-RS test score at the 8th visit.

Analysis statistical

Finally, test results were analyzed using SPSS 22 statistical software. A value of $P<0.05$ was considered significant and the 95% confidence interval was used to calculate the odds ratio. The final report was presented in the form of descriptive and analytical statistics. Independent t-tests and chi-square tests were used to compare the quantitative and qualitative variables, and analysis of covariance (ANOVA) was used to determine the effect of the intervention in the groups.

Results

This study included children aged 6-14 years who were referred to the psychiatric clinic of Yahyanejad Hospital as outpatients, 60 subjects were selected as a sample.

Demographic data

The mean and standard deviation of the age of the patients was 8.7± 1.94 with an age range of 6 to 14 years. The two groups showed no statistically significant differences in terms of demographic information, including age and gender (P = 0.157). A total of 44 of the patients were boys and 9 girls, of whom 22 (44.06%) boys and 4 (6.77%) girls were assigned to the atomoxetine group and 22 boys (37.28%) and 5 girls (11.86%) were assigned into the methylphenidate group. There were 86.7% boys and 13.3% girls in the atomoxetine group and 75.9% boys and 24.1% girls in the methylphenidate group. Both groups were homogeneous by gender distribution and no statistically significant difference was observed between them (P = 0.287).

Comparison of the effects of atomoxetine and methylphenidate on ADHD subtypes

As can be seen in Figures 1 and 2, 44 patients with combined ADHD participated in the study, of whom 21 received atomoxetine and 23 methylphenidate. The mean score of patients receiving atomoxetine was 78.4±7.5 before treatment, 57.8±13.6 after the fourth week, and 47.66±25.4 after the eighth week. The mean score of the patients receiving methylphenidate was 76.21±6.7 before the treatment, 52.3±14.2 in the fourth week, and 45.7± 20 in the eighth week.

There was no difference in the effect of the two drugs on the reduction of symptoms of patients with combined ADHD and the same therapeutic effect of the two drugs was observed in this subgroup (P-value=0.714).

A total of 7 inattentive ADHD patients also participated in the study of which 5 patients received atomoxetine and 2 patients received methylphenidate. The ADHD-RS scores of the atomoxetine group were as follows: 67.6±3.5 before treatment, 54.2±15.5 after the fourth week, and 46.8±12.7 after the eighth week. In the methylphenidate group, the pre-treatment score was 69.5±7.77, 48.5±9.19 in the fourth week, and 29.5±13.4 in the eighth week. No significant difference in therapeutic response was found between the two drugs (P-value=0.254).

Among patients with hyperactivity ADHD, there were only 2 cases who were not examined due to the small sample size.

Side effects frequency

Table 1 presents the frequency (in percent) of side effects during treatment for each of the groups receiving methylphenidate and atomoxetine. According to the table, the incidence of nausea and anxiety was significantly higher in the group receiving atomoxetine, while the incidence of palpitations was significantly higher in the group receiving methylphenidate.

Frequency of side effects after treatment

The side effects were assessed using a checklist completed in the fourth and eighth week after treatment. In the fourth week, side effects occurred

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in 6 (23%) patients in the atomoxetine group, while no side effects were reported in 19 cases. In the group receiving methylphenidate, side effects occurred in 20 (74%) patients, but 7 patients reported none. The side effects of the medication in the fourth week differed significantly between the two groups so fewer side effects were observed in the atomoxetine group (Table 2) (P-value = 0.001).

In the eighth week after treatment, side effects were observed in 7 (26%) and 5(18%) cases in the atomoxetine and methylphenidate groups, respectively. According to the findings, no significant difference was found between the two groups (Table 2) (P-value=0.53).

Table 1. Frequency of side effects in the two groups receiving methylphenidate and atomoxetine

Side Effects	Atomoxetine group N=27 Frequency (%)	Methylphenidate group N=26 Frequency (%)	P-Value
Anorexia	8(29%)	20(77%)	0.22
Abdominal pain	4(15%)	2(7%)	0.28
Insomnia	6(22%)	1(3%)	0.07
Nausea	1(3%)	0(0.0%)	0.04
Tic	1(3%)	2(7%)	0.39
Anxiety	2(7%)	0(0.0%)	0.03
Heart palpitation	0 (0.0%)	4(15%)	≤0.0001

Table 2. Comparison of the frequency of side effects in the fourth and eighth week after treatment

Drug	Week 4	Week 8
Atomoxetine	6 (23%)	7 (26%)
Methylphenidate	20 (74%)	5 (18%)
P-value	0.001	0.553

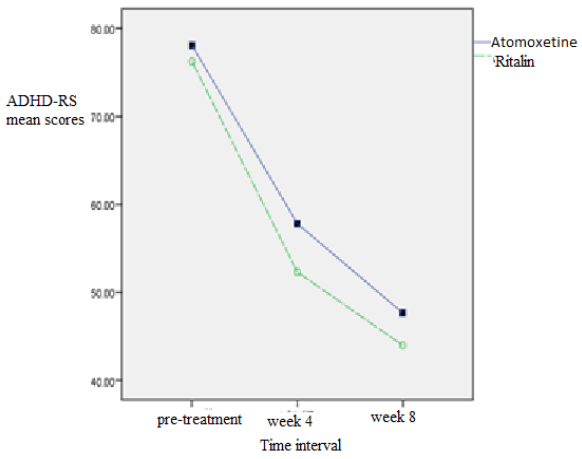

Fig 1. Comparison of the effect of atomoxetine and methylphenidate in the combined ADHD patients

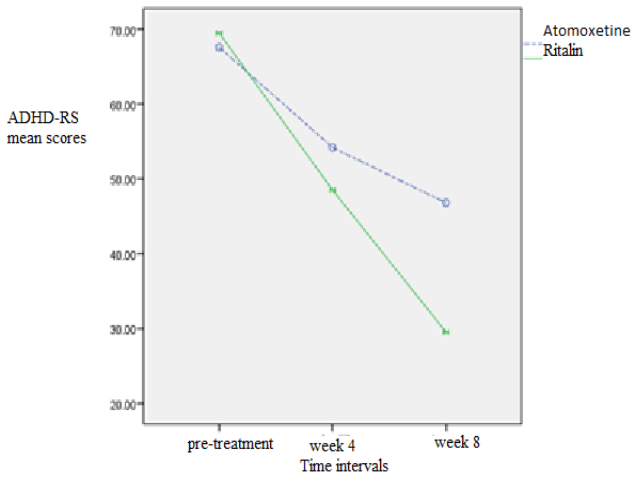

Fig 2. Comparison of the effect of atomoxetine and methylphenidate in inattentive ADHD patients

Discussion

Since no comparable study has been conducted in Iran to compare the efficacy and side effects of atomoxetine and methylphenidate, as well as the differences in metabolism and dosage and the ease of accessibility of the two drugs, the aim of the present study was to compare the therapeutic effects of methylphenidate and atomoxetine in the treatment of children with ADHD and to evaluate the side effects of these drugs.

In the two groups receiving atomoxetine and methylphenidate, the mean ADHD-RS score was

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significantly reduced at the fourth and eighth week post-intervention time intervals compared to pre-intervention scores. However, there was no statistically significant difference between the mean scores of the atomoxetine and methylphenidate groups, indicating that the efficacy of the two medications in treating ADHD patients is similar. Nevertheless, the results of Zhu et al. (2017) suggested that the short-term efficacy (eight weeks) and immunity of the two drugs were similar and no significant difference was observed between the atomoxetine and Ritalin groups [12].

In the current study, significant changes were also revealed in the mean value of the indicators before and after treatment with atomoxetine and methylphenidate. Grag et al. also came to results that are consistent with those of Zhu and the present study. They reported that the rate of improvement in ADHD symptoms was significantly different at the first visit and the eighth week after treatment, the mean score of Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) was not significant between the atomoxetine and methylphenidate groups, and both drugs demonstrated good efficacy and tolerability [12, 19].

Wang et al. (2013) studied 6-12-year-old children administered atomoxetine and methylphenidate daily and observed for 8 weeks. The results indicated that atomoxetine was as effective as methylphenidate [20]. Yildiz et al (2011) concluded that there was no significant difference in the response to methylphenidate and atomoxetine in ADHD patients; thus, both medications effectively improved symptoms [21]. In a meta-analysis by Hanwella et al. (2011), a similar degree of efficacy of methylphenidate and atomoxetine was found in ADHD patients; there was no significant difference between the two medications in improving symptoms [22]. The data obtained from the aforementioned studies are consistent with the results of the ongoing study. The study by Su et al. (2016) also provided similar results, i.e., both methylphenidate and atomoxetine improved the symptoms of Chinese children and adolescents with ADHD in a similar manner [23].

In the present study, the reduction in ADHD symptoms was estimated at 57% and 62% for the two medications. Since the reduction rate is higher than 30% for both drugs, methylphenidate and atomoxetine play an effective role in improving symptoms in the cases studied. Zhu et al. (2017) reported an efficacy of 11.5% and 7.7%, respectively and no significant difference was found between the two groups [12]. Thus, the results of the current study are confirmed, indicating the efficacy of the two medications in improving the symptoms of the disorder.

The division of the ADHD groups into three subgroups of hyperactivity (3.4%), inattention (15.3%), and combined (81.4%) was similar to the systematic and meta-analytic study conducted by Rezaei et al. (2016), which used data from 11 published articles and divided the ADHD cases into the subgroups of hyperactivity (11.5%), inattention (28.2%) and combined (76.3%) [24].

In the present study, there was no significant difference in therapeutic response between the group of boys treated with Ritalin and the group of boys treated with atomoxetine; both groups responded similarly. The same result was observed in the two groups of girls receiving Ritalin and Atomoxetine. Moreover, no significant relationship was seen between gender and response to treatment. However, Sonuga Barke et al. showed that females had better pharmacokinetic indices than males in terms of response to methylphenidate; the females had a better response 1.5 hours after taking the drug than the males, which lasted for three hours. This could be due to the role of sex hormones in dopamine function and response to stimuli, the slower emptying of the stomach, and the slower passage of food through the small intestine in women [25]. Further, it was concluded that the rate of symptom improvement and drug efficacy in the combined ADHD group receiving Ritalin was similar to that in the combined ADHD group receiving atomoxetine, and no significant difference was found. This was also observed in the two groups of inattentive ADHD cases receiving Ritalin and atomoxetine. The results of Garg et al. are in line with those of the ongoing study, so there was no significant difference between the two groups. Furthermore, no significant difference was observed

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in VADPRS scores before the intervention and at the eighth week [19].

The side effects of the medications were also evaluated in the fourth and eighth weeks. In the fourth week, it was 74% for methylphenidate and 23% for atomoxetine; thus, the side effects of atomoxetine were significantly lower than those of methylphenidate. In the eighth week, the side effect rate was 18% for methylphenidate and 26% for atomoxetine. There was therefore no statistically significant difference between the two groups. Anorexia nervosa, insomnia, abdominal pain, nausea, tics, and anxiety were the most common side effects of atomoxetine, while anorexia, palpitations, insomnia, abdominal pain, and tics were reported for methylphenidate. Besides, the incidence of nausea and anxiety was significantly higher in the atomoxetine group, while the incidence of palpitations was significantly higher in the methylphenidate group. In a systematic review study by Zhen Lv et al., insomnia, loss of appetite, and abdominal pain were reported as the most common complications of atomoxetine, while anorexia, dizziness, and abdominal pain were observed in the methylphenidate group. However, no significant difference was observed between the two groups in terms of the frequency of side effects [26]. Hanwella et al. [22] and Rezaei et al. [25] recommended that methylphenidate should not be administered in cardiovascular disorders and cardiac arrhythmias. This recommendation confirms our findings on the occurrence of cardiac complications (palpitations) in patients receiving methylphenidate.

Conclusion

The efficacy and tolerability of atomoxetine and methylphenidate were similar in the current study. Both medications were effective in reducing the clinical symptoms of ADHD, but there was no significant difference in treatment performance between the two. Based on the efficacy and tolerability of the drugs in treating and reducing the clinical symptoms of ADHD patients, it is recommended that atomoxetine and methylphenidate be administered in the treatment of the disorder unless specific side effects are reported or guidelines prohibit them for patients who have a co-occurring condition with ADHD. In addition, atomoxetine is better tolerated in the fourth week due to its fewer side effects.

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Author's contributions

Conceptualization and methodology: (Armon Massoodi, Angela Hamidia, Hemmat Gholinia, Seyedeh Maryam Zavarmousavi)

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Conflict of Interest

There is no conflict of interest.

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Ethical statements

All methods and procedures were approved by the Ethics Committee of Babol University of Medical Sciences under code MUBABOL.REC.1394.322 and IRCT20170606034348N1.

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