Original Article

Investigation of Efficacy of Short-Acting Methylphenidate (Ritalin) and Long-Acting (Matoride) on Symptoms of Attention Deficit Hyperactivity Disorder in Children Aged 6–18 Years: A Single-Blind, Randomized Clinical Trial

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Abstract

Background: This study aimed to evaluate the efficacy and safety of long-acting versus short-acting methylphenidate on the symptoms of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6–18 years. **Materials and Methods:** This single-blind, randomized clinical trial was conducted on 150 children and adolescents aged 6–18 years with ADHD based on the Diagnostic and Statistical Manual of Mental Disorder-5 criteria. The patients were randomly assigned to two groups (Matoride or Ritalin). In the first group, Ritalin was prescribed 2/3 times a day, and in the second group, Matoride was prescribed once a day for 3 weeks. The Conner's questionnaire was completed by the parents of the participants for evaluation of the performance and symptoms of ADHD in both groups at the beginning and 3 weeks after treatment. In addition, the incidence of any drug complications at the end of 3-week treatment period was evaluated. **Results:** There were no statistically significant differences between the two groups before the intervention ($P > 0.05$) in the dimensions of attention deficit, emotional reaction, behavioral disorder, learning disorder, and impulsivity. At the postinterventional periods, behavioral disorder of the Ritalin group was statistically significantly lower than that of the Matoride group ($P = 0.001$). This treatment did not have a statistically significant effect on the total score of Conners ($P = 0.255$). Complications were seen in 58 cases (77.3%) of Matoride group and 49 ones (67.1%) of the Ritalin group. Weight loss in the Ritalin group was higher than that of the Matoride group ($P = 0.019$). Compared to the Ritalin group, anxiety was higher in the Matoride group ($P = 0.022$). **Conclusion:** Given the similar effect of Matoride and Ritalin and no significant difference in drug complications, it seems that Matoride (slow release) can be used as an alternative to Ritalin (short acting).

Keywords: *Attention deficit hyperactivity disorder, long-acting methylphenidate, Matoride, Ritalin, short-acting methylphenidate*

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents, which affects the educational status, health, and social relationships of children.[1] In addition, in 60% of cases, in the absence of treatment, the disease continues until adulthood, causing academic and occupational problems and leading the person to risky behaviors and illicit drug use. The prevalence of this disorder is estimated to be 7%–8% in primary schoolchildren before maturity. The prevalence of ADHD in children and adolescents is about 5% and in adults, it is about 2.5%.[1,2] This disorder is a complex disorder with a multifactorial etiology, including multiple genetic and environmental variables.

The first step in the treatment of ADHD is stimulant, which has therapeutic effects on three areas of low attention, hyperactivity, and impulsivity. Two categories of stimulant drugs that have been approved by the Food and Drug Administration are amphetamines and methylphenidate. Stimulants increase the concentration of dopamine and norepinephrine in the synaptic cleft.[3-5] Methylphenidate acts by inhibiting norepinephrine-dopamine. Worldwide, methylphenidate is available in three forms

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including short-acting form, fast-acting form, and long-acting form. The fast-acting form (such as Ritalin) has a half-life of about 4 h and is prescribed to children two to three times a day. In contrast to the long-acting forms, slow-release (such as Matoride) form, which has a half-life of about 10–12 h, is prescribed once a day.[6,7]

According to a study performed by Steele *et al*. in 2006, the slow release of methylphenidate had a significant effect on the rapid onset of the effect of the patient's onset of symptoms and the severity of the symptoms of ADHD, while the profile of medical effects was similar in both groups.[8] Another study by Weiss *et al*. published in 2007 found that in both groups – fast acting and slow-release of methylphenidate – all parameters recovered and were approximately equal in size in both groups without any significant differences.[9]

In a randomized controlled trial conducted in 2012, Punja *et al*. investigated the studies conducted during 1950–2012 about the efficacy of methylphenidate (fast acting and slow release). The results of this study indicated that parents of children had considered slow-release type to be more effective to control ADHD. Experts considered the effect of short-acting methylphenidate to be more effective in controlling hyperactivity. Finally, they concluded that the slow-release methylphenidate type is slightly more effective than the short-acting type in controlling the symptoms of low attention and hyperactivity.[10] Finally, a study done by López and Leroux in 2013 found that long-acting and slow-release methylphenidate types have similar complications in tolerance and profile when compared to short-acting and rapid acting types and, on the other hand, improve the acceptance of treatment and have less potential for drug use.[11]

It seems that previous studies conducted in other countries analyzing the short-acting effect and long-acting effect of methylphenidate have not been sufficient, and most studies have compared the effects of two drugs (methylphenidate and amphetamines). On the other hand, no study had compared these two forms of methylphenidate drug in Iran, and hence, the long-acting effect of methorohydride and the short-acting effect of Ritalin need to be compared natively.

Keeping in mind that no study had been done to compare the effects of these two forms of methylphenidate drug in Iran and given that there is little information about the effects of these two drugs and their efficacy, this study was performed to evaluate the efficacy of Matoride drug versus Ritalin drug on the reduction of symptoms in children and adolescents with ADHD.

Materials and Methods

A single-blind, randomized clinical trial was conducted on 150 children and adolescents aged 6–18 years who had been approved by a pediatrician for pediatric psychiatry, hyperactivity disorder, and major psychiatric disorder, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria. In addition, patients and their family who do not cooperate in completing the interventional period, those receiving medications other than Matoride and Ritalin, those with severe or intolerable side effects (such as severe appetite loss and severe insomnia), those with severe allergic reactions to the drugs, and those having a physical illness (preventing drug use) were excluded from the study. Two patients were excluded from the study due to lack of cooperation from their families [Figure 1].

After obtaining the ethics code from the Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1397.058), registering the Iranian Registry of Clinical Trials (IRCT) number (IRCT20181113041638N1), and obtaining a written consent from the parent or guardian, ADHD was diagnosed based on the DSM-5 through a clinical interview conducted by the presenter (pediatric psychiatrist). Then, the patients were randomly assigned to an intervention group (treated by Matoride or Ritalin). At the time of entering the study, patients' demographic information such as age, gender, and level of education was recorded and the Conners questionnaire was completed by the parents to assess the symptoms of their child's ADHD. The Conners questionnaire has 26 questions, with the range of its total score varying from 26 to 104. If the score be above 24, it indicates the attention deficit disorder, and the disorder rate increases with score. This questionnaire has been evaluated in many previous studies both inside and outside of Iran and verified in terms of validity and reliability.[12,13]

In the first group, Ritalin was prescribed two or three times a day due to its short-acting duration, and in the second group, Matoride was prescribed once a day due to its slow-release duration. This intervention was performed in both groups for 3 weeks.

Medications were prescribed as a single dose. The children before going to school were prescribed Ritalin at a dose of 10 mg and Matoride at a dose of 18 mg in the morning. The child's performance after school hours was evaluated by the Conners Parents' questionnaire. In this case, the short-acting efficacy of Ritalin was not problematic and both drugs were evaluated during their half-life.

It should be noted that patients enrolled in this study had ADHD diagnosis and took Matoride or Ritalin for the first time.

In addition, considering the nature of these two drugs (short acting and slow release), the different prescription rates of these two drugs during the day, the lack of availability of these two drugs in Iran, and the with using the similar color, smell, and appearance, the present study was conducted as a single-blind, randomized clinical trial. However, these two drugs were removed from the plate

for 3 weeks and placed in envelopes and were named with codes A and B. Therefore, the patient was not aware of the type of the drug used. In addition, the resident pediatric psychiatric who was responsible for collecting information and the statistic specialist did not know the nature of the two groups. Therefore, the blindness conditions were met in this study.

The Conners Parents' questionnaire was completed by parents for evaluation of the performance and symptoms of ADHD in both groups and 3 weeks after treatment. In addition, the incidence of any drug complications such as weight loss, recurrence, insomnia, nightmares, feeling bored, ticking, headache, anxiety, reduced appetite, dizziness, variable mood, and delusional symptoms were evaluated at the end of the 3-week treatment period simultaneously with completing the questionnaire.

Finally, the collected data were entered into SPSS software (version 25; SPSS Inc., Chicago, Ill., USA). Data shown mean ± SD or frequency (frequency percentage). And Chi-square test, Fisher's exact test, independent sample *t*-test, and Univariate analysis at the level of inferential statistics. In all analyses, the significance level was considered at <0.05.

Results

In the present study, there were 19 (25.3%) girls and 56 (74.7%) boys in the Matroide group, with a mean age of 10.13 ± 2.51 years, and 26 (35.6%) girls and 47 (64.4%) boys in the Ritalin group, with a mean age of 10.42 ± 3.10 years ($P > 0.05$) [Table 1].

On the other hand, the assessment of children with ADHD based on the Conners questionnaire showed that there were no statistically significant differences between the two

Table 1: Baseline characteristics in the two groups

Characteristics	Matoride (*n*=75)	Ritalin (*n*=73)	*P*
Sex, *n* (%)			
Girl	19 (25.3)	26 (35.6)	0.212*
Boy	56 (74.7)	47 (64.4)	
Age (years)	10.13±2.51	10.42±3.10	0.530**
Education status, *n* (%)			
Preschool†	68 (90.7)	58 (79.4)	0.145***
Elementary	3 (4)	8 (10.9)	
Intermediate	4 (5.3)	7 (9.7)	

Data are shown mean±SD or *n* (%). †Age <7 years, *Use of Fisher's exact test, **Used of independent sample *t*-test, ***Use of χ^2. SD: Standard deviation

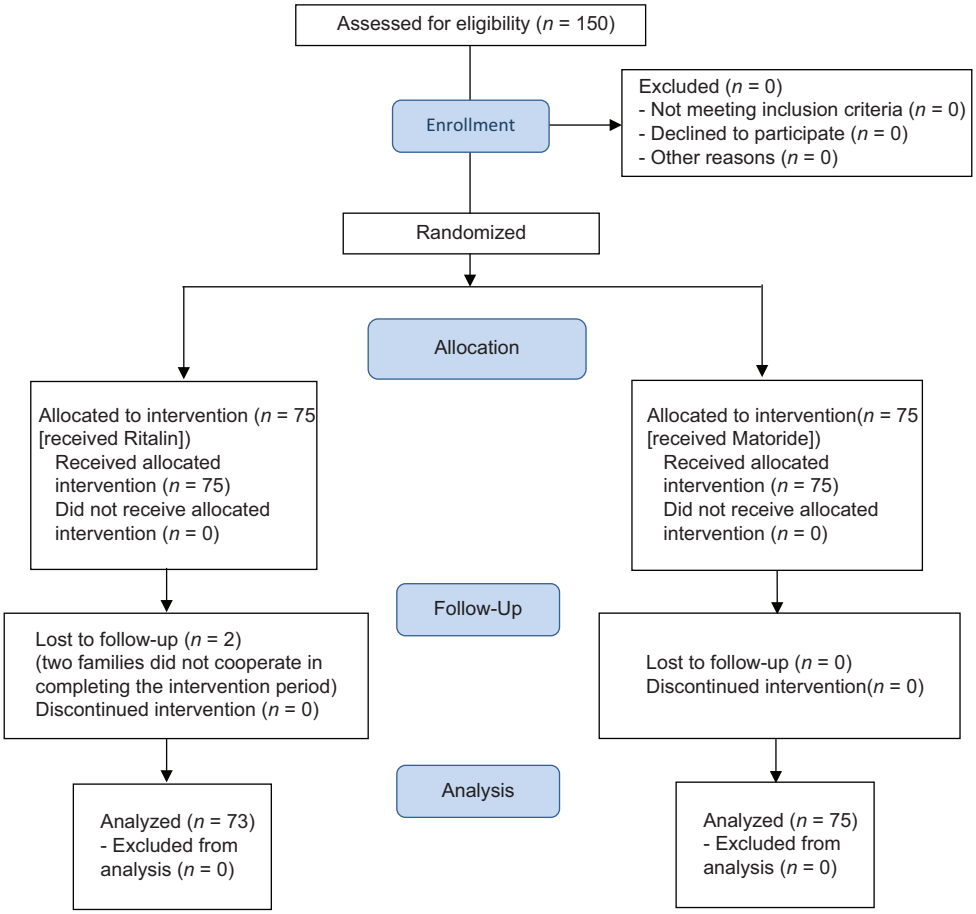

Figure 1: Consort patient flow diagram

groups before the intervention ($P > 0.05$) in the dimensions of attention deficit, emotional reaction, behavior disorder, learning disorder, and impulsivity. In the postinterventional period, the two groups did not differ significantly in terms of mentioned factors, but there was only a significant difference in the behavioral disorder of the Ritalin group with a mean of 10.57 ± 3.14 that was lower than the Matoride group with a mean of 11.91 ± 1.46 ($P = 0.001$). In addition, the results of the multivariate analysis showed that the intervention group had a significant role in the behavioral disorder ($P = 0.025$), and in the other considered dimensions, the effectiveness of both groups was similar in reducing the symptoms of ADHD ($P > 0.05$) [Table 2]. On the other hand, according to the results of univariate analysis, treatment provided did not have a significant effect on the total score of Conners questionnaire in the postinterventional phase compared to that of before the intervention (with adjusted confounding factors such as age and sex) ($P = 0.255$) [Figure 2].

Finally, the evaluation of drug complications showed that 58 cases (77.3%) in the Matoride group and 49 cases (67.1%) in the Ritalin group had side effects ($P = 0.200$). Hence, complications such as reducing appetite, weight loss, drowsiness, variable mood, and feelings bored were the most prevalent. In addition, in the Ritalin group, weight loss was higher compared to that of the Matoride group (Matoride: 10.7% vs. Ritalin: 28%; $P = 0.019$). In contrast, patients receiving Matoride experienced higher anxiety level than Ritalin-receiving patients (Matoride: 18.7% vs. Ritalin: 5.5%; $P = 0.022$) [Table 3].

Discussion

While the therapeutic effect of short-acting methylphenidate has been well established, the effectiveness and safety of long-acting formulations that are more expensive in the market is still controversial.

Medication treatment is very effective in reducing the symptoms of ADHD when the optimal dose and side effects are effectively addressed. Generally, stimulant medications (methylphenidate and amphetamines) are more effective than nonstimulants, and are therefore used first unless there is a strong contraindication. Among them, particular mention to Ritalin SR tablets with a 5–6 h' duration of action and Matoride with a long-acting methylphenidate product and 10–12 h' duration of action, which usually lasts about 8–10 h in practice.[14]

This clinical trial study aimed at evaluating benefits offered by long-acting versus short-acting Ritalin to children with ADHD. It suggested the improvements of ADHD symptoms and quality of life (QoL), confirmed good tolerability and safety, and revealed longer effect duration compared with those of previous treatments. The results of

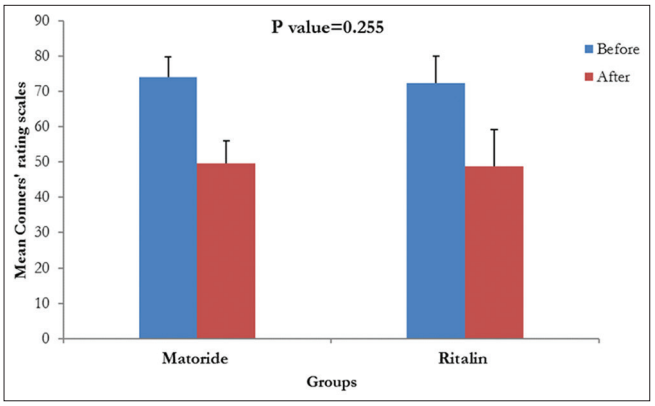

Figure 2: The mean of total score of Conners scale between the two groups

Table 2: Comparison of the mean score of attention deficit hyperactivity disorder based on the Conners scale in the two groups

Variables	Matoride (n=75)	Ritalin (n=73)	P*	P**
Attention deficit				
Before	39.96±3.49	39.15±3.23	0.145	0.727
After	26.53±4.48	25.59±5.53	0.257	
Emotional reaction				
Before	16.96±1.94	16.97±3.27	0.981	0.975
After	12.48±1.38	12.39±2.74	0.800	
Behavioral disorder				
Before	15.76±2.58	14.71±3.76	0.051	0.025
After	11.91±1.46	10.57±3.14	0.001	
Learning disorder				
Before	15.57±1.84	15.45±1.78	0.687	0.081
After	9.32±2.19	9.92±2.27	0.104	
Impulsivity				
Before	50.59±5.03	48.82±6.56	0.067	0.734
After	34.48±4.33	33.16±7.73	0.200	

Data are shown mean±SD. *Use of independent sample t-test, **Use of univariate analysis with adjusted age and sex. SD: Standard deviation

Table 3: Comparison of the frequency distribution of complications in the two groups

Complication	Matoride (n=75), n (%)	Ritalin (n=73), n (%)	P*
Reduced appetite	38 (50.7)	36 (49.3)	0.869
Recursive phenomenon	0	5 (6.8)	0.027
Loss of weight	8 (10.7)	19 (28)	0.019
Insomnia	17 (22.7)	13 (17.8)	0.541
Nightmare	2 (2.7)	2 (2.7)	0.978
Dizziness	2 (2.7)	7 (9.6)	0.095
Variable mood	13 (17.3)	16 (21.9)	0.538
Feeling bored	15 (20)	21 (28.8)	0.252
Anxiety	14 (18.7)	4 (5.5)	0.022
Delusional symptoms	1 (1.3)	5 (6.8)	0.114
Induction of tick	3 (4)	5 (6.8)	0.491
Headache	6 (8)	13 (17.8)	0.089
Other	4 (5.3)	3 (4.1)	0.726

Data are shown, n (%). *Use of Fisher's exact test

this study conducted on 150 children and adolescents aged 6–18 years with ADHD in the two groups of receiving Matoride and Ritalin showed that, according to Conner's questionnaire, there was a reduction in the symptoms, but no significant difference was seen in the dimensions of attention deficiency, emotional reaction, learning disorder, and impulsivity ($P > 0.05$). In contrast, the reduction of behavior disorder was statistically significantly higher in the Ritalin group than the Matoride group ($P < 0.05$). These findings are in accordance with many studies, for example, the data presented in the study by Cascade *et al*. showed that the clinical advantages of long-acting medications for ADHD are ahead of the curve compared to many psychiatrists and primary care providers regarding its utilization in children and adolescents. It showed that once-daily morning use of long-acting ADHD medications resulted in adequate treatment efficacy for the entire day. The benefits of this dose are that the children do not have to referee to a busy school nurse or school office to take their medications, nor are they forced to go out from the class in order to receive an additional dosage of short-acting ADHD medication. There is also less likelihood of forgetting because the administration of medications at home in the morning is supervised.[15]

While our study demonstrates a slight preference toward the long-acting than the short-acting methylphenidate on certain core symptoms, depending on the environment, we recognize that our results depend on the samples and the family situations such as social and economic. Our study found no difference in the reported adverse events between the two formulations, but this warrants cautious interpretation. The side effects of these two drugs were 77.3% in the Matoride group and 67.1% in the Ritalin group, with more prevalent complications such as decreased appetite, weight loss, insomnia, mood disorder, and feeling bored. Although the overall incidence of complications was not significant between the two groups, in more detail, weight loss in the Ritalin group was significantly higher than that of the Matoride group. In contrast, the anxiety of patients in the Matoride group was greater than that of the patients in the Ritalin group.

In a systematic review by Punja *et al*., the findings indicated that according to parent reports, the long-acting formulations have a modest effect on the severity of inattention/overactivity and hyperactivity/impulsivity.[10] Another study by Haertling *et al*. was done to evaluate the effectiveness and safety of a long-acting, once-daily, two-phase formulation of methylphenidate (Ritalin LA®) in schoolchildren and revealed that Ritalin LA in children with ADHD under routine practice conditions improved Clinical Global Impression and QoL.[14]

Long-acting ADHD medications may also be less prone to contribute to the development of the behavior of drug abuse or dependence. It can be due to the slower rise and fall of methylphenidate or MPH, amphetamine, and dexamphetamine levels in the brain that may contribute to decreased potential of drug abuse.[15] To examine this hypothesis, two studies compared short-acting and long-acting MPH formulations. In healthy volunteers, the effects of oral immediate-release (40 mg) and osmotic-release MPH were studied.[16] Although these two formulations had almost similar average peak-drug concentrations and dopamine-transporter blockade, the immediate-release formulation reached the targets several hours earlier than osmotic-release formulation. It suggested that immediate-release MPH has a more rapid drug absorption and central drug activity versus osmotic-release MPH. This point is noteworthy that the immediate-release formulation achieved significantly greater popularity ratings compared with the osmotic-release formulation.[17] The reported prescribing pattern in adults shows that some psychiatrists and primary care providers have not completely take the advantage of long-acting ADHD medications. It should be noted that often a day in the life of adolescents and adults is full of activities and responsibilities including work and/or educational hours associated with parental/social activities in the evening. Many patients report that with the usage of long-acting medications, their children's mental focus remains clearer throughout the day. They have also stated that sometimes in the early evening, the negative impacts of the peak–trough effects that are often seen with twice- or thrice-daily dosing of immediate-release ADHD medications would be minimizing.[18,19] It is observed that for the same reason, the hyperactive symptoms are better controlled in many cases with long-acting ADHD medications.

According to the results of the current study, evaluating the risks and benefits of the various ADHD medications, and discussing these explicitly with the patients and their families, it is concluded that the safety and tolerability of long-acting medications are similar to short-acting medications and seem to have comparatively lower risk of abuse and diversion,[20,21] which may be associated with significant improvements in medication adherence. Hence, long-acting medications can be considered a preferred choice for ADHD. However, short-acting medications may yield more flexibility regarding the dose frequency, titration, and tolerability and can be taken on as a needed basis when coverage is only requested for a few hours.

Finally, the lack of long-term follow-up of the administration of these two drugs and lack of full cooperation by parents for accurately and fully performing the protocol were the limitations of the present study that were unavoidable.

Conclusion

The results of the study indicate a same reduction of symptoms of ADHD in both groups that received Matoride and Ritalin. The conduct disorder of patients who received Ritalin was significantly lower than those

received Matoride. Moreover, side effects were slightly and not significantly different in both groups. Therefore, it can be concluded that the tolerance and side effect profile of long-acting, slow-release drugs (e.g., Matoride) was similar to those of short-acting and fast/instant release drugs (e.g., Ritalin), but they improve acceptance for treatment and have less potential for abuse. Hence, these drugs can be recommended to use for patients, and we suggest further research in this respect.

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Conflicts of interest

There are no conflicts of interest.

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