

Comparison of the effects of methylphenidate and the combination of methylphenidate and risperidone in preschool children with attention-deficit hyperactivity disorder

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric disorder among preschool children but the number of controlled clinical trials regarding psychopharmacological treatment in this age group is limited. The aim of this study was to compare methylphenidate with the combination of methylphenidate and risperidone in preschool children with ADHD. Forty-two preschool children, aged 3–6 years, diagnosed with ADHD by a child and adolescent psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision criteria, were enrolled in a 6-week, single-blind clinical trial and administered with methylphenidate (5–30 mg/dl) or the combination of methylphenidate and risperidone (0.25–2 mg/dl) in Iran. Treatment outcomes were assessed using the Conners' Rating Scale and Clinical Global Impression (CGI) Scale at baseline and 3 and 6 weeks after starting the drugs administration. Side effects were rated by a checklist and body weight was measured at each visit. There were no significant differences between the two protocols in Parent Conners' Rating Scale scores ($P > 0.05$) and CGI scores ($P > 0.05$). Both groups showed a significant improvement in ADHD symptoms over the 6 weeks of treatment for Parent Conners' Rating Scale ($P < 0.001$). The combination group used significantly lower doses of methylphenidate compared to the other group ($P = 0.002$). The most common adverse effects were anorexia (21.7%) and daytime drowsiness (17.4%) in combination treatment group and insomnia (33.3%) and anorexia (25%) in methylphenidate group. Risperidone and methylphenidate may be effective and well tolerated in preschool children with ADHD, and adding risperidone to methylphenidate may decrease the occurrence of some side effects of methylphenidate such as insomnia and anorexia and lower the dose of methylphenidate may be needed to control symptoms.

Key words: Attention-deficit hyperactivity disorder, methylphenidate, preschool children, risperidone

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INTRODUCTION

Chronic disease has a significant impact on the physical and mental health of patients and their families.^[1,2]

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Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children.^[3] ADHD is highly prevalent in Iran, and there are obstacles to accessing mental health services.^[4] Children with ADHD are predisposed to academic failure, substance abuse, and social adjustment problems.^[5] Care and effective treatment can improve the quality of life considerably.^[6-8] Sympathomimetics are the first-line medications for ADHD, and methylphenidate is one of the most frequently used drugs of this class.^[9]

Methylphenidate is the first-line psychopharmacological treatment for preschool ADHD in the Preschool Psychopharmacology Working Group algorithm,^[10] but the Preschool ADHD Treatment Study showed that the effect size in preschoolers is smaller than in older children.^[5,10] This age group shows higher rates of emotional adverse effects such as nervousness, irritability, and crying as well.^[11-13] Loss of appetite, short duration of action (3–4 h), and rebound phenomenon are some issues that limit the use of methylphenidate to treat ADHD.^[3] The number of controlled clinical trials conducted on stimulant drugs in preschool children is limited.^[5]

In addition, other pharmacological strategies such as mood stabilizers and antipsychotic drugs have been used for ADHD.^[14] Risperidone has been reported to be an effective and safe drug for disruptive behavior disorders (DBDs) and ADHD in children.^[15] Effect of the combination of risperidone and methylphenidate has already been investigated in some studies.^[16,17]

In the few studies which used risperidone in preschool children, it was found to be an effective and tolerable drug for this age group although they showed considerable weight gain and increased level of prolactin.^[5,18] The use of atypical antipsychotics has been risen significantly for treating DBDs in children,^[19] and positive effects of this class of drugs for disruptive behavior have increased their use in children with ADHD.^[20]

As methylphenidate can cause insomnia, loss of appetite and emotional side effects which can be problematic, especially in preschool children, adding risperidone to it may improve some of these negative side effects and lower doses of methylphenidate may be needed to control symptoms of ADHD. As there are limited data about the use of this combination treatment in preschool children, we decided to conduct this study.

MATERIALS AND METHODS

This study was a single-blind randomized controlled trial conducted at a clinic of child psychiatry affiliated with the Shahrekord University of Medical Sciences in Shahrekord, Iran, in 2015. The study protocol was

approved by the respective institutional research center. The study population consisted of preschool children with ADHD comorbid with DBDs. The sample size was decided to be 21 children in each group selected based on convenience sampling from children referred to the clinic. The parents provided written informed consent for their children's participation in the study after they were informed about the procedures and purposes. Participants were randomly assigned to one of the treatment groups of methylphenidate alone (Group 1) and methylphenidate plus risperidone (Group 2).

Inclusion criteria were being 3–6 years old, suffering hyperactive/impulsive or mixed subtype of ADHD comorbid with DBDs diagnosed by a child psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision criteria, and exclusion criteria having mental retardation or other developmental disorders and any physical disorder, and being on treatment with any psychotropic drug during the last 4 weeks. Besides that, if children showed significant or intolerable adverse effects during the treatment, they were excluded from the study.

Data were collected using a demographic data questionnaire, revised Conners' Parent Rating Scale-short form, clinical global scale severity and improvement (CGS-S and CGS-I), and a checklist of medication side effects and body weight measurement. The primary assessment instrument was Conners' Parent Rating Scale-revised, which consists of 27 items and four subscales. Each item is scored as 0–3. This scale has been translated into Persian and standardized in Iran.^[21] The CGS-S and CGS-I scores of the disorder range from 0 to 7. In this study, 68 parents of children who met the inclusion criteria were approached, of whom 47 consented to participate in the study. Methylphenidate was started at a dose of 2.5 mg twice daily and was increased by 2.5–5 mg each week based on the treatment response and the patient's tolerance, to a maximum of 20/day.^[3] Risperidone was started with a single dose of 1.25 mg/day and was increased by 0.25–0.5 mg each week to a maximum dose of 2 mg/day.^[22] For blinding, the assessing psychiatrist was blind to group assignment of the participants. Before starting the drug, Conners' scale score, CGI-S score, and weight were measured for each patient. Measurements were repeated after 3 and 6 weeks of treatment.

Independent *t*-test was used for comparison of age and Conners' Rating Scale scores between the two groups at baseline. Chi-square test was used to compare gender between the two groups. Mann-Whitney test was used for comparison of methylphenidate dose at weeks 3 and 6, and CGI-S scores at baseline. Two-way repeated measures analysis of variance (time × treatment interaction) was run for Conners' Rating Scale and its subscales. The two groups were considered between-subjects factor (group)

and the measurements during treatment the within-subjects factor (time). Furthermore, repeated measures analysis of variance (time \times body weight) was conducted to compare body weight between two groups. Mann–Whitney test was used to compare CGS-I at weeks 3 and 6 of assessment.

RESULTS

Forty-seven children with ADHD aged 3–6 years participated in the study. Forty-two of 47 participants (89.36%), 21 in each group, completed the trial. No significant differences were identified between the two groups in age ($t = 0.128$, $df = 40$, $P = 0.90$), ADHD subtypes ($P = 0.66$), and gender ($t = 1.27$, $df = 1$, $P = 0.26$) [Table 1].

There was no significant difference in the mean body weight between the two groups at baseline ($t = 1.42$, $df = 40$, $P = 0.16$). The within-subject effect was significant ($F = 8.80$, $df = 1.22$, $P = 0.003$ 0.15). However, neither interaction (weight and group of the treatment) ($F = 1.22$.06, $df = 2$, $P > 0.05$) nor intersubject effect (group of the treatment) was significant ($F = 1.73$, $df = 1$, $P = 0.19$).

No significant differences were observed between the two treatments in the Conners' Parent Rating Scale scores ($t = -0.025$, $df = 40$, $P = 0.98$) and CGS-S scores ($P = 0.29$) at baseline before the intervention [Tables 2]. Repeated measures ANOVA, one for Conners' Parent Rating Scale and three for its subscales were done [Table 2].

For parent Conners' Scale total score, the within-subject effect was significant ($F = 31.62$, $df = 2$, $P < 0.001$). However, neither interaction (time and group of the treatment) ($F = 0.27$, $df = 2$, $P > 0.05$) nor intersubject effect (group of the treatment) was significant ($F = 0.42$, $df = 1$, $P > 0.05$) [Table 3].

For hyperactivity/impulsivity subscale, only the within-subject effect was significant ($F = 40.41$, $df = 2$, $P < 0.001$), but neither interaction (time and group of the treatment) ($F = 0.33$, $df = 2$, $P > 0.05$) nor intersubject effect (group of the treatment) was significant ($F = 0.01$, $df = 1$, $P > 0.05$) [Table 3].

For inattention subscale, the within-subject effect was significant ($F = 6.04$, $df = 2$, $P < 0.001$). However, neither interaction (time and group of the treatment) ($F = 0.16$, $df = 2$, $P > 0.05$) nor intersubject effect (group of the treatment) was significant ($F = 0.16$, $df = 1$, $P > 0.05$) [Table 3].

For oppositional defiant disorder subscale, only the within-subject effect was significant ($F = 25.58$, $df = 1.70$, $P < 0.001$). However, neither interaction (time and group of the treatment) ($F = 0.30$, $df = 1.70$, $P > 0.05$) nor intersubject effect (group of the treatment) was significant ($F = 1.73$, $df = 1$, $P > 0.05$) [Table 3]. The mean dose of methylphenidate

was significantly lower in the combination treatment group at week 6 of treatment ($P = 0.002$), but not at week 3 ($P = 0.16$).

Based on CGI-I scores in the methylphenidate group, six patients (28.6%) at week 3 and 13 patients (61.9%) at week 6 experienced much or very much improvement. In the combination treatment group, eight patients (38.1%) at week 3 and 16 patients (76.2%) at week 6 experienced much or very much improvement. CGI-I scores were not statistically different between the two groups at week

Table 1: Demographic data

Variables	Group 1*	Group 2**	P
Gender (%)			
Female	3 (14.29)	6 (28.57)	0.26
Male	18 (85.71)	15 (71.43)	
ADHD subtypes (%)			
Combined	19 (90.48)	17 (80.95)	0.66
Hyperactive/impulsive	2 (9.52)	4 (19.05)	
Age, year	4.52 \pm 1.24	4.47 \pm 1.16	0.90
Body weight			
Baseline	17.93 \pm 3.68	16.44 \pm 3.08	0.16
Week 3	17.91 \pm 3.48	16.55 \pm 2.98	>0.05
Week 6	18.11 \pm 3.37	17.02 \pm 2.88	

*Methylphenidate group, **Methylphenidate plus risperidone group.
ADHD: Attention-deficit hyperactivity disorder

Table 2: Mean (standard deviation) scores on Conners' Parent Rating Scale and drug dose

Variables	Group 1	Group 2	P
Conners' total score			
Baseline	52.95 \pm 10.36	53.05 \pm 14.31	>0.05
Week 3	43.29 \pm 15.96	40.14 \pm 14.67	
Week 6	33.85 \pm 15.22	30.52 \pm 15.81	
Hyperactivity subscale			
Baseline	13.95 \pm 2.82	14.10 \pm 3.28	>0.05
Week 3	10.95 \pm 4.63	10.19 \pm 4.40	
Week 6	7.14 \pm 4.21	7.52 \pm 3.46	
Inattention subscale			
Baseline	9.47 \pm 4.31	9.19 \pm 4.78	>0.05
Week 3	8.28 \pm 4.55	7.42 \pm 3.9	
Week 6	6.67 \pm 3.98	6.67 \pm 3.79	
Oppositional defiant disorder subscale			
Baseline	13.90 \pm 3.95	13.33 \pm 4.18	>0.05
Week 3	11.00 \pm 3.97	9.29 \pm 4.10	
Week 6	8.76 \pm 3.86	7.24 \pm 3.75	
Dose of methylphenidate (mg)			
Week 3	13.8 \pm 5.7	11.3 \pm 5.5	0.002
Week 6	17.9 \pm 7.17	11.9 \pm 8.9	
Dose of risperidone (mg)			
Week 3	0	0.60 \pm 0.26	-
Week 6	0	0.79 \pm 0.32	

Table 3: Side effects reported by parents

Side effect	Groups	
	1* (%)	2** (%)
Sedation	0	4 (17.4)
Insomnia	8 (33.3)	1 (4.3)
Anorexia	6 (25)	5 (21.7)
Nervousness	1 (4.2)	2 (8.7)
Agitation	2 (8.3)	0
Phobia	0	2 (8.7)
Enuresis	0	3 (13.0)
Total	17 (70.8)	17 (73.9)

*Methylphenidate group, **Methylphenidate plus risperidone group

3 ($\chi^2 = 0.43$, $df = 1$, $P = 0.37$) and week 6 ($\chi^2 = 1.003$, $df = 1$, $P = 0.25$).

Two parents in combination group decided to discontinue the medication before week 3 due to severely increased appetite (one patient) and sleepiness (one patient). The most common adverse effects in this group were anorexia (21.7%) and sedation (17.4%). Three parents in risperidone group discontinued medication due to decreased appetite (one patient), agitation (one patient), and nervousness and aggression (one patient). The most common adverse effects in this group were insomnia (33.3%) and anorexia (25%) [Table 3].

DISCUSSION

Results of this study showed that in both groups, the total and subscale scores of Conners' Rating Scale were significantly reduced, but there was no significant difference between the two groups. Both protocols were well tolerated and no serious side effects occurred. In the study of Arabgol *et al.*, risperidone was compared with methylphenidate in preschool children with ADHD in a 6-week, double-blind clinical trial. Results showed that there was no significant difference between the two protocols in the Parent ADHD Rating Scale scores and Parent Conners' Rating Scale scores. They concluded that risperidone monotherapy might be effective and well tolerated in preschool children with ADHD. The most common adverse effects seen with risperidone were daytime drowsiness and anorexia, and with methylphenidate anorexia, nervousness, and disturbed sleeping.^[16]

In the study of Safavi *et al.*, comparing risperidone with aripiprazole in ADHD preschool children, both medications were relatively safe and effective; however, some patients experienced reduced effectiveness of the medications during the 6 weeks of the trial.^[5]

The results of a retrospective analysis of 44 cases showed that bitherapy decreased the symptoms of ADHD and conduct disorder, sleep disorders, and anxiety. Regarding

the safety of the bitherapy, a compensation effect on weight gain and appetite was observed in 70% and 50% of patients, respectively. They concluded that bitherapy appears to be particularly effective on ADHD with conduct disorder symptoms. Although tolerance may limit its use, the benefit/risk ratio seems favorable for a number of children.^[17]

Another study evaluated 52-week clinical outcomes of children with co-occurring ADHD, DBD, and serious physical aggression who participated in a prospective, longitudinal study that began with a controlled, 9-week clinical trial comparing the relative efficacy of stimulant medication versus stimulant plus risperidone. The results showed that only 43% of participants in the augmented group and 36% in the basic group still adhered to their assigned regimen (not significant). Both treatment strategies were associated with clinical improvement at follow-up, and primary behavioral outcomes did not differ significantly. The participants in the augmented group were more likely to have a CGI severity score of 1–3 (i.e, normal to mildly ill) at follow-up than those in the basic group. The augmented group had elevated prolactin levels, and the basic group lost weight over time. Findings were generally similar whether group assignment was conducted randomly or according to follow-up treatment status.^[16]

Aman *et al.* study showed that adding risperidone to methylphenidate results in significant improvement in antisocial behaviors in school-aged children with ADHD. They concluded that risperidone causes moderate but variable improvement, does not have severe adverse effects, and can be used combined with stimulant drugs.^[23] In our study, inconsistent with Aman *et al.*'s study, adding risperidone to methylphenidate did not cause significant improvement of symptoms. This may be explained by the fact that in Aman *et al.*'s study, children received psychostimulant for 3 weeks, titrated for optimal effect, and if improvement was likely at the end of week 3, either placebo or risperidone was added; however, in the present study, one group received the combination from baseline, and patients in the combination treatment group used lower doses of methylphenidate than the methylphenidate alone group.

In our study, the most frequent side effects in methylphenidate group were insomnia, loss of appetite, agitation, and nervousness, but in the combination group, the most frequent side effects were loss of appetite and sedation. Regarding weight variation, the combination group gained more weight than methylphenidate group, yet with no significant difference. Adding risperidone to methylphenidate may decrease the frequency of adverse effects such as insomnia, anorexia, weight loss, and nervousness. Moreover, in the combination treatment group, the patients needed lower doses of methylphenidate

which can alleviate side effects in the patients who cannot tolerate higher doses of methylphenidate to control symptoms.

In this study, as with similar studies, patients showed no serious side effects.

CONCLUSIONS

The results of the present study show that risperidone and methylphenidate may be effective and well tolerated in preschool children with ADHD. Adding risperidone to methylphenidate may decrease the occurrence of some side effects of methylphenidate such as insomnia and anorexia and lower doses of methylphenidate may be needed to control symptoms.

Recommendations

We recommend further studies with larger sample size, cross-over design, and longer follow-up as well as to compare risperidone with other atypical antipsychotics and methylphenidate, or behavioral interventions for the treatment of behavioral disorders in preschool children.

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Conflicts of interest

There are no conflicts of interest.

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