Comparing the Effectiveness of Risperidone with Aripiprazole as a Combination Therapy in Attention-Deficit Hyperactivity Children with Oppositional Defiant Disorder

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Research

Keywords: Risperidone, Aripiprazole, ADHD, ODD, Children.

Posted Date: January 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-148639/v1>

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Abstract

Background: This study intends to compare the effectiveness of Risperidone with Aripiprazole as a combination therapy in Attention-deficit hyperactivity (ADHD) children with oppositional defiant disorder, treated with Methylphenidate.

Methods: This is a double-blind clinical experiment. The sample size was determined as 60 (40 for the intervention group and 20 for the control group) by random sampling. The data collecting instrument was Parent's ADHD Rating Scale, Clinical Global Impression-Severity (CGI-S), demographic information checklist, and drug's side-effects checklist for this study. Repeated measurement multivariate analysis was used as a statistical method to compare the quantitative variables in both intervention and control groups using SPSS18 software.

Results: The results of this study indicated that there is a substantial difference between scores in ADHD and oppositional defiant disorder (ODD) groups after 8 weeks ($F=2.34$, $p>0.03$).

Conclusion: Based on the results of the present study, Aripiprazole in combination with Methylphenidate have a higher effect on reducing ADHD and ODD symptom.

Trial registration: IRCT20160530028182N5; Registered 6 February 2018, <https://en.irct.ir/trial/22916>

Background

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatry disorders, which begins with the 5–12% prevalence at childhood (1). This disorder is a kind of neurodevelopmental problem that appears as the permanent attention deficit or hyperactivity and impulsivity behavior in which the brain cannot process unrelated information and important aspects (2). The inattention, hyperactivity, and impulsivity symptoms in ADHD are more severe than expected concerning the age and growth stage of a child. The clinical symptoms appear before 12 years old age and at least in two places (e.g. school and home), and disturb the social and educational function of the child (3, 4). ADHD is more common amongst the boys (2 to 1) than girls (9 to 1) (Sadock & Sadock, 2008), and its prevalence is reported as 2% in the primary care clinics to 59% in paediatric psychiatry clinics before the school time (5).

The risk of afflicting this disorder is high in first-degree relatives (6). The studies about the twins demonstrated that the role of heritage is 75% for catching this disorder (7, 8). This disorder can continue even in adulthood and it is necessary to treat it (9). The main reason of this disorder is not recognized yet, but various studies have referred to its relation with genetic and considered it as fetal injuries and dysfunction of neural transporters, especially for dopaminergic and adrenergic systems, also psychosocial factors are important factors for this disorder (10). Various studies have revealed that there is high comorbidity of disruptive disorders with ADHD (11, 12). For example, the oppositional defiant disorder has 60% comorbidity with ADHD (13, 14). The studies have shown that oppositional defiant

disorder (ODD) with the combination of ADHD can decrease the well-being, and increase the social and individual problems compare to ADHD without ODD (15), and also would cause many difficulties at home, school, and social environments; consequently, treating this disorder is essential (16).

Similar to Methylphenidate, Neural system stimulants are the first-line psychopharmacological treatments for ADHD (17). It has been proved that Methylphenidate is very effective in three-fourths of ADHD children with few side-effects. A conducted survey has presented that almost 75% of ADHD children treated with Methylphenidate have indicated significant progress in their classroom attentions and academic performances (10).

The side-effects of this drug are headache, nausea, insomnia, rebound symptom, and exacerbate tics in children with the movement tic history (10). Regarding the non-response of about 30% of children to Methylphenidate, consuming at least one dose per a day in the school, is necessary for considering other medicines (17). Hence, the use of uncommon antipsychotics to treat the children disruptive behavior is increasing (12). The positive effects of uncommon antipsychotics are seen as its usage for treating disruptive behavior, and ADHD children. A study has demonstrated the effectiveness and safety of Risperidone with and without psycho-stimulants for children. Adding Risperidone to the stimulant demonstrated that it provided better control for hyperactivity compared to stimulant alone, and this combination did not increase side-effects (18).

In a review article about the effects of second-generation antipsychotics on children and adults, it was displayed that Risperidone was used in 43% of studies, and it was very beneficial, especially for ADHD children (19). Risperidone is a safe and effective drug for controlling the disruptive behavior of children (20). Aripiprazole is one of the uncommon antipsychotic medicines, which is effective for the children and adolescents behavioral disorders treatment, and for who suffering autism spectrum disorders (21), tic (18), schizophrenia (22), and bipolar disorder (23).

This drug is a relative agonist of D2 receptors and 5HT_{1A} serotonin (23). It increases prolactin levels less than other uncommon antipsychotics (24). Aripiprazole relative antagonist increases the weight less than other uncommon antipsychotics (25). In a conducted study, Aripiprazole was an effective drug with worthy tolerance for ADHD and behavioral disorder symptoms (26). Aripiprazole and Risperidone are both from the same therapeutic class and also the same effectiveness, but their side-effects are different. Using Aripiprazole instead of Risperidone, the risk of metabolic syndrome becomes very low. There are few studies about the effectiveness of this medicine on ADHD. Regarding the high prevalence of ADHD (1), its high comorbidity with oppositional defiant disorder (27), the importance of treatment, and since there is no study about the comparison of Aripiprazole and Risperidone along with Methylphenidate, as a result, this research is conducted in order to attain the effectiveness of Risperidone and Aripiprazole in combination with Methylphenidate.

Methods

This study was a double-blind clinical trial. The population of the study was children with ADHD and ODD, who were selected based on DSM-5 criteria amongst those who visited in Psychiatric Clinic of Be'sat Hospital, Sanandaj-Iran in 2018. The sample size for each group was determined by considering a 5% first-type error and a 2% second-type error. The sample size was 60 (40 for the intervention group and 20 for the control group).

Sample selection

This is a double-blind clinical trial and experimental intervention (the patient and physician were not aware that patients are in case and control groups) on ADHD and ODD children. The disorder was diagnosed by the paediatric psychiatrist or psychiatric expert by using a non-structured clinical interview based on DSM-5 criteria. The study population consisted of 60 children with ADHD who visited the psychiatric clinic of Be'sat hospital in Sanandaj by considering inclusion and exclusion criteria. After an explanation about the steps and attaining the written consent of parents and oral consent of children, the patients entered into the study and excited when they wish. The harshness of symptoms before beginning was assessed by the ADHD Rating Scale. Before starting the treatment, physical examination was done in order to measure heartbeat, blood pressure and weight.

Grouping, Allocation, and Blinding

Regarding the nature of the study, the researcher distributed the patients into three groups i.e. group 1, 2, and 3 and referred them to the treatment authority with this code. Risperidone, Aripiprazole, and placebo (starch) were placed in the same capsules, and delivered to the patients in the pre-prepared packets based on the codes of 1 to 60 by the pharmacy. Therapeutic dose of 10mg Methylphenidate, made by Novartis Company, was prescribed for the first week (daily, one-fourth in the morning and one-fourth in the evening), second week (daily, 1/2 in the morning and 1/2 in the evening) and then (daily, one dose in the morning and one in the evening) based on the tolerance of patient. Therapeutic dose of 1mg Risperidone, made by Sobhan Company, was prescribed for the first week (daily, one-fourth in the morning and one-fourth in the evening), second week (daily, 1/2 in the morning and 1/2 in the evening) and then (daily, one dose in the morning and one in the evening) based on the tolerance of patient along with Methylphenidate. Therapeutic dose of 5mg Aripiprazole, made by Sobhan Company, was prescribed for the first week (daily, one-fourth in the morning and one-fourth in the evening), second week (daily, 1/2 in the morning and 1/2 in the evening) and then (daily, one dose in the morning and one in the evening) based on the tolerance of patient along with Methylphenidate.

Therapeutic dose of placebo (starch), was prescribed for the first week (daily, one-fourth in the morning and one-fourth in the evening), and second week (daily, 1/2 in the morning and 1/2 in the evening) and then (daily, one dose in the morning and one in the evening) along with Methylphenidate. Clinical global impression and Parent ADHD Rating Scale were accomplished by the participants before starting the cure and in weeks 2, 4, and 8 in order to determine the severity of ADHD symptoms. The side-effects were also documented in weeks 2, 4, and 8 after starting the study in side-effects form. Other observed side-effects that were not in the form were also documented.

Measurement

A) Parent's ADHD Rating Scale

It is a valid and reliable tool to evaluate the severity of ADHD symptoms and the response of children, which has two versions: parent and teacher. This scale contains 18 phrases about attention deficit and impulsivity-hyperactivity. The respondent should specify the rate of recurrence of each phrase or symptom in a Likert 4-point scale (0 to 3). From the results of this scale, we acquire three scores (inattention, hyperactivity-impulsivity and total). The internal consistency of this scale was 85% in 92% and its retest reliability in the interval of 4 weeks (28, 29).

B) Clinical Global Impression Severity (CGI-S)

This scale measures the severity of disease and the response rate to treatment of the psychological disorders, especially in the studies (30). Therapists use CGI-S to measure the disease' severity that has 7 sub-scales including: Normal, not at all ill; Borderline mentally ill; mildly ill; moderately ill; markedly ill; severely ill and extremely ill.

C) Demographic Information Checklist

This checklist includes the information like age, gender, education, occupation of parents and weight which was completed by the interviewer during the interview.

D) Side-effects checklist

This checklist is provided to check the probable side-effects in which previously reported side-effects of Methylphenidate, Risperidone, and Aripiprazole are documented.

Data analysis

The descriptive and inferential statistical methods are used to analyze the data in this research. Mean, frequency and standard deviation were applied in descriptive level in this research. Repeated measurement multivariate test was used to compare the quantitative variables in both intervention and study groups using SPSS-18 Software in inferential statistical method. The significance level was 0.05.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committees of the Kurdistan Universities of Medical Sciences (Iran) with number (IR.MUK.REC.1395.135). Also this study is registered in clinical trial of Iran site (<http://irct.ir/>) with code IRCTID: IRCT20160530028182N5. Prior to participation, participants provided written informed consent.

Results

As Table 1 shows, there is no significant relationship between the study groups and age ($p > 0.21$). In addition, There is no relationship between the gender and the studied groups ($p > 0.72$). There was no significant relationship between the occupation, education of parents and the family history of attention deficit and hyperactivity in different studied groups (Table 1).

Table 1
Participants' demographic characteristics by type of treatments of ADHD

Variables	Methylphenidate + Risperdone	Methylphenidate + Placebo	Methylphenidate + Aripiprazole	P-value
Age, years	8.57 ± 1.89	8.23 ± 1.78	8.70 ± 1.99	0.21 <
Gender				> 0.05
Girl, n (%)	(3) 27.27	2 (18.18)	6 (54.54)	
Boy, n (%)	16 (34.78)	19 (41.3)	11 (23.91)	
Father's job				> 0.58
Unemployed, n (%)	0 (0)	1 (4.8)	1 (5.9)	
Employed, n (%)	19 (100)	20 (96.2)	16 (94.1)	
Mother's job				> 0.30
Unemployed, n (%)	19 (100)	21 (100)	16 (94.1)	
Employed, n (%)	0 (00)	0 (0)	1 (5.9)	
Education level(F)				> .15
≥Diploma, n (%)	16 (84.2)	20 (96.2)	17(100)	
≤Bachelor, n (%)	3 (16.8)	1 (4.8)	0 (0)	
Education level (M)				> 0.08
≥Diploma, n (%)	19 (100)	21(100)	15 (88.2)	
≤Bachelor, n (%)	0(0)	0(0)	2 (11.8)	
Family history of ADHD				> 0.08
Father, n (%)	7 (36.8)	10(47.6)	3(17.6)	
Mother, n (%)	0(0)	1(4.8)	1(6.9)	
Both of them, n (%)	0(0)	1(4.8)	1(6.9)	
None of them, n (%)	12 (63.2)	6(28.6)	8(47.1)	
Drug dose				
1 week dose	0.5 mg/day*	5 mg/day**	2.5 mg/day***	
2-week dose	1 mg/day	10 mg/day	5 mg/day	

Variables	Methylphenidate + Risperdone	Methylphenidate + Placebo	Methylphenidate + Aripiprazole	P-value
3,4,5,6,7 and 8 weeks doses	2 mg/day	20 mg/day	10 mg/day	

Based on Fisher Exact Test, there were no significant relationship between three groups of Methylphenidate and Risperidone, Methylphenidate and Placebo and Methylphenidate with Aripiprazole in drug complications ($p > 0.23$) are shown in Table 2.

Table 2
The comparison of complications observed between the three groups during the study

Type of complication	Methylphenidate and Risperidone	Methylphenidate and Placebo	Methylphenidate and Aripiprazole	P-Value
Week 2				> 0.230
Somnolence	0(0)	1(50)	1(50)	
Week 4				
Headache	0(0)	1 (100)	0 (0)	
Stomachache	1(50)	0(0)	1(50)	
Week 8				
Somnolence	1(100)	0(0)	0(0)	

Parent Adhd Rating Scale

Regarding that the Mauchly's sphericity test was rejected in the combination of ADHD (Total) with ODD (Mauchly's $W = 0.753$, $df = 5$, $p = 0.021$), therefore, Greenhouse-Geisser test was used that the results of the test demonstrated that there is a significant difference between the mean of the groups after 8 weeks in ADHD and ODD ($f = 2.34$, $p < .03$) (Table 3). In this regard, diagram (1) reveals the difference between the mean and standard deviation of ADHD and ODD among all three groups. Because Mauchly's sphericity test was rejected in ADHD (Inattention subtype) with ODD (Mauchly's $W = 0.380$, $df = 5$, $p = 0.001$), Greenhouse-Geisser test was used that its results demonstrated that there is no significant difference in the mean of the groups after 8 weeks in Inattention subtype with ODD ($f = 1.68$, $p > 1.26$). In fact, after ending the study, ADHD (Inattention subtype) with ODD have shown the same reduction in all three groups (Table 3).

As Mauchly's sphericity test was rejected in ADHD (hyperactivity-impulsivity subtype) with ODD (Mauchly's $W = 0.462$, $DF = 5$, $p = 0.001$), Greenhouse-Geisser test was used. The results of this test demonstrated that there is no significant difference between the mean scores of groups after the interval of 8 weeks in hyperactivity-impulsivity subtype ($f = 899$, $p > 0.45$). In fact, after ending the study, ADHD

(hyperactivity-impulsivity subtype) with ODD, has demonstrated the same reduction in all three groups (Table 3).

Clinical Global Impression Severity

Finally, Table 3 shows the results of mean difference in a global scale in the interval of 8 weeks in ADHD with ODD. The results demonstrated that there is no significant difference ($f = 1.06$, $p = 0.3.73$).

Table 3

The results of Repeated Measure ANOVA analysis considering the comparison of the mean severity of symptoms in the studied groups at baseline, 3 and 6

Variables	Risperidone	Placebo	Aripiprazole	F	P
Parent ADHD Rating Scale (Inattention) with ODD					
Baseline(M ± SD)	57.312 ± 9.99	53.95 ± 9.71	52.46 ± 9.61	1.31	> 0.06
Week 2(M ± SD)	49.62 ± 9.43	50.65 ± 9.38	43.33 ± 9.18		
Week 4 (M ± SD)	41.00 ± 11.39	46.95 ± 10.34	41.53 ± 8.07		
Week 8 (M ± SD)	43.31 ± 8.80	44.75 ± 11.85	41.46 ± 10.30		
Parent ADHD Rating Scale (Hyperactivity/Impulsivity) with ODD					
Baseline(M ± SD)	121.50 ± 20.66	124.90 ± 26.15	52.46 ± 9.65	3.41	> 0.01
Week 2(M ± SD)	51.93 ± 9.61	50.65 ± 9.38	41.93 ± 11.20		
Week 4 (M ± SD)	40.25 ± 12.82	49.15 ± 10.42	41.53 ± 8.07		
Week 8 (M ± SD)	42.43 ± 12.35	47.50 ± 12.55	36.00 ± 9.35		
Parent ADHD Rating Scale(Total) with ODD					
Baseline(M ± SD)	88.06 ± 12.09	84.45 ± 13.89	79.73 ± 15.39	2.34	< 0.03
Week 2(M ± SD)	76.87 ± 14.04	78.20 ± 13.59	63.66 ± 13.51		
Week 4 (M ± SD)	61.31 ± 18.01	73.10 ± 15.15	60.33 ± 11.67		
Week 8 (M ± SD)	65.56 ± 15.15	70.55 ± 11.67	58.86 ± 11.69		
Clinical Global Impression					
Week 2(M ± SD)	27.81 ± 5.65	27.40 ± 6.06	24.06 ± 7.60	1.06	> 0.378

Variables	Risperidone	Placebo	Aripiprazole	F	P
Week 4 (M ± SD)	22.50 ± 6.75	25.90 ± 6.08	21.40 ± 4.32		
Week 8 (M ± SD)	23.06 ± 6.707	24.80 ± 7.68	21.40 ± 5.30		

Discussion

ADHD is neurodevelopmental disorder with the symptoms like attention deficit, hyperactivity and impulsivity. In children, this disorder results in the disruption in interpersonal communications (31). These children show the negative experiences in their relationship with their friends. In addition, their relationship with their family and teachers is instable and disrupted (32, 33). This issue is important as much that in some cases, the unsuitable behavior of these children destroys the relationship between their families and their relatives (31). Therefore, identifying the suitable treatment methods is an important concern of psychiatrists and other medical cadre members. According to the importance of this issue, this study aimed at comparing the effectiveness of Risperidone with Aripiprazole as a combination therapy in children with ADHD treated with Methylphenidate.

There were differences in the demographic information of three studied groups. The male gender in the placebo group was dominant and the number of fathers was higher in the group treated with Risperidone and placebo and most mothers were treated with Aripiprazole. There was the highest mean age in the children treated with Aripiprazole, and there was also the highest mean age of fathers in placebo group and there was also the highest mean age among the mothers treated with Risperidone. A few percents of each group suffered the side-effects that only sleepiness can be observed in the group treated with Risperidone; sleepiness and vomiting, and in placebo group, sleepiness and headache were observed in group treated with Aripiprazole. In a study, the most common side-effect was nausea, vomiting and confusion in Risperidone group, and increasing appetite and sleepiness in Aripiprazole group (34) and in the other study, there was no clear side-effect in the group treated with Aripiprazole and weight gain was observed in a group treated with Risperidone (35). In the studies conducted by Lamberti et.al (2016), and Safavi et.al (2016), prolactin level is decreased in the group treated with Aripiprazole and increased in the group treated with Risperidone, although there was no side-effect in this study (36, 37).

The results of this study demonstrated that there was no significant relationship between the combination of Methylphenidate with Risperidone, Aripiprazole and placebo groups in ADHD with ODD ($p > 0.05$), while, there was a significant difference ($p = 0.023$) between the combination of Methylphenidate with Aripiprazole and Methylphenidate with placebo groups in total scores of ADHD without ODD. In addition, the mean of ADHD scores and its' subtypes along with ODD in group treated by Aripiprazole was better compared to the placebo and Risperidone groups. The Risperidone group was better than the placebo group. The results of this research were not consistent with the results of other studies (34, 37, 38).

There was no difference about the effectiveness of these two drugs in these studies. In the study conducted by Zeni et.al (39), the effectiveness of Methylphenidate alone was higher compared to its combination with Aripiprazole. The difference of this research results and other studies was the difference in the sample size and simultaneous consumption of these drugs with Methylphenidate, because these drugs were used and compared alone in these studies. It should be noted that all these studies have considered children younger than 6 years age old but the 6–12 years old age group has been studied in this research. In the study conducted by Safavi et.al (2016), ADHD disorder has been related to the bipolar disease (37). This can be one of the other inconsistency causes of this research with the previous findings. But the results of this study were consistent with the results obtained of the studies conducted by Kumar et.al (2017) and Lamberti et.al (2016) in which the effectiveness of Aripiprazole was much better than Risperidone (35, 36), although in this study these two drugs were compared among schizophrenia patients and adults; ADHD was associated with autism in a study conducted by Lamberti et.al (2016) (36). There was no significant statistical difference between the combination therapy (Risperidone and Aripiprazole with Methylphenidate) in ODD treated in three groups. But the mean scores of ODD reduced by passing the time and mean ODD scores in group treated with Aripiprazole was lower than placebo and Risperidone groups. Also, the mean of ODD scores in Risperidone group was lower compared to the placebo group.

Our study had several limitations. One of the limitations of the study was the dose of drugs used. In this study, Risperidone was used with 2 mg/day dose and Aripiprazole with 10 mg/day dose. Selecting different doses could report different results. The next limitation was the assurance of adherence to the medication regimen of the studied samples. Also, since there was no research conducted about the effects of these medicines on ODD, we could not compare its results with the results obtained of other studies.

Conclusion

The results demonstrated that Aripiprazole in combination with Methylphenidate have higher effect on reducing ADHD and ODD symptoms compared to Risperidone with Methylphenidate and Methylphenidate alone groups. There is no significant different in side-effects in three groups. Therefore, it can be used with other medicines by conducting more studies in this field and proving the effectiveness of Aripiprazole on treating ADHD and ODD in long-term.

Abbreviations

ADHD

Attention-deficit hyperactivity

CGI-S

Clinical Global Impression-Severity

ODD

Oppositional defiant disorder

Declarations

Acknowledgments

The authors are thankful of the deputy and director of research and other collaborators who were participated in all stages of the research. Moreover, we are thankful of all the patients who participated in this project.

Authors' contributions

FY, RGG and SM conceived the survey; ASM, FR and KH conceptualized and designed the survey. ST and SM collected and analysed the data. RGG and FY wrote the manuscript. FR and SM reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding

This work was supported by funding from the Kurdistan University of Medical Science (No. 1395.135). The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed Consent Informed consent was obtained from parents of all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest.

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Figures

Figure 1

the mean and standard deviation difference of ADHD with ODD ($f=2.34$, $p<0.03$)