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Comparative Study on the Effect of Risperidone and its Combination with Naltrexone in Pediatric Patients with Autistic Spectrum Disorders: A Clinical Trial Study

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Abstract

Background

Autistic spectrum disorder (ASD) refers to a syndrome associated with persistent impairments in communication skills, social interactions, and so forth. Given the approval of risperidone and naltrexone by U.S. Food and Drug Administration (FDA) for ASD cases and extant controversy concerning their pertained side effects, this double-blind, placebo-controlled, crossover clinical trial with 2-treatment, 2-sequence, 2-period design was intended to evaluate the behavioral effectiveness of individual risperidone and its combination with naltrexone in autistic children aged 4-12 years old.

Materials and Methods

A total of 30 autistic children were recruited in this study, and then equally assigned into groups A and B. The first group underwent co-treatment with risperidone and naltrexone, while group B was instructed to use placebo and risperidone for 8 weeks. After a washout period of two weeks, treatments were crossed over for another 8 weeks. The behavioral changes were assessed applying the childhood autism rating scale (CARS).

Results

There were five out of 30 cases at the risk of drop-out due to side effect in group A, while only three failed to complete the trial in group B. The effect size of the combined treatment was greater than the individual which was manifest in the total score of CARS, improved 4-week listening response, and 8-week general impressions.

Conclusion

According to the results, naltrexone can be a promising candidate for the management of behavioral symptoms in autism children.

Key Words: Autism, Children, Crossover design, Naltrexone, Risperidone.

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1- INTRODUCTION

Autism spectrum disorders (ASD) are a clinical condition characterized by permanent impairments in communications and social interactions, along with restrictive desires and repetitive behaviors (1, 2). The prevalence of ASD has increased due to its modified definition from a single disorder to a spectrum of conditions (3). Almost 1.5% of eight-year children in several regions of United States were reported to be affected by ASD (4). A recent study by Samadi et al. indicated that the overall prevalence rate of autism among five-year Iranian children was 6.26 per 10,000 (5). The long course as well as poor prognosis of this medical condition has always posed a challenge to families and the society (6, 7). Almost two-third of these patients is afflicted with a severe disability in adulthood and thus will be dependent to their family and related institutions for the whole lifetime (3). Accordingly, proper and early treatment plays a crucial role in the quality of life and prognosis of these patients (8).

Recently, applying psychotropic treatments for children with ASD has been established (9-11). However, the overuse of these antipsychotics may be associated with adverse effects, including hyperprolactinemia (12, 13). Greenhill et al. reviewed the results of 196 studies about pharmacological treatment of ASD in children. They found that there has been no active surveillance for adverse effect measurements (14). Furthermore, there have been other side effects regarding the application of psychotropic medications such as, delayed puberty, growth problems, and cognitive impairments (15). Although the available pharmacological and non-pharmacological treatments have failed to completely eradicate the symptoms pertained to ASD, they can be effective in alleviating these symptoms (6, 16). Risperidone and aripiprazole are the two drugs that have approved by the United States Food and Drug Administration (FDA) to be used in intensive behavioral intervention for ASD children (17-19). It has been shown that these two drugs can improve the symptoms, namely aggression, hyperactivity, fidget, self-injury, and irritability (6, 18-20). Risperidone and other recent antipsychotics were demonstrated to cause weight gain (21). Despite such undesirable consequences, the long-term positive behavioral benefits of risperidone outweigh the adverse effects (22). Evidence about the administration of naltrexone in practice is controversial. Various studies have reported the beneficial effects of naltrexone on the decrease in some symptoms such as hyperactivity, irritability, and self-injury. However, no significant improvement was shown in communications and social interactions (6, 16, 23-25).

It is also suggested that naltrexone can be used in persistent behavioral symptoms (16). Desjardins et al. observed an increased transient negative behavior upon the treatment with naltrexone (16). On the contrary, there have been some reports indicating that the low dose of naltrexone can significantly reduce hyperactivity, irritability, and even social communication (26, 27). Besides, it was associated with marked improvements in the self-injury behavior (28). In light of such conflicting evidence with respect to the application of naltrexone for treating ASD, this double-blind, randomized, placebo-controlled, cross-matched trial was intended to compare the effects of individual risperidone, and its combination with naltrexone in children with ASD aged 4-12 years.

2- MATERIALS AND METHODS

2-1. Participants

This double-blind, placebo-controlled, crossover clinical trial was performed on a sample of convenience consisting of 30

children who were referred to the psychiatry ward or the clinic of the Ebn-e-Sina hospital, Mashhad city, North East of Iran, and diagnosed with autism or autistic spectrum disorders. This sample size was calculated based on the following formula:

$$n = \frac{1}{d^2}(z_{\alpha/2} + z_{\beta})^2$$

With a statistical power of 0.80, reliability coefficient of 0.9 and effect size of 0.3. The inclusion criteria were as follow: a) being aged 4-12 years; b) having autistic spectrum disorder; d) being under no treatment with antipsychotic drugs, risperidone or naltrexone for at least 8 weeks before the study commencement. The exclusion criteria included having severe medical illnesses, history of severe drug allergy to naltrexone or risperidone, and onset of the severe side effects related to the treatment.

2-2. Instruments

Before and during the treatment, the participants were evaluated using the childhood autism rating scale (CARS). It is a clinical scale that determines the severity of autism, helps in the diagnosis, and evaluates the treatment outcome through serial assessments. The scale is used to observe and subjectively rate fifteen items, including relationship to people, imitation, emotional response, body use, object use, adaptation to change, visual response, listening response, taste-smell-touch response and use, fear or nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response, and general impressions. Each of the items has 7 scores ranging from 1 (normal for the child's age) to 4 (severely abnormal) with intervals of 0.5 (29). Its Persian version is well developed in clinical settings. Mohammadi and Zarafshan reported a Cronbach's alpha coefficient of 0.76 (30).

2-3. Procedure

The participants were randomly divided into a 1:1 ratio to groups A and B. Randomization was conducted by a researcher who was not involved in the study and used random numbers from statistical tables. The first group was treated with naltrexone (0.5-1.5 mg/kg of body weight daily in the form of either 25 or 37.5 mg capsule), and risperidone (0.5-2 mg/day in the form of 1 mg tablet) for eight weeks followed by a two-week washout period.

Thereafter, they were administered the similar dose of risperidone along with a placebo identical in color and size to naltrexone capsules for another eight weeks. The placebo was made in the Pharmacy School in the Mashhad University of Medical Sciences. It contained starch and was designed to achieve an appearance and taste similar to naltrexone. Group B received risperidone and placebo for the first eight weeks prior to the washout period. In the second eight weeks, they underwent risperidone and naltrexone. During washout, both groups were exposed to risperidone. All the drugs were packed in similar boxes and neither the psychologist nor the patients were aware of the contents.

2-4. Outcome measures

The CARS mean score was considered as the outcome measures which were recorded at baseline, weeks 4, 8, 10, 14, and 18. Data collection was performed by a clinical psychologist who was independent from the study and blinded to the patient's group allocation. Any adverse events or treatment failure were also recorded by this psychologist. If any adverse event was observed that could affect participation in the trial, the physician in charge of care of the subjects would be informed by the parents. According to predetermined regulations, the trial researcher was then notified and

the event was recorded in the case-report form. In case that the event was manageable or not related to the trial, a series of therapeutic interventions was implemented. When it was life-threatening and likely related to the trial, the trial coordinator was called within 24 h to decide on this serious case. Decision-making process was performed by at least two members of the trial team who defined factors that would rule out participation. Those participants, whom the team decided to be excluded from the trial, underwent evidence-based therapies.

2-5. Statistical analysis

The data were fed into SPSS software (version 15, SPSS Science, Apache Software Foundation, USA). Normal distribution was tested by means of the Kolmogorov-Smirnov test. The demographic characteristics of the patients were compared between the two groups by using the nonparametric Mann-Whitney U test and Chi-squared test. As for the comparisons of the CARS variables, the MIXED procedure in SAS was utilized due to the crossover design. Repeated measures ANOVA were performed to determine the effect of sequence, treatment, and period. A p-value below 0.05 was considered significant.

2-6. Ethical considerations

This study was approved by the Ethical Committee for Medical Research affiliated to the Mashhad University of Medical Sciences with the identification number IRCT.201108155280N5 at the Iranian Clinical Trial Registry (IRCT.ir). Written parental permission was obtained prior to the study. The drugs used in the study, their side effects, and symptoms of the adverse drug reactions were thoroughly explained in this forms. The parents were asked to call the physician in charge if any pertained symptoms appeared.

3- RESULTS

This study recruited 30 patients who were eligible based on the inclusion criteria to enter into the 20-week drug therapy intervention. They were then allocated into groups A and B as shown in **Figure.1**. Of all the subjects, a half was allocated to group- A and the other 50% served as group- B. **Table.1** indicated that they were comparable in terms of the demographic characteristics (i.e., age, gender, and parental education) ($p>0.05$). The major age category was 4-6 year in group A (41.7%), and 7-9 years in group B (45.4%). Moreover, there was female predominance in the study with the striking 1.8 female/male ratio. A number of eight subjects withdrew from this trial. Five subjects were from group A, who reported severe side effects due to naltrexone, such as constipation (n=2), reduced communication and increased symptoms of autism (n=2), and sleepiness (n=1). Of these eight subjects, three from group B failed to complete the trial during the first period.

They experienced frustration and restlessness (n=1), stereotyped movements (n=1), fecal incontinence (n=1), angioedema and shortness of breath (n=1), and skin dryness (n=2). **Table.2** shows the comparison of baseline, 4-week, and 8-week mean scores. Of all 15 parameters defined in CARS, only listening response on week 4 and general impression on week 8 were associated with a marked difference ($p=0.050$). The results of repeated measures ANOVA in **Table.3** indicated that there was a significant difference between two groups regarding treatment effect ($p=0.050$), while no considerable difference was observed in period effect and sequence effect ($p>0.05$). Moreover, the effect sizes were 0.6 and 0.4 for groups A and B, respectively.

Table-1: Characteristics of the study participants at enrolment

Variables		Group A	Group B	P-value*
Age category in year, number (%)	4-6	5 (41.7)	3 (30.0)	1.000
	7-9	4 (33.3)	6 (60.0)	
	10-12	3 (25.0)	1 (10.0)	
Males, number (%)	-	9 (75.0)	8 (80)	1.000
Maternal Education level, number (%)	Primary	5 (41.6)	5 (50.0)	0.974
	High school	6 (50)	2 (20.0)	
	University	1 (3.3)	3 (30.0)	
Paternal Education level, number (%)	Primary	6 (50.0)	2 (20.0)	0.228
	High school	5 (41.7)	5 (50.0)	
	University	1 (8.3)	3 (30.0)	

* Chi-square test.

Table-2: Parameters of CARS during treatment with naltrexone-risperidone and risperidone-placebo administered to groups A and B, in order for 8 weeks

Variables		Result by study group, Mean (SD)				P-value*
		Group A		Group B		
		1st period	2nd period	1st period	2nd period	
Relationship to people	Baseline	2.1(0.7)	2.0(0.8)	2.8(0.4)	2.4(0.7)	0.402
	4 weeks	2.3(0.9)	1.6(0.5)	2.5(0.6)	2.3(0.7)	0.974
	8 weeks	2.3(0.9)	1.8(0.8)	2.5(0.6)	2.0(0.6)	0.722
Imitation	Baseline	2.6(0.8)	2.5(1.0)	2.5(0.6)	2.3(0.8)	0.071
	4 weeks	2.5(0.8)	2.2(0.7)	2.5(0.9)	2.4(0.7)	0.974
	8 weeks	2.5(0.8)	2.3(0.9)	2.5(0.8)	2.0(0.5)	0.771
Emotional response	Baseline	2.7(0.4)	2.3(0.8)	3.0(0.2)	2.6(0.6)	0.053
	4 weeks	2.3(0.7)	2.2(0.6)	2.4(0.5)	2.8(0.7)	0.364
	8 weeks	2.3(0.7)	2.2(0.9)	2.4(0.5)	2.6(0.8)	0.418
Body use	Baseline	2.5(0.7)	2.7(0.7)	2.6(0.4)	2.2(0.9)	0.401
	4 weeks	2.6(0.7)	2.8(0.9)	2.6(0.7)	2.7(0.7)	0.418
	8 weeks	2.6(0.7)	2.5(0.9)	2.6(0.7)	2.3(0.9)	0.539
Object use	Baseline	2.5(0.6)	2.5(0.8)	2.6(0.5)	2.4(0.6)	0.215
	4 weeks	2.4(0.7)	2.2(0.6)	2.3(0.5)	2.3(0.7)	0.628
	8 weeks	2.4(0.7)	2.1(0.7)	2.3(0.5)	2.3(0.6)	0.107
Adaptation to change	Baseline	2.4(0.6)	2.2(1.0)	2.7(0.5)	2.7(1.0)	0.063
	4 weeks	2.7(0.8)	2.2(0.9)	2.3(0.9)	2.0(0.9)	0.228
	8 weeks	2.7(0.8)	2.1(0.9)	2.3(0.9)	2.2(0.9)	0.821
Visual response	Baseline	2.3(0.5)	2.3(0.6)	2.5(0.4)	2.1(0.7)	0.111
	4 weeks	2.3(0.6)	2.3(0.7)	2.4(0.5)	2.4(0.5)	0.069
	8 weeks	2.5(0.6)	2.0(0.6)	2.4(0.5)	1.9(0.4)	0.314
Listening response	Baseline	2.4(0.6)	2.3(0.6)	2.7(0.5)	2.0(0.3)	0.309
	4 weeks	2.4(0.4)	2.0(0.6)	2.1(0.5)	2.1(0.4)	0.050†
	8 weeks	2.4(0.4)	2.1(0.7)	2.1(0.5)	2.0(0.4)	0.123
Taste-smell-touch response and use	Baseline	2.4(0.6)	2.7(0.7)	2.4(0.4)	2.1(0.8)	0.210
	4 weeks	2.7(0.8)	2.7(0.6)	2.5(1.11)	2.4(0.5)	0.821
	8 weeks	2.7(0.8)	2.3(0.7)	2.5(1.1)	2.2(0.05)	0.254
Fear or nervousness	Baseline	2.4(0.6)	3.0(0.8)	3.1(0.4)	2.7(0.4)	0.672
	4 weeks	2.7(0.8)	2.9(0.8)	2.9(0.7)	2.7(0.6)	0.228
	8 weeks	2.7(0.8)	2.4(0.5)	2.9(0.7)	2.4(0.8)	0.107
Verbal communication	Baseline	2.7(0.7)	2.6(0.9)	3.2(0.4)	2.4(0.8)	0.107
	4 weeks	2.9(0.8)	2.4(0.6)	2.8(0.8)	2.5(0.6)	0.069

	8 weeks	2.9(0.8)	2.5(0.8)	2.8(0.8)	2.4(0.4)	0.093
Non-verbal communication	Baseline	2.6(0.9)	2.5(0.8)	2.5(0.6)	2.5(0.6)	0.062
	4 weeks	2.6(0.7)	2.5(0.6)	2.4(0.5)	2.4(0.4)	0.069
	8 weeks	2.6(0.7)	2.4(0.7)	2.4(0.5)	2.2(0.5)	0.093
Activity level	Baseline	2.8(0.5)	2.2(0.6)	2.7(0.4)	2.0(0.6)	0.918
	4 weeks	2.3(0.6)	1.9(0.5)	2.2(0.3)	2.1(0.4)	0.872
	8 weeks	2.3(0.6)	1.8(0.6)	2.2(0.3)	1.8(0.5)	0.628
Level and consistency of intellectual response	Baseline	2.1(0.5)	2.7(0.4)	2.5(0.6)	2.8(0.8)	0.078
	4 weeks	2.5(0.6)	2.6(0.6)	2.8(0.4)	2.8(0.7)	0.821
	8 weeks	2.5(0.6)	3.0(0.5)	2.8(0.4)	2.8(0.5)	0.582
General impressions	Baseline	3.0(0.6)	2.8(0.8)	3.2(0.5)	2.4(0.5)	0.095
	4 weeks	2.9(0.6)	2.8(0.5)	2.6(0.6)	2.3(0.3)	0.539
	8 weeks	2.9(0.6)	2.5(0.8)	2.6(0.6)	2.4(0.4)	0.050†

a Mann-Whitney U test; † Statistically significant.

Table-3: Total score of CARS during treatment with naltrexone-risperidone and risperidone-placebo administered to groups A and B, in order for 8 weeks

Variables		Result by study group, Mean (SD)				P-value, F*		
		Group A		Group B		Treatment effect	Sequence effect	Period effect
		1st period	2nd period	1st period	2nd period			
Total score	Baseline	37.5(6.1)	37.2(5.7)	40.6(2.8)	80.1(11.6)	0.207, 1.70	0.764, 0.09	0.989, <0.001
	4 weeks	38.2(5.5)	35.2(5.2)	37.0(3.4)	78.1(9.3)			
	8 weeks	76.3(10.9)	34.0(6.9)	128.5(14.4)	33.2(3.5)	0.050†, 4.27	0.311, 1.08	0.339, 0.96

* Repeated measures ANOVA test; † statistically significant at $p<0.05$.

4- DISCUSSION

This 2-sequence, 2-treatment, 2-period study was designed to investigate the effectiveness of individual risperidone or its combination with naltrexone in lowering the symptoms of ASD according to CARS. To the best of our knowledge, this is the first study design which also included placebo. Co-treatment with naltrexone and risperidone was more likely to drop out due to side effects than an administration of risperidone and placebo. The findings of the present trial unraveled that the effect size of the combined treatment was greater than individual risperidone at week 8. Moreover, treatment effect was associated with marked improvement at week 8. The combination of naltrexone with risperidone led to a significant enhancement in listening response at week 4, which, further, remained unchanged at week 8. Also, a marked improvement was observed in general impressions following co-administration of naltrexone and risperidone at week 8. What is more, non-considerable enhancements were reported in visual response. In a similar study design, Willemsen-Swinkels et al. observed that 4-week treatment with 1 mg/kg naltrexone caused a notable reduction in hyperactivity and irritability. Furthermore, stereotypic behaviors and social interactions were found with no improvement, which was consistent with our results and those documented by Ghanizadeh (31, 32). Another double-blind placebo-controlled crossover trial by Kolmen et al. substantiated the finding that the use of naltrexone carried no significant impact on the communication skills, either verbal or non-verbal (33). In contrast with ours, Williams et al. highlighted a minimal improvement in social interactions caused by daily dose of 1.5 mg/kg naltrexone over 4 weeks (34).

5- CONCLUSION

In relation to the previous clinical trial using naltrexone for autistic children, our study has a larger sample size, longer follow-up duration, and more observation intervals (4 weeks). However, the main limitation of the present study regards the use of only one validated and reliable instrument (CARS). In conclusion, this study demonstrated an interventional relationship between autistic symptoms and co-treatment with naltrexone and risperidone.

6- CONFLICT OF INTEREST: None.

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