Buspirone versus Methylphenidate in the Treatment of Children with Attention- Deficit/ Hyperactivity Disorder: Randomized Double-Blind Study

Mohammad-Reza Mohammadi[1], Poopak Hafezi[1], Ali Galeiha[2], Reza Hajiaghaee[3], and Shahin Akhondzadeh[1]

[1] *Psychiatric Research Centre, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Research Center for Behavioral Disorders and Substance Abuse, Hamadan University of Medical Sciences, Hamadan, Iran*

[3] *Institute of Medicinal Plants (ACECR), Tehran, Iran*

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Abstract- A recent randomized clinical trial showed buspirone efficacy in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children. However, results from a recent multi-site controlled clinical trial of transdermal buspirone failed to separate it from placebo in a large sample of children with ADHD. Therefore, due to these inconsistent findings, this study was designed to assess the efficacy of buspirone in the treatment of children with ADHD compared to methylphenidate in a double blind randomized clinical trial. Forty outpatients with a DSM-IV-TR diagnosis of ADHD were study population of this trial. Subjects were recruited from an outpatient child and adolescent clinic for a 6 week double blind, randomized clinical trial. All study subjects were randomly assigned to receive treatment using tablet of buspirone at a dose of 20-30 mg/day depending on weight (20 mg/day for < 30kg and 30 mg/day for > 30kg) (group 1) or methylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for < 30kg and 30 mg/day for > 30kg (group 2) for a 6 week double blind, randomized clinical trial. The principal measure of outcome was the Teacher and Parent ADHD Rating Scale IV. Patients were assessed at baseline and at 21 and 42 days after the medication started. Significant differences were observed between the two groups on the Parent and Teacher Rating Scale scores. The changes at the endpoint compared to baseline were: -8.95±8.73 (mean±SD) and −15.60±7.81 (mean±SD) for buspirone and methyphenidate, for Parent ADHD Rating Scale. The changes at the endpoint compared to baseline were: −9.80 ±7.06 (mean±SD) and -22.40±9.90 (mean±SD) for buspirone and methyphenidate, respectively for Teacher ADHD Rating Scale. The difference between the buspirone and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group. The results of this study suggest that administration of buspirone was less effective than methylphenidate in the treatment of ADHD.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood behavioral condition characterized by persistent symptoms of inattention, hyperactivity, and impulsivity. The ADHD prevalence was once estimated to be 3 to 5% of school-age children (1), but more recent studies place the figure closer to 7 to 8% of school-age children (2).

There are both pharmacological and non-pharmacological treatments for ADHD for both children and adults (3). Pharmacological approaches to treatment are the most common, and typically consist of stimulant medication, such as methylphenidate, dexmethyl-phenidate, mixed amphetamine salts and lisdexamfetamine dimesylate (LDX) (3,4). However, non-stimulants such as atomoxetine, clonidine and guanfacine have also been found to be efficacious in

Corresponding Author: Shahin Akhondzadeh
Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran.
Tel: 98 21 88281866, Fax: +98 21 55419113, E-mail: s.akhond@neda.net

treating ADHD (3,4). Between 10 to 30% of those affected with ADHD may not respond to stimulants or may not be able to tolerate associated side effects such as appetite suppression, sleep disturbance, mood difficulties, or exacerbation of comorbid tic disorders (5). In addition, there is ongoing concern that treatment of ADHD with stimulant medications lead to increased risk of substance abuse and dependence (5).

In such instances or when families are unwilling to consider a stimulant, non-stimulant medications may be appealing (5). Several non-stimulant medications that affect noradrenergic and/or dopaminergic pathways have demonstrated efficacy in the treatment of ADHD (3,6). Buspirone is an anxiolytic agent and possesses an antidepressant action. It displays high affinity and selectivity for the serotonin 5-HT1A receptor subtype (7). The neurochemical and clinical effects of buspirone represent both its pre-synaptic and pos-tsynaptic actions. It also has an affinity for 5-HT2 receptors, which might contribute to its therapeutic efficacy (7). Because of its dopaminergic effects, it was supposed that buspirone might also be effective in treating ADHD (3). An open clinical trial of 12 children with ADHD treated with buspirone 0.5 mg/kg/day (range 15 to 30 mg/day) in two divided doses suggested that it helps to reduce hyperactivity, impulsivity and oppositionality (8). In addition, a recent randomized clinical trial showed its efficacy in the treatment of ADHD in children (9). However, results from a recent multi-site controlled clinical trial of transdermal buspirone failed to separate it from placebo in a large sample of children with ADHD (6). Therefore, due to these inconsistent findings, this study was designed to assess the efficacy of buspirone in the treatment of children with ADHD compared to methylphenidate in a double blind randomized clinical trial.

Materials and Methods

Trial design

This was a single-center, 6-week, randomized, double-blind, parallel-group clinical trial conducted in the outpatient child and adolescent psychiatry clinics at Roozbeh Psychiatric Hospital (Tehran, Iran) from June 2010 to December 2011.

Participants

Subjects included 40 outpatients (28 boys and 12 girls) between the ages of 6-14 who clearly met the DSM-IV-TR diagnostic criteria for ADHD. At screening, investigators conducted a psychiatric evaluation with the DSM-IV-TR criteria for ADHD and the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview and performed a complete medical history and physical examination (10,11). Additional inclusion criteria included total and/or subscale scores on Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for patient's age and gender (12). The ADHD-RS-IV has been used extensively in Iran and offers valid measurement of attention and behavioral problems in school-age children (13-18). The patients were recruited from the outpatient child and adolescent clinic at Roozbeh Psychiatric Hospital. The diagnosis of ADHD was confirmed by a child and adolescent psychiatrist before participants were initiated into the study. All patients had combined subtype of ADHD and were newly diagnosed. Parents were carefully interviewed and asked to rate the severity of the DSM-IV-TR ADHD symptoms that their children displayed at home. Children were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I); any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation (I.Q <70). In addition, patients were excluded if they had a clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs the last 6 months. Additional exclusion criteria were hypertension or hypotension. To participate, parents and children had to be willing to comply with all requirements of the study. After a description of the procedures and purpose of the study, written informed consent was obtained from each patient's parent or guardian. Informed consent was received before the administration of any study procedure or dispensing of study medication in accordance with the ethical standards of the investigative site's institutional review board and with the Helsinki declaration of 1975, as revised in 2000. The study was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (Grant No: 8643). This trial is registered with the Iranian Clinical Trials Registry (IRCT201011101556N17)

Interventions

Patients were randomly assigned to receive buspirone tablets 20-30 mg/day depending on weight (20 mg/day for patients<30 kg and 30 mg/day for patients>30 kg) or methylphenidate (Ritalin®, Novartis,

Switzerland) 20–30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) for 6 weeks.

Outcomes

Symptoms were rated using the Parent and Teacher ADHD-RS-IV at baseline and week 3 and 6 (12). It assesses the 18 symptoms of ADHD based on DSM-IV-TR on a 4-point scale. The primary outcome measure was the change in the scores of parent and teacher version of ADHD-RS-IV from baseline to week 6 in each group. (19). Adverse effects were systematically recorded at each visit using a checklist that comprised 20 side effects.

Randomization, allocation concealment, and blinding

Patients were randomized in a 1:1 ratio (blocks of four) using a computerized random number generator. Allocation was concealed from the rater and the participants using sequentially numbered, opaque, and sealed envelopes. Random allocation and clinical rating of the patients was done by different individuals. The patient and his/her parents, the clinician referring physician, the physician who prescribed the medication and rated the patients, and the statistician were blind to allocation.

Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups (buspirone and methylphenidate) as a between-subjects factor (group) and the three measurements during treatment as the within-subjects factor (time) were considered. This was done for Parent and Teacher ADHD Rating Scale scores. Results are presented as mean±SD. Differences were considered significant with $P \leq 0.05$. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was performed. To consider the final difference between the two groups, at least a score of 5 on the Teacher and Parent ADHD Rating Scale, S=5 and power=0.8, the sample size was calculated at least 15 patients in each group.

Results

A total of 53 patients were screened, 7 of which did not meet the eligibility criteria. Forty-six eligible patients were randomly assigned to either methylphenidate (n=23) or buspirone (n=23), six of which dropped out before the first follow-up visit. Forty patients completed the study. Table 1 summarizes baseline characteristics of the patients. All patients were drug-naive. No significant differences were identified between patients randomly assigned to the group 1 or 2 conditions with regard to basic demographic data including age, gender and weight (Table 1).

Parent ADHD rating scale

The mean ± SD scores of the two groups are shown in Figure 1. There were no significant differences between two groups at day 0 (baseline) on the Parent ADHD Rating Scale (t=0.53, df=38, P=0.59). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor (F=4.58, df=1, P=0.009). The time/treatment interaction was significant (groups by time interaction, F=4.54, df=1.50, P=0.02) (total score). The changes at the endpoint compared to baseline were: −8.95±8.73 (mean±S.D.) and -15.60±7.81 (mean±S.D) for buspirone and methyphenidate, respectively (total score). A significant difference was observed on the reduction of scores of the Parent ADHD Rating Scale at Week 6 compared to baseline in the two groups (t=2.53, df=38, P=0.01).

Teacher ADHD rating scale

The mean ± SD scores of two groups are shown in Figure 2. No significant differences were observed at baseline on the Teacher ADHD Rating Scale (t=0.13, df=38, P=0.89) (total score). The difference between the two groups was significant as indicated by the effect of group, the between-subjects factor (F=14.70, df=1, P<0.001).

Table 1. Baseline data.

	Buspirone Group	Methylphenidate Group
Girl	8	7
Boy	12	13
Age (mean ± SD)	10.05 ± 2.60 (year)	9.70 ± 3.18 (year)
Weight (kg)	36.00±12.08	33.00±11.92

Table 2. Clinical complications and side effects.

Complications	Busropion	Ritalin	*P*-value
Abdominal pain	3	5	0.69
Dizziness	4	2	0.66
Decreased appetite	2	9	0.03
Tic	3	4	1.00
Insomnia	1	9	0.008
Dry mouth	1	3	0.60
Headache	2	9	0.03
Vomiting	2	2	1.00

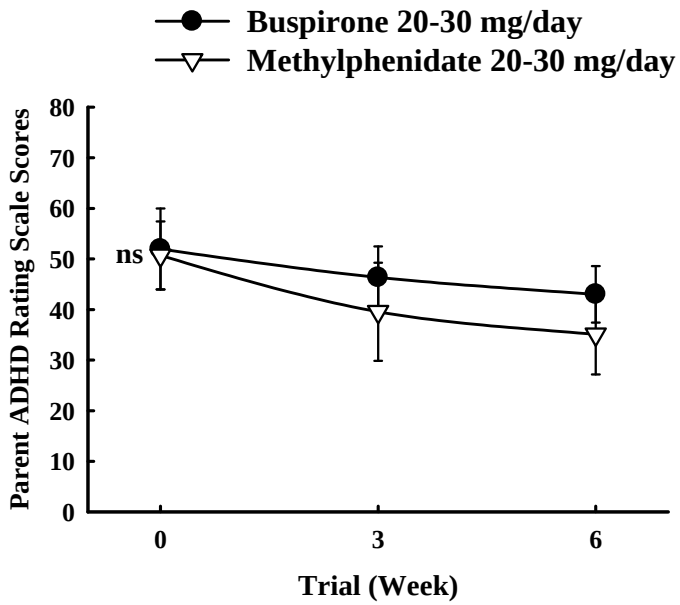

Figure 1. Mean ± SD scores of two protocols on the Parent ADHD Rating Scale-IV. ns: non-significant.

The time/treatment interaction was significant (groups by time interaction; Greenhouse–Geisser, F=15.46, df=1.46, *P*=0.001). The changes at the endpoint compared to baseline were: −9.80±7.06 (mean±SD) and −22.40±9.90 (mean±SD) for buspirone and methyphenidate, respectively. A significant difference was observed on the reduction of scores of the Teacher ADHD Rating Scale at week 6 compared to baseline in the two groups (t=4.62, df=38, *P*=0.001).

Clinical complications and side effects

A number of probable side effects were studied (Table 2). Ten side effects were observed over the trial that all of them were mild to moderate and tolerable. The difference between the buspirone and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group.

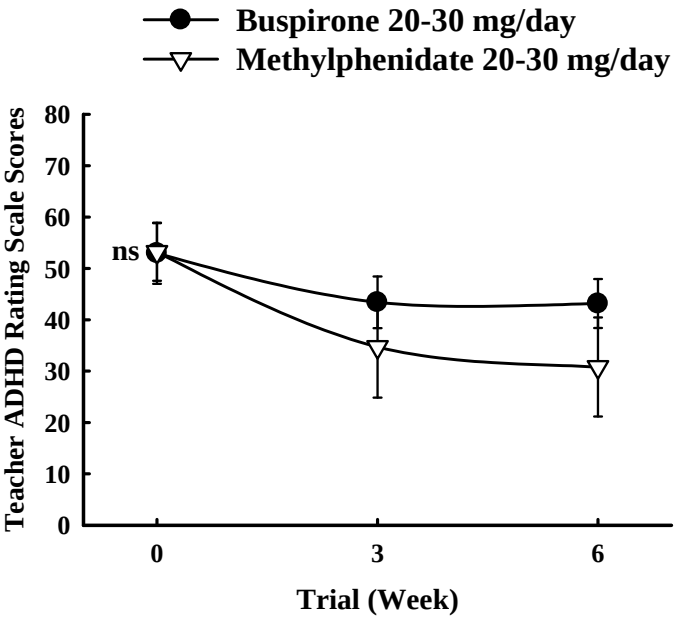

Figure 2. Mean ± SD scores of two protocols on the Teacher ADHD Rating Scale-IV. ns: non-significant.

Discussion

There are many data that support stimulant medications, such as methylphenidate and amphetamine, as effective treatments of ADHD in children (2). However, Stimulant can be associated with significant negative effect, notable appetite suppression, weight loss and sleep disturbance. Stimulant medication remains the most effective and widely prescribed ADHD treatment (6). Considering stimulant side effects and questions regarding the long-term safety of stimulant treatment, as well as personal preference to avoid stimulant medication, has led many parents to seek alternative medical therapies (4).

The results of this study suggest that administration of buspirone has no comparable efficacy in comparison with methylphenidate in the treatment of ADHD. Nevertheless, in our study, those in the buspirone group experienced fewer adverse events than the methylphenidate group in particular regarding decreased appetite, headache and insomnia. This trial used similar enrollment criteria and the same rating scales as our previous trials to monitor improvement in symptoms over the course of the study (20, 21). Our results are in contrast with the study of Davari-Ashtiani *et al.*, who reported beneficial application of buspirone in the treatment of thirty four children and adolescent with ADHD for 6 weeks in a randomized trial (9). Nevertheless, the effect size in that study was small and our sample size was relatively bigger that study. A recent multi-site controlled clinical trial of transdermal buspirone failed to separate it from placebo in a large sample of children with ADHD that our study is line with this report (6). This was a negative trial but what could be the value for our negative findings? There is no doubt, modern medicine needs to evidence based medicine. The relatively short duration (6 weeks) and small sample size of this trial are limitations of this study. In conclusion, the results of this study do not support the application of buspirone in the treatment of ADHD.

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