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Original Article

A randomized parallel-controlled study of curative effect and safety of atomoxetine and methylphenidate in treatment of ADHD in children

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Abstract: Objective: To compare the curative effect and safety of atomoxetine and methylphenidate in treatment of attention deficit hyperactivity disorder (ADHD) in children. Methods: One hundred and four children with ADHD treated in our hospital from February 2014 to January 2016 were included in this study. They were divided into atomoxetine group (52 cases) and methylphenidate group (52 cases) according to the design method of the randomized single-blind parallel controlled trial. Both groups were respectively treated with atomoxetine and methylphenidate for 8 weeks. Curative efficacy was evaluated through the changes of recorded scores of ADHD Rating Scale-IV: Parent Version (ADHDRS-IV-Parent: Inv), Conners' Parent Rating Scale-Revised: Short Form (CPRS-R: S) and Clinical Global Impression of ADHDSeverity (CGI-ADHD-S) before and after treatments. Cohen's d, an effect size index, and the Treatment Emergent Symptom Scale (TESS) were used to evaluate and compare the safety of the two treatments. Results: The response rates of atomoxetine group and methylphenidate group were 71.2% and 78.8% (P=0.365), respectively; and the dropout rates were 11.5% and 7.7% (P=0.506), which were not significantly different. A statistically significant decrease from baseline was observed in the postoperative scores of both groups in comparison with the preoperative ones (P<0.001). It had significant clinical significance, but there was no significant difference in curative effect between the two treatments. No serious adverse event occurred during the treatment, and the most common adverse events in two groups were loss of appetite, lethargy and nausea. The incidence of lethargy of atomoxetine group was significantly higher than that of methylphenidate group (P=0.027). Conclusion: The short-term efficacy and safety of atomoxetine in the treatment of ADHD in children is similar to that of methylphenidate, and the long-term efficacy and safety of the two treatments need to be further verified by more randomized controlled trials.

Keywords: Attention deficit hyperactivity disorder, atomoxetine, methylphenidate, children

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common psychological and behavioral disorder in children and adolescents, which is characterized by inattention, hyperactivity and impulsivity [1]. A recent meta-analysis showed that the prevalence of ADHD in children and adolescents was 6.26% in China, similar to the results of foreign studies [2, 3]. And the proportion of children who had sustained symptoms to adulthood was about 60% [4]. ADHD could cause a serious impact on children's learning, emotion, development and life [5, 6]. Thus, it is very important to play the therapeutic intervention for children with ADHD. The common treatment methods include drug therapy, cognitive-behavioral therapy, sensory integration training and so on. The drug therapy of ADHD mainly includes central stimulant, antidepressant, antihypertensive drugs, etc. Methylphenidate, a kind of central nervous system stimulant drugs, is commonly used in the treatment of ADHD. It can improve the core symptoms of inattention, hyperactivity and impulsivity quickly and effectively. However, in some patients, the effect is not good, and the use of large doses of drugs may cause the symptoms of anxiety, tension, mental disorder and so on, resulting in the poor compliance of patients [7]. In addition, long-

term use of central stimulants has potential risks of addiction and abuse [8]. Therefore, searching for effective and safe treatments of ADHD has become the main focus of the current research.

Atomoxetine is the first non-central stimulant drug approved for the treatment of children with ADHD. It can selectively inhibit the reuptake of noradrenaline by presynaptic amine pump. Besides, it has a significant effect on children with inattention and hyperactivity [9, 10]. Since its listing in China in 2007, it has been gradually used in the treatment of children with ADHD. In this study, methylphenidate was used as a contrast medium to evaluate the clinical efficacy and safety of atomoxetine in the treatment of children with ADHD. The results were as follows.

Materials and methods

General information

One hundred and four children with ADHD treated in our hospital from February 2014 to January 2016 were enrolled in this study. Inclusion criteria: patients who aged from six to fourteen and conformed to the ADHD diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). And the scores ofCGI-ADHD-S of these patients were all higher than 4 points. The informed consent of the children's guardians was obtained. Exclusion criteria: patients who had the psychiatric disorders of mental retardation, autism, schizophrenia, pervasive developmental disorder and so on; patients who didn't respond to methylphenidate treatments previously; and those who had serious physical diseases in heart, lung and other organs. The randomized single-blind parallel controlled method was adopted in this research. All children and their patients didn't know the grouping and types of therapeutic drugs. The research program was approved by the Hospital Ethics Committee.

Therapeutic methods

One hundred and four patients were randomly divided into methylphenidate group and atomoxetine group, 52 cases for each group. If patients took the central nervous system stimulants before the experiment, a week of drug elimination was given to them. If not, patients could be treated with atomoxetine directly. The initial dose of methylphenidate group was 0.2 mg/kg per day, and then gradually increased to 0.5 mg/kg. The drugs should be taken after breakfast every day. The initial dose of atomoxetine group was 0.5 mg/kg per day then gradually increased to 1.2 mg/kg according to the children's condition and tolerance. The maximum daily dose was no more than 1.4 mg. Both groups were treated continuously for eight weeks. Finally, the average dose of atomoxetine and methylphenidate were 1.32 mg/kg and 0.55 mg/kg per day respectively.

Outcome measures

Efficacy evaluation: At baseline and the end of eighth week, ADHDRS-IV-Parent:Inv filled up by parents was used as the main index for efficacy evaluation. The treatment could be considered as effective when reduction rate was greater than or equal to 40% [11]. Reduction rate = (baseline scores-postoperative scores)/baseline scores*100%. The second efficacy evaluation criteria includedCPRS-R: S and CGI-ADHD-S.

The parents who filled up the form all lived with their children for a long time and were familiar with their living and learning conditions. When they filled up the form, the trained professionals made a detailed description of the content and requirements of the scale to them. After the completion of the form, the trained professionals checked one by one to ensure the reliability and authenticity of the information.

Safety assessment: All the patients underwent routine physical examinations, vital signs measurements, laboratory tests (hepatic and renal functions, electrolyte, blood biochemical, blood and urine routine examinations) and electrocardiography examinations before and after treatment. Treatment emergent symptom scale (TESS) was used to record the adverse events during the treatment. At the same time, medication compliance was recorded and analyzed.

Statistical analysis

The scale score was expressed as mean ± standard deviation ($\bar{x}$ ± S). The differences

Table 1. Baseline demographicand clinical features of the two groups

Variables	Atomoxetine group (n=52)	Methylphenidate group (n=52)	χ^2/t	P
Age	9.92 (2.98)	9.75 (3.14)	0.283	0.778
Gender (Male/Female)	32 (78.0)/9 (22.0)	29 (70.7)/12 (29.3)	0.576	0.614
Weight (kg)	37.8 (6.7)	36.1 (5.9)	1.373	0.173
Height (cm)	133.2 (11.2)	135.3 (14.8)	0.816	0.416
Blood pressure				
SBP	101.2 (11.9)	103.4 (12.1)	0.935	0.352
DBP	64.1 (6.5)	66.2 (7.2)	1.561	0.122
Type of ADHD				
Inattention	27 (51.9)	24 (46.2)	1.165	0.559
H-I	13 (25.0)	18 (34.6)		
Combined	12 (23.1)	10 (19.2)		
Comorbidity				
CD (with/without)	9 (17.3)/43 (82.7)	5 (9.6)/47 (90.4)	1.321	0.390
PD (with/without)	1 (1.9)/51 (98.1)	2 (5.8)/50 (94.2)		0.618*

Note: *Fisher's exact test, SBP: systolic blood pressure; DBP: diastolic blood pressure; H-I: Hyperactivity-Impulsive; CD: conduct disorder; PD: panic disorder.

Table 2. Compliance and effective rate of both groups

Group	Number of cases (n)	Dropout rate (n/%)	Effective rate (n/%)
AG	52	6 (11.5)	37 (71.2)
MG	52	4 (7.7)	41 (78.8)
P value		0.506	0.365

Note: AG: atomoxetine group; MG: methylphenidate group.

between two groups at baseline, pre-and post-treatment were examined by independent-sample t test. The comparison of categorical variables was performed using the two-sided chi-square test or Fisher's exact test. Cohen's d was used as an effect size index (clinical significance): d≥0.8 meant the large effect size, 0.5≤d<0.8 represented the medium effect size, 0.2≤d<0.5 indicated the small effect size. The data were analyzed according to the Intent-To-Treat principle (ITT). If the patients dropped out during the study, it would be analyzed according to the last measurement data. Significance level was P<0.05 (two tailed).

Results

Basic information

The baseline and clinical characteristics of patients in two groups are shown in **Table 1**. There was no difference between the two groups in patients' gender, age, height, weight and blood pressure. The proportion of inattention type, hyperactivity-impulsive type and combined type were 51.9%, 25.0% and 23.1% in atomoxetine group and 46.2%, 34.6%, and 19.2% in methylphenidate group, respectively. The comorbidity rates of tic disorder and panic disorder were 17.3% and 1.9% in atomoxetine group, 9.6% and 5.8% in methylphenidate group, respectively. There was no statistically significant difference (P>0.05).

Treatment effect

Six cases of atomoxetine group and 4 cases of methylphenidate group were dropped out respectively during the eight-week treatment. Dropout rates were 11.5% and 7.7% (**Table 2**), without significant difference between two groups (P=0.506). The dropout in the atomoxetine group included 4 cases of drug side effects and 2 cases of no satisfactory efficacy, and there were 3 cases of drug response and 1 case of different concepts between family members in methylphenidate group. At eighth week of treatment, according to evaluation criteria of ADHDRS-IV-Parent: Inv, the effective rates reached 71.2% and 78.8% respectively, showing no statistical significance (P=0.365).

At the end of treatment, a significant decrease from baseline was observed in two groups in scores of ADHDRS-IV-Parent: Inv, 2 subscales

Table 3. The changes of scoresbefore and after treatments in two groups

Variable	Atomoxetine group					Methylphenidate group					Inter-group comparison of difference
	Pre-treatment	Post-treatment	Difference	Cohen's d	*P* value	Pre-treatment	Post-treatment	Difference	Cohen's d	*P* value	
ADHDRS											
Total	38.5 (7.4)	23.3 (4.1)	15.2 (6.9)	2.57	<0.001	37.5 (7.9)	20.1 (4.8)	17.4 (9.7)	2.76	<0.001	0.093
Inattention	22.8 (5.9)	11.7 (3.1)	11.1 (3.9)	2.38	<0.001	23.1 (6.8)	10.8 (3.7)	12.3 (4.1)	2.27	<0.001	0.129
H-I	15.7 (4.3)	8.6 (3.4)	7.1 (3.1)	1.85	<0.001	14.1 (4.2)	7.2 (2.3)	6.9 (3.1)	2.02	<0.001	0.743
CPRS-R: S											
LP	13.6 (3.7)	7.2 (3.4)	6.4 (3.9)	1.82	<0.001	13.4 (3.8)	7.4 (3.9)	6.0 (3.7)	1.62	<0.001	0.593
H-I	11.7 (3.8)	6.6 (3.2)	5.1 (2.8)	1.47	<0.001	11.0 (4.1)	5.1 (3.0)	5.9 (2.5)	1.66	<0.001	0.127
Confrontation	10.1 (3.6)	5.1 (3.1)	5.0 (2.1)	1.50	<0.001	10.9 (4.5)	6.1 (2.9)	4.8 (2.2)	1.28	<0.001	0.636
ADHD index	28.3 (6.4)	14.3 (5.0)	14.0 (4.1)	2.46	<0.001	27.5 (6.7)	12.4 (5.3)	15.1 (4.4)	2.52	<0.001	0.190
CGI-ADHD-S	5.7 (1.1)	3.4 (1.3)	2.3 (1.5)	1.93	<0.001	5.3 (1.3)	2.5 (1.4)	2.8 (1.6)	2.09	<0.001	0.103

Note: ADHDRS: ADHD Rating Scale-IV: Parent Version; H-I: Hyperactivity-Impulsion; CPRS-R: S: Conners' Parent Rating Scale-Revised: Short Form; LP: learning problems.

Table 4. The adverse reactions during treatment in two groups

Adverse reactions	Atomoxetine group (n=52)	Methylphenidate group (n=52)	*P* value
Loss of appetite	30 (57.7)	24 (46.2)	0.239
Lethargy	19 (36.5)	10 (17.3)	0.027
Nausea	10 (19.2)	8 (15.4)	0.604
Headache	8 (15.4)	5 (9.6)	0.374
Dizziness	8 (15.4)	4 (7.7)	0.220
Abdominal pain	5 (9.6)	4 (7.7)	0.727
Fever	4 (7.7)	6 (11.5)	0.506
Vomiting	6 (11.5)	2 (3.8)	0.269
Twitch	0 (0)	2 (3.8)	0.618
Insomnia	4 (7.7)	8 (15.4)	0.220
Itch of skin	9 (17.3)	7 (13.5)	0.587

and CPRS-R: S (ADHD index, learning problems, hyperactivity-impulsion and confrontation), with considerable clinical significance. It was found that *P* values were all lower than 0.001 after examinations of paired t test before and after treatment. Before the treatment, the scores of CGI-ADHD-S were 5.7 in atomoxetine group and 5.3 in methylphenidate group. At the end of treatment, the scores decreased to 3.4 and 2.5 respectively (P<0.001), indicating that the severity degree of symptoms was changed from "obvious" to "slight". There was no statistical significance in difference values between the two groups before and after the above treatment, showing that the two treatments had similar curative effect (**Table 3**).

Safety evaluation

There were no serious adverse events in both groups during the treatment period, 4 patients in atomoxetine group and 3 in methylphenidate group discontinued treatment at sixth week due to a significant loss of appetite and lethargy. The most common untoward reaction of two groups was loss of appetite, and the difference was not statistically significant (P>0.05). The incidence of lethargy in atomoxetine group was conspicuously higher than that of methylphenidate group (P=0.027). There were no differences in the occurrence rate of other untoward reactions in two groups (**Table 4**). Furthermore, no difference was found between two groups in other vital signs, laboratory tests or electrocardiography examinations, etc.

Discussion

ADHD is one of the most common behavioral disorders in children and has wide and negative impacts on learning, social intercourse and life. The pathogenesis may be related to the metabolic disorders of central catecholamine neurotransmitter dopamine (DA) and norepinephrine (NA). At present, in some clinical guidelines or practice recommendations, methylphenidate and other central nervous system stimulants are still the first-line drugs in treatment of severe ADHD [12-14]. However, some studies have demonstrated that methylphenidate has abuse potential and is relevant to many kinds of untoward reactions, such asemotional change, involuntary spasm, the increase of heart rate and so on [15-17]. Besides, some children are still intolerant or unresponsive to methylphenidate. And parents are not willing to choose methylphenidate because they think methylphenidate is a kind of mental stimulants, which belongs to controlled substances. Therefore, clinically, the non-central stimulant drugs, with better curative efficacy and fewer side effects, are required for the treatment of children with ADHD.

In recent years, some studies have shown that atomoxetine, an antidepressant drug, has similar efficacy, safety and tolerability with methylphenidate. Atomoxetine can effectively improve the core symptoms of ADHD and ameliorate the comorbidity of ADHD, such as anxiety and depression, without the occurrence of abuse or addiction [18, 19]. A meta-analysis, which analyzed 13 articles concerning the treatment of ADHD with atomoxetine, showed that among 272 children with ADHD, the score of ADHDRS-IV-Parent: Inv was significantly reduced in the majority of children, with minor side effects, and only 4% children discontinued treatment due to obvious side effects [20]. A recent meta-analysis containing 11 randomized trials showed that the standardized mean difference between the methylphenidate group andatomoxetine group was 0.09 (95% CI: -0.06, 0.25), which was not statistically significant [19]. In this study, the effective rates of atomoxetine group and methylphenidate group at the eighth week were 71.2% and 78.8%, respectively, and there was no significant difference between the

two groups. The scores of ADHDRS-IV-Parent: Inv, subscales, CGI-ADHD-S and CPRS-R: S were recorded, the changes of each index before and after the treatment of atomoxetine were statistically significant, but there was no statistically significant difference between atomoxetine group and methylphenidate group. The effect size of the two groups indicated that the curative efficacy was significant, which was in line with the results of other reports [21, 22].

At present, reports about the incidence of adverse events in the two groups are not exactly the same. The results of the meta-analysis showed that the discontinuation rates of drugs and the occurrence of adverse events were similar in both group [23], and a single-arm study found that the incidences of loss of appetite and insomnia in methylphenidate group were higher than that of atomoxetine group, while the incidences of anorexia, nausea, lethargy and dizziness were significantly higher in the atomoxetine group [24]. No serious adverse events were observed during the treatment in this study. The most common adverse reactions in two groups were loss of appetite, lethargy and nausea. However, there was no significant difference in the incidence of adverse reactions between the two groups, except for the lethargy, whose incidence was obviously higher in atomoxetine group. Overall, the severity degree of the adverse effects, caused by atomoxetine and methylphenidate, were mild or moderate, so there was no significant difference in safety [25].

In summary, the randomized single-blind design is adopted in this study and it is further confirmed that the efficacy and safety of atomoxetine are comparable to those of methylphenidate in the treatment of children with ADHD. However, there are still some limitations in this study.For example, randomized single-blind design can avoid bias of subjects, but can not avoid the bias of doctors or researchers. In addition, the sample size is small, and only short-term efficacy and safety are evaluated. Therefore, the long-term efficacy and safety of atomoxetine in children with ADHD requires more randomized double-blind controlled trials with a larger sample size to verify.

Disclosure of conflict of interest

None.

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