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Original Research Article

Effect of Tiaoxie Yizhi Formula combined with atomoxetine and biofeedback therapy of school-age children with attention deficit hyperactivity disorder

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Abstract

Purpose: *To investigate the effect of Tiaoxie Yizhi Formula combined with atomoxetine and biofeedback therapy on the Swanson, Nolan, and Pelham-IV Rating Scale (SNAP-IV) score as well as Clinical Global Impression (CGI) score of school-age children with attention deficit hyperactivity disorder (ADHD).*
Methods: *Clinical data of 85 school-age children with ADHD who were admitted to Dushu Lake Hospital from April 2019 to June 2022 were analyzed retrospectively. Patients treated with biofeedback therapy and atomoxetine for 1 month were defined as control group (n = 42), while those treated with Tiaoxie Yizhi Formula in addition to what was given control group were defined as study group (n = 43). Efficacy, Traditional Chinese Medicine (TCM) symptom scores, SNAP-IV score, CGI score and cerebral electrophysiological indices were compared between the groups. The scores of the main and secondary syndromes were also compared between two groups.*
Results: *Treatment response rate in study group was significantly higher than in control group ($p < 0.05$). There was no significant difference in scores of the main syndromes and secondary syndromes, SNAP-IV score or CGI score between the two groups before treatment ($p > 0.05$). However, scores of the two groups decreased significantly after treatment, and study group had significantly lower scores than control group ($p < 0.05$). There was no significant difference in sensorimotor rhythms (SMR) waves, β waves, or θ waves between the two groups before and after treatment ($p > 0.05$).*
Conclusion: *Tiaoxie Yizhi Formula plus atomoxetine plus biofeedback therapy improves ADHD symptoms more than biofeedback therapy and atomoxetine combination as shown by the reduction in TCM, SNAP-IV and CGI scores. However, investigations will need to be carried out using a larger sample size in order to validate these findings.*

Keywords: *Attention deficit hyperactivity disorder (ADHD), Tiaoxie Yizhi Formula, Biofeedback therapy, Swanson, Nolan, Pelham-IV rating scale*

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), also known as "childhood hyperactivity syndrome", is a common mental disorder in childhood, especially in school-aged children, characterized by excessive activity and a lack of attention The exact cause of ADHD is still

unclear, but it is likely influenced by a combination of genetic, neurological and environmental factors. Genetic factors include variations in genes related to neurotransmitter regulation, neurological factors involve imbalances in brain structure and neurotransmitters, while environmental factors such as maternal smoking, premature birth and family environment may also play a role. Overall, ADHD is a complex disorder with multiple factors involved in its underlying pathology [1]. Epidemiological surveys have shown that the prevalence of ADHD in China is about 3 - 10 %, with higher rates in males than females [2]. Core symptoms of ADHD, such as attention deficit and hyperactivity, affect cognitive function and hinder learning and daily life processes [2]. Currently, there are three main treatments for ADHD namely: neuro-feedback therapy, medication and behavioral therapy. Behavioral therapy for ADHD focuses on helping individuals change their behavior patterns and improve their learning skills. It involves setting routines, providing clear instructions, using rewards and consequences, managing the environment and teaching coping strategies. It aims to enhance self-control, confidence and daily functioning [3].

Neurofeedback therapy is the non-pharmacological treatment method recommended both domestically and internationally, which improves the stability, attention and reaction speed of children to some extent and also has good application effects [3]. Atomoxetine is a serotonin–norepinephrine reuptake inhibitor (SNRI) that inhibits norepinephrine reuptake, which has been used and is known to have significant effects in treating childhood hyperactivity disorder. It works by inhibiting the reuptake of norepinephrine, a neurotransmitter that regulates attention and impulse control. Common side effects include nausea, decreased appetite and dry mouth [3]. With the continuous development of integrated Chinese and Western medicine, the advantages of traditional Chinese medicine in clinical practice are gradually being revealed [4].

Traditional Chinese medicine intervention for ADHD mainly focuses on dialectical treatment and whole-body regulation, with fewer adverse reactions and more precise curative effects than Western medicine treatment. The main manifestations of ADHD in children are short concentration time, scattered attention, irritable personality and restlessness. So the treatment focuses on supplementing the spleen, reinforcing the kidney and regulating willpower [5]. In order to provide safer and more effective treatment for ADHD children, this study retrospectively analyzed the use of the combination of regulating willpower, atomoxetine and neurofeedback therapy in treating school-aged children with ADHD.

METHODS

General information

A retrospective analysis was conducted on clinical data of 85 school-aged children with ADHD admitted to Dushu Lake Hospital affiliated with Soochow University, Suzhou, China, from April 2019 to June 2022. Western medicine diagnostic criteria, in "Diagnosis and Treatment Guidelines for Attention Deficit Hyperactivity Disorder in Children and Adolescents" [5], was used. In addition, traditional Chinese medicine diagnostic criteria, which is in accordance with diagnostic criteria for ADHD in "Guidelines for Diagnosis and Treatment of Common Pediatric Diseases in Traditional Chinese Medicine", was also used [6]. Furthermore, this study was approved by the ethics committee of Dushu Lake Hospital affiliated with Soochow University (approval no. Y-20-1). Signed written informed consent was obtained from patients and/or guardians.

Inclusion criteria

Patients who met clinical diagnostic criteria of both Chinese and Western medicine, were aged 6 - 12 years old, had not taken relevant psychiatric treatment drugs, or had not participated in related trials were included in the study.

Exclusion criteria

Accompanying organ dysfunction, organic diseases such as neurological and cardiovascular diseases, failure to complete medication within the specified time, and withdrawal midway or allergy/intolerance to the drugs used in treatment were the criteria used to exclude patients from the study. According to the treatment methods used, patients were divided into two groups. Patients treated with biofeedback therapy and atomoxetine for 1 month were defined as control group (n = 42), while those treated with Tiaoxie Yizhi Formula in addition to what was given control group were defined as study group (n = 43).

Treatment procedures

Control group was administered biofeedback therapy combined with atomoxetine. Specifically, an autogenic feedback system (AutogenicA620)

was used to increase fast wave beta and inhibit slow wave theta, while strengthening the sensory-motor rhythm (SMR) in the brainwave of somatosensory motor area. The device was used to collect the child's brainwaves and provide real-time feedback in the form of images.

Relevant indicators were recorded, including relative power of SMR wave, beta wave, and theta wave. Treatment included five stages: Stage 1 was baseline assessment and goal-setting stage (2 minutes); stages 2 – 5 were feedback treatment stages, with a treatment time and frequency of 5 – 7 min per session, 3 – 5 times per week, for one course of intervention (20 sessions in total).

Dosage and frequency of atomoxetine administered (Jiangsu Zhengda Fenghai Pharmaceutical Co., Ltd., H20133346) was based on patient's body weight, with an initial dose of 40 mg twice daily for patients with body weight > 70 Kg, and later adjusted to 80 mg after 3 days, depending on patient's condition; for patients with body weight ≤ 70 Kg, initial dose was 0.5 mg/Kg twice per day, which was later adjusted after 3 days according to patient's condition, up to a maximum of 1.2 mg/kg.

Study group was treated with Tiaoxie Yizhi Formula in combination with biofeedback therapy and atomoxetine. Tiaoxie Yizhi Formula consisted of 6 g each of chaihu and yinyanghuo, 12 g each of shengdihuang and zhiyuanzhi, 15 g of nüzhenzi, and 9 g of zhuru, with 3 g of huanglian, decocted in water and taken orally once daily for 2 weeks. Frequency of biofeedback therapy and the operation were consistent with those in control group every day.

Evaluation of parameters/indices

Traditional Chinese medicine (TCM) symptom score

The TCM symptom scores of the main and secondary symptoms, in both groups were observed pre- and post-treatment. The main symptoms include inattention and hyperactivity, while secondary symptoms include night sweats, insomnia with excessive dreams, dry mouth as well as hot palms and soles [7].

Swanson, Nolan, and Pelham Rating Scale, 4ht edition (SNAP-IV)

The scale consists of 26 items and three subscales of hyperactivity/impulsivity, oppositional-defiant behavior and inattention. Each item has a score range of 0 – 3 points, and the total score ranges of ≤ 13 points, 13 – 17 points, 18 – 22 points and 23 – 27 points corresponded to normal, mild abnormality, moderate abnormality and severe abnormality, respectively [7].

Clinical Global Impression scale (CGI) score

The physician evaluates the clinical severity of the patients before and after treatment using CGI. The scale includes two subscales namely Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I), with a total score range of 0 – 7 points and higher scores indicate more severe diseases [8].

Electrophysiological indicators

The indicators include SMR wave, beta wave and theta wave. The changes in brainwave frequencies were recorded and compared before and after treatment in both groups.

Efficacy assessment

Referring to the "Current Status of Traditional Chinese Medicine Syndrome and Key Research on Syndrome-based Chinese Medicine" [9] and "Treatment of ADHD in Children" [10], the treatment efficacy (E) in the two groups was compared. The formula is shown in Eq 1.

A decrease of ≥ 90 % in traditional Chinese medicine syndrome score and SNAP-IV score after treatment compared to before treatment is considered clinical control; a decrease of ≥ 60 % was considered significantly effective, a decrease of ≥ 35 % is considered effective, while a decrease of < 35 %, no decrease, or an increase, with a SNAP-IV score of 23 – 27 points is considered ineffective.

$$E = 1– (NI/NC)100 \quad \text{..... (1)}$$

where E = effective rate of treatment; NI = number of ineffective patients; and NC = number of patients.

Statistical analysis

Statistical Packages for the Social Sciences (SPSS) 20.0 was used for analysis. Descriptive statistics were presented as mean ± standard deviation (SD), *t*-tests were used for comparisons within and between groups for continuous variables, and frequency (percentage) was used for categorical variables, with chi-square tests used for comparison. Significance level was set at $p < 0.05$.

RESULTS

Biodata of the groups

There were 42 patients in control group, including 32 males and 10 females; their ages ranged from 7 - 12 years, with a mean age of 9.57 ± 1.12 years; disease duration was from 6 months to 2 years, with a mean duration of 1.05 ± 0.31 years; ADHD type was combined type in 23 patients, impulsive/hyperactive type in 5 patients, inattentive type in 14 patients. There were 43 patients in study group, including 35 males and 8 females; age: 6 - 11 years, mean age of 8.97 ± 1.07 years; disease duration was from 10 months to 2 years, with a mean duration of 1.13 ± 0.26 years; ADHD type was combined type in 24 patients, impulsive/hyperactive type in 5 patients, inattentive type in 14 patients. There was no statistically significant difference in general information between the two groups (p > 0.05) and they were comparable.

Treatment efficacy

The effective rate of treatment in study group was 93.02 % (40/43), which was significantly higher than control group's 76.19 % (32/42) (p < 0.05), as shown in Table 1.

Traditional Chinese medicine syndrome (TCM) scores

There was no significant difference in the traditional Chinese medicine syndrome scores of the main and secondary symptoms before treatment between the two groups (p > 0.05). However, after treatment, the scores for both the main and secondary symptoms in both groups decreased significantly, with Study group having a lower score than control group (p < 0.05), as shown in Table 2 and Table 3.

SNAP-IV scores

There was no significant difference in SNAP-IV scores before treatment between the groups (p > 0.05). After treatment, the scores in both groups significantly decreased, with study group having a lower score than control group (p < 0.05), as shown in Table 4.

CGI scores

There was no significant difference (p > 0.05) in CGI scores before treatment between groups but there was a significant decrease in CGI scores after treatment. Study group had lower scores than control group (p < 0.05), as shown in Table 5.

Neurophysiological indicators

There was no significant difference (p > 0.05) in SMR, beta and theta wave values before treatment. After treatment, however, there was a significant increase in SMR and theta wave, while a significant decrease in beta wave was observed in both groups, as shown in Table 6.

DISCUSSION

ADHD is a common disruptive behavioral disorder in children and some symptoms may persist into adulthood, causing serious social, mental, and academic impacts [1]. Although there has been some progress in the treatment of ADHD, research shows that 40 to 50 % of children with the disorder continue to exhibit symptoms into adulthood [11].

Table 1: Comparison of therapeutic effects between the groups (n (%))

Group	n	Clinical control	Significantly effective	Effective	Ineffective	Effective rate
Control	42	12(28.57)	13(30.95)	7(16.67)	10(23.81)	32(76.19)
Study	43	18(41.86)	15(34.88)	7(16.28)	3(6.98)	40(93.02)
X^2						4.647
P-value						0.031

Table 2: Comparison of the scores of TCM syndrome differentiation of the main symptoms between the groups

Group	n	Inattentiveness		Hyperactivity	
		Before treatment	After treatment	Before treatment	After treatment
Control	42	6.79±1.53	5.11±0.76[a]	7.23±0.98	5.07±0.63[a]
Study	43	6.83±1.47	4.73±0.58[a]	7.16±0.87	4.28±0.41[a]
T		0.123	2.595	0.348	6.868
P-value		0.903	0.011	0.728	<0.001

Note: Compared with before treatment in the same group, [a]p < 0.05.

Table 3: Comparison of the scores of TCM syndrome differentiation of secondary symptoms between the two groups

Group	n	Night sweats		Insomnia with frequent dreaming		Dry mouth		Hot sensations in the palms and soles	
		Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	42	1.46±0.51	0.34±0.07[a]	1.89±0.62	0.46±0.08[a]	2.11±0.65	0.35±0.10[a]	1.96± 0.64	0.35±0.06[a]
Study	43	1.50±0.53	0.13±0.02[a]	1.92±0.65	0.21±0.05[a]	1.99±0.72	0.16±0.07[a]	2.03±0.68	0.11±0.03[a]
T		0.354	18.901	0.218	17.320	0.806	10.168	0.488	23.407
P-value		0.724	<0.001	0.828	<0.001	0.423	<0.001	0.627	<0.001

Note: Compared with before treatment in the same group, [a]$p < 0.05$

Table 4: Comparison of SNAP-IV scores between the two groups

Group	n	Hyperactivity-Impulsivity		Oppositional Defiant Disorder		Inattention		Total score	
		Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	42	9.36±3.14	5.49±1.52[a]	6.57±1.62	5.06±1.06	7.93±3.55	5.61±2.13[a]	23.86±4.53	16.16± 2.85[a]
Study	43	9.61±3.31	3.28±1.29[a]	6.30±1.59	3.82±0.86[a]	8.16±3.42	3.33±2.05[a]	24.07±4.60	10.43± 2.77[a]
T		0.357	7.233	0.775	5.929	0.172	5.029	0.212	9.400
P-value		0.722	<0.001	0.440	<0.001	0.864	<0.001	0.833	<0.001

Note: Compared with before treatment in the same group, [a]$p < 0.05$

Table 5: Comparison of CGI scores between the two groups

Group	n	CGI-S		CGI-I		Total score	
		Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	42	3.11±0.46	2.01±0.36[a]	2.05±0.40	1.21±0.23[a]	5.16±0.86	3.22±0.59[a]
Study	43	3.01±0.44	1.05±0.22[a]	2.02±0.47	0.47±0.14[a]	5.03±0.91	1.97±0.36[a]
T		1.024	14.874	0.414	17.965	0.677	11.822
P-value		0.309	<0.001	0.680	<0.001	0.501	<0.001

Note: Compared with before treatment in the same group, [a]$p < 0.05$

Table 6: Comparison of the neurophysiological indicators between the groups

Group	n	SMR wave		β wave		θ wave	
		Before treatment	***After treatment***	***Before treatment***	***After treatment***	***Before treatment***	***After treatment***
Control	42	6.11±1.13	6.83±0.86[a]	24.96±3.52	19.68±4.47[a]	6.76±1.18	8.16±0.72[a]
Study	43	6.15±1.17	6.91±0.75[a]	25.03±3.46	19.52±4.52[a]	6.81±1.21	8.11±0.78[a]
T		0.160	0.457	0.092	0.164	0.193	0.307
P-value		0.873	0.649	0.927	0.870	0.848	0.760

Note: Compared with before treatment in the same group, [a]$p < 0.05$

Therefore, exploring effective methods to treat ADHD in children and reducing the harm caused by their behavioral problems when they reach adulthood is particularly important. Impaired neurocognitive function is the main cause of ADHD and stimulants have been the main medication used in the past for ADHD treatment. They relieve symptoms and improve cognitive function to some extent, but long-term use can lead to various adverse reactions such as headaches and loss of appetite [12]. Traditional Chinese medicine (TCM) has gradually gained popularity in clinical practice due to its advantages of minimal adverse reactions and significant efficacy [4]. The appropriate tune-up and control method is selected based on the classification of the disease and then treated with Tiaoxie Yizhi Formula (regulating willpower formula). On the other hand, multiple studies have shown that non-pharmacological treatment methods such as biofeedback therapy and pharmacological treatment, for example, atomoxetine, have good effects in the clinical treatment of ADHD [13-15]. However, the effectiveness of these three treatments combined in school-age children with ADHD remains to be explored. Therefore, this study adopted a combination of Tiaoxie Yizhi Formula (regulating willpower formula), atomoxetine and biofeedback therapy to treat school-age children with ADHD.

The results suggest that a combination of Tiaoxie Yizhi Formula (regulating willpower formula), atomoxetine and biofeedback therapy significantly improves treatment efficacy and reduces TCM syndrome scores in children with ADHD. In TCM, ADHD falls under the categories of "forgetfulness" and "dirty restlessness" [4]. Due to the complex pathogenesis of the disease, Tiaoxie Yizhi Formula was selected based on the theory of combined syndrome differentiation and disease differentiation. The formula consists of multiple Chinese herbs, including Chaihu, which enhances children's attention; Shengdihuang and Huanglian, which have the function of calming and soothing the mind and balancing heart and kidney function; Yin Yang Huo, which warms and tonifies the body; Zhiyuanzhi, which nourishes the heart and calms the mind; and Nvzhenzi and Zhuru, which soothes and nourishes the liver, regulates the lungs and nourishes the kidneys as well. The combination of these herbs enhances intelligence and strengthens the willpower [16]. Furthermore, biofeedback therapy and atomoxetine have been shown to also be effective in the clinical treatment of ADHD.

Comparison of SNAP-IV scores and CGI scores between the two groups showed a decrease in both groups after treatment, with study group showing a greater decrease than control group. This suggests that the three treatments combined can significantly reduce SNAP-IV and CGI scores in children with ADHD. Biofeedback therapy works by applying operant conditioning, measuring brain activity through sensors placed on the scalp to record the child's autonomic nervous system and muscle activity, then processing the brainwave frequency signals through a computer and feeding them back to the child. The child selectively inhibits or enhances certain brainwaves during audio-visual games, which can change their brainwave patterns over time and improve self-regulation function to some extent [17]. Relevant studies suggest that both the resting and task-related brain function of children with ADHD show reduced activity in the

left frontal gyrus and atomoxetine improves symptoms such as lack of attention and cognitive function by enhancing neurotransmitter reversal effects associated with synaptic norepinephrine transport inhibition, thus reducing clinical symptoms of ADHD and lowering SNAP-IV and CGI scores [18].

Some scholars believe that the main symptoms in school-age children with ADHD are hyperactivity and impulsivity due to poor coordination between the spleen and the mind [18] and Tiaoxie Yizhi Formula enhances mental clarity, strengthens the spleen and supports kidney function, while the combination of atomoxetine and biofeedback therapy significantly reduces SNAP-IV and CGI scores. After treatment, SMR, beta, and theta wave values in both groups improved significantly compared with those before treatment, which suggests that the combination of the three methods enhances children's brainwave activity and increases arousal levels, consistent with the findings of Liu *et al* [19].

CONCLUSION

Tiaoxie Yizhi Formula with atomoxetine and biofeedback therapy improve treatment efficacy, reduces TCM syndrome scores, SNAP-IV scores and CGI scores, as well as enhances the EEG activity of pediatric patients to a certain extent. However, due to limited sample size and relatively simple grouping method in this study, the results may be limited to a certain extent. Additional studies are required using a larger sample size and expanding the scope of the investigation.

DECLARATIONS

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Ethical approval

This study was approved by the ethics committee of Dushu Lake Hospital affiliated with Soochow University (approval no. Y-20-1).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Wanyan Yao and Jing Cai contributed equally to this work.

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