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Efficacy of clonidine in the treatment of children with tic disorder co-morbid with attention deficit hyperactivity disorder

K.-D. ZENG[1], G.-L. WANG[1], Y. YUAN[1], W. ZHANG[2], X.-H. HUANG[1], B. HU[1]

[1]Department of Pediatrics, The Affiliated Yichun People's Hospital of Yichun University, Yichun, Jiangxi, China
[2]Department of Obstetrics and Gynecology, The Affiliated Yichun People's Hospital of Yichun University, Yichun, Jiangxi, China

Abstract. – OBJECTIVE: The current research was designed to assess the efficacy of clonidine in the treatment of children with tic disorder co-morbid with attention deficit hyperactivity disorder.

PATIENTS AND METHODS: A total of 154 children with tic disorder co-morbid with attention deficit hyperactivity disorder admitted to our hospital from July 2019 to July 2022 were recruited and assigned to receive either methylphenidate hydrochloride plus haloperidol (observation group) or clonidine (experimental group), with 77 cases in each group. Outcome measures included clinical efficacy, Yale Global Tic Severity Scale (YGTSS) scores, Conners Parent Symptom Questionnaire (PSQ) scores, and adverse events.

RESULTS: Clonidine was associated with markedly higher clinical efficacy vs. methylphenidate hydrochloride plus haloperidol ($p<0.05$). Clonidine offered more significant mitigation of the tic disorder vs. methylphenidate hydrochloride plus haloperidol, as evinced by the lower kinetic tic scores, vocal tic scores, and total scores ($p<0.05$). Children exhibited markedly milder tic symptoms after clonidine monotherapy vs. those with dual therapy of methylphenidate hydrochloride and haloperidol, suggested by the lower scores of character problems, learning problems, psychosomatic disorders, hyperactivity/impulsivity, anxiety index, and hyperactivity index ($p<0.05$). Clonidine features a higher safety profile than methylphenidate hydrochloride plus haloperidol by reducing the incidence of adverse events ($p<0.05$).

CONCLUSIONS: Clonidine effectively alleviates tic symptoms, reduces attention deficit and hyperactivity/impulsivity in children with tic disorder co-morbid attention deficit hyperactivity disorder, and features a high safety profile.

Key Words:
Clonidine, Tic disorder co-morbid with attention deficit hyperactivity disorder, Efficacy observation, High safety profile.

Introduction

Tic disorder is a neuropsychiatric movement disorder of undetermined etiology that predominantly develops in childhood and adolescence and features a clear genetic predisposition[1]. Children with tic disorder mostly present recurrent, involuntary, purposeless motor or vocal twitching of one or more parts of the muscles[2]. Moreover, tic disorder is typically concomitant with multiple behavioral disorder issues, such as attention deficit hyperactivity disorder (ADHD), sleep disorders, and mood disorders[3]. It has been reported[4] that co-morbidity of ADHD is the main cause of functional impairment in children with tic disorders, for which pharmacological and psychological interventions are usually recommended[5]. Haloperidol and thiopurine provide symptom mitigation of tics but poor therapeutic efficiency for attention deficit and hyperactivity[6]. Central stimulant drugs can alleviate the symptoms of attention deficit and hyperactivity in children but result in aggravation of tic symptoms[7]. Moreover, the co-administration of the aforementioned drugs is associated with significantly increased risks of adverse events[8]. Thus, efficient drugs for both tic disorder and ADHD are urgently necessitated. Clonidine is a clinically used antihypertensive drug and has been used in the neuropsychiatric field for the treatment of children with tic disorders, ADHD, and other psychiatric disorders since the 1980s[9]. It has been largely reported[10,11] that clonidine exhibited significant efficiency in the management of tic disorder and ADHD; however, little knowledge is available related to the efficacy of clonidine in the treatment of children with tic disorder co-morbid

Corresponding Author: Bing Hu, MD; e-mail: hutotoch38551@163.com

with attention deficit hyperactivity disorder. Thus, the current study was performed to evaluate the clinical efficiency of clonidine.

Patients and Methods

Participants

A total of 154 children with tic disorder co-morbid with attention deficit hyperactivity disorder admitted to our hospital from July 2019 to July 2022 were recruited and assigned to receive either methylphenidate hydrochloride plus haloperidol (observation group) or clonidine (experimental group), with 77 cases in each group. This study was reviewed and approved by Ethics Committee of The Affiliated Yichun People's Hospital of Yichun University, No. Y2397911. The patients signed the relevant informed consent forms.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Children were clinically diagnosed with tic disorder and attention deficit hyperactivity disorder; (2) children had not received other psychotropic drug interventions before enrollment; (3) the children's families were informed about the study and signed the relevant informed consent forms.

Exclusion criteria: (1) children with allergies or contraindications to the study drugs; (2) children with abnormal liver and kidney function; (3) children with systemic or immune diseases; (4) children with epilepsy, abnormal or delayed brain development; (5) children with chorea, hepatomegaly, or delayed movement disorders; (6) children with ocular and nasal allergic diseases; (7) children with psychiatric or cognitive disorders; (8) children who are unable to cooperate fully with the study.

Treatment Methods

(1) Children in the observation group received methylphenidate hydrochloride plus haloperidol. Methylphenidate hydrochloride (Shanghai Shang-Pharma Xinyi Pharmaceutical Co., Ltd., Shanghai, China, State Pharmacopoeia H31021539) was administered in the morning at a dose of 10 mg once daily, and haloperidol (Ningbo Dahongying Pharmaceutical Co., Ltd., Ningbo, Zhejiang, China, State Pharmacopoeia H33020585) was administered at an initial dose of 0.25 mg, twice daily. The dosage could be strengthened as appropriate to a maximum dose of 3 mg daily if no significant response was observed.

(2) Children in the experimental group received 25-50 μg of oral clonidine hydrochloride tablets (Changzhou Pharmaceutical Factory Co., Ltd., Changzhou, China, State Drug Administration H32021681) once daily. The dosage could be increased as appropriate if no significant response was documented, with a maximum dose of 5 μg/(kg·d). The children in both groups returned to the hospital for a follow-up visit every Saturday from 15:00 to 16:00, during which the relevant medical personnel evaluated the treatment effect and adverse reactions of the children and regulated the dosage of medication.

The duration of the treatment for both groups was 12 weeks.

Outcome Measures

(1) clinical efficacy: cured: the child's Yale Global Tic Severity Scale (YGTSS) score was reduced by ≥80% after treatment; markedly effective: the child's YGTSS score was reduced by 50-79% after treatment; effective: the child's YGTSS score was reduced by 30-49% after treatment; ineffective: the child's YGTSS score was reduced by less than 30% after treatment.

(2) YGTSS score[12]: before and after treatment, the child's motor and vocal tics scores were assessed using the YGTSS score. The scores were based on the number, frequency, intensity, compounding, and disturbance of the child's tics, and the scores for both motor and vocal tics on this scale were 50. The two tic scores of the child were summed to obtain the total YGTSS score.

(3) Conners Parent Symptom Questionnaire (PSQ) score[13]: the PSQ scale was used to assess the child's symptoms and concomitant problems before and after treatment, and the scale was completed by the parents based on the child's daily behavioral performance. The PSQ scale includes 6 domains: character problems, learning problems, psychosomatic disorders, hyperactivity/impulsivity, anxiety index, and hyperactivity index, and higher scores of the children indicate a more severe symptomatic condition.

(4) Adverse events: The adverse events included in this study for observation included drowsiness, dizziness and headache, irritability, decreased appetite, and hyperphagia.

Statistical Analysis

SPSS 25.0 statistical software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis of the obtained data, and GraphPad Prism 8 (GraphPad Software, San Diego, CA,

Table I. Patient characteristics.

	Observation (n = 77)	Experimental (n = 77)	t/χ^2	*p*
Sex			0.347	0.556
Male	59	62		
Female	18	15		
Age (year)	9.79 ± 2.37	9.92 ± 2.41	-0.337	0.737
Disease duration (month)	21.32 ± 4.23	21.29 ± 4.36	0.043	0.966
Tic disorder types				
Transient	11	13	0.197	0.657
Chronic	49	46	0.247	0.619
Tourett's syndrome	17	18	0.037	0.848
Symptom types				
Attention deficit	36	39	0.234	0.629
Hyperactive/impulsive	10	8	0.252	0.616
Mixed	31	30	0.027	0.869

USA) was employed to plot the graphics. The measurement data were expressed as (and examined using the *t*-test. Count data were expressed as cases (%) and analyzed using the Chi-square test. Significant differences were indicated by $p<0.05$.

Results

Patient Characteristics

In the observation group, there were 59 male and 18 female cases, aged 5-13 (9.79±2.37) years, with a duration of disease of 3-35 (21.32±4.23) months, 11 cases of transient tic disorder, 49 cases of chronic tic disorder, 17 cases of Tourett syndrome tic disorder. There were 36 cases of attention deficit, 10 cases of hyperactivity/impulsivity, and 31 cases of mixed type. In the experimental group, there were 62 male and 15 female cases, aged 6-13 (9.92±2.41) years, with a duration of disease of 3-34 (21.29±4.36) months, 13 cases of transient tic disorder, 46 cases of chronic tic disorder, 18 cases of Tourett syndrome tic disorder. There were 39 cases of attention deficit, 8 cases of hyperactivity/impulsivity, and 30 cases of mixed type. The two groups showed no significant disparity in terms of patient features ($p>0.05$) (Table I).

Clinical Efficacy

The total efficiency of treatment in the observation group was 88.31% (68/77), of which 4 cases were cured, 36 cases were markedly effective, 28 cases were effective, and 9 cases were ineffective. The total efficiency of treatment in the experimental group was 97.40% (75/77), of which 9 cases were cured, 42 cases were markedly effective, 24 cases were effective, and 2 cases were ineffective. Clonidine was associated with markedly higher clinical efficacy *vs.* methylphenidate hydrochloride plus haloperidol ($p<0.05$) (Table II).

YGTSS Scores

The motor tic scores before and after treatment in the observation group were (37.92±7.35, 15.33±3.42), vocal tic scores were (11.74±2.89, 4.13±0.98), and total scores were (49.66±10.24, 19.46±4.40). The motor tic scores before and after treatment in the experimental group were (37.69±7.43, 10.24±2.27), vocal tic scores were (11.53±2.92, 2.32±0.54), and total scores were (49.22±10.35, 12.56±2.81). Clonidine offered more significant mitigation of the tic disorder *vs.* methylphenidate hydrochloride plus haloperidol, as evinced by the lower kinetic tic scores, vocal tic scores, and total scores ($p<0.05$) (Figure 1).

Table II. Clinical efficacy [n (%)].

Group	N	Cured	Markedly effective	Effective	Ineffective	Total efficiency
Observation	77	4	36	28	9	88.31% (68/77)
Experimental	77	9	42	24	2	97.40% (75/77)
χ^2	-	-	-	-	-	4.797
p	-	-	-	-	-	0.029

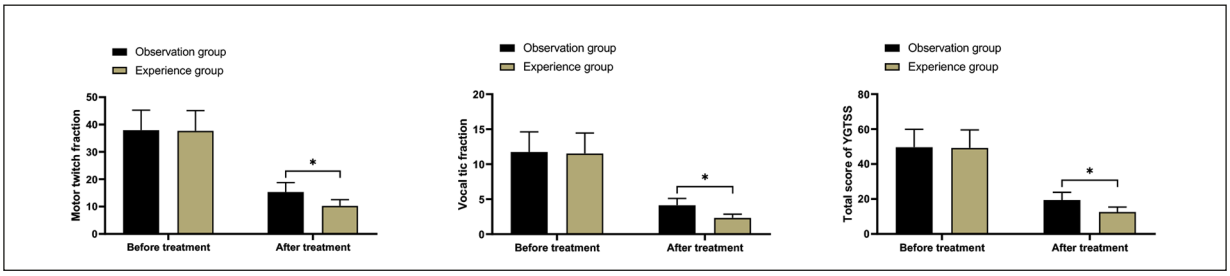

Figure 1. YGTSS scores ($\bar{x} \pm s$, points). *Indicates $p < 0.05$.

PSQ Scores

In the observation group, the pre and post-treatment character problems scores were (1.52±0.39, 1.02±0.31), learning problems scores were (2.21±0.65, 1.47±0.42), psychosomatic disorders scores were (0.93±0.31, 0.52±0.27), hyperactivity/impulsivity scores were (2.39±0.35, 1.67±0.29), anxiety index scores were (0.69±0.45, 0.46±0.23), and hyperactivity index scores were (2.05±0.47, 1.39±0.34). In the experimental group, the pre and post-treatment scores of character problems were (1.48±0.37, 0.73±0.22), learning problem scores were (2.18±0.63, 1.04±0.26), psychosomatic disorders were (0.91±0.34, 0.28±0.15), hyperactivity/impulsivity were (2.35±0.41, 1.02±0.32), anxiety index scores were (0.67±0.48, 0.25±0.17), and the hyperactivity index scores were (2.09±0.42, 0.93±0.23). Children exhibited markedly milder tic symptoms after clonidine monotherapy *vs.* those with dual therapy of methylphenidate hydrochloride and haloperidol, suggested by the lower scores of character problems, learning problems, psychosomatic disorders, hyperactivity/impulsivity, anxiety index, and hyperactivity index (p<0.05) (Figure 2).

Adverse Events

The incidence of adverse events in the observation group was 41.56% (32/77), including 11 cases of drowsiness, 7 cases of dizziness and headache, 4 cases of irritability, 6 cases of decreased appetite and 4 cases of hyperphagia. The incidence of adverse events in the experimental group was 18.18% (14/77), including 6 cases of drowsiness, 3 cases of dizziness and headache, 2 cases of irritability, 2 cases of decreased appetite, and 1 case of hyperphagia. Clonidine features a higher safety profile than methylphenidate hydrochloride plus haloperidol by reducing the incidence of adverse events (p<0.05) (Table III).

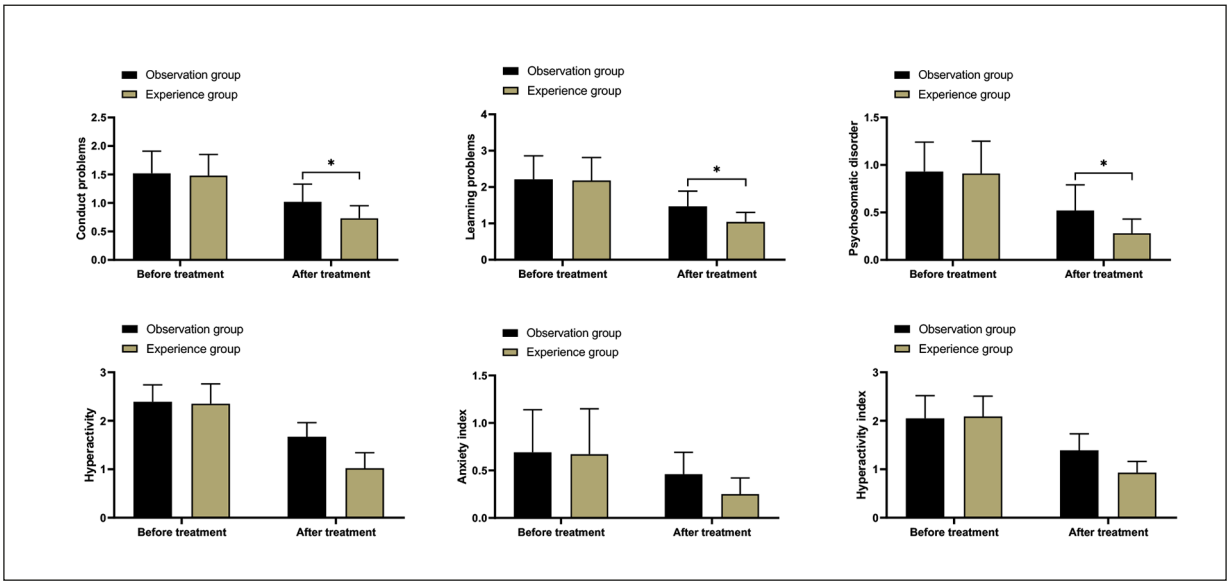

Figure 2. PSQ scores ($\bar{x} \pm s$, points). *Indicates $p < 0.05$.

Table III. Adverse events [n (%)].

Adverse events	Observation (n = 77)	Experimental (n = 77)	χ^2	*p*
Drowsiness	11	6	-	-
Dizziness and headache	7	3	-	-
Irritability	4	2	-	-
Loss of appetite	6	2	-	-
Hyperphagia	4	1	-	-
Incidence (%)	41.56% (32/77)	18.18% (14/77)	10.043	0.002

Discussion

The treatment of tic disorder co-morbid with ADHD is a major clinical challenge, and the pathogenesis and mechanisms of the two disorders remain poorly understood. Research[14] suggested that tic disorder and ADHD may severely compromise the psychological, physical, daily life, and social functioning of the child. At the present stage, the management of ADHD co-morbid with tic disorder primarily involves pharmacological interventions, which, however, remain controversial in clinical practice. Central stimulants are common drugs for treating children with ADHD, such as methylphenidate hydrochloride. It has been reported[15] that central stimulants could promote the release of norepinephrine and the neurotransmitter dopamine in children, thus boosting the expression of norepinephrine and synaptic gap dopamine levels. However, a study[16] revealed an increased risk of tic aggravation after the use of central stimulant drugs. Moreover, endorsed by clinical guidelines, haloperidol plus central stimulants are recommended to avoid tic symptoms, whereas the regimen has been found[17] to cause toxic side effects and adverse events in children. In another trial[18], significant mitigation of tic disorder and ADHD symptoms has been observed after clonidine monotherapy, and the efficacy is potentiated in the case of comorbidities. Clonidine is an α_2 agonist that effectively agonizes central postsynaptic membrane α_2 receptors in the hypothalamus and delayed brain, thereby agonizing inhibitory neurons and suppressing peripheral sympathetic nerve activity. In addition, clonidine can agonize peripheral sympathetic presynaptic membrane α_2 receptors and reduce the expression of norepinephrine in peripheral nerves, thus alleviating the symptoms of hyperactivity and attention deficit in children with tic disorder co-morbid ADHD[19].

The results of the present study showed that clonidine was associated with markedly higher clinical efficacy *vs.* methylphenidate hydrochloride plus haloperidol, which was consistent with previous research[20], suggesting the potent activity of clonidine in children with tic disorder co-morbid with ADHD. Bloch[21] showed that children using clonidine had significantly better alleviation in tic symptoms and behavioral disorders such as attention deficit and hyperactivity/impulsivity than children using methylphenidate. In the current study, children exhibited markedly milder tic symptoms after clonidine monotherapy *vs.* those with dual therapy of methylphenidate hydrochloride and haloperidol, suggested by the lower scores of character problems, learning problems, psychosomatic disorders, hyperactivity/impulsivity, anxiety index, and hyperactivity index, which were in line with the prior research[21]. Furthermore, clonidine features a higher safety profile than methylphenidate hydrochloride plus haloperidol by reducing the incidence of adverse events, which was consistent with a previous trial[22], in which clonidine also resulted in a significantly lower incidence of adverse events. The results evinced the high safety profile of clonidine.

Conclusions

Clonidine effectively alleviates tic symptoms, reduces attention deficit and hyperactivity/impulsivity in children with tic disorder co-morbid attention deficit hyperactivity disorder, and features a high safety profile.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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None.

Informed Consent

The patients signed the relevant informed consent forms.

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Ethics Approval
This clinical study has been approved by the Ethics Committee of The Affiliated Yichun People's Hospital of Yichun University (Ethics approval number: No. Y2397911).

ORCID ID
Bing Hu: 0009-0001-8235-5176.

Authors' Contribution
K.-D. Zeng: conceptualization, methodology, software; G.-L. Wang: data curation, writing-original draft preparation. Y. Yuan: visualization, investigation. W. Zhang: Supervision. X.-H. Huang: software, validation. B. Hu: writing-reviewing and editing.

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