

Retrospective Study on the Therapeutic Effect of Repetitive Transcranial Magnetic Stimulation Combined with Tiapride Hydrochloride Tablets in Children with Attention Deficit Hyperactivity Disorder

ABSTRACT

Objective: This study aimed to explore the application effect of repetitive transcranial magnetic stimulation (rTMS) combined with tiapride hydrochloride tablets in children with attention deficit hyperactivity disorder (ADHD).

Methods: The medical records of 197 children with ADHD in our hospital from January 2022 to January 2023 were retrospectively analysed. Seven children who did not meet the inclusion criteria were excluded, and 190 children were finally included in this retrospective study. Based on the different clinical therapeutic methods, these children were divided into tiapride ($n=64$), rTMS ($n=64$), and combination ($n=62$) groups. The clinical effects of different therapeutic schemes were compared. The clinical effectiveness and the scores of Swanson, Nolan, and Pelham Rating Scale Version IV (SNAP-IV), Conners Parent Symptom Questionnaire (PSQ), and Weiss Functional Impairment Rating Scale—Parent Report (WFIRS-P) were compared among the 3 groups.

Results: There was no significant difference in gender, age, course of disease, weight, and WISC-IV score among the combination, tiapride, and rTMS groups (all $P > .05$). The effective rate of treatment in the combination group (93.55%) was significantly higher than that in the tiapride group (78.13%) and the rTMS group (81.25%). There was a significant difference in the comparison of the combination group with the tiapride group ($P = .013$) and the rTMS group ($P = .038$). Before treatment, no significant difference existed in the scores of attention deficit symptoms and hyperactivity disorder symptoms among the 3 groups (all $P > .05$). After 3 months of treatment, the difference score of the combination group before and after treatment was significantly higher than that of other 2 groups (all $P < .001$). Before treatment, no significant difference was found in the scores of conduct problems, learning problems, psychosomatic disorders, impulsive hyperactivity, anxiety and hyperactivity index among the 3 groups (all $P > .05$). After treatment, the combination group had significantly higher difference score before and after treatment than other 2 groups (all $P < .001$). There was no significant difference in WFIRS-P scores among the 3 groups before treatment (all $P > .05$). After treatment, the difference score in the combination group before and after treatment was significantly higher compared with other 2 groups (all $P < .001$).

Conclusion: Transcranial magnetic stimulation combined with tiapride hydrochloride tablets had a positive effect on improving the condition of children with ADHD, with certain clinical promotion value.

Keywords: Attention deficit hyperactivity disorder, repetitive transcranial magnetic stimulation, tiapride hydrochloride tablets, therapeutic effect

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric diseases in children and adolescents, with more than 5% morbidity.¹ The disease with complex



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symptoms often has defects in executive function and exercise capacity.² If treatment measures for ADHD are not actively taken, it causes a greater burden on the individual, family, and society. It further exerts a significant impact on the quality of life and daily function of children with ADHD. The risk of severe adverse outcomes increases in children with ADHD, including poor educational outcomes, injuries and accidents, family conflicts, and criminal behavior.³ Attention deficit hyperactivity disorder is a neurodevelopmental disorder, and difficulties in objective diagnosis of the disease may lead to overdiagnosis or underdiagnosis.⁴ This has brought great challenges to clinical treatment, so it is very important to explore an efficient treatment plan.

Drug therapy has been proven to effectively reduce the core symptoms of ADHD and is gradually becoming a first-line treatment.⁵ Bachmann CJ et al⁶ have pointed out in their study that tiapride is one of the 10 most commonly used antipsychotic drugs in pediatrics in Germany. In addition to conventional drug therapy, ADHD can be treated by other complementary and alternative medicine methods, for example, neuromodulation provides stimulation to targeted areas of the brain.⁷ Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive diagnostic and therapeutic technique that has shown benefits for various mental disorders, such as autism spectrum disorder, ADHD, obsessive-compulsive disorder, seizures, and psychosis.⁸

Many clinical studies have been conducted on the single application of tiapride hydrochloride tablets and rTMS in ADHD. However, reliable results for confirming the application effect of tiapride hydrochloride tablets combined with rTMS in children with ADHD are lacking. On this basis, a retrospective study was conducted to compare the effects of tiapride hydrochloride tablets, rTMS, and their combination in the treatment of ADHD. The study aimed to provide more choices for the subsequent treatment of the disease.

Material and Methods

Research Objects

The medical records of 197 children with ADHD in our hospital from January 2022 to January 2023 were retrospectively analyzed. Seven children who did not meet the inclusion criteria were excluded, and 190 cases were finally included. According to different therapeutic methods, they were divided into the following groups: tiapride (received tiapride hydrochloride tablets; n=64), rTMS (received rTMS treatment; n=64), and combination (received rTMS combined with tiapride hydrochloride tablets; n=62).

MAIN POINTS

- Based on the above research results, we inferred that the implementation of rTMS combined with tiapride hydrochloride tablets in children with ADHD can improve their condition to a certain extent.
- rTMS combined with tiapride hydrochloride tablets exerts a positive effect on improving the social function of children with ADHD, which is conducive to their return to society.
- rTMS combined with tiapride hydrochloride tablets can improve the behavioral ability of children with ADHD to a certain extent, with clinical practicability.

Inclusion Criteria

1. Children met the diagnostic criteria of ADHD in children in the Diagnostic and Statistical Manual of Mental Disorders.⁹
2. Children had complete medical records.
3. The score of Wechsler Preschool and Primary Scale of Intelligence Fourth Edition (WISC-IV) was >85 points.
4. Children had normal cognitive function.
5. Children first received EEG biofeedback therapy.

Exclusion Criteria

1. Children had other mental illnesses, such as autism and schizophrenia.
2. Children had nervous system diseases or brain organic lesions, such as epilepsy and brain trauma.
3. Children had metal implants in the brain, such as cochlear implantation, skull implantation, or heart-stent implantation.
4. Children lacked clinical data.

Ethics: This study has been approved by the Committee of The People's Hospital of Rongchang District (Approval No: 202354, Date: August 1, 2023). This study was a retrospective analysis, so obtaining the informed consent of ADHD children and their families was unnecessary.

Therapeutic Measures

Tiapride Group: The children with ADHD in this group were treated with tiapride hydrochloride tablets (Shandong Renhetang Pharmaceutical Co., Ltd.; specifications: 100 mg × 100 tablets/bottle; NMPA approval no. H32026011; batch no. 14202246169; origin: Linyi, Shandong, China), with oral administration at 50 mg/time and 2 times/day, and the therapeutic time was 3 months.

Transcranial Magnetic Stimulation Group: The children with ADHD in this group received rTMS treatment. The therapeutic instrument was a magnetic-field stimulator (manufacturer: Wuhan Yiruide Medical Treatment Equipment New Technology Co., Ltd.; model: YRD CCY-I; origin: Wuhan, Hubei, China). The treatment frequency was 1 time/day, 20 min/time, 5 times/week, for 3 months.

1. The metal objects on the children's body were removed, and children were instructed to remain in a supine position and keep the limb relaxed.
2. Motion threshold refers to the minimum magnetic-stimulation intensity that can induce the target muscle to produce motor evoked potential. The measurement methods were as follows. The children sat with their hands on their thighs and palms facing up, and then an '8'-shaped coil was placed on the right side of the brain. Intermittent single-pulse stimulation was carried out on children, and the motor response of their left thumb was observed. The motion threshold was the intensity that can cause the movement response of the thumb.
3. The parameter settings were as follows: Frequency: 10 Hz; stimulation: 4 seconds; interval: 26 seconds; motion threshold: 100%; 2000 pulse stimulation in single treatment.
4. The stimulation site was the right dorsolateral prefrontal cortex (moving forward by 5 cm from the coil position during the measurement of the motion threshold).

Combination Group: The ADHD children in this group were treated with tiapride hydrochloride tablets combined with rTMS, and the treatment time was 3 months. The usage of tiapride hydrochloride tablets is same as tiapride group, and the therapeutic method of rTMS is same as rTMS group.

Research Indicators

General Data: The general data of children with ADHD included gender, age, course of disease, weight, and WISC-IV scores.

Evaluation of Therapeutic Effect in Clinical Settings: The effective rate was the total number of cases with significant and effective effects/total number of cases in each group \times 100%. The evaluation criteria were as follows.

1. Significant. Attention disorder, excessive activity, and impulsivity, learning difficulties, and other symptoms disappeared completely, with no effect on the life of children with ADHD.
2. Effective attention disorder, excessive activity, and impulsivity, learning difficulties, and other symptoms all improved, with less effect on the life of children with ADHD.
3. Ineffective. The above symptoms did not improve or even aggravated, and the life of children with ADHD was seriously affected.

Assessment of Attention Deficit Hyperactivity Disorder Symptoms: Swanson, Nolan, and Pelham Rating Scale Version IV (SNAP-IV),¹⁰ was used to assess the severity of ADHD in children. The difference scores of 3 groups before and after treatment were compared (difference score = score after 3 months of treatment score before treatment). The scale was filled out by parents of ADHD children. This scale contained 9 questions of attention deficit symptom and 9 questions of hyperactivity symptom, and the score range of each question was 0-3 points. The score meanings were as follows: 0 point indicated complete absence of symptoms, 1 indicated occasional symptoms, 2 indicated frequent symptoms, and 3 indicated constant symptoms. The average value was calculated to assess disease severity. The average score of 0-1.0 point was normal, 1.1-1.5 was mild, 1.6-2.0 was moderate, and 2.1-3.0 was severe.

Assessment of Adaptive Behavior Ability: The Parent Symptom Questionnaire (PSQ),¹¹ was used to screen and assess children's behavioral problems, particularly in relation to ADHD. The difference scores of 3 groups before and after treatment were compared (difference score = score after 3 months of treatment score before treatment). The scale was created by C. K. Conners, an American child psychiatrist. The children's parents filled out the PSQ. This scale had a total of 48 items, and the items were classified into 6 dimensions as

follows: conduct problems, learning problems, psychosomatic disorders, impulsive hyperactivity, anxiety, and hyperactivity index. The score for each question was 0-3 points, and the sum of the scores for each dimension was divided by the number of items to obtain the average score. A higher average score indicated that ADHD children had worse improvement in behavioral ability.

Assessment of Social Function: The Weiss Functional Impairment Rating Scale—Parent Report (WFIRS-P) scale¹² was used to evaluate the specific social function of children with ADHD. The difference scores of 3 groups before and after treatment were compared (difference score = score before treatment – score after treatment). The scale was filled out by parents of ADHD children. The scale included dimensions of family, learning and school, life skills, self-management, social activities, and adventure activities. Each question was scored by 0-3 points, and the average of the total score was used to evaluate social function. A higher score indicated that children with ADHD had worse social function.

Statistical Analysis

The data of this study were calculated and processed using Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc.; Chicago, IL, USA). The categorical data were indicated by [n (%)] and detected by the χ^2 test. The Shapiro–Wilk method was used to determine whether the continuous variables conformed to the normal distribution. The continuous variables that did not conform to the normal distribution were expressed by Median (Q1, Q3). Kruskal–Wallis *H*-test was used to test the differences in age, course of disease, weight, and WISC-IV among the 3 groups. Other continuous variables, such as SNAP-IV, PSQ, and WFIRS-P scores were detected by Mann–Whitney *U*-test, and pairwise comparisons were performed among the 3 groups. The causal group (within the group) of continuous variables was detected by Wilcoxon signed rank test (Tables 3-5, comparison of *P* values in each group before and after treatment). *P* < .05 indicated that the difference was statistically significant.

Results

General Data

No distinct difference in gender, age, course of disease, weight, and WISC-IV score existed among the combination, tiapride, and rTMS groups (*P* > .05), as shown in Table 1.

Evaluation of Clinical Therapeutic Effect

The effective rate of treatment in the combination group (93.55%) was obviously higher than that in the tiapride (78.13%) and rTMS (81.25%) groups, with statistical significance (*P* < .05). There was no

Table 1. Comparison of General Data Among the 3 Groups [Median (Q1, Q3), n (%)]

Projects		Tiapride Group (n = 64)	rTMS Group (n = 64)	Combination Group (n = 62)	<i>P</i>
Gender	Male	45 (70.31)	49 (76.56)	48 (77.42)	.603 ^a
	Female	19 (29.69)	15 (23.44)	14 (22.58)	
Age (years)		10.00 (8.25,11.00)	10.00 (8.00,11.00)	9.50 (8.00,11.00)	.897 ^b
Course of disease (months)		28.00 (15.00,42.75)	31.00 (20.00,45.00)	32.00 (18.00,45.25)	.579 ^b
Weight (kg)		33.04 (26.04,38.09)	31.65 (27.26,37.41)	34.11 (26.91,39.47)	.684 ^b
WISC-IV scores (points)		100.00 (95.25,105.00)	99.00 (95.00,102.75)	100.00 (93.00,103.25)	.747 ^b

WISC-IV scores, Wechsler Intelligence Scale for Children-Fourth Edition scores; rTMS, repetitive transcranial magnetic stimulation.

^arepresented the *P* value obtained by the chi-square test. ^bshowed the *P* value obtained by Kruskal–Wallis *H* test.

Table 2. Comparison of Effective Rates of Clinical Treatment Among the 3 Groups [n (%)]

Groups	① Tiapride group	② rTMS Group	③ Combination Group	$P_{① \text{ vs } ③}$	$P_{② \text{ vs } ③}$
n	64	64	62	.013	.038
Significant	12 (18.75)	18 (28.13)	26 (41.94)		
Effective	38 (59.38)	34 (53.13)	32 (51.61)		
Ineffective	14 (21.88)	12 (18.75)	4 (6.45)		
Effective rate	50 (78.13)*	52 (81.25)	58 (93.55)		

*Indicated that compared with the data in rTMS group, $P > .05$. rTMS, repetitive transcranial magnetic stimulation.

①, Tiapride group; ②, rTMS group; ③, Combination group.

significant difference in the effective rate of treatment between the tiapride and rTMS groups ($P > .05$), as shown in Table 2.

Evaluation of Attention Deficit Hyperactivity Disorder Symptom

Before treatment, no obvious difference existed in the scores of attention deficit symptoms and hyperactivity disorder symptoms among the tiapride, rTMS, and combination groups ($P > .05$). The scores of 3 groups after 3 months of treatment were significantly lower than those before treatment ($P < .001$). The difference score of the combination group before and after treatment was significantly higher than that of the other 2 groups, with a statistically significant difference ($P < .001$), as shown in Table 3.

Assessment of Adaptive Behavior Ability

Before treatment, no distinct difference in the scores of conduct problems, learning problems, psychosomatic disorders, impulsive hyperactivity, anxiety, and hyperactivity index existed among the tiapride, rTMS, and combination groups ($P > .05$). After treatment, the scores of the 3 groups were significantly lower than those before treatment ($P < .001$). The difference score of the combination group was distinctly higher than that of the other 2 groups before and after treatment, and the rTMS group had a higher difference score than the tiapride group, with a statistically significant difference ($P < .001$), as shown in Table 4.

Assessment of Social Function

Before treatment, no obvious difference in WFIRS-P scores existed among the tiapride, rTMS, and combination groups ($P > .05$). After treatment, the scores of the 3 groups all decreased compared with those before treatment, with a statistically significant difference ($P < .05$). The difference score of the combination group was obviously higher than that of the other 2 groups before and after treatment, with a significant difference ($P < .001$), as shown in Table 5.

Discussion

This study found that rTMS combined with tiapride hydrochloride tablets can effectively improve the clinical symptoms of children with ADHD and improve their adaptability and social function. This therapy is beneficial in alleviating the condition of children.

Attention deficit hyperactivity disorder is a disease that occurs in childhood, characterized by a pervasive pattern of inattention and/or impulsive hyperactivity that usually continues into later life.¹³ Tiapride, a benzamide drug, acts as a selective dopamine antagonist for dopamine D2 and D3 receptors. It is recommended as a first-line drug in China.¹⁴ A retrospective study has proven that tiapride and

Table 3. Comparison of Swanson, Nolan, and Pelham Rating Scale Version IV (Scores Among the 3 Groups [Median (Q1, Q3), Points])

Projects	Attention Deficit Symptoms			Symptoms of Hyperactivity Disorder			Comparison of Difference Scores		
	(1) Before treatment	(2) After 3 months of treatment	(3) Difference score	(1) Before treatment	(2) After 3 months of treatment	(3) Difference score	$P_{① \text{ and } ②}$	$P_{① \text{ and } ③}$	$P_{② \text{ and } ③}$
Time points									
①Tiapride group (n=64)	1.83 (1.71,1.94)	1.19 (1.12,1.26)	0.63 (0.50,0.80)	1.87 (1.78,1.96)	0.78 (0.73,0.84)	1.09 (0.98,1.17)	<.001	<.001	<.001
②rTMS group (n=64)	1.92 (1.76,2.02)	1.09 (1.03,1.17)	0.81 (0.66,0.92)	1.86 (1.78,1.99)	0.76 (0.66,0.85)	1.12 (0.98,1.26)	<.001	<.001	<.001
③Combination group (n=62)	1.86 (1.68,2.05)	0.76 (0.67,0.86)	1.08 (0.96,1.29)	1.90 (1.80,1.96)	0.63 (0.53,0.69)	1.29 (1.22,1.34)	<.001	<.001	<.001

Table 4. Comparison of Parent Symptom Questionnaire Scores [Median (Q1,Q3), Points]

Time Points	(1) Before Treatment	(2) After 3 Months of Treatment	(3) Difference Score	$P_{①\text{ and }③}$	$P_{②\text{ and }③}$	$P_{①\text{ and }②}$	$P_{(1)\text{ and } (2)}$	$P_{(1)\text{ and } (2)}$
①Tiapride group (n = 64)	7.80 (7.59,8.00)	5.78 (5.57,5.96)	2.07 (1.76,2.30)	<.001	<.001	<.001	<.001	
②rTMS group (n = 64)	7.85 (7.55,7.97)	5.33 (5.12,5.56)	2.47 (2.14,2.77)					<.001
③Combination group (n = 62)	7.71 (7.55,7.95)	3.97 (3.78,4.15)	3.75 (3.55,4.03)					

rTMS, repetitive transcranial magnetic stimulation.

Table 5. Comparison of Weiss Functional Impairment Rating Scale—Parent Report (WFIRS-P) Scores [Median (Q1,Q3), Points]

Time points	(1) Before Treatment	(2) After 3 months of Treatment	(3) Difference score	$P_{①\text{ and }③}$	$P_{②\text{ and }③}$	$P_{①\text{ and }②}$	$P_{(1)\text{ and } (2)}$	$P_{(1)\text{ and } (2)}$
①Tiapride group (n = 64)	5.73 (5.09,6.27)	4.65 (4.14,5.04)	1.15 (0.52,1.78)	<.001	<.001	.235	<.001	
②rTMS group (n = 64)	5.59 (5.02,6.20)	4.47 (3.97,4.98)	1.30 (0.71,1.90)					<.001
③Combination group (n = 62)	5.59 (5.02,6.09)	2.90 (2.41,3.50)	2.43 (2.09,3.23)					

rTMS, repetitive transcranial magnetic stimulation.

topiramate are effective in reducing convulsions in patients with Gilles de la Tourette syndrome.¹⁵ After treatment with tiapride and topiramate, some behavioral and emotional problems of children with ADHD were obviously alleviated.

Transcranial magnetic stimulation is an antidepressant therapy whose development has been supported by extensive clinical studies.¹⁶ Transcranial magnetic stimulation is a non-invasive therapeutic form of brain intervention, which is effective for major depressive disorder.¹⁷ Lefaucheur JP et al¹⁸ reported that rTMS is widely used to treat depression, chronic pain, migraine, stroke, and other neurological and psychiatric diseases. Cao P et al¹⁹ believed that rTMS, atomoxetine hydrochloride, and their combined therapy can effectively improve the core symptoms and executive function of children with ADHD. Compared with the single treatment, the combined treatment has significant therapeutic advantages.

Clinical reports on combining the 2 methods of treating ADHD are few. This study further explored the effect of rTMS combined with tiapride hydrochloride tablets in treating children with ADHD to find an effective therapeutic scheme. Results showed that the scores of SNAP-IV, PSQ, and WFIRS-P in ADHD children treated with tiapride hydrochloride tablets, rTMS, and combined treatment were obviously lower than those before treatment, with a statistical significance. The scores of the above scales decreased more obviously in ADHD children receiving combined treatment. The effective rate of treatment in the observation group (93.55%) was higher than that in the tiapride (78.13%) and rTMS (81.25%) groups, and the difference was significant. The factor scores of attention deficit and hyperactivity disorder symptoms can reflect the effect of clinical treatment. Tiapride hydrochloride tablets can inhibit the midbrain limbic system and dopaminergic nerve hyperfunction, which has an antagonistic effect on neuromotor disturbance of striatal dopamine. The principle of rTMS is as follows. The pulse current is introduced into the coil placed above the head, then the pulse magnetic field is generated around the coil. The pulse magnetic field generates an induced current in the head, which stimulates the brain tissue regularly and repeatedly. rTMS adjusts the blood circulation of the cerebral cortex as a whole, which contributes to the fine growth of nerves and adjusts the functional activities of corresponding brain regions. In addition, rTMS promotes the release of dopamine in the striatum, stimulates the prefrontal cortex to increase excitability,²⁰

enhances the inhibition of hyperactivity and impulsive behavior, with obvious sedative and stabilizing effects, and distinctly improves the symptoms of children with ADHD. Transcranial magnetic stimulation combined with tiapride hydrochloride tablets can also antagonize the movement disorder of the striatal dopaminergic nerve, promote the evoked potential of central nervous cells, further improve the excitability of central cells, and release central neurotransmitters.²¹ This combined treatment further enhances the ability of the nervous system to adapt to external reactions and improves social adaptability.

However, this study also had some deficiencies. We selected a small sample size and developed only a single-center retrospective study. Accordingly, the sample size will be expanded, and multicenter studies will be carried out in the future to further confirm the therapeutic effect. Limited by the research condition, this experiment followed up ADHD children in a short time and analyzed the effect only after 3 months of treatment, lacking long follow-up information. Thus, the follow-up time needs to be further extended to track the long-term effects of combined therapy.

In summary, the combined use of rTMS and tiapride hydrochloride tablets had a better effect than a single application in the treatment of ADHD. This combination can significantly improve the clinical symptoms, adaptive behavior ability, and social function of children with ADHD, thereby providing more reference and direction for the selection of follow-up treatment options.

Availability of Data and Materials: Data to support the findings of this study are available on reasonable request from the corresponding author.

Ethics Committee Approval: This study has been approved by the Committee of The People's Hospital of Rongchang District (Approval No: 202354, Date: August 1, 2023).

Informed Consent: As this study is a retrospective study, it is not necessary to obtain informed consent of patients.

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