Research Paper

Analysis of Clinical Efficacy, Negative Emotions and Cognitive Function of Sertraline Combined with Repetitive Transcranial Magnetic Stimulation for Depression and Anxiety

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To explore the effects of sertraline combined with repetitive transcranial magnetic stimulation on clinical efficacy, negative emotions and cognitive function in adolescent patients with depressive disorders and anxious features was the objective of this study. This study selected 119 adolescent individuals with depressive disorders and anxious features who were admitted to The First Affiliated Hospital of Air Force Military Medical University from April 2019 to April 2022 and followed up for 1 y. All the individuals were divided into control (n=55) and research groups (n=64). The control group received sertraline and a research group receiving sertraline with repetitive transcranial magnetic stimulation. The clinical efficacy, negative emotions, cognitive function, adverse event rate and recurrence rate were comparatively analyzed. Among them, negative emotions were mainly assessed by the Hamilton depression and anxiety scales scores. Similarly, cognitive function was evaluated by the Montreal cognitive assessment scale and Wisconsin card sorting test and adverse event rate was statistically analyzed by observing nausea, anorexia, dizziness and drowsiness. Compared with the control group, the total effective rate of the research group was significantly higher; scores of Hamilton depression and anxiety, number of wrong answers and persistent errors were significantly lower after treatment. Montreal cognitive assessment score, total number of replies, number of number of correct answers and number of number of classifications completed were significantly higher after treatment. No notable difference was identified between groups in the adverse event rate. However, the recurrence rate within 12 mo was lower in the research group. Sertraline combined with repetitive transcranial magnetic stimulation has a definite clinical effect on adolescent patients with depressive disorders and anxious features, which can significantly relieve anxiety and depression, and improve cognitive function while not increasing the risk of adverse drug events, with a lower 1 y recurrence risk.

Key words: Sertraline, anxiety, repetitive transcranial magnetic stimulation, depression, 5-hydroxytryptamine, cognitive function, selective serotonin reuptake inhibitor

Depression is a mental health disorder that ranks 3rd leading cause of disability after diarrhoeal diseases and respiratory infections, predominating adolescents and often with anxious features[1,2]. Depressive disorders in adolescents are primarily manifested as depression, decreased appetite, weight change, lack of sleep and energy loss, which have varying degrees of negative impact on the normal learning and social life of adolescents[3,4]. In addition to its high incidence, the disease is also associated with a certain risk of recurrence. Family history of depression, negative cognitive style, negative life events and study or life pressure are all referred as pathogenic factors[5,6]. Adolescent patients with depressive disorders and anxious features may suffer from self-injury, suicide and aggressive behavior if they are not promptly and effectively intervened[7-9]. At present, the 1st-line drugs for this disease are mainly 5-hydroxytryptamine and norepinephrine reuptake inhibitors, but they include some limitations such as slow onset of effect and unsatisfactory improvement of Cognitive Function (CF)[10]. Therefore, it is necessary to continue to explore novel effective treatment schemes for adolescent patients with depressive disorders and anxious features.

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Sertraline (STL) is a Selective Serotonin Reuptake Inhibitor (SSRI), which has a certain ameliorative effect on depression without significantly increasing the risk of suicide and is more responsive, and tolerated in adolescent patients than tricyclic antidepressants[11,12]. STL has been reported in previous studies to have the best efficacy and safety along with high acceptability in children and adolescents with major depressive disorders[13]. The antidepressant effect of STL can be realized by actively regulating the formation of hypothalamic neuroprecursor cells and the survival of newly formed neurons or by simultaneously regulating 5-hydroxytryptamine and Indoleamine 2,3-Dioxygenase (IDO) activity in the central nervous system to participate in the metabolic regulation of monoamine neurotransmitters in the brain[14,15]; repetitive Transcranial Magnetic Stimulation (rTMS) is a widely used non-invasive neuromodulation therapy with neuroprotective action, which can be used for the treatment of depressed patients[16]. In the depression rat model experiment, it has been demonstrated to reduce depression-like behaviors, nerve cell apoptosis and astrocyte reduction by participating in the activation of the fibroblast growth factor 2/FGF Receptor 1/ phosphorylated-Extracellular signal Regulated Kinase (FGF2/FGFR1/p-ERK) axis[17]. A study suggests that rTMS can be used to treat adolescent depression and is particularly suitable in combination with antidepressants to help improve long-term tolerability of STL[18].

In view of the limited research on the influence of STL with rTMS on the clinical efficacy, Negative Emotions (NEs) and CF of adolescent patients with depressive disorders and anxious features, this report attempts to analyze it to optimize the treatment and management of such patients.

MATERIALS AND METHODS

General data:

119 adolescent patients with depressive disorders and anxious features who were treated in The First Affiliated Hospital of Air Force Military Medical University from April 2019 to April 2022 were selected and were assigned into control and research groups. The control group (n=55) received STL treatment while the research group (n=64) received STL+rTMS treatment. The cohorts selected were not statistically different in the general data ($p>0.05$), showing clinical comparability. The hospital's ethics committee approved the research study.

Inclusion criteria: Treatment-naive patients who met the diagnostic criteria for depressive disorders, with first episode; patients who scored≥17 in Hamilton Depression Scale (HAMD) and patients whose Hamilton Anxiety Scale (HAMA) score was ≥15 were included in the study.

Exclusion criteria: Patients having the history of depression; patients having history of allergy to the medication used in the study; patients having strong suicidal tendency; patients having comorbidities towards other serious physical diseases or cognitive impairment; patients showing abnormal Electroencephalogram (EEG) or metal implantation in the body and patients who depicted self-injury behavior during the trial were excluded from the study.

Treatment method:

The control group was given STL hydrochloride (Zoloft, Pfizer Pharmaceuticals, Co., Ltd) (specification of 50 mg×14 tablets and approval no: H10980141). The drug was administered orally after breakfast, with the dose being 25 mg/day on 1st 3 d and 50 mg/day from 4-7 d. The effective dose of 100-150 mg/day was achieved within 2 w if there were no significant adverse reactions. The treatment lasted for 12 w.

Similarly, the research group was treated with rTMS on the basis of the control group. A magnetic field therapy apparatus (model: CCY-I, Yiruide Medical Equipment New Technology Co., Ltd.) was used for treatment, with the patient lying flat on the treatment bed. The site of action was the patient's left Dorsolateral Prefrontal Cortex (DLPFC) and the treatment parameters were set as follows, frequency of 10 Hz, stimulation intensity of 80 % of the motor threshold, stimulation interval for 20 s, and stimulation time of 1 s. The patients were treated for 30 min each time, once/day for 5 d. The two groups received a total of 20 sessions lasting for 4 w.

Observation indicators:

The clinical efficacy, NEs, CFs, adverse event rate and recurrence rate were comparatively analyzed between the two groups.

Clinical efficacy: The HAMD score reduction rate, which was the percentage of the difference between the pre- and post-treatment score, was used as the evaluation criterion. HAMD-24 score reduction of >80 %, 50 %, ~80 %, and <50 % was considered as markedly effective, effective, and ineffective,

respectively. The overall effective rate was calculated as the sum of markedly effective and effective patient cases as a percentage of total cases.

NE: Patients' anxiety and depression were evaluated by HAMA scale with a score range of 0-56 and HAMD scale ranging from 0-68, respectively. The scores of both scales were proportional to the patient's anxiety or depression levels.

CF: Patients were assessed for CF before and after treatment using the Montreal Cognitive Assessment (MoCA) scale and Wisconsin Card Sorting Test (WCST). The former has a total score of 30, with lower scores suggesting worse CF and a score <26 indicating the presence of cognitive impairment. It mainly evaluates the executive function of subjects' frontal lobe through 128 cards with different colors, form and number of figures, including five items namely, total number of replies, number of correct answers, wrong answers, persistent errors and number of classifications completed.

Adverse event rate: The adverse events such as nausea, anorexia, dizziness, drowsiness etc., were observed and recorded, and the rate of total incidence was calculated.

Recurrence rate: The recurrence rates of both the groups were statistically analyzed after 6 mo and 12 mo of follow-up. The follow-up methods included medical records inquiry, visit and telephone visit.

Statistical methods:

In this study, both the measurement data and count data were imported into Statistical Package of Social Sciences (SPSS) version 24.0 software package for statistical analysis. The mean±Standard Error of Mean (SEM) was used for statistical description of the measurement data. T-test and paired t-test were adopted for intra- and inter-group comparisons, respectively. Count data was expressed by percentage. The comparison between both the groups was made by Chi-square (χ^2) test and $p<0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Base line data of 119 adolescents with depressive disorders and anxious features was studied. 119 adolescent patients with depressive disorders and anxious denoted no significant inter-group difference was determined in gender, age, disease course, age of onset, years of education and parents' education level ($p>0.05$) (Table 1).

Clinical efficacy of patients of both the groups was analyzed. The total effective rates of the control and research groups were 76.36 % and 93.75 %, respectively, indicating evidently higher clinical effectiveness of the combination therapy ($p<0.05$) (Table 2).

TABLE 1: GENERAL INFORMATION OF PATIENTS WITH DEPRESSIVE DISORDERS AND ANXIOUS FEATURES

Factors	Control group (n=55)	Research group (n=64)	χ^2/t	p
Gender (male/female)	22/33	31/33	0.853	0.356
Age (y)	14.56±1.58	14.92±1.83	1.139	0.257
Disease course (mo)	13.13±5.54	14.84±6.84	1.482	0.141
Age of onset (y)	13.18±2.02	13.00±2.06	0.480	0.633
Education (y)	7.18±1.78	7.66±2.34	1.243	0.216
Patient's education level (junior/senior high school or technical secondary school/university and above)	17/25/13	25/25/14	0.885	0.642

TABLE 2: CLINICAL EFFICACY OF PATIENTS OF THE TWO GROUPS

Factors	Control group (n=55)	Research group (n=64)	χ^2/t	p
Markedly effective	30 (54.55)	44 (68.75)		
Effective	12 (21.82)	16 (25.00)		
Ineffective	13 (23.64)	4 (6.25)		
Total effectiveness	42 (76.36)	60 (93.75)	7.302	0.007

NEs of the patients of both the groups were assessed comparatively. This study employed HAMD and HAMA scales to assess patients' depression and anxiety, respectively. The data showed no marked difference between the research and control groups prior to intervention ($p>0.05$); both scale scores reduced statistically after intervention ($p<0.05$), with even lower HAMD and HAMA scores in the research group ($p<0.05$) (fig. 1).

CF of the patients in both the groups were compared and recorded. Using the MoCA and WCST scales. No significant difference was found in pre-interventional MoCA scores between groups ($p>0.05$); an obvious increase was observed in the score after the intervention ($p<0.05$), with a higher score in the research group *vs.* control group ($p<0.05$). Similarly, the pre-interventional WCST score did not differ much between the groups in terms of the total number of replies, correct answers, wrong answers, persistent errors and number of classifications completed ($p<0.05$). After the intervention, the total number of replies, wrong answers and persistent errors in both the groups decreased significantly, while the number of correct answers and number of classifications completed increased significantly. Moreover, the research group had evidently lower wrong answers and persistent errors while higher total number of replies, correct answers and classifications completed than the control group after the intervention. All the above results are statistically significant ($p<0.05$) (fig. 2).

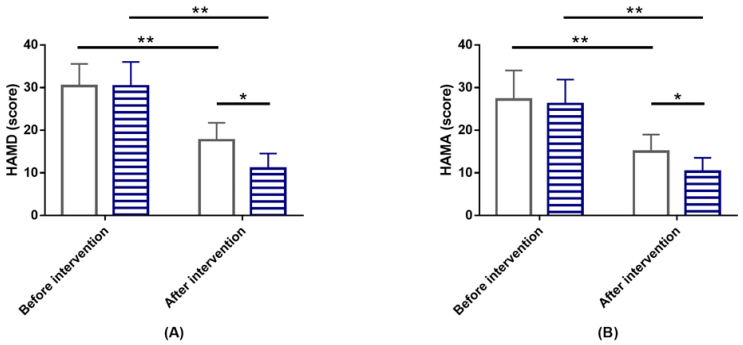

Fig. 1: Comparison of post-interventional negative emotion scores between research and control groups, (A): HAMD and (B): HAMA score
Note: *p<0.05 and **p<0.01, respectively, ( ): Control and ( ): Research group

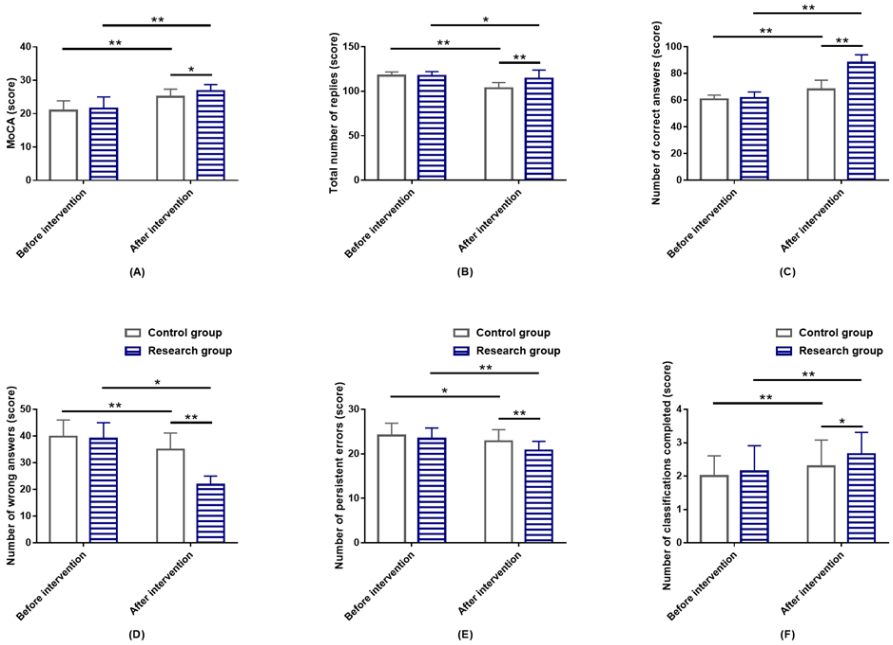

Fig. 2: Comparative analysis of cognitive function of patients in the two groups after intervention, (A): Higher MoCA scores; (B): Higher number of total replies; (C): Higher number of correct answers; (D): Lower number of wrong answers; (E): Lower number of persistent errors and (F): Higher number of classifications completed in research group than the control group
Note: *p<0.05 and **p<0.01, respectively, ( ): Control and ( ): Research group

Adverse event rates in the patients of the two groups were assessed. Both the groups experienced adverse events such as nausea, anorexia, dizziness and drowsiness. The data showed no significant inter-group difference in the total adverse event rate between the research and control groups after treatment (p>0.05) (Table 3).

Recurrence rate of the patients in the two groups were assessed. The recurrence rates of the control and research groups were found to be 10.91 % and 6.25 % after 6 mo of follow-up, respectively, with no significant difference (p>0.05). However, the recurrence rates of the control and research groups were 25.45 % and 9.38 %, respectively, after 12 mo of follow-up, with significant difference (p<0.05) (Table 4).

Adolescence is an important stage of adolescent personality formation and psychological development with great emotional ups and downs, during which physical, psychological and cognitive changes predispose them to depression, anxiety and other psychological disorders[19,20]. According to statistics, as high as 34 % of teenagers aged between 10-19 in the world may suffer from depressive disorders[21]. Therefore, it is of great practical significance to explore effective intervention methods for the prevention and treatment of adolescent patients with depressive disorders and anxious features and to improve their physical and mental health.

This study assumes that the clinical effect of STL+rTMS is superior to that of STL alone in the treatment of adolescent depression with anxious features and conducts relevant analysis for validation. Primarily, our research data revealed an obviously higher total effective rate of treatment in the research group (93.75 %) compared with the control group (76.36 %), indicating that STL+rTMS can significantly improve clinical efficacy in adolescents with depressive disorders and anxious features. In the research of Liu *et al.*[22], STL combined with cognitive behavioral therapy for the treatment of adolescent depression not only contributes to a high remission rate, but also significantly reduces depressive and anxiety symptoms, which is similar to our research results. Subsequently, the HAMD and HAMA scores in the research group reduced markedly after intervention, lower than those in the control group, indicating that STL+rTMS has a significant effect on relieving depression and anxiety in adolescent patients with depressive disorders and anxious features. A study in rats shows that rTMS has some ameliorating effect on depression and anxiety-like behaviors in epileptic rats[23]. In terms of CF, MoCA score of patients in the research group was significantly higher than that before treatment and in the control group. In addition, the post-interventional total number of replies, number of correct answers and classifications completed in the WCST score were significantly higher in the research group, while the number of wrong answers and persistent errors were lower, suggesting that STL+rTMS intervention is beneficial to improve CF in adolescents with depressive disorders and anxious features. In the study of Chen *et al.*[24], the combination of STL+rTMS in the treatment of adolescent patients with 1st-episode major depressive disorder not only improves the early improvement rate and efficacy, but also has a positive impact on the reduction of depressive symptoms and the improvement of CF, which is consistent with our research results. Furthermore, the two groups did not differ much in the incidence of adverse events such as nausea, anorexia, dizziness and drowsiness (p>0.05), indicating that STL+rTMS intervention for adolescent patients with depressive disorders and anxious features would not increase the risk of adverse events, with a certain safety profile.

TABLE 3: ADVERSE EVENT RATES IN PATIENTS OF THE TWO GROUPS

Factors	Control group (n=55)	Research group (n=64)	χ^2/t	p
Nausea	2 (3.64)	3 (4.69)		
Anorexia	1 (1.82)	1 (1.56)		
Dizziness	1 (1.82)	2 (3.13)		
Drowsiness	1 (1.82)	1 (1.56)		
Total	5 (9.09)	7 (10.94)	0.111	0.739

TABLE 4: RECURRENCE RATE IN PATIENTS OF THE TWO GROUPS

Factors	Control group (n=55)	Research group (n=64)	χ^2/t	p
After 6 mo follow-up	6 (10.91)	4 (6.25)	0.834	0.361
After 12 mo follow-up	14 (25.45)	6 (9.38)	5.470	0.019

STL, as an anti-depression SSRI therapy, will inevitably lead to the above complications to some extent, but for teenagers, it is more important to take a safer therapy[25]. In the study of Demirtas-Tatlidede *et al.*[26], rTMS for the long-term treatment of refractory depression has a sustainable antidepressant effect with an average duration of nearly 5 mo and is well tolerated, showing certain long-term effectiveness and safety. The safety and effectiveness of rTMS has also been demonstrated in the treatment of 11 patients of drug-resistant bipolar depression[27]. As far as disease recurrence is concerned, we identified no significant inter-group difference in the recurrence rate after 6 mo of follow-up but a statistical difference between the research group (9.38 %) and the control group (25.45 %) during the 12 mo follow-up, suggesting that STL+rTMS intervention is helpful to reduce the recurrence risk of adolescent patients with depressive disorders and anxiety within 12 mo.

Conclusively, STL combined with rTMS can help to improve the clinical efficacy, relieve depression and anxiety, and enhance the CF of patients, which is a medication scheme that is beneficial to reduce the recurrence risk within 12 mo while ensuring treatment safety and providing new options for the treatment of such patients.

Conflict of interests:

The authors declared no conflict of interests.

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