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Retrospective Study

Repetitive transcranial magnetic stimulation combined with olanzapine and amisulpride for treatment-refractory schizophrenia

INTRODUCTION

Schizophrenia, a heterogeneous progressive mental illness that may lead to cognitive impairment in patients, has a great negative impact on the patient's social interaction and work^[1]. The etiology of the disease is complicated and has been linked to environmental factors, hereditary factors, cortical excitation-to-inhibition imbalance, and subcortical dopamine dysfunction^[2]. Schizophrenia is prone to occur in early adulthood, and its symptoms are classified as positive symptoms, such as hallucinations, delusions, and speech disorders, and negative symptoms, such as emotional retardation, abulia, and social barriers^[3]. The overall prevalence of schizophrenia is approximately 0.4%, and the mortality rate of schizophrenia patients is 2–4 times that of the general population^[4,5]. Treatment-refractory schizophrenia (TRS), accounting for approximately 30% of the total schizophrenia cases, has a poor treatment response and prognosis despite treatment with antipsychotic drugs, which also poses great clinical challenges^[6,7]. Nevertheless, it is a compelling responsibility of physicians to explore effective treatment options for TRS.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation method, induces local neuronal activation in the brain regions *via* electromagnetic induction of electric fields, thus ameliorating the abnormal connections between the brain regions to a certain extent^[8,9]. According to the research by Zhu *et al*^[10], rTMS has a significant long-term ameliorating effect on working memory defects in schizophrenia

patients. Olanzapine (OLZ) and amisulpride (AMI) are both first-line antipsychotic drugs, which are highly effective in reducing the Positive and Negative Syndrome Scale (PANSS) scores and alleviating the mental symptoms of the patients^[11]. OLZ is not only a 5-hydroxytryptamine 2A/2C antagonist affecting the glucolipid metabolism^[12] but also an efficient AMP-activated protein kinase (AMPK) activator that enhances the AMPK activity in the hypothalamus, thus mediating energy homeostasis and metabolic modulation during neuronal activity^[13,14]. As for AMI, it is beneficial in relieving depressive symptoms and major negative symptoms as well as enhancing the patient's quality of life (QOL)^[15].

We proposed that the combination of rTMS and OLZ + AMI has certain beneficial clinical effects in TRS patients.

MATERIALS AND METHODS

Patient information

This study selected 114 TRS patients who received treatment at the First Affiliated Hospital of Zhengzhou University between July 2019 and July 2022. Among them, 54 cases were included in the control group (Con group) treated with modified electroconvulsive therapy (mECT) and 60 cases in the research group (Res group) treated with rTMS; the patients in both groups received OLZ + AMI therapy. The patients in the Res and Con groups presented similar demographic data ($P > 0.05$), suggesting clinical comparability and feasibility during follow-up research.

Inclusion criteria: The inclusion criteria for this study were that patients of both groups fulfill the TRS diagnostic criteria and present complete medical records with no treatment-associated contraindications.

Exclusion criteria: Patients with a history of allergy to the study medications, serious diseases such as heart, lung, or kidney dysfunction, and mental retardation that

hindered compliance and cooperation were excluded. Furthermore, pregnant and lactating women and drug abusers were excluded from this study.

Methods

The Con group patients were treated with mECT and OLZ + AMI, as described here. The patients received mECT 2–3 times a week using Thymatron ECT therapeutic apparatus. The treatment frequency could be adjusted to once weekly according to the treatment effect up to maximum 8 times during the treatment course. Regarding medications, the initial oral dose of OLZ was 5 mg once daily, and the drug dose could be gradually increased to 10–15 mg/d, depending on patient tolerance, for a total period of 8 wk. AMI was administered orally at an initial dose of 200 mg/d and increased according to patient tolerance and efficacy but not beyond a maximum daily dose of 1200 mg for a total period of 8 wk.

The Res group received rTMS combined with OLZ + AMI. An rTMS therapeutic instrument was used for treatment. The coil of the instrument was placed on the patient's forehead on the left, tangential to the scalp. The dorsolateral left frontal lobe was stimulated according to the threshold stimulation intensity of 80%–110% of the motor threshold, and the frequency was set at 20 Hz. The treatment time was 20 min, once a day, 5 times a week for 8 wk. OLZ and AMI were administered in the same way as that in the Con group.

Outcome measures

Clinical effectiveness: The PANSS scores were compared before and after treatment between the Res and Con groups. A decrease of more than 80% in the PANSS score was considered a “marked response,” a decrease of 50%–79% was considered a “response,” and failure to meet the above reduction criteria was considered as “non-response.” The overall response rate (ORR) was the percentage of the sum of the number of “marked response” and “response” patients among the total number of cases.

Safety: We observed and recorded the number of cases of drowsiness, headache, nausea, vomiting, and memory impairment and calculated the overall incidence.

Severity of schizophrenia: All patients were assessed for schizophrenia severity using the PANSS (total score: 98) with positive and negative subscales. The higher the score, the more serious the symptoms of schizophrenia.

Cognitive function: The cognitive function (CF) of patients was evaluated using the Montreal Cognitive Assessment (MoCA), mainly comprising eight items such as visuospatial/executive ability, memory, naming, and attention. On the 30-point scale, lower scores suggested worse CF.

QOL: The QOL of schizophrenia patients was evaluated using the Schizophrenia Quality of Life Scale (SQLS), comprising psychosocial factors (15 items, total score: 60), motivation and energy (7 items, total score: 28), and symptoms and adverse reactions (8 items, total score: 32). The score was inversely associated with the patient's QOL.

Statistical analysis

This study used Statistical Product and Service Solutions version 19.0 for data analysis; P -values < 0.05 were considered statistically significant. Sex and other categorical variables, expressed as the number of cases/percentages ($n/\%$), were compared between the groups using the χ^2 test. Continuous variables, such as the PANSS scores, expressed as means \pm SE, were compared between the groups using the t -test.

RESULTS

General information

Sex, age, course of the disease, family history, marital status, and educational level did not differ significantly between the Res and Con groups, indicating possible comparability between them ($P > 0.05$) (Table 1).

Comparison of therapeutic effectiveness

The ORRs of the Con and Res groups were 72.22% and 93.33%, respectively, demonstrating significantly higher efficacy of rTMS and OLZ + AMI than that of mECT and OLZ + AMI ($P < 0.05$) (Table 2).

Comparison of safety

Observation and records of the occurrence of drowsiness, headache, nausea, vomiting, and memory impairment in both cohorts showed that the incidence of adverse events was statistically higher in the Con group than in the Res group (25.93% vs 8.33%, $P < 0.05$) (Table 3).

Comparison of mental symptoms

Analysis of the mental symptoms using the PANSS revealed that the scores did not differ significantly between the groups before treatment ($P > 0.05$). However, the scores reduced significantly after treatment in both groups ($P < 0.05$), with the Res group exhibiting lower scores than those of the Con group ($P < 0.05$) (Figure 1A).

Comparison of CF

The CF, analyzed using the MoCA, did not differ significantly between the groups before treatment ($P > 0.05$). However, the MoCA scores increased significantly in both cohorts after treatment ($P < 0.05$), with higher scores in the Res group than in the Con group ($P < 0.05$) (Figure 1B).

Comparison of QOL

The QOL assessment using the SQLS showed that the two groups did not differ statistically in the QOL before treatment ($P > 0.05$). However, the post-treatment QOL improved significantly, manifesting as significantly reduced SQLS scores in various

dimensions ($P < 0.05$), with the Res group exhibiting better QOL (lower SQLS scores) than that of the Con group ($P < 0.05$) (Figure 2).

DISCUSSION

TRS, a chronic mental disorder, is associated with an increased risk of metabolic syndrome, including hypertension and diabetes, as well as cardiovascular diseases and death in patients^[16]. The difficulty in treating this disease lies in the fact that a significant proportion of patients do not respond well to non-clozapine antipsychotic drugs, ECT, or other enhancement strategies, imposing an economic burden on families and the healthcare system^[17,18].

This study comparatively analyzed the effectiveness and safety of two treatment modalities for TRS, mECT and OLZ + AMI (Con group) *vs* rTMS and OLZ + AMI (Res group), to provide clinical support and references for the formulation of effective treatment strategies for TRS patients to improve their clinical outcomes and reduce medical costs. Our research results identified a significantly higher ORR in the Res group than in the Con group (93.33% *vs* 72.22%), indicating the superior therapeutic effectiveness of rTMS and OLZ + AMI than that of mECT and OLZ + AMI for TRS. Kahn *et al*^[19] reported that 45% of the 93 patients receiving AMI and 44% of those receiving OLZ achieved “response” in the first stage of treatment, indicating that AMI or OLZ monotherapy induced less than satisfactory effects in TRS patients. Currently, there are limited studies on AMI + OLZ combination therapy, most of which focus on the comparison of AMI or OLZ monotherapy. For instance, Men *et al*^[20] demonstrated equivalent clinical efficacy and safety of AMI and OLZ in the treatment of schizophrenia. In our study, the total incidence of drowsiness, headache, nausea, vomiting, and memory impairment was significantly lower in the Res group than in the Con group (8.33% *vs* 25.93%), suggesting that rTMS contributes to fewer adverse events and is more cost-effective when compared with mECT in the treatment of TRS patients.

Additionally, we analyzed and compared the mental symptoms, CF, and QOF of the cohorts before and after treatment using the PANSS, MoCA, and SQLS, respectively.

The Res group showed significantly reduced PANSS and SQLS scores after treatment. Moreover, the post-treatment scores in the Res group were significantly lower than those before treatment and those in the Con group. On the other hand, the MoCA scores increased significantly in the Res group, and the post-treatment scores were higher than those before treatment and those in the Con group. This suggests that the combination of rTMS and OLZ + AMI has a significant effect on the improvement of mental symptoms, CF, and QOL in TRS patients. An open-label clinical study indicates that OLZ and AMI have positive and equivalent effects on ameliorating the negative symptoms and cognitive impairment in schizophrenia patients^[21]. Currently, antipsychotics alone cannot fully relieve social cognitive impairment and enhance functional outcomes in patients with mental illnesses, while rTMS is highly effective in improving their CF and mental symptoms^[22]. Li *et al*^[23] reported that a combination of rTMS and family intervention plays a synergistic role in schizophrenia patients, which is conducive to ameliorate the patients' negative symptoms and CF. Additionally, an animal study confirmed that rTMS elicits an antidepressant effect by enhancing the endogenous cannabinoid signaling transduction and up-regulating the endogenous cannabinoid 1 receptor and diacylglycerol lipase- α in the hippocampal astrocytes and neurons in rats under chronic and unpredictable stress^[24]. It has also been noted that rTMS may modulate the cortical plasticity by affecting the permanent changes in the excitability of the cerebellar-thalamic-cortical pathway and that its mechanism of action in TRS could be related to its promotion of interconnection of the remote areas in the neural network system^[25].

This study has several limitations that require further consideration. First, this was a single-center retrospective study; hence, the inclusion of more cases from multiple centers would be beneficial to improve the accuracy of the research results. Second, basic experiments should be supplemented to explore the underlying mechanism of the combination of rTMS and OLZ + AMI in treating TRS to understand this therapy and TRS better. Finally, the supplement of multivariate analyses influencing the efficacy of rTMS and OLZ + AMI in the treatment of TRS will help to gain deeper

insights regarding the pathways to enhance treatment efficacy. Future studies improving the aforementioned limitations are warranted.

CONCLUSION

Thus, rTMS in combination with OLZ + AMI may be preferred over the combination of mECT and OLZ + AMI for treating TRS, as the former has a clinical ORR as high as 93.33% and an adverse event rate as low as 8.33%. Moreover, this therapy has outstanding effects in relieving mental symptoms and improving CF and QOL; hence, it should be considered widely in clinical practice.

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Figure Legends

Figure 1 Comparison of the mental symptoms and the cognitive function between the groups. A: Comparison of the mental symptoms; B: Comparison of the cognitive function. PANSS: Positive and Negative Syndrome Scale; MoCA: Montreal Cognitive Assessment. ^a $P < 0.05$.

Figure 2 Comparison of the quality of life between the groups. A: Comparison of the quality of life between the two groups from the psychosocial society aspect; B: Comparison of the quality of life between the two groups from the motivation and energy aspect; C: Comparison of the quality of life between the two groups from the aspect of symptoms and adverse reactions. ^a $P < 0.05$; ^b $P < 0.01$.

Table 1 Demographic information, n (%)

Categories	Control group (n = 54)	Research group (n = 60)	χ^2/t value	P value
Sex			0.069	0.793
Male	32 (59.26)	37 (61.67)		
Female	22 (40.74)	23 (38.33)		
Age (yr)	40.07 \pm 7.01	41.28 \pm 8.74	0.810	0.420
Course of the disease (yr)	19.56 \pm 7.55	18.93 \pm 5.83	0.501	0.617
Family medical history			0.252	0.616
Yes	6 (11.11)	5 (8.33)		
No	48 (88.89)	55 (91.67)		
Marital status			0.381	0.537
Married	33 (61.11)	40 (66.67)		
Single	21 (38.89)	20 (33.33)		
Educational level			1.481	0.224
Below high school	30 (55.56)	40 (66.67)		
High school and above	24 (44.44)	20 (33.33)		

Table 2 Comparison of the therapeutic effectiveness of the two treatment methods, *n* (%)

Indicators	Control group (<i>n</i> = 54)	Research group (<i>n</i> = 60)	χ^2 value	<i>P</i> value
Marked response	19 (35.19)	36 (60.00)	-	-
Response	20 (37.04)	20 (33.33)	-	-
Non-response	15 (27.78)	4 (6.67)	-	-
Overall response	39 (72.22)	56 (93.33)	9.120	0.003

Table 3 Comparison of the safety of the two treatment methods, *n* (%)

Indicators	Control group (<i>n</i> = 54)	Research group (<i>n</i> = 60)	χ^2 value	<i>P</i> value
Drowsiness	4 (7.41)	1 (1.67)	-	-
Headache	4 (7.41)	1 (1.67)	-	-
Nausea	3 (5.56)	2 (3.33)	-	-
Vomiting	2 (3.70)	1 (1.67)	-	-
Memory impairment	1 (1.85)	0 (0.00)	-	-
Total	14 (25.93)	5 (8.33)	6.333	0.012

12%

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