Key Words: schizophrenia, rivastigmine, psychopathology, randomized controlled trial, quality of life

Efficacy of Rivastigmine Augmentation on Positive and Negative Symptoms, General Psychopathology, and Quality of Life in Patients with Chronic Schizophrenia: A Randomized Controlled Trial

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ABSTRACT *~ The study aimed to assess Rivastigmine augmentation on positive and negative symptoms (PNSs), general psychopathology, and quality of life in patients with chronic Schizophrenia. A double-blind, parallel-design, randomized, placebo-controlled trial of 60 schizophrenia patients was conducted. Intervention group received rivastigmine 3 mg/day + Treatment as Usual (TAU) and the control group: TAU + placebo. Negative and positive symptoms, general psychopathology; and quality of life were measured using Positive and Negative Symptom Scale (PANSS) and Manchester Short Assessment of Quality of Life (MANSA). T-test, ANOVA, and the general univariate linear model tests were used for the analyses. Out of 60 participants, 52 (86.6%) were male. At baseline, no significant relationship was found for demographic and clinical characteristics between intervention and control groups. Between-group analysis indicated that all outcome measures PNSs, general psychopathology symptoms, and QoL score in rivastigmine group was significantly improved ($p = 0.001$). According to within-group analysis, a significant association was found between Rivastigmine and placebo*

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groups in PNSs ($p < 0.05$). Rivastigmine augmentation improved PNSs and psychopathology in schizophrenia patients. However, no significant association found for improving the life quality after 8 weeks treatment.
Psychopharmacology Bulletin. *2024;54(2):15–27.*

Introduction

Schizophrenia is a severe mental illness that is characterized by significant changes in behavior, emotion, personality and insight.[1] The prevalence (median) of schizophrenia was reported 4.0 per 1000 for lifetime.[2] Schizophrenia patients' often suffer from memory problems, attentional shortages, and executive dysfunction. Despite a variety of bio-psychological treatments, only a low percentage of patients with schizophrenia fully recover, and most of them remain with chronic symptoms and problems for lifelong.[3]

Signs and symptoms of schizophrenia vary, however in general schizophrenia patients have signs of hallucinations or disorganized speech, delusions, and reflect an impaired ability to function.[4] Among chronic schizophrenia patients, a large proportion of the acute symptoms resolved with or without treatment, and longitudinal studies show average improvement in function over the years.[5] Investigations showed that positive symptoms often continue or recur in chronic patients, but a number of schizophrenia patients have negative symptoms in the acute phase or in the first episode.[6,7]

Despite the fact that dopamine has been considered the significant neurotransmitter participated in the pathogenesis of schizophrenic symptoms, several findings demonstrated cholinergic neurons roles in the disease process.[8] Evidence suggests that rivastigmine, donepezil, and galantamine can delay cognitive features of Alzheimer's patients,[9] clozapine,[10] and also adjuvant therapy[11] alleviated cognitive, negative and positive symptoms (NPSs) of schizophrenia patients.[12] Nevertheless, some evidence demonstrated that donepezil treatment was related to uncertain modify in the symptoms.[13]

The severity of cognitive impairments in antemortem among schizophrenia patients was reported to have a relationship with the reduction in brain choline acetyltransferase levels during postmortem assessment.[14] Therefore, it is an effective option treatment with a cholinesterase inhibitor for motivating the activity of the nicotinic and muscarinic receptors.

A study found that treatment with rivastigmine improved cerebellar activity and impressed attentional processes.[15] Case report studies indicated that rivastigmine treatment can improve refractory visual hallucinations in schizophrenia patient.[16,17] However, some findings

cannot find significant associations between rivastigmine augmentations on antipsychotics for decreasing cognitive impairments.[18] A study indicated that Memantine add-on to risperidone therapy was not correlated with NPSs in schizophrenia patients.[19,20]

However, Randomized Controlled Trials (RCTs) reported that rivastigmine treatment improved cognitive impairments, but it cannot alleviate negative and positive symptoms of schizophrenia.[6] Because of poor facilities of communities and families for maintaining and caring for schizophrenia cases, and many impairment features of the disease, the quality of life of patients has decreased.[21–23] Moreover, the impact of rivastigmine augmentation on the quality of life (QoL) of schizophrenia patients is poorly understood.[8]

As a result of the existing contradictions, as well as the limited investigations on schizophrenia patients' quality of life, conducting double-blinded RCTs can clarify the role of rivastigmine augmentation on schizophrenia patients' clinical symptoms and their life quality. A double-blind, parallel design RCT is conducted to evaluate the role of rivastigmine augmentation on PNSs, psychopathology symptoms and QoL in schizophrenia patients.

Methods

Study Design

A double-blind and randomized placebo-controlled trial was conducted at Razi Psychiatric Hospital, Tabriz in 2020–21. The study population was chronic Schizophrenia patients of any sex. A total of 60 chronic Schizophrenia patients (30 patients in each group) who had medical records and were Hospitalized at Razi Psychiatric Hospital were randomized into two groups.

The sample size was determined by considering $\alpha = 0.05$, Power $(1-\beta) = 80\%$, and 20% clinically significant difference based on previous studies.[12] The current study examines the efficacy and clinical outcomes of Rivastigmine augmentation on PNSs and QoL in patients with chronic schizophrenia.

Study Groups and Intervention

After a comprehensive explanation of the study process and written informed consent, eligible participants were randomized into two groups of intervention and control. The control group was given TAU + placebo and the intervention group was given Rivastigmine 3 mg per day (1.5 mg twice per day) + TAU. TAU was the current

antipsychotic drugs including one of the routine antipsychotics such as Risperidone, chlorpromazine, and Olanzapine. Study groups were followed up and treated for 8 weeks. Outcomes were evaluated 3 times: baseline (before), 4 weeks, and 8 weeks (after).

Eligibility Criteria

Inclusion criteria were chronic schizophrenia patients diagnosed at least two years previously, patients treated with routine antipsychotics, and having at least one negative symptom. Schizophrenia diagnosis is measured using the DSM-5.[24] Exclusion criteria were mental disabilities (IQ less than 70), substance use disorder, comorbidity of any psychiatric disorders, and/or neurological or medical disease, use of long-acting injectable antipsychotics, and Electroconvulsive Therapy (ECT) in the last two weeks.

Randomization and Masking

Schizophrenia patients were randomly allocated in 1:1 ratio arms (intervention and control). The randomization schedule was developed by an independent person (statistician). Patients, psychiatrists (investigators), and the Hospital staffs and nurses were blinded for the study groups and the recommended medications. Medications in each group were filled into similar sizes, colors, and capsules. A unique treatment number to identify each carton and contained capsules of the investigational medicinal products were used. The cartons of intervention and placebo groups were undistinguishable in appearance. No patients or investigators could guess or report that they could distinguish between intervention and placebo groups. Figure 1 shows the randomizations and study group assignments.

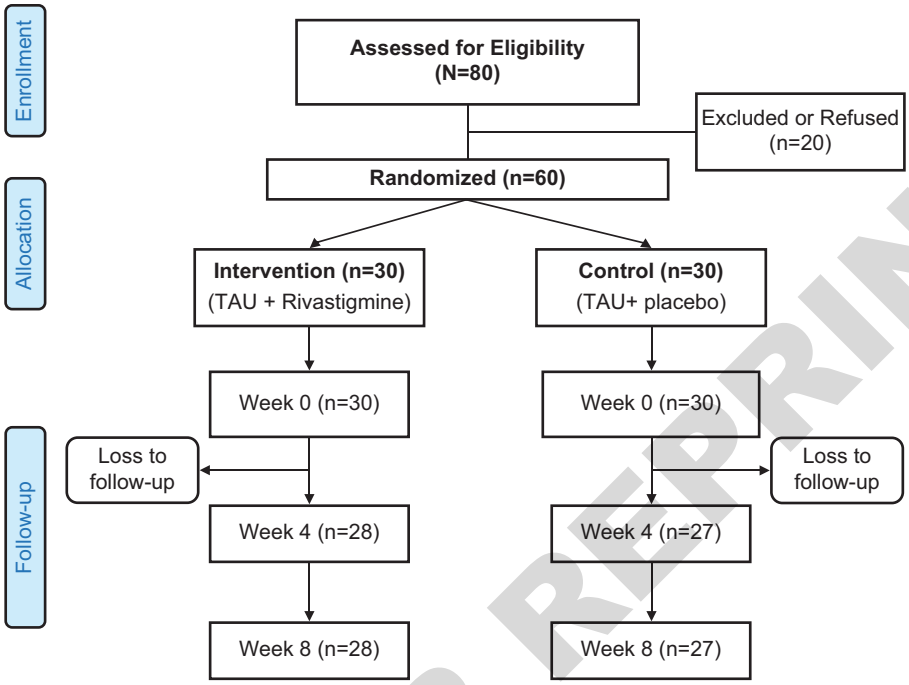
An investigational medicinal carton is allocated based on sequential treatment number order, after the randomization. Compliance with investigational medication was assessed by monitoring investigational medicinal consumption and daily audit by staffs.

Outcomes

Primary outcome was alternation in PNSs; and the general psychopathology symptoms of PANSS. The secondary outcome is alternation in the quality of life of the participants. Outcomes are evaluated three times at baseline (before), 4 weeks, and 8 weeks (after). There were no adverse reactions or morbidity and mortality outcomes to stop trial.

FIGURE 1

Consort Flow Chart



Measurements

We evaluated PNSs, and general psychopathology using Positive and Negative Symptom Scale (PANSS).[25] PANSS comprises 30 questions and three subscales including 7 questions positive symptoms, 7 questions negative symptoms, and 16 questions general psychopathology. PANSS instrument uses a 7-point Likert-type scale (absent, minimal, mild, moderate, moderate severe, severe, and extreme). Among Iranian population, PANSS was validated by Ghamari-Givi et al[26] and Abolghasemi[27] using Cronbach's Alpha test ($\alpha = 0.80$). Manchester Short Assessment of Quality of life (MANSA) was used to assess the quality of life.[28] MANSA instrument have been validated and used among Iranian population and in Tabriz (the study area). [29]

Statistical Analyses

We analyzed using SPSS software with version 22.0, Chicago, IL, USA. Chi-square (χ^2) test is calculated for comparing binary variables. Exact Fisher test was used, when at least one cell of 2×2 table have less than 5 frequencies.

Student T-test were performed to display distribution of positive, negative, and psychopathology symptoms scores between. Repeated measure test was used for intra-groups analyses of outcome scores before, median (4 weeks), and after (8 weeks). P-value less than 5% was considered significant. Person correlation coefficient was performed for comparing baseline and after (endpoint) changes in the study outcome.

Results

The baseline characteristics of participants by intervention and control groups were tabulated in Table 1. A total of 60 chronic schizophrenia patients were participated. Two individuals in the intervention and three individuals in the control groups drop out of the study due to loss to follow-up (Figure 1). Out of 60 schizophrenia patients, 52 (86.6%) were males. In both intervention and placebo groups, the same number of males and females had been participated ($p = 0.999$). The mean age of participants in rivastigmine and placebo groups was 36.5 ± 6.96 and 37.13 ± 6.06 ($p = 0.709$), respectively. No significant relationship was found between groups at baseline.

Table 2 displays the comparison of outcome measure scores among group analyses. A significant correlation was found between Rivastigmine and placebo groups in positive symptoms (at 4 and 8 weeks) and negative symptoms at three stages in baseline, week 4, and week 8 ($P < 0.05$).

Table 3 demonstrates the within-group analyses by repeated measure ANOVA test. The results show that all outcome measures

TABLE 1

Baseline (Week = 0) Characteristics of the Participants

VARIABLES		INTERVENTION (RIVASTIGMINE + TAU) N = 30	CONTROL (TAU + PLACEBO) N = 30	P-VALUE
Age	Mead ± SD	36.5 ± 6.96	37.13 ± 6.06	0.709
Sex	Female	4	4	0.999
	Male	26	26	
Marital Status	Married	6	9	0.822
	Single	21	19	
	Widow and Divorced	3	2	
Occupation	Unemployment	19	24	0.121
	Worker or free	13	6	
Educational level	Primary school	22	26	0.646
	Secondary school	4	3	
	Academic	4	1	
	No	0	0	
Number of admissions	⩾ 3	18	23	0.267
	< 3	12	7	

TABLE 2

Comparison of Outcome Measures Score Based on Between Group's Analyses

VARIABLES		INTERVENTION (RIVASTIGMINE + TAU) N = 28	CONTROL (TAU + PLACEBO) N = 27	T/Z	P-VALUE
PANSS-positive score	Baseline	8.5 ± 1.43	8.9 ± 0.944	Z = −1.61	0.110
	Week 4	8.17 ± 1.12	8.88 ± 0.96	−2.25	0.029
	Week 8	7.85 ± 0.84	8.70 ± 0.91	−3.56	0.001
PANSS-negative score	Baseline	35.53 ± 5.09	30.83 ± 4.30	3.85	0.001
	Week 4	34.42 ± 9.14	30.18 ± 3.99	2.21	0.031
	Week 8	32.46 ± 4.00	30.07 ± 3.67	2.30	0.025
PANSS-general psychopathology score	Baseline	28.93 ± 3.62	27.00 ± 2.22	Z = −1.88	0.060
	Week 4	26.53 ± 2.60	26.62 ± 1.94	−0.151	0.880
	Week 8	25.35 ± 3.04	26.11 ± 1.64	Z = −1.57	0.116
MANSA-Quality of life score	Baseline	55.93 ± 4.00	56.00 ± 3.30	−0.141	0.889
	Week 4	56.6 ± 3.78	56.62 ± 3.09	−0.024	0.981
	Week 8	57.64 ± 3.78	57.14 ± 3.00	0.535	0.595

TABLE 3

Comparison of Outcome Measures Score Based on Intra-Group Analyses (Repeated Measures ANOVA)

VARIABLES		INTERVENTION (RIVASTIGMINE + TAU) N = 28	F	P-VALUE	CONTROL (TAU + PLACEBO) N = 27	F	P-VALUE
PANSS-positive score	Baseline	8.5 ± 1.43	3.57	0.005	8.9 ± 0.944	2.14	0.138
	Week 4	8.17 ± 1.12			8.81 ± 0.96		
	Week 8	7.80 ± 0.84			8.70 ± 0.91		
PANSS-negative score	Baseline	35.53 ± 5.09	13.30	0.001	30.83 ± 4.30	2.95	0.071
	Week 4	34.42 ± 9.14			30.18 ± 3.90		
	Week 8	32.46 ± 4.00			30.07 ± 3.67		
PANSS-general psychopathology score	Baseline	28.93 ± 3.62	14.02	0.001	27.00 ± 2.22	5.32	0.012
	Week 4	26.53 ± 2.60			26.62 ± 1.94		
	Week 8	25.35 ± 3.04			26.11 ± 1.64		
MANSA-Quality of life score	Baseline	55.93 ± 4.00	8.48	0.001	56.00 ± 3.30	4.41	0.023
	Week 4	56.60 ± 3.72			56.62 ± 3.09		
	Week 8	57.64 ± 3.78			57.14 ± 3.00		

PANSS-positive symptoms (p = 0.005; F = 3.57), PANSS-negative symptoms (p = 0.001; F=13.30), general psychopathology symptoms (p = 0.001; F = 14.02) and QoL score (p = 0.001; F = 8.84) in rivastigmine group is significantly improved. In the placebo group (routine antipsychotics), intra-group analyses revealed a noteworthy progress in the general psychopathology symptoms (p = 0.012; F = 5.32), and QoL (p = 0.023; F = 4.41) after 8 weeks treatment period. However, a significant association between PANSS-PNSs was not found.

Figures 2 and 3 demonstrates changes in PANSS PNSs based on the study assessment times. Treatment with rivastigmine reduced positive and negative scores in comparison with the placebo group and improved symptoms. Regarding the quality of life, no significant changes between baseline and week 4 were observed, however, after 8 weeks, QoL score was increased in rivastigmine group (Figure 4).

FIGURE 2

Comparison of Changes in Positive Symptoms Between Groups at Baseline, Week 4, and Week 8 (p = 0.005)

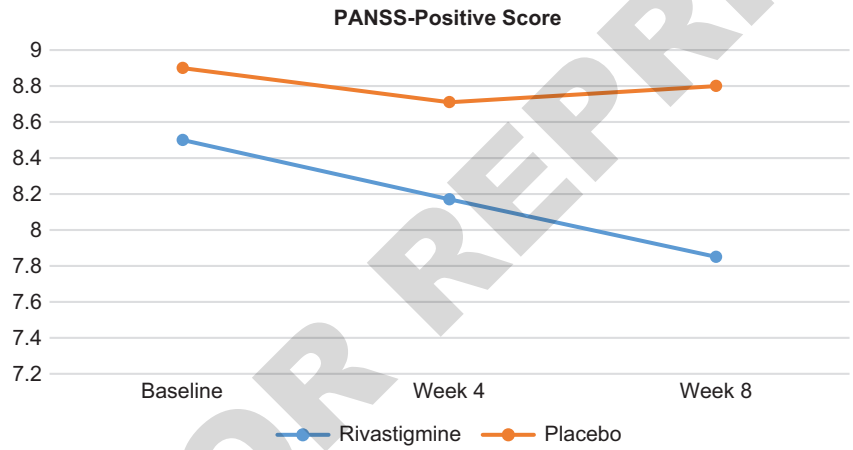


FIGURE 3

Comparison of Changes in Negative Symptoms Between Groups at Baseline, Week 4, and Week 8

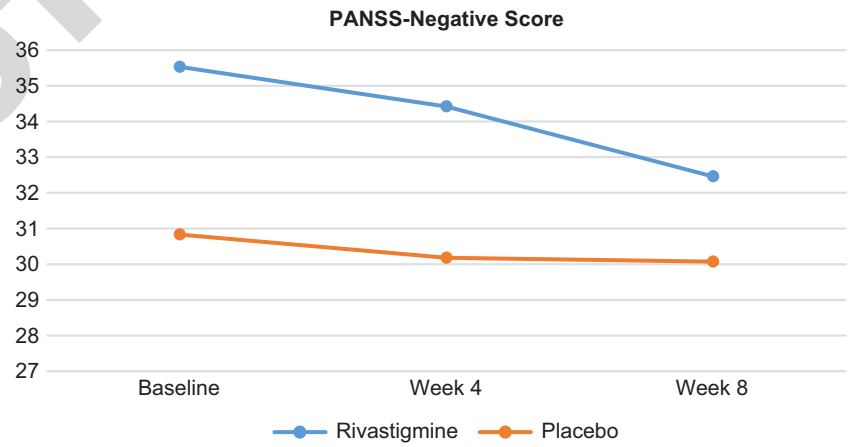
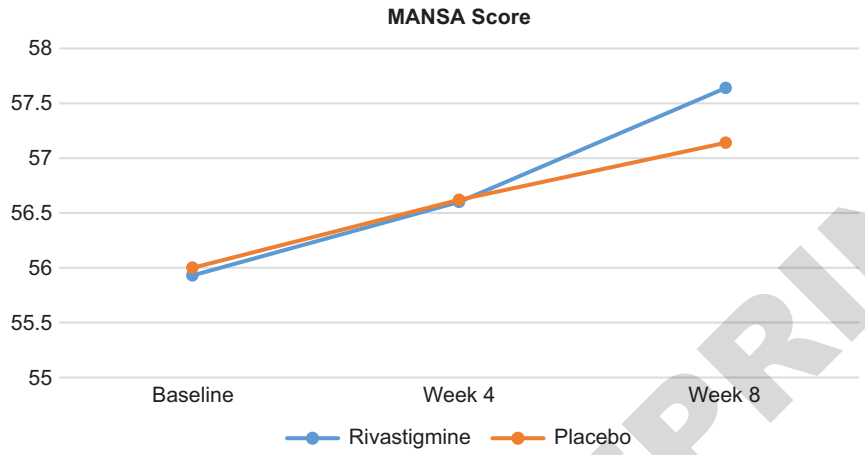


FIGURE 4

Comparison of Changes in Quality of Life Score (MANSA) Between Groups at Baseline, Week 4, and Week 8



Discussion

The double-blinded RCT of rivastigmine for; 3 mg per day; augmentation of antipsychotics demonstrated a significant progress in PANSS scores and QoL in patients with chronic schizophrenia. Findings recommended that rivastigmine augmentation improves the cognitive functions among schizophrenia patients.[12,30] Nevertheless, some studies were unable to find a significant progress in PANSS negative and positive symptoms.[18,30]

In this study rivastigmine augmentation treatment (3 mg per day for 8 weeks) improved PANSS positive and negative symptoms. Lenzi et al.[8] in Italy, reported cognitive enhancement after treatment with rivastigmine in schizophrenia patients (12 mg per day for 12 months). Attention and memory improvement and problem-solving by improving social and professional functions were found in Hussain et al.[31] study. Functional magnetic resonance imaging revealed that rivastigmine improved cerebellar activity and inclined attentional processes in patients with schizophrenia.[15]

Sachin et al. found positive effects from Acetylcholinesterase inhibitors for the treatment of visual hallucinations among schizophrenia cases in accordance with the present trial.[17] It is a significant result that needs further high-sample-size studies. Likewise, Singh et al. found that Acetylcholinesterase inhibitors were favorable antipsychotics, which revealed a positive effect over antipsychotics and placebo in the

general psychopathology and negative symptoms and cognitive function in PANSS.

Regarding QoL, the effect of rivastigmine augmentation on the QoL was poorly understood. In this trial, at the end of 8 weeks, MANSA score for QoL had modified in both rivastigmine and placebo groups. However, the score of QoL was higher in rivastigmine group than in the placebo group.

Currently, QoL is an important outcome for schizophrenia patients. However, the treatment options and effective factors that affect the life quality of patients who agonize from this severe mental disorder is not fully understood.

The correlation between mental disorders and psychological symptoms, and quality of life among schizophrenia patients have been investigated more extensively.[32] Nevertheless, studies have yet to clarify how important Acetylcholinesterase inhibitors (treatment) especially rivastigmine are in regard to life quality, and which treatment holds the strongest relation to the quality of life.

This trial is one of the rarest double-blinded trials to evaluate the efficacy rivastigmine augmentation on antipsychotics in PNSs; and general psychopathology symptoms in schizophrenia patients. The findings of the intra-group analysis reveal that rivastigmine augmentation has a significant, positive association with QoL in schizophrenia, by promoting general psychopathology reliably evolving as the robust contributor to enhancing the QoL.

Furthermore, it deserves to investigatethe relationship between PNSs with QoL in schizophrenia patients. Some findings demonstrated that PNSs are not connected with the life quality of all groups of schizophrenia patients equally.[32,33] However, such symptoms may be principally detrimental to the QoL in research on patients getting treatment in the field, and positive symptoms are only poorly associated with the quality of life in investigations of cases in the early stages of the disease. Such results can grasp several significant values for dealing progress and future QoL studies among schizophrenia patients.

According to the studies in the literature, general psychopathology has the robust link with the QoL,[33,34] this recommends that nonpsychotic symptoms and signs are central goals for treatments pointing to advance QoL for schizophrenia patients.

The findings suggest that there is a strong link between psychopathology values and QoL, which may be the result of subjective ratings being unduly affected by mood.[33,34] The effects of these signs and symptoms on QoL measurement are unclear, and it is uncertain whether they should be considered genuine targets for quality-of-life treatments. This study supports the latter because both objective and

subjective measurements of life quality are highly correlated with general psychopathology.

Limitations

The present study had some limitations. There were several antipsychotics used in Treatment as Usual for schizophrenia patients. To diminish this confounder, most of the participating patients have received Risperidone in the current study. Another concern was given negative symptoms rating scales are close to being quality of life measures (overlap), and usually improve when positive symptoms improve. Therefore, to attribute the impact of the current treatment is a treatment for both may problematic. Although the QoL score (secondary endpoint) was improved after 8 weeks of treatment with rivastigmine however, the effect size was minor and we found no significant association for QoL in comparison with the control group. As the findings have shown, the symptoms of schizophrenia improve over time. On the other hand, the use of routine treatment in the control group also helps this recovery. Besides, it may find impartments in the QoL by rivastigmine augmentation in the long term (more than 8 weeks), and this can be a departure point for future investigations.[1,35]

Conclusion

This double-blinded RCT supports the rivastigmine (3 mg/day) augmentation of TAU antipsychotics as a strategy to improve PNSs and cognitive function in patients with schizophrenia. However, no significant association found for improving the QoL after 8 weeks of treatment. ✤

Declarations

Ethics Approval and Consent to Participate

The trial was registered in the Iranian RCT website to number [IRCT20190530043769N1], date [26/01/2021], registration number [1399.53], and electronic address: https://fa.irct.ir/trial/39935. Ethics committee of Tabriz University of Medical Sciences was approved the protocol to number of IR.TBZMED.REC. 1399.923. Informed consent was obtained before the study.

Conflicts of Interests

There is no competing interests.

Funding

This study was funded by Tabriz University of Medical Sciences.

Author's Contributions

All authors were involved in the conception, development, or review of the manuscript, or they played a significant role in the acquisition, analysis, and interpretation of the data, or both. All authors took part in manuscript development and gave substantial revision suggestions, and they all approved the final submitted version.

Acknowledgments

The authors gratefully acknowledge the Clinical Research Development Unit of Al-Zahra Research and Treatment Center for its research consulting services.

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