Mirtazapine Combined with Paroxetine Can Improve Sleep Quality and Inflammatory Factor Levels in Patients with Postpartum Depression

Running title: Combinatory Effect of Mirtazapine and Paroxetine

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Abstract

Objective: To determine the effect of a combination of mirtazapine and paroxetine on postpartum depression.

Methods: Totally, 103 patients with postpartum depression admitted to our hospital from January 2017 to March 2019 were enrolled in this study and randomly assigned to Groups A and B. Patients in Group A (n = 49) were treated with paroxetine, while those in Group B (n = 54) were treated with mirtazapine, in addition to paroxetine. The sleep quality, treatment outcome, and inflammatory factors in the two groups were evaluated after treatment.

Results: Group B patients experienced milder depression and better sleep quality and showed lower levels of inflammatory factors than Group A patients (all $p < 0.05$).

Conclusion: Mirtazapine combined with paroxetine can effectively improve the sleep quality of patients with postpartum depression and lower the levels of inflammatory factors.

Keywords: Mirtazapine; paroxetine; postpartum depression; sleep quality; inflammatory factors.

Tob Regul Sci.™ 2022; 8(1): 1300-1311
DOI: doi.org/10.18001/TRS.8.1.103

Introduction

For new families, during the transition from new parents to experienced parents, health-related supervision of the infant is a special opportunity for shared growth. This period is challenging for both the father and mother, and its demands may exceed the available resources of the family. Such an imbalance may lead to depression in the mother [1]. Postpartum depression is a serious mental illness that has not been fully studied and diagnosed, either clinically or experimentally. It is the most common complication of delivery and has a negative impact on mothers; postpartum depression-related suicide accounts for approximately 20% of postpartum deaths [2]. Moreover, postpartum depression weakens the mother-infant interaction, which may disturb infant development. Generally, the attachment, sensitivity, and rearing pattern of mothers are crucial to the healthy development of social, cognitive, and behavioral skills in infants; however, mothers with depression usually show less attachment and sensitivity and more cruel or destructive parenting behaviors, which may have harmful effects on infants [3]. Postpartum depression is mostly treated with evidence-based psychotherapy and medication [4]. Paroxetine, a selective serotonin re-uptake inhibitor (SSRI) [5], is considered one of the preferred antidepressants during breastfeeding [6]. However, one study has shown that paroxetine is related to cardiac anomalies and that most antidepressants are excreted in breast milk at a low level, thus usually not being compatible with breastfeeding [7]. Therefore, it is necessary to choose a safer and more effective treatment. Mirtazapine is an antidepressant that can occasionally be used to treat anxiety, nausea, and vomiting and to gain weight, when necessary [8]. Among the potential suitable antidepressants, mirtazapine is an attractive choice because of its strong tolerance, low cost, high availability, and other potential strengths [9]. According to some studies, mirtazapine, a tetracyclic antidepressant with unique therapeutic mechanisms [10], can deliver additional benefits to patients with insomnia or anxiety [11]. This study was designed to determine the effect of mirtazapine in combination with paroxetine on postpartum depression.

Materials and Methods

General data

Totally, 103 patients with postpartum depression admitted to our hospital from January 2017 to March 2019 were enrolled in the present study and randomly assigned to Groups A and B. In the entire research center, according to the order in which patients were selected, they were assigned to Groups A and B according to a predetermined randomization plan. The randomization plan was generated by referring to the random comparison table or using a calculator or computer, following the simple random method. Group A patients (n = 49) were treated with paroxetine, while Group B patients (n = 54) were treated with mirtazapine, in addition to receiving the same treatment as patients in Group A (**Figure 1**).

Exclusion and inclusion criteria

The inclusion criterion for the study was a diagnosis of postpartum depression [12].

Informed consent forms were signed by patients and their family members and approval obtained from the Ethics Committee of The Second Affiliated Hospital of Shantou University Medical College.

Patients with alcohol dependence or psychiatric history, those for whom the study drugs were contraindicated, those who had received related antipsychotics or antidepressants before the study, those with serious suicidal tendency, and those with severe comorbid heart, brain, liver, kidney, or blood system diseases were excluded from the study.

Treatment methods

Patients in Group A were orally administered paroxetine at a dose of 20 mg/day, once a day, for six consecutive weeks. In contrast, patients in Group B were orally administered mirtazapine at a dose of 15 mg/day, once a day, for six consecutive weeks based on the treatment administered to Group A patients. Moreover, patients in the two groups were administered drug-based psychotherapy, and their psychological state and its dynamic changes were evaluated to determine the underlying issues. The staff was instructed to actively communicate with patients to assist them in performing meaningful tasks and finding their own value, help them in rebuilding their cognition, and guide them in letting go of their emotions and relaxing their minds. In addition, the staff was instructed to assist them in strengthening their emotional connection with their babies, help them in stepping into the role of motherhood, and encourage their families to provide emotional support and meticulous care, to promote their recovery.

Outcome measures

The Hamilton Depression Rating Scale (HAMD) and Edinburgh Postnatal Depression Scale (EPDS) were used to evaluate depression in the patients from the two groups [13,14]. Higher HAMD and EPDS scores indicate more severe depression. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the sleep quality (time for falling asleep, sleep time, sleep disorder, hypnotic drugs, sleep efficiency, sleep condition, and daytime functioning) in patients from the two groups after treatment, with 3 points for each parameter [15]. A higher PSQI score indicates a worse sleep quality. In addition, the efficacy of treatment in the two groups was assessed according to the reduction rate of the HAMD score [13] as follows: cured: good mood, disappearance of depression state, and HAMD score reduction > 75%; markedly effective: significant improvement in mood, significant alleviation of depression, and HAMD score reduction between 51% and 75%; effective: improvement in mood, alleviation of depression, and HAMD score reduction between 25% and 50%; and ineffective: no change in mood, depression or aggravation of the conditions, and HAMD score reduction < 25%. Total effective rate = (total number of patients with ineffective treatment)/total number of patients × 100%. Venous blood (5 mL) samples were collected from each patient of the two groups before and after treatment, allowed to stand for 20 min, and then centrifuged at 10 × *g* and 4°C for 15 min (BMH Instruments Co., Ltd., Beijing, China) to separate the serum. The serum was rapidly

frozen in liquid nitrogen and stored at -80°C for further analysis. Serum levels of the inflammatory factors interleukin-6 (IL-6) and interleukin-1β (IL-1β) were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Elisa Biotechnology Co., Ltd., Suzhou, China). The MOS 36-Item Short-Form Health Survey (SF-36) was adopted to score the quality of life (physiological functioning [PF], mental health [MH], vitality [VT], and role emotional [RE]) of the patients of the two groups [16]. The survey has a full score of 100 points, and a higher score indicates better quality of life.

Statistical analyses

Data were statistically analyzed using SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). Quantitative data are expressed as the mean ± standard deviation ($\bar{x}$ ± SD). Comparisons between groups were performed using the t-test, and comparisons within groups before and after treatment were performed using the paired t-test. Enumeration data are expressed as [n(%)], and comparisons between groups were performed using the chi-square test. $p < 0.05$ was considered to indicate a statistically significant difference.

Results

General data of the two groups

There was no notable difference between the two groups regarding the general data, including their own information and delivery mode (all $p > 0.05$) (**Table 1**).

Sleep quality of the two groups after treatment

The sleep quality scores of Group B patients were higher than those of Group A patients after treatment (all $p < 0.05$) (**Table 2**).

Levels of inflammatory factors in the two groups before and after treatment

IL-6 levels before and after treatment in Group A patients were 18.48 ± 4.28 and 12.37 ± 5.21 pg/mL, respectively, while those in Group B patients were 19.27 ± 4.13 and 9.11 ± 3.91 pg/mL, respectively. Additionally, IL-1β levels in Group A patients before and after treatment were 16.58 ± 5.29 and 10.31 ± 5.72 pg/mL, respectively, while those in Group B patients were 17.04 ± 5.32 and 7.18 ± 4.84. pg/mL, respectively. The results showed that after treatment, the levels of inflammatory factors in both groups decreased notably, with Group B patients having notably lower levels than Group A patients (both $p < 0.05$) (**Figure 2**).

HAMD scores of the two groups before and after treatment

The HAMD scores of Group A patients before and after treatment were 35.68 ± 3.85 and 24.18 ± 3.15 points, respectively, while those of Group B patients before and after treatment were 36.13 ± 3.71 and 16.29 ± 2.94 points, respectively. Therefore, before treatment, there was no notable HAMD score difference between the two groups. However, after treatment, the HAMD scores of both groups were notably reduced, with Group B patients having notably lower HAMD scores than Group A patients ($p <$

0.05) (**Figure 3**).

EPDS scores of the two groups before and after treatment

The EPDS scores of Group A patients before and after treatment were 23.18 ± 3.28 and 14.52 ± 2.43 points, respectively, while those of Group B patients were 22.89 ± 3.32 and 9.73 ± 2.74 points, respectively. Therefore, before treatment, there was no notable EPDS score difference between the two groups; however, after treatment, the EPDS scores of both groups were notably reduced, with Group B patients having notably lower EPDS score than Group A patients ($p < 0.05$) (**Figure 4**).

Comparison of adverse reactions between the two groups

The incidence of adverse reactions in Group B patients was notably lower than that in Group A patients ($p < 0.05$) (**Table 3**).

Efficacy of treatment in the two groups

The effective treatment rate of Group B patients was notably higher than that of Group A patients ($p < 0.05$) (**Table 4**).

Comparison of the quality of life scores between the two groups after treatment

The PF, MH, VT, and RE scores of Group A patients were 68.83 ± 4.29, 71.46 ± 5.28, 72.14 ± 4.14, and 64.48 ± 3.32, respectively, and those of Group B patients were 72.74 ± 5.13, 78.34 ± 4.85, 81.33 ± 3.91, and 75.46 ± 4.16, respectively. Therefore, the quality of life scores of Group B patients were higher than those of Group A patients (all $p < 0.05$) (**Figure 5**).

Discussion

Postpartum depression is a serious emotional disorder in women [17]. Women are twice as likely as men to experience severe depression; however, the risk is only limited to the period of their childbearing age. This sex-based risk difference is partly due to the burden women face regarding pregnancy, delivery, and upbringing of children [18]. One study has indicated that women with postpartum depression have a less positive interaction with their infants and a more negative view on their behavior. This leads to an increased risk of early interruption of exclusive breastfeeding, which is positively correlated with child malnutrition [19]. Therefore, postpartum depression, which weakens people's nerves warrants studies for more related knowledge and treatment strategies. According to the severity of symptoms, the standard treatment for postpartum depression needs to separate psychotherapy from medication. Some studies have reported that the non-traditional psychotherapy model is presently dominant, while data on other complementary therapy strategies are seriously lacking. Further research is needed to identify cost-effective alternative therapies for postpartum depression [20].

Paroxetine is the most effective and specific SSRI, which binds to the allosteric site of the 5-serotonin transporter. It inhibits the reuptake of norepinephrine to a lower

extent [21]. Mirtazapine is a postsynaptic drug that enhances serotonergic neurotransmission mediated by norepinephrine and 5-HT1A by antagonizing central α-2-autoreceptor and alo-adrenergic receptors [22]. In our study, we used paroxetine combined with mirtazapine to treat postpartum depression and evaluated its effect. The results showed that this combined treatment significantly reduced the depression score and adverse reactions in patients and significantly improved their sleep quality and quality of life. According to one study, in addition to the effect of paroxetine, the efficacy of treatment may be related to some functions of mirtazapine, which can not only help to relieve depression and improve the function of the nervous system but also regulate gastrointestinal movement or sensory function [23]. Another study reported that the addition of mirtazapine seems promising for improving sleep quality and the quality of life [24]. Collectively, these findings suggest that paroxetine combined with mirtazapine can effectively improve the quality of sleep and life of patients with postpartum depression.

IL-6 is a cytokine with hematopoietic function, which is involved in hematopoiesis, metabolic regulation, autoimmunity, and acute immune reaction [25]. It regulates host defense through various immune stimulation mechanisms, such as controlling mononuclear cells and their differentiation into macrophages, regulating the differentiation of antigen-dependent B cells, increasing the production of IgG by B cells, and promoting Th2 response by inhibiting Th1 polarization [26]. The pro-inflammatory cytokine IL-1β is associated with a persistent immune response and can give rise to several severe central nervous system diseases [27]. Postpartum depression may cause changes in the immune response. In our study, after treatment, the levels of IL-6 and IL-1β in Group B patients were both significantly lower than those in Group A patients. Collectively, these results suggest that paroxetine combined with mirtazapine can markedly lower the levels of inflammatory factors. Moreover, the results of our study showed that paroxetine combined with mirtazapine is more effective than paroxetine alone. This may be explained by the fact that the antidepressant effect of paroxetine mainly depends on inhibition of the serotonin transporter (SERT) and the smallest norepinephrine transporter (NET).

The addition of mirtazapine to paroxetine enhanced SERT inhibition and slightly enhanced NET inhibition, thus enhancing the antidepressant effect of paroxetine [28]. These results indicate that the addition of mirtazapine to paroxetine is effective in treating postpartum depression.

In summary, our research has verified that paroxetine combined with mirtazapine can effectively improve the sleep quality and inflammatory factor levels in patients with postpartum depression. However, only a limited number of inflammatory factors were analyzed, which is a limitation of the current study; thus, we will continue to conduct research and update our results.

Acknowledgements: None.

Conflicts of interest: The authors declare that there is no conflict of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Table 1 Comparison of general data between the two groups ($\bar{x}$ ± SD) [n(%)]

Items	Group A (n=49)	Group B (n=54)	t/χ2 value	P value
Age (Y)	32.58±3.97	33.19±3.48	0.830	0.408
Height (cm)	165.31±4.12	166.48±4.26	1.414	0.160
Nationality			0.403	0.525
Han nationality	43 (87.76)	45 (83.33)		
Minority nationality	6 (12.24)	9 (16.67)		
Education level			0.026	0.871
<senior high school	21 (42.86)	24 (44.44)		
≥ high school and above	28 (57.14)	30 (55.56)		
Delivery times			0.021	0.884
First delivery	32 (65.41)	36 (66.67)		
Not the first delivery	17 (34.69)	18 (33.33)		
Delivery mode			0.000	0.990
Cesarean section	19 (38.78)	21 (38.89)		
Eutocia	30 (61.22)	33 (61.11)		
Baby sex			0.084	0.770
Male	24 (48.98)	28 (51.85)		
Female	25 (51.02)	26 (48.15)		
Feeding pattern			0.085	0.769
Breast milk	41 (83.67)	44 (81.48)		
Milk powder	8 (16.33)	10 (18.52)		

Table 2 Comparison of sleep quality between the two groups after treatment ($\bar{x}$ ± SD)

Item	Group A (n = 49)		Group B (n = 54)		t	P-value
	Before treatment	After treatment	Before treatment	After treatment		
Time for falling asleep	2.62±0.13	1.78±0.18*	2.54±0.11#	1.19±0.11*	20.28	<0.001
Sleep time	2.23±0.21	1.69±0.13*	2.45±0.17#	1.05±0.18*	20.5	<0.001
Sleep disorder	2.14±0.22	1.83±0.27*	2.29±0.19#	1.12±0.19*	15.55	<0.001
Hypnotic drugs	2.78±0.27	2.14±0.28*	2.45±0.14#	1.43±0.13*	16.76	<0.001
Sleep quality	2.22±0.09	1.86±0.15*	2.01±0.12#	1.21±0.11*	25.24	<0.001
Sleep efficiency	2.30±0.95	1.91±0.22*	1.98±0.34#	1.16±0.19*	18.56	<0.001
Daytime functioning	1.99±0.13	1.68±0.25*	1.57±0.51#	0.89±0.16*	19.28	<0.001

*P<0.05 compared with those before treatment

P>0.05 compared with group A

Table 3 Comparison of adverse reactions between the two groups [n(%)]

Evaluation of adverse reactions	Group A (n = 49)	Group B (n = 54)	X2	P-value
Dizziness	2 (4.08)	1 (1.85)	-	-
Blurred vision	1 (2.04)	0 (0.00)	-	-
Sleepiness	2 (4.08)	1 (1.85)	-	-
Nausea and vomiting	2 (4.08)	0 (0.00)	-	-
Constipation	1 (2.04)	0 (0.00)	-	-
Fever	3 (6.12)	2 (3.70)	-	-
Total incidence	11 (22.45)	4 (7.41)	4.671	0.030

Table 4 Comparison of efficacy of treatment between the two groups [n(%)]

Evaluation of adverse reactions	Group A (n = 49)	Group B (n = 54)	X2	P-value
Cured	9 (18.37)	22 (40.74)	-	-
Markedly effective	12 (24.49)	18 (33.33)	-	-
Effective	11 (22.45)	6 (11.11)	-	-
Ineffective	17 (34.69)	8 (14.81)	-	-
Effective treatment rate	32 (65.31)	46 (85.19)	5.523	0.018

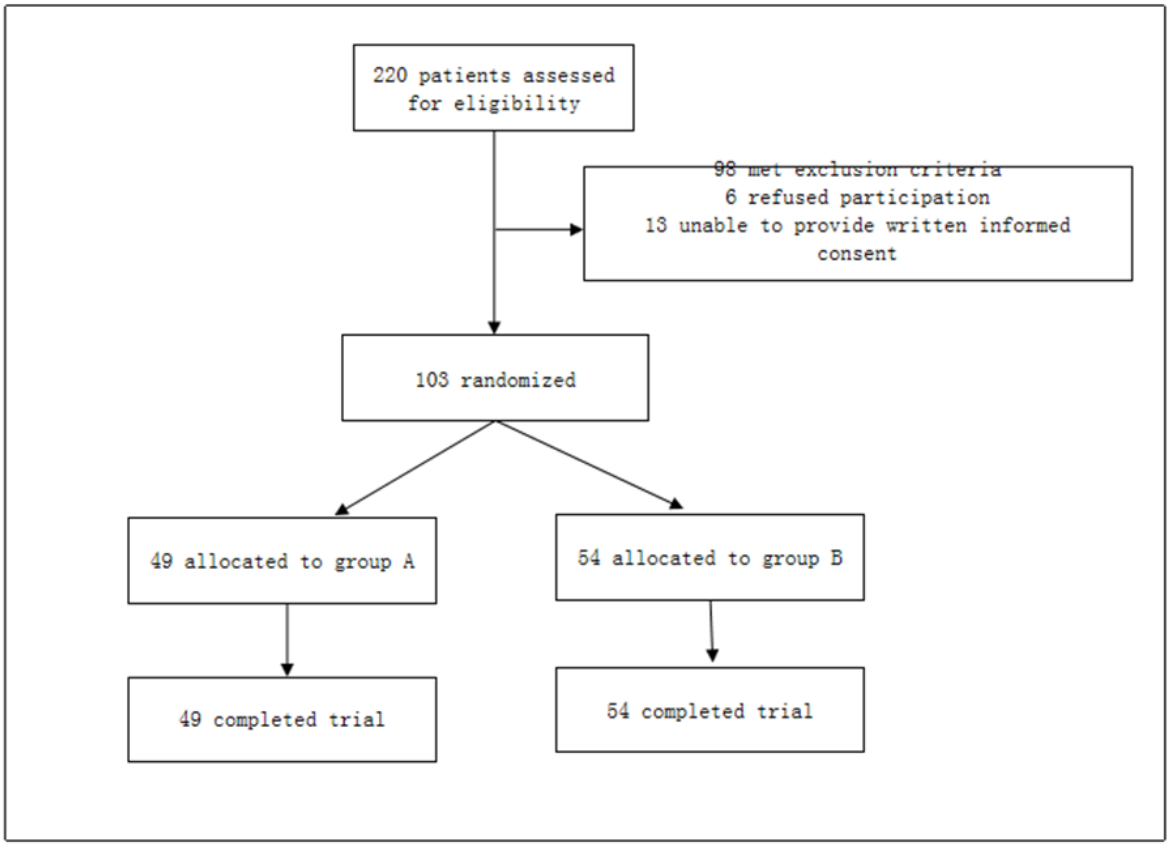

Figure 1 Flow chart of patient enrollment.

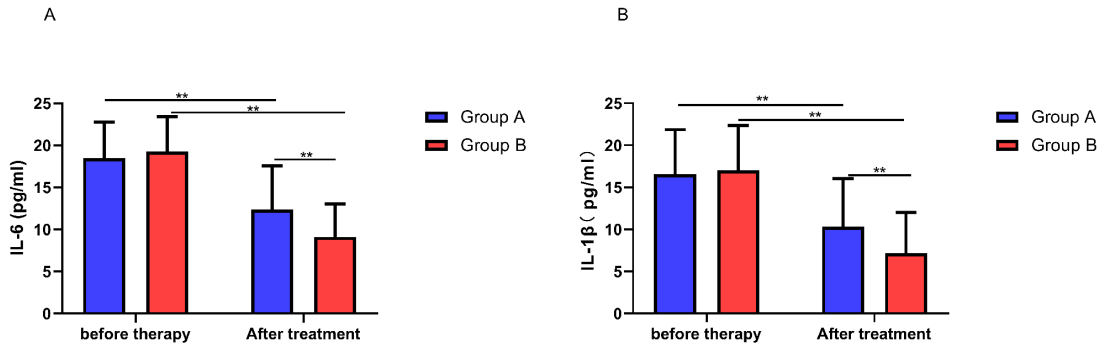

Figure 2 Levels of inflammatory factors in the two groups before and after treatment

Before treatment, there was no notable difference in the levels of inflammatory factors between the two groups; however, after treatment, these levels decreased notably in both groups. The levels in Group B patients were significantly lower than those in Group A patients (both $p < 0.05$). Note: $^{**}p < 0.05$. A, IL-6 levels in the two groups before and after treatment. B, IL-1β levels in the two groups before and after treatment.

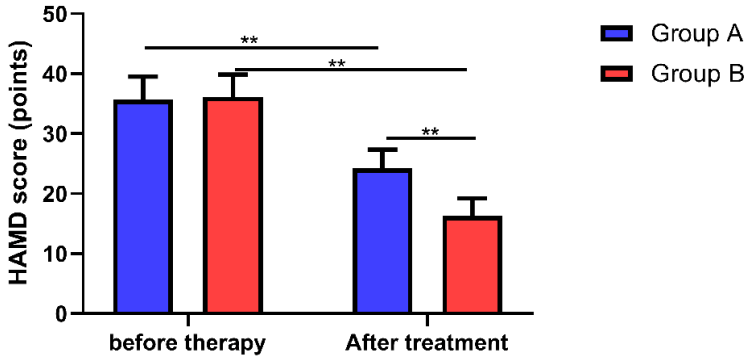

Figure 3 HAMD scores of the two groups before and after treatment

Before treatment, there was no notable difference in the HAMD score between the two groups; however, after treatment, the HAMD scores of both groups were notably reduced, and the mean HAMD score of Group B patients was lower than that of Group A patients ($p < 0.05$). Note: $^{**}p < 0.05$.

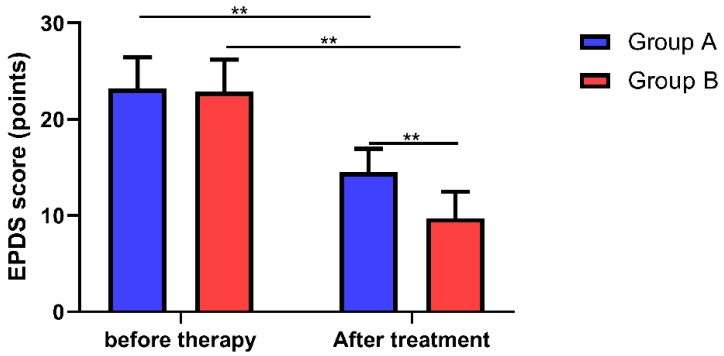

Figure 4 EPDS scores of the two groups before and after treatment

Before treatment, there was no notable difference in the EPDS scores between the two groups. However, after treatment, the EPDS scores of both groups were notably reduced, and the mean EPDS score of Group B patients was lower than that of Group A patients.
($p < 0.05$). Note: **$p < 0.05$.

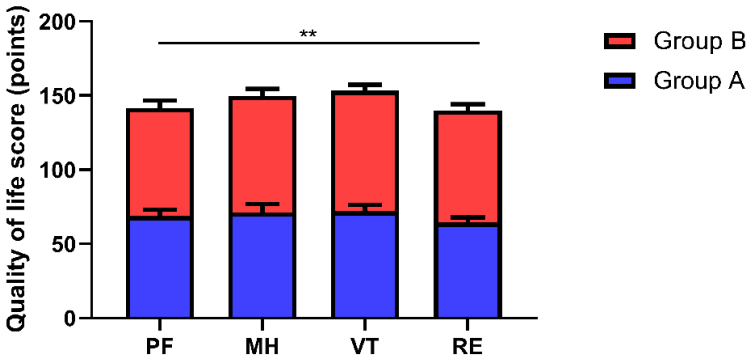

Figure 5 Comparison of quality of life scores between the two groups after treatment

After treatment, the related quality of life scores of Group B patients were higher than those of Group A patients (all $p < 0.05$). Note: **$p < 0.05$.