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Original Research Article

Effect of the combination of cognitive behavioral therapy and oral paroxetine hydrochloride in patients with post-stroke depression

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Abstract

Purpose: *To determine the effects of combined use of cognitive behavioral therapy (CBT) and paroxetine hydrochloride tablets in patients with post-stroke depression (PSD), and its effect on scores on Hamilton Rating Scale for Depression (HAMD) and Stroke Specific Quality of Life Scale (SS-QOL).*
Methods: *Clinical data for 96 patients with PSD who were treated in Dongying Traditional Chinese Hospital, Dongying City, China from June 2018 to June 2019 were retrospectively analyzed. Patients who met the inclusion criteria were divided into treatment group (TG, n = 48) and reference group (RG, n = 48) based on odd and even hospitalization numbers. Both groups received conventional treatment, but RG patients were in addition given clopidogrel, while TG received CBT in combination with paroxetine hydrochloride tablets. Clinical indices were evaluated in both groups before and after treatment. Moreover, therapeutic effects in the two different treatment methods on PSD, as well as on Hamilton Rating Scale for Depression (HAMD) and Stroke Specific Quality of Life Scale (SS-QOL) scores were analyzed.*
Results: *After treatment, TG had lower HAMD score ($p < 0.001$), lower scores on modified Rankin scale, and few incidences of adverse reactions at 3, 7, 15 and 30 days of treatment ($p < 0.05$), but higher total clinical effectiveness and mean SS-QOL score ($p < 0.05$), when compared with RG.*
Conclusion: *Combined use of CBT and oral paroxetine hydrochloride tablets may be a promising strategy for treating depression and enhancing the quality of life of PSD patients, as it greatly improves neurological deficit and prognosis. However, further clinical trials should be carried out prior to introducing it in clinical practice.*

Keywords: *Cognitive behavioral therapy (CBT), Paroxetine hydrochloride, Cerebral stroke, Depression, HAMD score, Quality of life*

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INTRODUCTION

Data from an authoritative international survey indicate that cerebral stroke, ischemic heart disease and chronic obstructive pulmonary disease are the top three causes of premature death in China [1]. Cerebral stroke is an acute cerebrovascular disease triggered by local brain

tissue damage due to cerebral vasculopathy [2]. Hemoperfusion of local brain tissue is reduced due to vascular blockage and rupture, as a result of which patients present with aphasia and hemiplegia. The disease may result in post-stroke depression (PSD) in some patients. Post-stroke depression (PSD) manifests mainly as depression and decreased mobility which may lead to some problems in rehabilitation, impairment of sociability-related functions, and decline in quality of life [3]. At present, tricyclic anti-depressants are used for treating PSD in clinics. However, poor tolerance of the drug has been observed in some patients, resulting in poor long-term treatment effects.

Cognitive Behavior Therapy (CBT) is a short-term psychotherapy method that corrects patients' poor cognition and eliminates bad emotions and bad behaviors by changing their thoughts and actions [4]. Cognitive Behavior Therapy (CBT) has been widely used in the treatment of depression, and it has produced good curative effect [5]. Paroxetine hydrochloride is a 5-hydroxytryptamine (5-HT) re-uptake inhibitor which is more selective than the traditional tricyclic and monoamine oxidase inhibitor antidepressants, and its efficacy has been confirmed in diabetes mellitus complicated with depression [6]. At present, there is limited literature on the effect of combined use of CBT and paroxetine hydrochloride in treating PSD. Thus, this research was performed to determine the efficacy of the combined therapy on PSD.

METHODS

Case selection

The clinical data of 96 PSD patients who were treated in the Neurology Department of Dongying Traditional Chinese Hospital, Dongying City, China from June 2018 to June 2019, were retrospectively analyzed. Patients who met the inclusion criteria were divided into treatment group (TG, n = 48) and reference group (RG, n = 48) based on odd and even hospitalization numbers. This study was approved by the ethics committee of Dongying Traditional Chinese Hospital (approval no. 20180415), and complied with the guidelines of Declaration of Helsinki [7].

Inclusion and exclusion criteria

Inclusion criteria

Patients in the following categories were included in the study: those who met the diagnostic criteria for cerebral stroke as outlined in *Cerebral Stroke Diagnosis and Treatment* [8], and were confirmed with CT angiography and color Doppler ultrasound; patients who met the diagnostic criteria of depression as specified in *Chinese Classification of Mental Disorders Version 3* [9], with depression symptoms for over 15 days; patients with clear consciousness, normal comprehension and expression ability unencumbered by aphasia; those who had no hemorrhagic problems, and patients who signed informed consent forms.

Exclusion criteria

The excluded patients were allergic to the drug, patients with a history of schizophrenia or neurotic disorders, those who had severe cardiorenal dysfunction, and patients with brain tumors. In addition, patients who had severe cognitive impairment, resulting in inability to cooperate with the researchers during the study, were excluded.

Criteria for drop-out

Patients were removed from the study under one or more of the following conditions: loss to follow-up, family request for withdrawal, diagnosis of psychiatric disorders (e.g., mania after taking drugs) other than PSD during the study, experience of adverse events that made it inappropriate for the subject to continue participating in the study, inability of the patient to tolerate the toxic side effects of drugs, and use of another drug.

Pre-study evaluation

The course of cerebral stroke and depression in the two groups was evaluated before treatment, and the data were recorded. Further analysis was carried out if no significant between-group difference in the clinical data was observed.

Treatments

In this retrospective study, the two groups were given routine treatment. Based on the patients' clinical condition, antihypertensive, lipid-lowering, and anti-infection treatments were used to maintain electrolyte and acid-base balance. For patients with brain edema, mannitol was used for dehydration treatment in order to reduce intracranial pressure. Moreover, the patients were given neurotrophic, anti-platelet aggregation, and anticoagulant treatments, as well as parenteral or enteral nutrition support and psychological nursing according to their nutritional and physical conditions. In addition to conventional treatment, patients in RG received oral sertraline hydrochloride tablets (Pfizer

Pharmaceuticals Co. Ltd; NMPA approval no. H10980141; specification: 50 mg x 14 tablets) at a dose of 5 mg/day in the first week. The dose was increased to 50 mg/day within one week, and 50 - 200 mg/day at weeks 2 - 8, with subsequent increment at a rate of 25 mg/week, which was maintained at weeks 9 – 24.

Patients in TG received combination of CBT and paroxetine hydrochloride tablets. Individual CBT treatment was carried out according to the requirements and principles outlined in *Cognitive Behavioral Therapy Manual* [10]. The physicians who administered the CBT treatment were equipped in the treatment of mental and psychological diseases, following requisite CBT training.

The CBT treatment involved three parts. The first part involved training on physiological relaxation which was designed for hyperpnea due to anxiety. The training was meant to change shallow and fast hyperpnea into slow and deep abdominal breathing. The second part was cognitive reconstruction. It was aimed at pointing out misinterpretation by patients and helping them to recognize the nature of the problem, thereby alleviating their symptoms of worrying through behavioral tests. The last part was prohibition of anxious behavior, problem-solving, and time management. It was the responsibility of the patients to receive the training. The core of the treatment plan was "worry exposure", which allowed patients to deal with personal concerns within a certain time, through the established principle of repeated, step-by-step and targeted treatment. The whole treatment was carried out 12 times, each time for 50-70 min. In the 1st and 2nd times, treatment relationship was established, the clinical data of patients were collected, and the plan was formulated. Relaxation training and cognitive correction were carried out between the 3rd and 6th times, while cognitive reconstruction was performed step-by-step between the 7th and 10th times. The 11th and 12th times were used for consolidating curative effects and preventing recurrence. The CBT treatment lasted for 24 weeks, during which weeks 1-8 were used for weekly acute treatment, while weeks 9-24 were used for maintenance treatment (4 times in total, once every 2 weeks in weeks 9-12, and once every 6 weeks in weeks 13 - 24).

Patients orally took paroxetine hydrochloride tablets (Zhejiang Huahai Pharmaceutical Co. Ltd; NMPA approval no. H20031106; specification: 20 mg ×10 tablets × 2 packs/box). Starting with an initial dose of 10 mg/day, the dose was increased to 20 mg/day within one week, and 20 - 50 mg/day in weeks 2 – 8 at an incremental rate of 10 mg/week, which was maintained in weeks 9 - 24.

Evaluation of indices/parameters

Depression

The degree of depression in the patients before and after treatment was evaluated in line with the Hamilton Rating Scale for Depression (HAMD) [11]. The assessment was jointly done by two raters with requisite professional training. The HAMD is convenient in clinical practice, and it has good reliability. The total score reflected the severity of the patients' condition. Lower scores indicated less severe condition: ≥ 24 points indicated *severe depression*, 17 - 24 points indicated *depression*, while 7 - 17 points and < 7 points indicated *possible depression* and *normality*, respectively.

Neurological deficits

The modified Rankin Scale with scores of 0-5 points [12] was used to evaluate the degree of neurological deficit at different time points (before treatment, and at 3, 7, 15 and 30 days of treatment). Higher scores indicated more serious neurological defects.

Treatment effectiveness

The treatment was *markedly effective* if a patient's HAMD score decreased by more than 75 % after treatment, and if the patient completely cooperated with the treatment, and their negative emotions were completely alleviated. The treatment was deemed *effective* if HAMD score decreased by 25-75 % after treatment, and the patient basically cooperated with the treatment, and their negative emotions were improved to some extent. In contrast, the treatment outcome was classified as *ineffective* if there were no changes in the patient's negative emotions, or if the patient's condition took a turn for the worse. Total treatment effectiveness (TE) was calculated as shown in Eq. 1:

$$TE\ (\%) = \frac{(ME + E)}{T} \times 100 \quad \ldots\ldots\ldots (1)$$

where *TE* = total treatment effectiveness; *ME* = number of markedly effective cases; *E* = number of effective cases; *T* = total number of cases.

Quality of life (QOL)

Patients' ***QOL*** was evaluated before and after treatment, in line with the Stroke Specific Quality of Life Scale (SS-QOL) [13]. The SS-QOL

included 12 aspects such as language, mood, and sociability, with a total of 78 items and 240 points. Higher scores indicated higher ***QOL***.

Adverse reactions

The incidence of adverse reactions in the course of treatment were monitored and recorded.

Statistical analysis

The data were processed using SPSS version 24.0 software, while graphs/images were prepared using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data are expressed as numbers and percentages [n (%)], and were analyzed using χ^2 test, while measurement data are expressed as mean ± SD, and were analyzed by *t*-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Patients and dropout cases

Ninety-six PSD patients were enrolled in this study. The subjects comprised 48 patients in TG and 48 patients in RG. By the end of the 24th week, a total of 10 patients dropped out in the two groups, with four cases from TG, and 6 cases from RG. These data are shown in Figure 1.

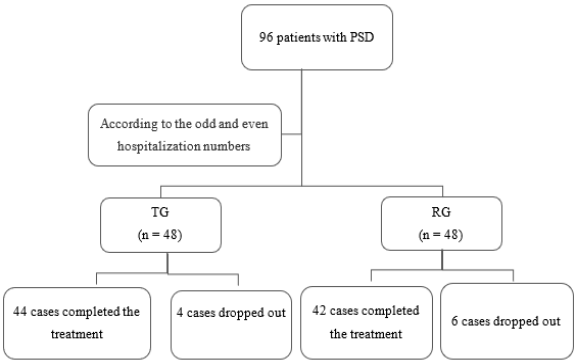

Figure 1: Patients used in the study, and drop-out cases

Baseline data of patients

No notable differences were found in patient data such as sex ratio, mean age, and the course of cerebral stroke and depression between the two groups ($p > 0.05$; Table 1).

Table 1: Baseline data of patients

Variable	TG	RG	χ^2/t	*P*-value
Gender [n (%)]			0.042	0.837
Male	27 (56.25)	26 (54.17)		
Female	21 (43.75)	22 (45.83)		
Mean age (years)	57.82±3.42	57.74±3.51	0.113	0.910
BMI (kg/m^2)	21.26±1.25	21.35±1.31	0.344	0.731
Course of cerebral stroke (years)	3.21±0.46	3.24±0.52	0.299	0.765
MMSE score (points)	26.37±2.36	26.41±2.42	0.082	0.935
Course of depression (months)	2.26±2.17	2.32±2.15	0.136	0.892
Pathological types			0.445	0.505
Ischemia	32 (66.67)	35 (72.92)		
Hemorrhage	16 (33.33)	13 (27.08)		
Ethnicity			0.546	0.460
Han	45 (93.75)	43 (89.58)		
Non-Han	3 (6.25)	5 (10.42)		
Marital status				
Unmarried	2 (4.17)	1 (2.08)	0.344	0.557
Married	42 (87.50)	44 (91.67)	0.447	0.504
Divorced	4 (8.33)	3 (6.25)	0.154	0.695
Residential area			0.168	0.682
Urban	23 (47.92)	21 (43.75)		
Rural	25 (52.08)	27 (56.25)		
Educational degree				
Junior college degree and above	5 (10.42)	9 (18.75)	1.338	0.247
Senior high school degree	20 (41.67)	14 (29.17)	1.640	0.200
Middle school degree and below	23 (47.92)	25 (52.08)	0.167	0.683

HAMD scores

Before treatment, the HAMD scores were 19.71 ± 1.69 and 20.00 ± 2.22 in TG and RG, respectively. After treatment, the HAMD scores were 7.85 ± 1.49 and 10.48 ± 1.81 in TG and RG, respectively. No significant difference was observed in the HAMD scores between TG and RG before treatment (p > 0.05). However, compared with RG, the HAMD score of TG after treatment was significantly lower (p < 0.001).

Modified Rankin scores

No notable between-group difference was shown in scores on the modified Rankin Scale before treatment (p > 0.05). However, the scores of modified Rankin scale at 3, 7, 15 and 30 days of treatment were significantly lower in TG than in RG, as shown in Table 2.

Treatment effectiveness

The total treatment effectiveness was higher in TG than in RG (p < 0.05).

SS-QOL scores

Before treatment, the average SS-QOL scores were 119.58 ± 4.68 points in TG and 120.75 ± 3.53 points in RG. After treatment, the average SS-QOL scores were 205.38 ± 5.40 points in TG and 179.65 ± 7.21 points in RG (t = 19.789, p < 0.001, Figure 2 B).No remarkable between-group difference was shown in mean SS-QOL scores before treatment (p > 0.05). However, after treatment, the average SS-QOL score of TG was notably higher than that of RG (p < 0.001; Figure 2).

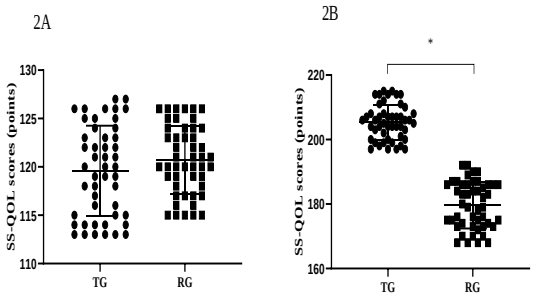

Figure 2: Comparison of SS-QOL scores before and after treatment (mean ± SD, n = 48). ***Note:*** Figure 2 A shows the comparison of SS-QOL scores of the two groups before treatment

Incidence of adverse reactions

The incidence of adverse reactions in TG was lower than that in RG (p < 0.05, Table 4).

Table 2: Modified Rankin Scale scores at different time points

Group	Before treatment	3 days of treatment	7 days of treatment	15 days of treatment	30 days of treatment
TG	3.75±0.79	3.04±0.80	2.00±0.71	1.69±0.55	0.92±0.54
RG	3.77±0.90	3.42±0.77	2.63±0.64	2.10±0.63	1.31±0.69
t	0.116	2.371	4.566	3.397	3.084
P	0.908	<0.05	<0.001	<0.05	<0.05

Table 3: Treatment effectiveness (%)

Group	Markedly effective	Effective	Ineffective	Total effectiveness {n (%)}
TG	28 (58.33)	17 (35.42)	3 (6.25)	93.75 (45/48)
RG	22 (45.83)	18 (37.50)	8 (16.67)	83.33 (40/48)
χ^2				4.360
P-value				0.037

Table 4: Incidence of adverse reactions

Adverse reaction	TG	RG	χ^2	*P*-value
Fatigue	1 (2.08)	1(2.08)		
Nausea	1(2.08)	1(2.08)		
Intestinal reaction	1(2.08)	2 (4.17)		
Palpitation	0 (0)	2 (4.17)		
Headache	0 (0)	1 (2.08)		
Xerostomia	0 (0)	1 (2.08)		
Acute dystonia	0(0)	2 (4.17)		
Total incidence	6.25% (3/48)	20.83% (10/48)	4.360	0.037

DISCUSSION

Post-stroke depression (PSD) is a common complication of cerebral stroke. A study of medical psychological characteristics has shown that more than 40 % of cerebral stroke patients have depression symptoms, and the incidence of PSD is higher than that in other people [14]. Clinical studies have found that depression, which occurs 2 months after cerebral stroke, has clinical manifestations of impaired thought and poor cognitive ability, sadness, and pseudo-dementia, all of which seriously affect the prognosis of patients [15]. Therefore, it is important to give psychological care and implement other intervention methods such as use of drugs for PSD patients in order to mitigate depression and improve their quality of life.

At present, the pathogenesis of PSD is not very clear, but the consensus is that it is triggered by disorders in secretion of neurotransmitters in the brains of patients. The affected neurotransmitters comprise dopamine, norepinephrine and 5-hydroxytryptamine. Therefore, it can be inferred that effective regulation of the secretion of these neurotransmitters may be beneficial in the treatment of PSD patients [16]. The frequently-used antidepressant, sertraline hydrochloride (in tablet formulation) effectively reduces depressive symptoms in patients, and relieves persistent fatigue symptoms and anxiety state. However, long-term use of sertraline hydrochloride leads to decreased body resistance which negatively affects the prognosis and rehabilitation of patients [17]. Cognitive behavioral therapy (CBT) is unique amongst the various psychotherapy methods: not only does it emphasize that cognitive activities are crucial in the onset and outcome of psychological or behavioral problems, it also has the advantages of integrity and guidance through the application of various cognitive correction techniques and behavioral therapy techniques during the treatment. Therefore, CBT is suitable for various psychological disorders. Indeed, its treatment effectiveness has been confirmed in recurrent abortion depression [18]. The biochemical changes associated with depression symptoms involve functional defects in 5-hydroxytryptamine (5-HT). Therefore, Western drug treatment is used to inhibit the reuptake of 5-HT. Paroxetine hydrochloride (tablet formulation), a 5-HT reuptake inhibitor, blocks the reuptake of 5-HT via its suppressive effect on the presynaptic membrane, enhances the levels of 5-HT, and alleviates bad emotions in patients. Some studies have demonstrated that paroxetine hydrochloride effectively relieved the clinical symptoms of depression [19,20].

In this study, cognitive behavioral therapy (CBT) was used in combination with paroxetine hydrochloride tablets in patients with PSD, and the HAMD score was used to evaluate the degree of depression before and after treatment in both groups. The results showed an obvious between-group difference in HAMD scores after treatment, and the HAMD score of TG was significantly lower than that of RG. This demonstrated that the combined therapy was better than conventional drug treatment in reducing the degree of depression in patients with PSD. The SS-QOL score is a key index widely used in China to objectively evaluate the quality of life of patients with cerebral stroke, and it makes up for the deficiencies in other scales.

The present study also showed that the mean post-treatment SS-QOL score was higher in TG than in RG, indicating that the combined treatment method clearly delivered better results in PSD patients, with respect to quality of life.

Limitations of this study

Although CBT is widely used in patients with depression, there are limited studies on its application in PSD. Moreover, this study did not evaluate the degree of depression in the included subjects before treatment. This limitation may cause bias in the results. Therefore, there is need for a more rigorous study design with a larger sample size to achieve systematic intervention measures.

CONCLUSION

Cognitive behavioral therapy (CBT) in combination with paroxetine hydrochloride tablets relieves depression and enhances the QOL of PSD patients. However, there is a need for further clinical trials prior to the introduction of this strategy in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Bin Tian, Shiwei Zhang and Zhan Gao conceived and designed the study, and drafted the manuscript. Bin Tian, Shiwei Zhang, Qingyong Li, Chengyong Sun, Ya'nan Wu and Hairong Yang collected, analyzed and interpreted the experimental data. Bin Tian and Zhan Gao revised the manuscript for important intellectual contents. All authors read and approved the final manuscript. Bin Tian and Shiwei Zhang contributed equally to this study.

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