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Original Article

Effect of comprehensive rehabilitation training on prevention of post-stroke dementia: a randomized controlled trial

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Abstract: To evaluate the difference in the prevention of cognitive impairment and the incidence of dementia in patients with initial stroke between comprehensive rehabilitation training (a combination of cognitive training, rehabilitation training and patient education) plus medical treatment and medical treatment alone. A total of 200 patients from April 2013 to April 2015 with initial onset of ischemic stroke were included. These patients were randomized into the experimental group (comprehensive rehabilitation training plus medical treatment) and control group (medical treatment alone) in a 1:1 ratio to receive treatment for 6 months and follow-up for 12 months. The proportion of patients with dementia, the changes from baseline of MMSE (Minimum Mental State Examination) and ADL (activities of daily living score) as well as the proportion of patients with anxiety and patient with depression were evaluated and compared between two groups. There was no significant difference in the proportion of patients with dementia between experimental group and control group at 3 months and 6 months. However, the proportion of patients with dementia in experimental group was significantly lower than control group at 12 months of follow-up (7.70% vs. 19.20%, P=0.041). The changes from baseline of MMSE (1.67±0.34, 95% CI: 1.59-1.75 vs. 5.22±0.31, 95% CI: 5.15-5.29, P<0.001) and ADL (2.73±0.20, 95% CI: 2.69-2.77 vs. 3.45±0.27, 95% CI: 3.39-3.51, P<0.001) in experimental group were significantly decreased when compared to control group at 12th months. In addition, the proportion of patients with anxiety in the experimental group was significantly lower than control group (24.70% vs. 44.60%, P=0.007); whereas no significant difference was observed in the proportion of patients with depression between experimental group and control group (43.20% vs. 45.80%, P=0.74). This study indicates that the comprehensive rehabilitation training reduces the incidence of post-stroke dementia as well as significantly prevents the cognitive function impairment, anxiety and improves activities of daily living in patients of stroke.

Keywords: Post-stroke dementia, comprehensive rehabilitation training, randomized controlled trial

Introduction

With high incidence and heavy disease burden, stroke ranks the second among worldwide mortality and third in disability rates of various diseases [1]. Stroke is highly correlated with dementia. The proportion of patients who develop post-stroke dementia (PSD) in patients with stroke is significantly higher than the patients without stroke (as control) [2]. The proportion of patients with post-stroke dementia one year after first stroke is up to 10%, and the proportion of patients with post-stroke dementia one year after recurrent stroke is as high as 30% [3, 4]. Cognitive training, rehabilitation training and regular check improve post-stroke cognitive function, physical function and mental state of patients [5-7]. However, currently, no studies have been conducted to determine whether these interventions decrease the proportion of patients develop dementia after stroke. This randomized, controlled study aims to evaluate the difference in the prevention of cognitive impairment and the incidence of dementia in patients with initial stroke between comprehensive rehabilitation training (a combination of cognitive training, rehabilitation training and patient education) plus medical treatment and medical treatment alone.

Materials and methods

Patients

A total of 200 patients who were admitted into the Neurology Department and Emergency

Department of Shanghai TCM-Integrated Hospital, Shanghai University of TCM between April 2013 and April 2015 with initial onset of ischemic stroke were recruited.

Inclusion criteria: 1. Patients with initial stroke (mainly ischemic stroke) confirmed by brain CT or MRI; 2. Patients who had no conscious disturbance and mental disturbance and were willing to cooperate with the evaluation and follow-up; 3. Patients who had at least one permanent caregiver in their family and there was no patients with dementia and mental disorders among their first-degree relatives; 4. Patients without dementia and stoke confirmed by screening using Minimum Mental State Examination (MMSE) scale according to the degrees of education of patients.

Exclusion criteria: 1. Patients who had severe physical diseases such as severe cardiac, pulmonary, hepatic and renal insufficiency; 2. Patients with concurrent malignancies; 3. Patients with severe hearing impairment; 4. Patients with aphasia caused by stroke; 5. Patients who were unable to walk due to severe dysfunction were excluded.

All patients who were enrolled into the study were willing to participate in this clinical study and singed the informed consent form. The study protocol had been reviewed and approved by the committee of Shanghai TCM-Integrated Hospital, Shanghai University of TCM.

Procedures

This was a single center, randomized, controlled clinical study. The patients were randomized into the experimental group (comprehensive rehabilitation training plus medical treatment) and control group (medical treatment alone) in a 1:1 ratio to receive treatment for 6 months and follow-up for 12 months.

The specific interventions were as follows:

Experimental group (comprehensive rehabilitation training plus medical treatment): 1. Patient education: A manual of the *Rehabilitation and Mental Health of Stoke* developed by our hospital was dispensed to the patients and their families for education at enrollment, and then once every two months for six months. 2. Cognitive training: Related research therapist (a trained, licensed occupational therapist with expertise in stroke rehabilitation) would visit the patient to provide instructions on cognitive training two weeks after enrollment, and then once a month for six months. 3. Rehabilitation training: a. Related research therapist would visit the patient to provide instructions to the relatives of the patient on massage and systemic coordinative training two weeks after enrollment, and then once every two months for 6 months. b. Patients were instructed to visit the rehabilitation department of our hospital to receive rehabilitation training including cerebral function, biofeedback, etc. once a week for six months. 4. Regular check: Patients were instructed to regularly undergo necessary biochemical examinations, including blood glucose, blood pressure and blood lipid to manage any abnormality timely once every two months for six months. 5. Medical treatment.

Control group: 1. Medical treatment alone.

Randomization

A randomization number was generated by SAS8.1 software. Patients were randomly divided into experimental group and control group in 1:1 ratio by the randomization number given by recruiting sequence.

Study outcomes

Primary endpoint: The difference in the number (%) of patients with dementia at the 12 months between the experimental group and control group (According to *Diagnostic and Statistical Manual of Mental Disorders* of American Psychiatric Association (DSM IV) [8]).

Secondary endpoint: The changes from baseline of MMSE (Minimum Mental State Examination) score [9] and ADL (ADL score by PULSES profile, activities of daily living score) [10] at the 12 months in experimental group and control group; and proportion of patients with anxiety (HAMA>7, Hamilton anxiety scale) [11] and patients with depression (HAMD>7, Hamilton depression scale) [12].

Statistics

Statistical analysis was conducted using SAS8.1 software. Student t test or Wilcoxon signed rank test was used to compare the difference of quantitative data. Chi-square test or Fisher exact test was used to compare the difference of qualitative data. The difference was considered statistically significant when $P<0.05$.

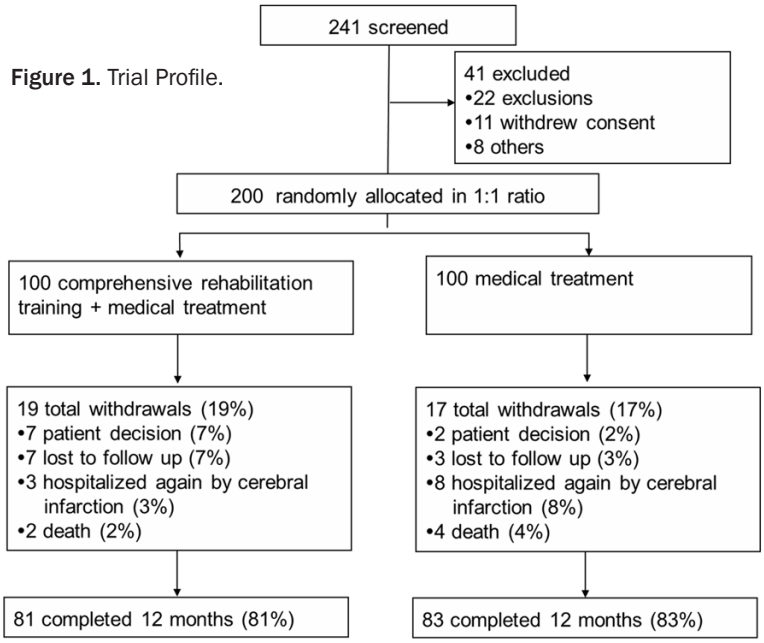

Figure 1. Trial Profile.

Table 1. Demographic and baseline disease characteristics of patients

Parameters	Comprehensive rehabilitation training + medical treatment (n=81)	Medical treatment (n=83)	*p* Value
Age (years)	64.86±9.04	63.01±12.17	0.226
Male (%)	41 (51%)	46 (55%)	0.538
Education duration (years)	5.89±3.31	6.19±3.19	0.549
Smoke (%)	27 (33%)	31 (37%)	0.591
Drink (%)	21 (26%)	26 (31%)	0.445
Hypertension (%)	75 (93%)	73 (88%)	0.316
Diabetes (%)	18 (22%)	25 (30%)	0.250
Intellectual work (%)	53 (65%)	65 (78%)	0.066
SSRS score	33.75±5.70	32.94±6.69	0.403
MMSE score	27.39±2.97	28.04±2.37	0.128
ADL score by PULSES	15.32±2.08	15.65±2.22	0.328
Anxiety (%)	6 (7%)	6 (7%)	0.965
Depression (%)	7 (9%)	9 (11%)	0.635

Data are presented as Mean values ± SD or percentages. A *p* Value <0.05 was considered statistically significant. Significance of the comparison is determined by the Student t test and the χ^2 test. SSRS: Social Support Rating Scales; ADL: Activities of Daily Living; Anxiety and Depression is defined as HAMA score >7 and HAMD score >7, respectively; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale.

Results

Characteristics of the participants and study completion

A total of 241 patients were screened, among which, 41 patients were excluded and 200 patients were enrolled (100 cases in experimental group and 100 cases in control group). In experimental group, 19 (19%) patients dropped out during the study (7 patients withdrew from the study, 7 patients lost the follow-up, 3 patients were hospitalized again due to cerebral infarction and 2 patients died); while in control group, 17 (17%) patients dropped out (2 patients withdrew from the study, 3 patients lost the follow-up, 8 patients were hospitalized again due to cerebral infarction and 4 patients died). Therefore, 164 patients finally completed the trial and were included into the final analysis (81 cases in experimental group and 83 cases in control group) (Trial profile seen in **Figure 1**).

There was no significant difference between experimental group and control group in age (64.86±9.04 vs. 63.01±12.17, P=0.226), gender (51% male vs. 55% male, P=0.538) and education duration (5.89±3.31 vs. 6.19±3.19, P=0.549) at baseline. No significant differences were seen in other baseline characteristics between two groups (P>0.05) (**Table 1**).

Primary endpoint-post stroke dementia

There was no significant difference in the proportion of patients with dementia between the experimental group and control group at the 3 months and 6 months (2.50% vs. 3.60%, P=0.670; 3.80% vs. 6.30%, P=0.490, respectively). The proportion of patients with dementia in the experimental group was significantly lower than that in the control group at the 12 months of follow-up (7.70% vs. 19.20%, P=0.041), as shown in **Figure 2**.

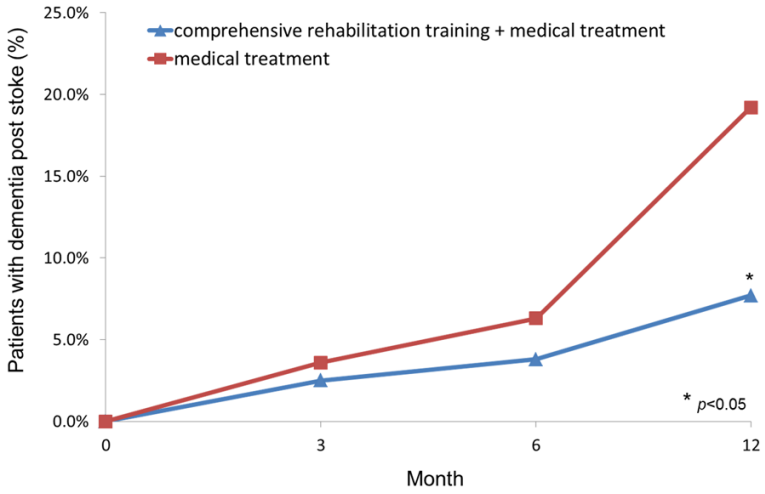

Figure 2. Proportion of patients with dementia post stroke.

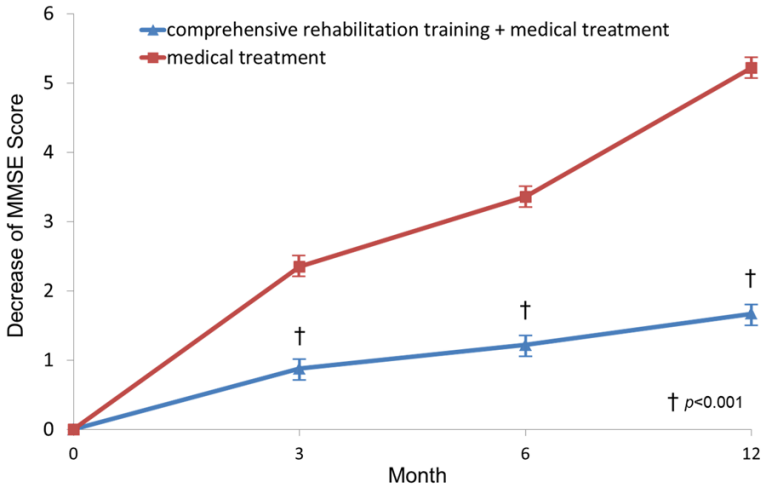

Figure 3. Decrease of MMSE score from baseline (Error bars are 95% CIs).

Secondary endpoint-MMSE, anxiety, depression and ADL

The change from baseline of MMSE score in experimental group was significantly decreased compared with control group at the 3 months (0.88±0.34, 95% CI: 0.8-0.96 vs. 2.35±0.27, 95% CI: 2.29-2.41, P<0.001). And at 12 months, the MMSE change was still reduced in experimental group than control group at the 12 months (the endpoint of the study, presented in **Figure 3**) (1.67±0.34, 95% CI: 1.59-1.75 vs. 5.22±0.31, 95% CI: 5.15-5.29, P<0.001).

There was no significant difference in the proportion of patients with anxiety or depression between experimental group and control group at baseline. After 12 months, the proportion of patients with anxiety in experimental group was significantly lower than that in control group (24.70 vs. 44.60%, P=0.007); whereas there was no significant difference in the proportion of patients with depression between experimental group and control group (43.20% vs. 45.80%, P=0.74) (Shown in **Figure 4**).

In addition, the change from baseline of ADL score in experimental group was significantly decreased compared to control group at the 3 months (1.32±0.27, 95% CI: 1.26-1.38 vs. 1.63±0.25, 95% CI: 1.58-1.68, P<0.001). This difference in ADL score change was also demonstrated at the 12 months (2.73±0.20, 95% CI: 2.69-2.77 vs. 3.45±0.27, 95% CI: 3.39-3.51, P<0.001) (**Figure 5**).

Conclusion

This study indicates that comprehensive rehabilitation training reduces the incidence of post-stroke dementia of patients and also significantly protects patients from the impairment of cognitive function, anxiety state and activities of daily living.

Stroke leads to decreased cognitive function and dementia in patients, in addition to the impairment in physical, cognitive and speech functions of patients [13]. A number of studies show that stroke is highly correlated to dementia, and they share common risk factors [14]. Stroke is more likely seen in patients with dementia, and patients with stoke are likely to develop dementia [15]. A meta-analysis shows that the probability of dementia in patients with stroke is 6%-32% [16]. The probability of dementia in patients with stroke was 3.5-5.8 times higher than patients without stroke [17]. The cognitive function of patients with stroke is

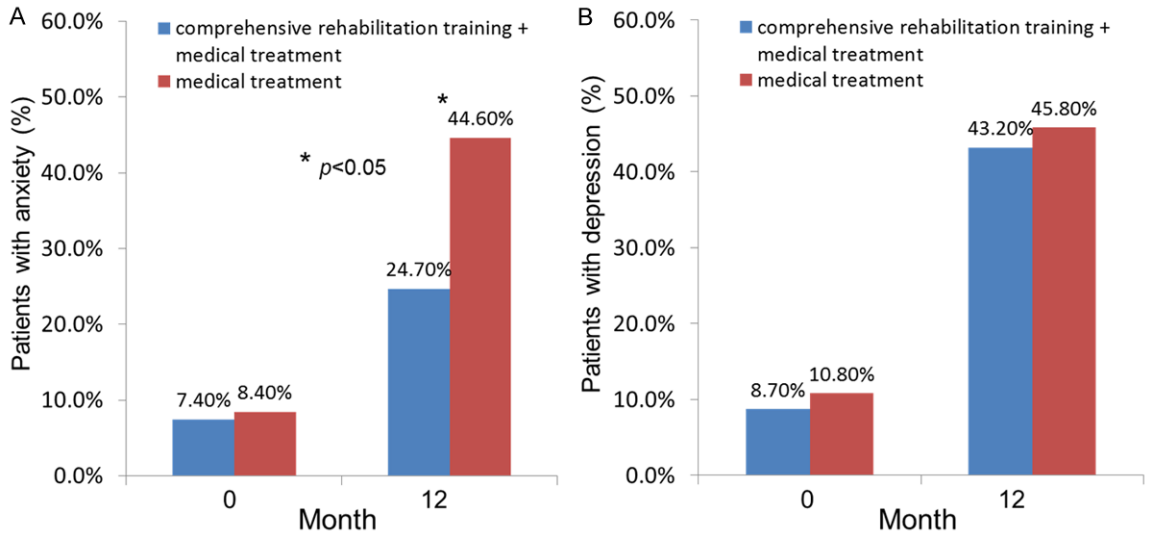

Figure 4. Proportion of patients with anxiety (A) and depression (B) by HAM score. (A) Patients with anxiety was defined as HAMA score >7; (B) Patients with anxiety was defined as HAMD score >7.

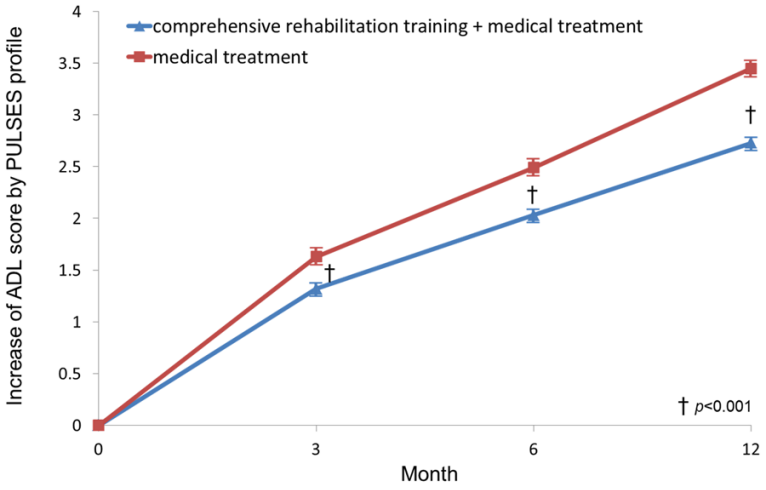

Figure 5. Increase of ADL score by PULSES profile from baseline (Error bars are 95% CIs).

usually impaired severely, and the risk of cognitive disorders increases at least 2 times due to stroke [17, 18]. Additionally, approximately 40% patients developed depression syndrome after stroke [19]. This is an independent predictive factor of long-term survival of patients with stroke [20].

Post-stroke dementia is caused by a lot of very complicated reasons, including vascular diseases or injuries, changes of brain cells, neural inflammatory, immunosuppression and so on [21-24]. Old age, low degree of education, recurrent stroke, high pre-stroke dependence and cognitive impairment are the high-risk factors leading to post-stroke dementia [25].

Systemic analysis showed that post-stroke cognitive training improves attention deficits of patients and increases the memory of patients [26-28]. In addition, studies showed that cognitive training also improves executive functions of patients [29]. Rehabilitation training improves self-care ability, communication skill and social skills of patients [5]. Two small scale studies showed that rehabilitation training relieved cognitive impairment of patients [30, 31]. It also improved the attention, memory and executive functions of patients [32]. Currently, no reports concerning the effect of cognitive training and rehabilitation training on the incidence of post-stroke dementia are available.

There are some limitations about this study: a. The duration of observation was 12 months, and the effect of comprehensive rehabilitation training on the incidence of dementia, cognitive function and anxiety of patients in a long term was not observed; b. Our study mainly focused on the patients with initial stroke, and the effect

of comprehensive rehabilitation training on patients with recurrent stroke needs to be further investigated.

This study indicates that the comprehensive rehabilitation training reduces the incidence of post-stroke dementia as well as significantly prevents the cognitive function impairment, anxiety and improves activities of daily living in patients of stroke.

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Disclosure of conflict of interest

None.

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