Am J Transl Res 2021;13(12):13803-13810
www.ajtr.org /ISSN:1943-8141/AJTR0138601

Original Article

Butylphthalide soft capsules combined with modified tonic exercise therapy on neurological function and ability of daily living of patients with stroke hemiplegia

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Received August 26, 2021; Accepted October 21, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objective: To explore the effect of butylphthalide soft capsules combined with modified tonic exercise therapy on neurologic function and the abilities of daily living in patients with stroke hemiplegia. Methods: In this retrospective trial, a total of 90 patients with stroke hemiplegia admitted to our hospital from January 2019 to January 2020 were enrolled and divided into a control group and an experimental group according to different treatment methods. The two groups were both treated with butylphthalide soft capsules, and the experimental group was additionally treated by modified tonic exercise therapy. The clinical efficacy, endothelial injury indicators, molecular indicators of oxidative stress, and adverse reactions of the two groups were compared. Generic Quality of Life Inventory-74 (GQOLI-74) was used to assess the quality of life of patients after treatment. The Fugl-Meyer Upper Extremity Assessment (FMA) was used to evaluate their limb function before and after treatment, the National Institute of Health Stroke Scale (NIHSS) was used to evaluate their brain nerve function before and after the treatment, and the activities of daily living (ADL) were employed to assess their activities of daily living before and after treatment. Results: After treatment, the experimental group outperformed the control group in terms of total clinical efficacy ($P<0.05$). The experimental group had significantly lower endothelial injury indicators and higher molecular indicators of oxidative stress than the control group (all $P<0.001$). The incidence of adverse reactions in the experimental group was lower than that in the control group ($P<0.05$). Higher GQOLI-74, FMA, and ADL scores and a significantly lower NIHSS score were obtained in the experimental group than the control group after treatment ($P<0.001$). Conclusion: For patients with stroke hemiplegia, butylphthalide soft capsule combined with modified tonic exercise therapy effectively improves their neurologic function, abilities of daily living, and quality of life.

Keywords: Butylphthalide, modified tonic exercise therapy, stroke, hemiplegia

Introduction

Stroke is a common disease in neurology with a high incidence of fatality and disability [1-3]. Stroke refers to a disease in which a sudden rupture or blockage of a blood vessel in the brain prevents blood from flowing to the brain and causes brain tissue damage [4-6]. Currently, its etiology is still poorly understood, and it is believed to be related to diabetes, atrial fibrillation, and poor living habits. The clinical manifestations of stroke are sudden fainting, poor communication ability, and unresponsiveness, which lead to hemiplegia and other complications without timely and appropriate treatment, seriously compromising the patient's quality of life [7, 8]. Stroke hemiplegia is mainly triggered by impaired brain function. Currently, drug therapy is the mainstay of treatment to improve intracranial pressure and cerebral edema in patients to stop progression of the disease [9, 10]. The clinical efficiency of conventional treatment is considered rather unsatisfactory. Butylphthalide is a synthetic drug with strong anti-ischemic effects by blocking pathologic processes of brain injury after ischemic stroke, and its mechanism of action includes the reduction of cerebral infarct area and cerebral edema, improvement of cerebral energy metabolism, and inhibition of neuronal apoptosis. However, its role in regulation of the inflammatory response after cerebral infarction remains elusive. The effectiveness of the introduction of modified tonic exercise therapy in the early post-infarction period for improving individual neurologic deficits in patients with cere-

bral infarction has been widely recognized, and its therapeutic mechanism may be related to an improvement of the microenvironment of the cerebral ischemic peripheral zone, pro-vascular regeneration, neuro-regeneration, and inhibition of apoptosis. Given the important role of the inflammatory response in post-infarction brain pathologic injury, modified tonic exercise therapy may play a role in post-ischemic immune modulation. It was found that modified tonic exercise therapy promotes the expression of inflammatory cytokines after cerebral ischemia and also inhibits the expression of adhesion molecules [8]. Butylphthalide soft capsules combined with modified tonic exercise therapy has demonstrated promising clinical efficiency in the treatment of stroke hemiplegia. Accordingly, this study was conducted to further explore the effects of this combination on the neurologic function and daily life of patients with stroke hemiplegia by enrolling 90 such patients admitted to our hospital from January 2019 to January 2020. The novelty of this study is that the combination of butylphthalein capsules with modified tonic exercise therapy contributes to the further improvement of neurologic function and their daily living abilities in patients with acute cerebral infarction. Results of this study provide further clinical evidence for the efficacy of butylphthalein capsules combined with modified tonic exercise therapy in acute cerebral infarction.

Materials and methods

General information

In this retrospective study, a total of 90 patients with stroke hemiplegia admitted to our hospital from January 2019 to January 2020 were enrolled and equally divided into a control group and an experimental group according to different treatment methods.

Inclusion criteria

(1) Patients who met the diagnostic criteria for stroke hemiplegia; (2) Patients who could stand and keep their balance independently for more than 1 min.

Exclusion criteria

(1) Patients with further deterioration; (2) Patients with mental or other cognitive disorders; (3) Patients with abnormal heart, lung, liver, or kidney function.

This study was approved by the hospital ethics committee (2018-12-19), and the patients and their family members signed an informed consent form after being fully informed of the purpose and process of the study.

Method

Patients in the two groups were given 0.2 g butylphthalide soft capsule (manufacturer: CSPC NBP Pharmaceutical Co., Ltd.; SFDA approval no.: H20050299; Specification: 0.1 g * 24/bottle), 3 times/d. Those in the experimental group were additionally given modified tonic exercise therapy. The specific measures were as follows: (1) The patients were given butylphthalide soft capsule with the same dosage and usage as the control group; (2) Patients were instructed to perform joint activities for 3 hours per day, and during the treatment period, the patient's upper extremity was limited to hand movements with an arm sling; (3) Patients were given shaping training to exercise their upper limb ability, and they were also instructed to perform exercises according to their actual condition, including screwing, holding wooden pegs, using spoons and chopsticks, and flipping cards, 3 h/d; (4) Patients were instructed to perform trunk muscle control exercises, hip joint control exercises, knee joint exercises, and passive activity connection, 1 h/d; (5) Patients were instructed to adopt shaping training to train the lower limb ability, including bounce walking, crossing obstacles, single-leg weight-bearing walking, and lower limb joint flexion and extension at a frequency of 3 h/d.

Patients in both groups were treated for 2 months.

Outcome measures

The clinical efficacy of the two groups was compared. A decrease in the patient's NIHSS score over 90% after treatment is considered a cure. A decrease in NIHSS score between 45% and 90% after treatment is considered markedly effective. A decrease in NIHSS between 8% and 44% after treatment is considered effective. A decrease in NIHSS score less than 8% after treatment is considered ineffective.

Table 1. General information in the two groups

	Experimental group (n=45)	Control group (n=45)	x^2 or t	*P*-value
Mean age (years)	61.25±3.32	61.33±3.29	0.115	0.909
Gender			0.194	0.660
Male	30 (66.67)	28 (62.22)		
Female	15 (33.33)	17 (37.78)		
BMI (kg/m^2)	26.27±1.59	25.89±1.63	1.119	0.266
Mean disease course (h)	6.12±1.21	6.13±1.11	0.041	0.968
Diseased site				
Basal ganglia	24 (53.33)	22 (48.89)	0.178	0.673
Brain stem	9 (20.00)	11 (24.44)	0.257	0.612
Brain lobe	7 (15.56)	6 (13.33)	0.089	0.764
Cerebellum	5 (11.11)	6 (13.33)	0.104	0.748
Past medical history			0.182	0.670
hypertension	27 (60.00)	25 (55.56)		
diabetes	18 (40.00)	20 (44.44)		
Place of residence			0.050	0.822
Urban area	31 (68.89)	30 (66.67)		
Rural area	14 (31.11)	15 (33.33)		

Total efficacy = (The number of patients with cured + markedly effective + effective)/Total number of patients ×100%.

The endothelial injury indicators of the two groups were compared. Fasting venous blood was collected from each patient in the two groups and centrifuged to obtain the serum. The serum levels of endothelin (ET)-1 and D-dimer (D-D), and soluble thrombomodulin (sTM) were determined using an enzyme-linked immunosorbent assay (ELISA).

Molecular indicators of oxidative stress were compared between the two groups. Early morning fasting venous blood was collected from each patient in the two groups and centrifuged to obtain the serum which was then stored at -80°C. According to the ELISA kit instructions, the levels of quinone oxidoreductase (NQO) 1 and heme oxygenase (HO)-1 in the serum were determined.

The incidence of adverse reactions of drugs, including dizziness, nausea, and loss of appetite, was compared between the two groups.

Total incidence = (The number of patients with dizziness + nausea + loss of appetite)/Total number of patients ×100%.

The quality of life of the two groups of patients was compared after treatment with reference to the Generic Quality of Life Inventory-74 (GQOLI-74) Evaluation Scale [11]. With a total score of 100 points, the scale covers four dimensions: psychological function, physical function, social function, and material life status. Higher GQOLI-74 score indicates a better quality of life.

The Fugl-Meyer Upper Extremity Assessment (FMA) Scale was used to compare the physical activity of patients before and after treatment [12]. With a total score of 100 points, the scale indicates extremely severe dysfunction with 54 points, severe dysfunction with 55-84 points, moderate dysfunction with 85-94 points, mild dysfunction with 95-99 points, and normal function with 100 points. A higher score indicates better recovery of the patient's limb movement ability.

The National Institute of Health Stroke Scale (NIHSS) was used to evaluate the brain nerve function of the two groups of patients before and after treatment [13], with a total score of 42 points. A higher NIHSS score indicates more severe neurological damage.

The activities of daily living (ADL) scale was used to compare the patients' ability of daily living before and after treatment [14]. With a total score of 100 points, patients without ability of daily living or unable to carry out physical activities score under 34 points, patients with severe dysfunction in ADL score 35-64 points, patients with moderate dysfunction in ADL score 65-74 points, patients with mild dysfunction in ADL score 75-94 points, and a score of 95-100 points indicates that patients have normal ADL. ADL score is positive correlated with the patient's ability for daily living.

Statistical analysis

The data obtained in this study were analyzed by SPSS20.0 and visualized into required figures by GraphPad Prism 7 (GraphPad Software, San Diego, USA). The results included count data and measurement data. The chi-square test was used to analyze the counted data. Two

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	n	Cured	Markedly effective	Effective	Ineffective	Total effectiveness
Experimental group	45	66.67% (30/45)	17.78% (8/45)	11.11% (5/45)	4.44% (2/45)	95.56% (43/45)
Control group	45	40.00% (18/45)	15.56% (7/45)	17.78% (8/45)	26.67% (12/45)	73.33% (33/45)
x^2						8.459
P-value						<0.05

Table 3. Comparison of endothelial injury indicators between the two groups (x±s)

Group	n	ET-1 (pg/ml)	D-D (μg/ml)	sTM (pg/ml)
Experimental group	45	3.68±0.75	0.43±0.03	5.25±1.02
Control group	45	5.02±1.13	0.71±0.07	8.71±2.72
t		6.628	24.663	7.989
P-value		<0.001	<0.001	<0.001

independent samples t-test was used for comparison between groups of measured data, and paired t-test was used for comparison of measurement data within group. P<0.05 was considered significant.

Results

Comparison of general information

There were no significant differences between the two groups of patients in average age, gender, body mass index (BMI), average course of disease, lesion location, past medical history, and place of residence (all P>0.05). See **Table 1**.

Comparison of clinical efficacy

Table 2 shows a significantly higher total clinical efficacy in the experimental group than that in the control group after treatment (P<0.05).

Comparison of endothelial injury indicators

The index of endothelial injury in the experimental group was lower than that in the control group after treatment (P<0.05), as listed in **Table 3**.

Comparison of molecular indicators of oxidative stress

After treatment, the molecular indicators of oxidative stress in the experimental group were higher than those in the control group (P<0.05, **Table 4**).

Comparison of the incidence of adverse reactions

Table 5 shows a lower incidence of adverse reactions in the experimental group than that in the control group (P<0.05).

Comparison of GQOLI-74 score

After treatment, the GQOLI-74 score of the experimental group was higher than that of the control group (P<0.05), as shown in **Table 6**.

Comparison of FMA score

The FMA score of the experimental group was higher than that of the control group after treatment (P<0.05), as presented in **Figure 1**.

Comparison of NIHSS score

After treatment, the NIHSS score of the experimental group was lower than that of the control group (P<0.05), as displayed in **Figure 2**.

Comparison of ADL score

After treatment, the ADL score of the experimental group was higher than that of the control group (P<0.05), as shown in **Figure 3**.

Discussion

Due to the varying nature and location of brain injury caused by stroke, stroke patients may experience varying degrees of cognitive impairment and motor deficits, with hemiparesis being the most common sequela [15, 16]. Relevant literature has found that appropriate treatment measures and rehabilitation therapy within 2 weeks after the onset of the disease can improve the neurologic function and rapid recovery of the patient [17, 18]. Clinically, Ureklin is effective in relaxing blood vessels by increasing cerebral blood hemoglobin content and alleviating inflammatory response. It

Table 4. Comparison of molecular indicators of oxidative stress between the two groups (x±s)

Group	n	NQO1		HO-1	
		Before treatment	After treatment	Before treatment	After treatment
Experimental group	45	0.49±0.08	1.23±0.27	0.47±0.06	1.23±0.23
Control group	45	0.48±0.07	0.75±0.16	0.46±0.07	0.85±0.15
t		0.631	10.259	0.728	9.283
P-value		0.529	<0.001	0.468	<0.001

Table 5. Comparison of the incidence of adverse reactions between the two groups [n (%)]

Group	n	Dizziness	Nausea	Loss of appetite	Total incidence
Experimental group	45	2.22% (1/45)	2.22% (1/45)	2.22% (1/45)	6.67% (3/45)
Control group	45	8.89% (4/45)	6.67% (3/45)	11.11% (5/45)	26.67% (12/45)
x^2					6.480
P-value					<0.05

Table 6. Comparison of GQOLI-74 scores between the two groups (x±s)

Group	n	Mental function	Physical function	Social function	Material life
Experimental group	45	81.44±5.72	84.28±5.78	84.25±6.53	85.63±6.98
Control group	45	62.11±4.68	61.22±4.65	64.88±4.25	64.25±5.71
t		17.545	20.823	16.677	15.904
P-value		<0.001	<0.001	<0.001	<0.001

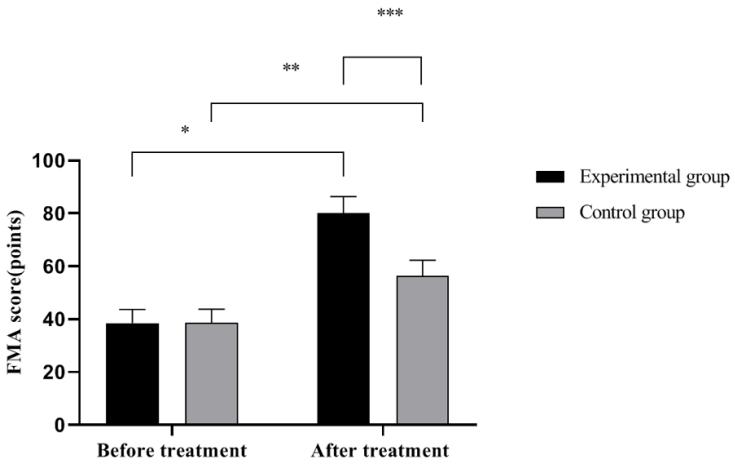

Figure 1. Comparison of FMA scores between the two groups (x±s). Note: The abscissa represents Before and After treatment, and the ordinate represents FMA score (points); The FMA scores of the experimental group before and after treatment were (38.53±5.16) points and (80.12±6.25) points, respectively; The FMA scores of the control group before and after treatment were (38.62±5.19) points and (56.37±5.93) points, respectively; Intra-group comparison showed a significant difference in the FMA scores of the experimental group before and after treatment (t=34.423, *P<0.05); Intra-group comparison showed a significant difference in the FMA scores of the control group before and after treatment (t=15.109, **P<0.01); Inter-group comparison showed a significant difference in FMA scores between the two groups of patients after treatment (t=18.492, ***P<0.001).

releases kininogen through hydrolysis, which is then converted into vasodilators and kinins to increase blood flow and improve the patient's nerve function [19-21]. However, the monotherapy efficiency of ureklin still remains unsatisfactory. Butylphthalide improves the patient's nerve function by effectively reducing the intracellular calcium concentration, inhibiting the release of glutamate and free radicals, and alleviating inflammatory reactions by increasing PGI2 in the patient's vascular endothelium. Moreover, the additional adoption of modified tonic exercise therapy can deliver a higher therapeutic effect to promote the recovery of the patient from the disease [22]. In this study, the treatment efficacy of both groups have been significantly improved, with a better improvement in the experimental group than that in

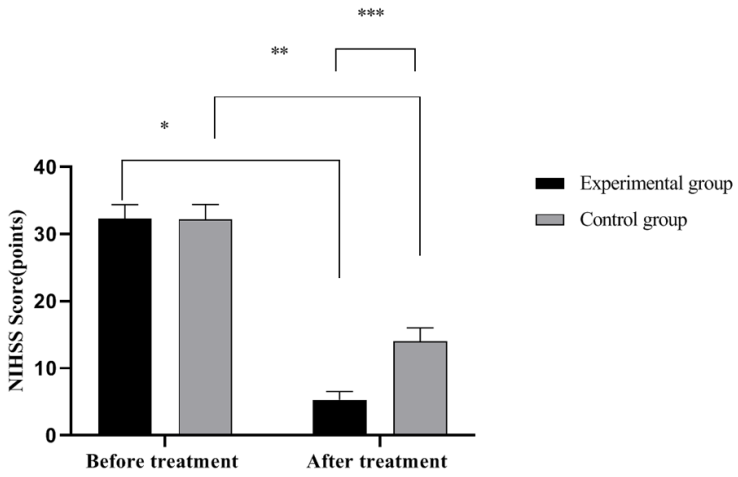

Figure 2. Comparison of NIHSS scores between the two groups (x±s). Note: The abscissa indicates Before and After treatment, and the ordinate indicates the NIHSS score (points); The NIHSS scores of the experimental group before and after treatment were (32.27±2.11) points and (5.32±1.22) points, respectively; The NIHSS scores of the control group before and after treatment were (32.18±2.23) points and (14.02±1.98) points, respectively; Intra-group comparison showed a significant difference in the NIHSS scores of the experimental group patients before and after treatment (t=74.174, *P<0.05); Intra-group comparison showed a significant difference in the NIHSS scores of the control group before and after treatment (t=40.849, **P<0.01); Inter-group comparison showed a significant difference in the NIHSS scores of the two groups of patients after treatment (t=25.094, ***P<0.001).

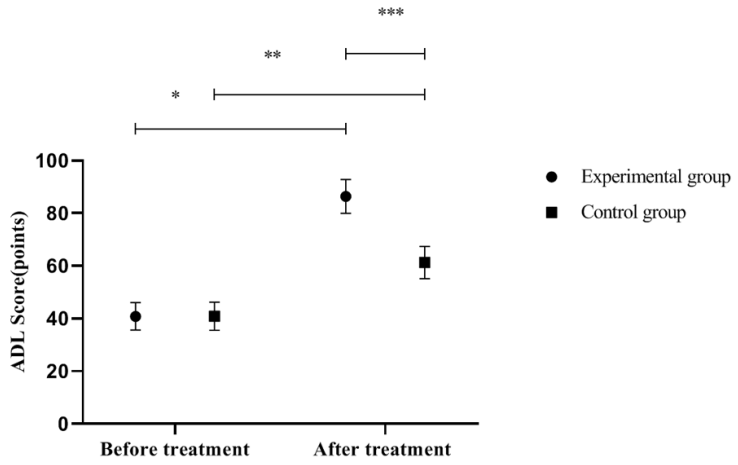

Figure 3. Comparison of ADL scores between the two groups (x±s). Note: The abscissa represents before and after treatment, and the ordinate represents ADL score (points); The ADL scores of the experimental group before and after treatment were (40.83±5.21) points and (86.37±6.45) points, respectively; The ADL scores of the control group before and after treatment were (40.85±5.32) points and (61.27±6.13) points, respectively; Intra-group comparison showed a significant difference in the ADL scores of the experimental group before and after treatment (t=36.845, *P<0.05). Intra-group comparison showed a significant difference in the ADL scores of the control group before and after treatment (t=16.877, **P<0.01). Inter-group comparison showed a significant difference in the ADL scores of the two groups of patients after treatment (t=18.922, ***P<0.001).

the control group, indicating a more robust therapeutic efficacy of butylphthalide soft capsules combined with modified tonic exercise therapy when compared with the single treatment method.

Endothelial injury is a major pathologic feature of stroke hemiplegia, and oxidative stress is a major pathologic change in the development of the disease. Relevant studies have found that insufficient coronary blood supply will damage the vascular endothelial function and thereby accelerate thrombosis. An increase in D-D level indicates that thrombosis persists in the patient due to the blood being in a hypercoagulable state. In addition, the aggravation of the patient's oxidative stress molecular response is closely related to the changes in Keap1-Nrf2/ARE pathway function. In the present study, excimer indicators were significantly higher in the experimental group than those in the control group, indicating a high effectiveness of the combination of butylphthalide soft capsules and modified tonic exercise therapy in alleviating myocardial ischemia, platelet aggregation, and progression of body oxidation-induced stress injury. The incidence of adverse reactions in the experimental group was significantly lower than that of the control group, indicating a high safety profile of butylphthalide soft capsule combined with modified tonic exercise therapy. Modified tonic exercise therapy is a major new type of rehabilitation method that constrains the patient's healthy limb movement and strengthens the movement of the affected limb. It is effective in alleviating the patient's dyskinesia and reorganizing the patient's cerebral cortex function [23]. Prior research has

found that neurologic damage in patients with stroke hemiplegia leads to dyskinesias, and modified tonic exercise therapy effectively improves the patient's limb function and ability to perform daily activities [24]. In addition, modified tonic exercise therapy involves the application of training movements in daily life to eliminate the symptoms of hemiplegia by adjusting the patient's joint and muscle strength. Continuous training substantially improves the function of the affected limb and promotes faster recovery, which ensures a better quality of life. Similar to the results of Yang et al. [25], the efficacy of butylphthalide in the treatment of acute cerebral infarction was investigated using NIHSS scores, GQOLI-74, FMA, and ADL scores, and it was found the treatment methods improved the NIHSS scores, GQOLI-74, FMA, and ADL scores. This fully reinforces that the combination of butylphthalide soft capsules and modified tonic exercise therapy can considerably boost the patients' ability of daily living. With the continuous research on the pathophysiologic mechanisms of cerebral infarction, the inflammatory response has received growing attention in the pathophysiologic process after cerebral ischemia, and inflammation-associated cytokines play an important regulatory role in the inflammatory response after cerebral ischemia. The limitation of this study lies in the absence of exploring the changes in inflammatory indexes, which will be investigated in future studies.

In summary, for patients with stroke hemiplegia, the application of butylphthalide soft capsules combined with modified tonic exercise therapy substantially enhances the patients' ability of daily living, quality of life, and neurologic function.

Disclosure of conflict of interest

None.

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