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Original Article

Effect of butylphthalide on neurological and cognitive functions in the sequential treatment of patients with acute cerebral infarction

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Abstract: Objective: This study aimed to investigate the effect of butylphthalide on cognitive and neurological functions in the sequential treatment of patients with acute cerebral infarction. Methods: A total of 83 patients with acute cerebral infarction admitted to our hospital from June 2018 to June 2019 were divided into the control group (CG, n=41) and the observation group (OG, n=42) by the random number table. Patients in CG were given conventional therapy, while patients in OG were managed with sequential treatment of butylphthalide in addition to the treatment given in CG. Results of neurological function, cognitive function, activities of daily living, as well as transcranial doppler ultrasonography of patients in the two groups were recorded. Results: (1) Neurological function score of OG after 1, 2, and 3 months of treatment were lower than that of CG (P<0.05); (2) Barthel index (BI) for activities of daily living of patients in OG after 1, 2, and 3 months of treatment was higher than those in CG (P<0.05); (3) Scores from the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) of cognitive function of patients in OG after 1, 2, and 3 months of treatment were significantly higher than those in CG (P<0.05); (4) The amount of collateral circulation, which had no significant difference between the two groups before the treatment (P>0.05), increased at the end of treatment in both groups and the amount in OG was more than that in CG, but the between-group variance showed no statistical significance (P>0.05); (5) 3 months after treatment, the cerebral artery Vm in OG was higher than that in CG, while the PI was lower than that in CG (P<0.05). Conclusion: Butylphthalide in the sequential treatment of patients with acute cerebral infarction dramatically improved the cerebral collateral circulation and cerebral blood flow, ameliorated the neurological and cognitive function in a more significant way, and improved the activities of daily living effectively.

Keywords: Acute cerebral infarction, butylphthalide, sequential treatment, neurological function, cognitive function

Introduction

Cerebral infarction is one of the most frequently encountered diseases in the elderly. In the recent years, aging of the population has increased the incidence of cerebral infarction. High morbidity, high disability rate and high mortality are the main characteristics of acute cerebral infarction, bringing a heavy burden to the families and society [1]. Clinical data showed that cerebral infarction has become the leading cause of death in cerebrovascular diseases, seriously threatening the health and life of patients [2].

Patients' brain tissues necrose due to hypoxia and ischemia. Once a softening lesion is formed, the central necrotic zone can never be saved. However, if necrosis has not occurred in the adjacent ischemic penumbra and local tissue can be remedied if an effective collateral circulation compensation is established [3, 4]. The brain tissues will be subjected to severe and irreversible damage if the blood flow is interrupted for more than half an hour. At this point, it is essential to rescue the ischemic penumbra and reconstruct the collateral circulation in the treatment of acute cerebral infarction [5]. In cases where the patient is in an appropriate time window, thrombolytic therapy may lead to a good prognosis, or vascular intervention could be used to restore the blood perfusion. Unfortunately, most patients miss the

timing for thrombolytic therapy and rely on drugs to establish the collateral circulation [6, 7].

Butylphthalide is considered to be valuable in the treatment of acute cerebral infarction. Specifically, the value it provides and the mechanisms it uses in the treatment of acute cerebral infarction have not been elaborated. In this study, 83 patients with acute cerebral infarction were enrolled to investigate the application values of butylphthalide in the sequential treatment of acute cerebral infarction.

Materials and methods

Materials

A total of 83 patients with acute cerebral infarction admitted to our hospital from June 2018 to June 2019 were divided into the control group (CG, n=41) and the observation group (OG, n=42) by the random number table. (1) Inclusion criteria: Patient who met the Standards of Diagnosis of Acute Cerebral Infarction by the Fourth Academic Conference of National Cerebral Vascular Disease [8]; patients with their first onset; patients with aortic atherosclerosis designated by Etiological Type; 18 years old or above; and signed informed consent, could be enrolled. (2) Exclusion criteria: Patients with hemorrhagic lesions found by CT examination; who received thrombolytic therapy; who used alprostadil or urinary kallindinogenase; during pregnancy or breastfeeding; who were allergic to the drugs used in this study; with disturbance of consciousness; had malignant tumor(s) were excluded. This study was approved by the Ethics Committee of our hospital.

Methods

Patients in CG received conventional treatment, including anti-platelet aggregation therapy [dipyridamole (persantine, Specifications: 25 mg * 100 tablets, SFDA Approval No. H44-020689, Manufacturer: Guangdong Huanan Pharma) oral 25-50 mg, 3 times a day] and lipid regulation [Atorvastatin Calcium Tablets (Specification: 5 mg/10 mg * 7 tablets, SFDA Approval No. J20160017, Manufacturer: Hisun Pfizer Pharmaceutical Co., Ltd.) orally 1 tablet a day], for 3 months.

Patients in OG were managed with sequential treatment with butylphthalide in addition to the conventional treatment as given in CG. One hundred ml of Butylphthalide and Sodium Chloride Injection (Specification: 100 ml, SFDA Approval No. H20100041, Manufacturer: Shijiazhuang Pharmaceutical Group dl-3-butylphthalide Pharmaceutical Co., Ltd.) was administered to the patients by intravenous drip, twice a day, and the time interval between the two administration was more than 6 hours, for half a month. Then the therapy was replaced by Butylphthalide Soft Capsules (Specification: 0.1 g * 24 capsules, SFDA Approval No. H20-050299, Manufacturer: Shijiazhuang Pharmaceutical Group dl-3-butylphthalide Pharmaceutical Co., Ltd.), 0.2 g caps 3 times a day for 2.5 months.

Observation indicators

(1) Neurological function: NIH Stroke Scale (NIHSS) [9] was used for evaluation before treatment, 1, 2 and 3 months after treatment of neurological function with 11 items including level of consciousness, best gaze, visual fields, facial palsy, left/right motor arm, and left/right motor leg. The total score range was 0-42. Scores are proportional to the neurologic impairment. A more serious neurological impairment represents a worse neurological function.

(2) Activities of daily living: Barthel index (BI) [10] was used for evaluation before treatment, 1, 2 and 3 months after treatment, for activities of daily living, including bowel/bladder control, stairs, feeding, bathing, dressing, grooming, transferring, toilet use, and mobility. Based on the severity under each variable, scoring of no impact, slightly affected, moderately affected, severe impact, and extreme impact, was given 0, +2, +4, +6, +8, and +10. The total scores are 100. The higher score indicates the better reflection of self-care ability.

(3) Cognitive function: Mini-Mental State Examination (MMSE) [11] and Montreal Cognitive Assessment (MoCA) [12] were used for evaluation of cognitive function before treatment, 1, 2, and 3 months after treatment. MMSE offers 30 questions covering the fields of recall, orientation, attention and calculation, language and memories. Under each question, a right answer was given +1, a wrong answer or not

knowing was given 0. The total score is 30. Scores below 27 indicated the presence of cognitive impairment. A lower score represents a more severe cognitive impairment. MoCA covers the assessment of attention, memory, naming, words and expressions, delayed recall, trail making, abstraction, visuospatial (clock), sentence paraphrasing, orientation, and visuospatial (cube). The total score is 30. Scores below 26 indicated the presence of cognitive impairment; but in case that the patients had less than 12 years of education, scores under 27 indicated the presence of cognitive impairment. A lower score indicates a more severe cognitive impairment.

(4) The establishment of the amount of collateral circulation [13]: Transcranial Doppler (TCD) was used before treatment and 3 months after treatment. Standards for establishment of the posterior communicating artery (PCoA): the velocity in the P1 segment of the affected posterior cerebral artery (PCA) increased by more than one-fifth compared with the contralateral side, and blood flows through the basilar artery and the P1 segment on the affected side increased significantly when the contralateral common carotid artery was compressed. Standards for establishment of the anterior communicating artery (ACoA): the direction of blood flow through the A1 segment, anterior cerebral artery on the affected side is reversed, while that from the opposite side is unchanged, and the velocity of flow increases significantly, but it still reduces at the affected A1 and M1 segments when the contralateral common carotid artery was compressed. Standards for establishment of the leptomeningeal anastomoses (LMA): the velocity in A1, P1 and P2 segments of the affected anterior cerebral artery (ACA) or the affected posterior cerebral artery (PCA) increased by more than 35% compared with the contralateral side. Standards for establishment of the collateral branches of the ophthalmic artery: the direction of blood flow on the affected side of ophthalmic artery is reversed; the velocity reduced when the ipsilateral blood vessels were compressed. The amount of collateral circulation was recorded as the sum of the amount of ACoA, PCoA, OA, and LMA collateral branches.

(5) Mean blood flow velocity (Vm) and pulse index (PI) were measured by TCD before and 3 months after treatment.

Statistical analysis

SPSS22.0 was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. Independent-sample *t* test was used for comparisons between groups. Enumeration data were expressed in [n (%)]. X^2 test was used for comparisons between groups, and ANVOA, F-test was used for intra-group comparisons. $P<0.05$ indicated statistical significance.

Results

General data

There were no significant differences between the two groups in terms of gender distribution ($X^2=0.015$, $P=0.903$), average age ($X^2=0.558$, $P=0.579$), occurrence of various diseases ($X^2=0.852$, $P=0.136$), education, course of disease, and cause of disease ($P>0.05$) (**Table 1**).

Neurological function

Before treatment, NIHSS scores were (22.35±4.19) in OG and (23.19±4.21) in CG. After 1, 2 and 3 months of treatment, the scores were reduced to (17.45±2.95), (14.23±2.34), and (9.86±3.08) in OG, and (20.34±3.03), (17.85±2.53), and (12.46±3.26) in CG, respectively. No significant difference was observed in scores before treatment ($t=0.911$, $P=0.365$). At 1, 2 and 3 months after treatment, OG had significantly lower scores than CG ($t=4.403$, 6.770, 3.736, $P=0.000$, 0.000, 0.000) (**Figure 1**).

Activities of daily living

There was little difference between the two groups with respect to BI scores for activities of daily living before treatment ($t=1.316$, $P=0.192$). At 1, 2 and 3 months after treatment, the BI scores in OG were higher than those in CG with statistical significance ($t=4.168$, 3.855, 4.195, $P=0.000$, 0.000, 0.000) (**Table 2**).

MMSE scores for cognitive function

Before treatment, MMSE scores were (22.39±2.18) in OG and (22.54±2.43) in CG. After 1, 2 and 3 months of treatment, the scores were respectively (26.83±1.84), (27.89±1.26), and (28.63±0.63) in OG, and (23.65±2.02), (25.03±1.13), and (27.41±0.93) in CG. No sig-

Table 1. General data of patients in both groups ($\bar{x}$ ± s)/[n (%)]

Variables		OG (n=42)	CG (n=41)	t/X^2	*P*
Gender	Male	19 (45.24)	18 (43.90)	0.015	0.903
	Female	23 (54.76)	23 (56.10)		
Age (years)		58.96±10.13	60.28±11.41	0.558	0.579
Course of disease (h)		4.68±2.19	4.71±2.26	0.061	0.951
Education (years)		13.56±2.82	13.83±2.49	0.462	0.645
Medical history	Hypertension	10 (23.81)	9 (21.95)	0.852	0.136
	Hyperlipidae-mia	11 (26.19)	10 (24.39)		
	Diabetes	6 (14.29)	7 (17.07)		
	Coronary heart disease	10 (23.81)	9 (21.95)		
	Cerebral stroke	5 (11.90)	6 (14.63)		
Cause of disease	Small artery occlusion	10 (23.81)	11 (26.83)	0.791	0.397
	Atherosclerosis	20 (47.62)	21 (51.22)		
	Cardiogenic cerebral embolism	8 (19.05)	6 (14.63)		
	Others	4 (9.52)	3 (7.32)		

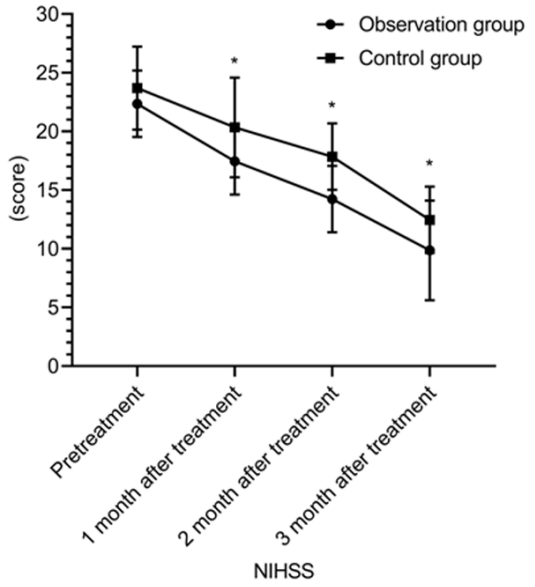

Figure 1. Scores of neurological function between the two groups. Before treatment, there was little difference between the two groups in terms of NIHSS scores (*P*>0.05). At 1, 2 and/or 3 months after treatment, NIHSS scores in OG were notably lower than those in CG (*P*<0.05 for all). * indicates *P*<0.05 from the comparison of NIHSS scores between the groups.

nificant difference was observed in scores before treatment (*t*=0.296, *P*=0.768). At 1, 2 and 3 months after treatment, the scores in OG were higher than those in CG (*t*=7.501, 10.878, 7.012, *P*=0.000, 0.000, 0.000) (**Figure 2**).

MoCA scores for cognitive function

No significant difference was observed in MoCA scores between the two groups before treatment (*t*=1.015, *P*=0.313). At the end of 1, 2 and/or 3 months of treatment, the MoCA scores in OG were higher than those in CG (*t*= 4.218, 8.558, 17.430, *P*=0.000, 0.000, 0.000) (**Table 3**).

The amount of collateral circulation

Before treatment, the number of open collaterals for ACoA, PCoA, OA, and LMA was 7, 5, 1, and 5 in OG, and 8, 4, 1, and 5 in CG, respectively. After treatment, the number of open collaterals for ACoA, PCoA, OA, and LMA was 12, 7, 2, and 10 in OG, and 11, 5, 1, and 9 in CG. There was not significant differences in collateral circulation before treatment between the two groups (X^2=0.114, 0.099, 0.000, 0.002, *P*=0.736, 0.753, 0.986, 0.968). Both groups showed an increase after treatment, but the difference was not significant (X^2=0.031, 0.335, 0.321, 0.041, *P*=0.859, 0.562, 0.571, 0.840) (**Figure 3**).

Blood flow velocity and pulse index

Before treatment, the Vm in the cerebral artery of patients was (106.38±5.13) cm/s in OG and (105.72±4.96) cm/s in CG; PI of patients was (0.82±0.13) in OG and (0.81±0.12) in CG. At 3 months after treatment, the Vm in the cerebral artery of patients was (117.82±3.26) cm/s in OG and (110.36±2.89) cm/s in CG; PI was (0.72±0.07) in OG and (0.78±0.09) in CG. Before treatment, there was little difference in Vm and PI between the two groups (*t*=0596, 0.364, *P*=0.553, 0.717). After 3 months of treatment, the Vm in the cerebral artery in OG

Table 2. BI scores for activities of daily living before and after treatment of patients in both groups ($\bar{x} \pm s$, points)

Groups	Cases	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
OG	42	38.69±5.46	56.86±6.39*	65.78±7.23*	79.82±8.13*
CG	41	37.15±5.19	51.37±5.57*	59.83±6.82*	72.63±7.46*
T		1.316	4.168	3.855	4.195
P		0.192	0.000	0.000	0.000

Note: *P<0.05, as compared with that before treatment.

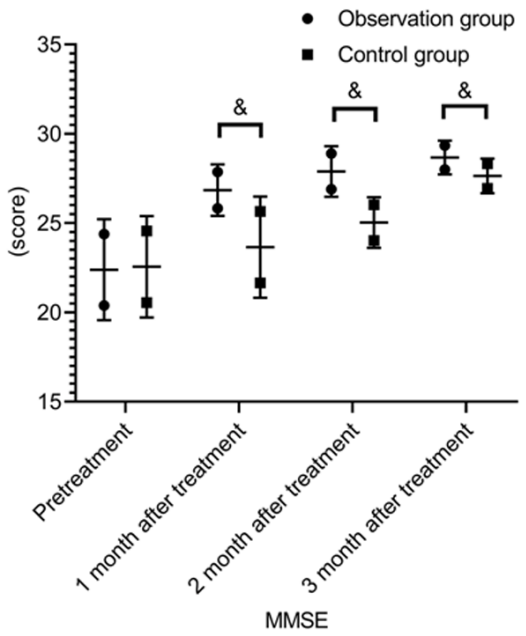

Figure 2. Scores of cognitive function between the two groups. Before treatment, there was little difference between the two groups in terms of MMSE scores (P>0.05). At 1, 2 and/or 3 months after treatment, MMSE scores in OG were notably higher than those in CG (P<0.05 for all). & indicates P<0.05 from the comparison of MMSE scores between the groups.

were higher than that in CG, while PI in OG was lower compared with the CG. The differences were statistically significant (t=11.022, 3.395, P=0.000, 0.001) (**Figures 4** and **5**).

Discussion

Although it is essential to rescue the ischemic penumbra for the treatment of acute cerebral infarction, effective methods such as thrombolysis or vascular intervention are subjected to limited time windows, which means that patients who fail to receive timely medical treatment lose the opportunity of thrombolysis and/or vascular intervention [14]. Besides, after the thrombolytic therapy, they could be prone to various severe complications such as re-occlusion, cerebral reperfusion injury, and intracranial hemorrhaging leading to death [15]. Furthermore, vascular intervention brings high surgical risks and hospitalization costs, and some patients may be reluctant to accept it [16]. Therefore, new therapies that are effective, have low-cost and high safety for the treatment of acute cerebral infarction are needed.

Butylphthalide is a self-developed drug in China with positive effects on different pathological stages of acute ischemic stroke [17]. Butylphthalide is a fat-soluble synthetic drug with unique anti-ischemic effects and multiple targets through the hemato-encephalic barrier [18]. Animal experiments showed that butylphthalide may increase the cerebral blood flow, contribute to the reconstruction of collateral microcirculation, and promote the recovery of brain cell function in rats with acute cerebral infarction [19]. Pathological studies have shown that butylphthalide has an effect on the mitochondria in nerve cells to increase the activities of superoxide dismutase, Ca^{2+}-Mg^{2+}-ATPase, and Na^{+}-K^{+}-ATPase, which can delay and even prevent lipid peroxidation. The release of cytochrome C is controlled by the regulation of the electron transport chain, and the caspase-3 activity is decreased so as to accelerate cell apoptosis [20]. Among the research with butylphthalide and its mechanism of actions, some animal experiments have indicated that butylphthalide plays a role in several pathological processes of stroke [21]. Butylphthalide weakens the permeability of the hemato-encephalic barrier in rats with cerebral infarction to relieve the pain of cerebral edema. At the same time, it elevates the expression of vascular endothelial growth factors. These, in turn, significantly improve the neurologic impairment and the size of cerebral infarction [22].

In this paper, the patients in OG were given sequential treatment with butylphthalide in addition to conventional therapy. The results sh-

Table 3. MoCA scores of cognitive function before and after treatment of patients in both groups ($\bar{x} \pm s$, points)

Groups	Cases	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
OG	42	23.63±2.13	27.02±1.63*	28.72±1.01*	29.12±0.35*
CG	41	23.15±2.18	25.62±1.38*	26.85±0.98*	27.45±0.51*
T		1.015	4.218	8.558	17.430
P		0.313	0.000	0.000	0.000

Note: *$P < 0.05$, as compared with that before treatment.

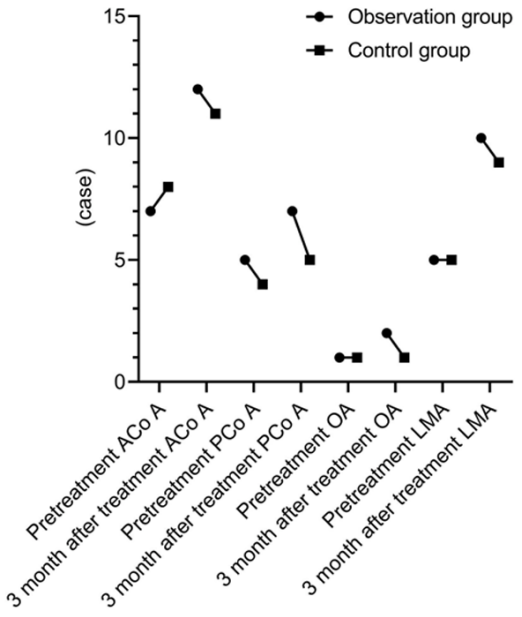

Figure 3. The amount of collateral circulation in both groups. Before treatment, there was little difference between the two groups in terms of the amount of collateral circulation from ACoA, PCoA, OA, and LMA (*P*>0.05). The same was applicable to that at the end of 3 months of treatment (*P>0.05*).

owed that at the end of 1, 2 and/or 3 months of treatment, the neurological scores, BI scores and MMSE and MoCA scores for cognitive function in OG were higher than those in CG (*P*<0.05), suggesting that sequential administration of butylphthalide reduces neurologic impairment and improves cognitive disorders. As a result, the activities of daily living of the patients have been improved. It could be explained by the fact that butylphthalide inhibits the reaction of xanthine-xanthine oxidase by suppressing the formation of glutamic acid and arachidonic acid, provides effective protection for neurons with the control of superoxide anions so as to achieve angiectasis and improve microcirculation, and accelerates the formation of new blood vessels by elevating the expression of hypoxia-inducible factor-1α and vascular endothelial growth factors. In this way, the neurological function, cognitive function, and activities of daily living of the patients were recovered and enhanced [23]. PI reflects the vascular resistance and reactive vasomotion, which was associated with peripheral systolic pressure, hypertension, age, and insulin resistance. Increased PI also indicates the cerebral blood perfusion [24]. Vm in the cerebral artery is used to estimate the cerebral perfusion, and a clear decrease of Vm indicates cerebral hypoperfusion [25]. In this study, the amount of collateral circulation established at 3 months after treatment in both groups was greater than that before treatment, and the circulation in OG was superior to that in CG. However, no statistical significance was found between the groups (*P*<0.05), which may be due to the small size of samples used in the study. Nevertheless, it was still confirmed that the sequential treatment of acute cerebral infarction with butylphthalide promotes the improvement of collateral circulation through the above three main collateral branches, and achieves microcirculation improvement through the behaviors on multiple pathological links. The reconstruction of collateral circulation also accelerates the recovery of neurological function [26].

In summary, butylphthalide in the sequential treatment of acute cerebral infarction significantly improves the collateral circulation and cerebral blood flow, while further accelerating the recovery of neurological and cognitive functions as well as improving the activities of daily living. However, this study also has certain limitations, which are reflected in the fact that it is a retrospective study with a small size of samples. In addition, the study on the mechanism of butylphthalide on acute cerebral infarction is not thorough and comprehensive enough. Further in-depth studies with large sample size should be carried out to focus on a prospective study and obtain more scientific and representative research conclusions, thus providing

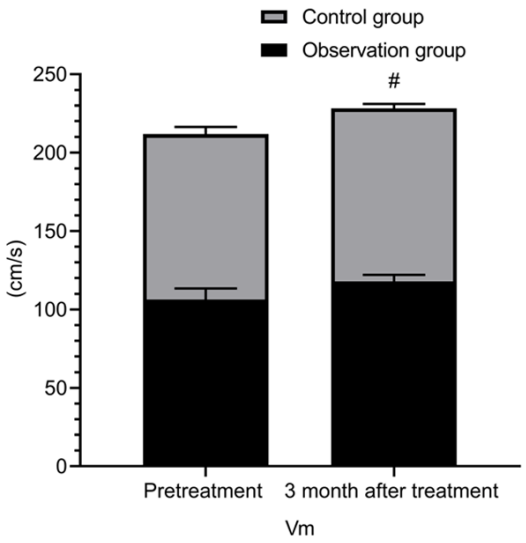

Figure 4. Vm in the cerebral artery of patients in both groups. Before treatment, there was little difference between the two groups with respect to Vm in the cerebral artery (P>0.05). At the end of 3 months of treatment, the Vm in OG was higher than that in CG (P<0.05). # indicates P<0.05 from the comparison of groups.

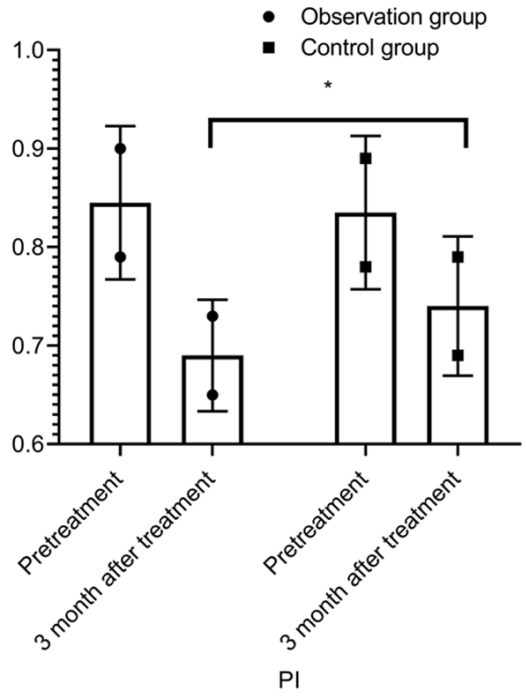

Figure 5. PI in the cerebral artery of patients in both groups. Before treatment, there was little difference between the two groups with respect to PI in the cerebral artery (P>0.05). At the end of 3 months of treatment, the PI in OG was lower than that in CG (P<0.05). * indicates P<0.05 from the comparison of groups.

more guidance for the treatment of patients with acute cerebral infarction.

Disclosure of conflict of interest

None.

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