The influence and clinical effect of Dl-3-butylphthalide on cerebral blood perfusion images in patients with acute ischemic stroke

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Abstract: Objective To observe the influence and clinical effect of Dl-3-butylphthalide on cerebral blood perfusion images in patients with artery stenosis or occlusion acute ischemic stroke. **Methods** 45 patients with artery stenosis or occlusion acute ischemic stroke were divided into control group (24 cases) and treatment group (21 cases) randomly, all the 45 patients were given standard treatment, and patients in treatment group were given Dl-3-butylphthalide soft capsules besides standard treatment. NIHSS, MMSE, serum hs-CRP and Hcy concentration and cerebral computed tomography perfusion were observed one month before and after treatment. **Results** 1.After one month of treatment, serum hs-CRP and Hcy concentration in treatment group decreased significantly compared with the control group ($P< 0.05$); 2. NIHSS and MMSE in treatment group improved significantly compared with the control group ($P< 0.05$); 3. regional cerebral blood flow (rCBF) of cerebral perfusion imaging in infarction center region increased significantly compared with prior treatment, and the growth rate was larger than the control group ($P< 0.05$), rCBF、rCBV of cerebral perfusion imaging in infarction ischemic penumbra region increased significantly compared with prior treatment, and the growth rate was larger than the control group. **Conclusion** The clinical effect of Dl-3-butylphthalide in patients with acute ischemic stroke is definite, Dl-3-butylphthalide improves the cerebral blood perfusion imaging in infarction center and ischemic penumbra region effectively, the improvement is much better in infarction ischemic penumbra region in the form of significant increase of rCBF and rCBV value.

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Introduction

With the development of CT technology and the improvement of processing function in recent years, CT perfusion (CTP) which aims to observe the cerebral blood flow perfusion conditions has been paid more and more attention. The common etiology of acute ischemic stroke is macroangiopathy, the infarction caused by cerebral artery stenosis or occlusion is more likely to happen, the condition is more serious, and the disability rate and recurrence rate is higher. This study aims to explore the effect of cerebral hemodynamics and investigate clinical effect of Dl-3-butylphthalide on cerebral blood perfusion images by observing the change of cerebral blood perfusion images in patients with acute ischemic stroke.

1. Materials and methods

1.1 general materials

45 patients with acute ischemic stroke who were hospitalized in the First Affiliated Hospital of Xinxiang Medical University from October 2012 to December 2013 were all middle cerebral artery disease. The entry criteria were as follows, patients were the first onset, onset time was less than 72 hours, the diagnosis met the diagnostic criteria of the Fourth National Academic Conference on cerebrovascular disease, and all patients were diagnosed by skull CT OR MRI. The exclusion criteria were as follows, 1. patients with cognitive dysfunction and nervous system diseases before onset, 2. patients with other system diseases such as heart disease, cancer and other diseases, patients who never used folic acid, vitamin B6 and vitamin B12 and other drugs before onset, 3. patients who could not complete the medication and cognitive function assessment scale for physical disabilities or serious illness.

1.2 methods

1. Survey of stroke scale was designed, including general materials on all patients. The conventional blood examination and serum Hcy concentration were determined by empty stomach blood in the morning of the second day after hospitalization. Serum biochemical, hs-CRP and Hcy concentration were detected by Hitachi 7060 automatic biochemical analyzer. Serum Hcy concentration was detected by assay kit (Mike biological technology Co. ITD) enzymatic cycling method (reference value was 0-10umol/ L). Serum hs-CRP was detected by immune turbidimetric test (reference value was 0～3 mg/ L). 2. All the patients were scored. Patients who meet the criteria were

evaluated by trained neurological physicians using NIHSS and MMSE one month after hospitalization. 3.Skull MRI were examined by Philips Intera Achieva 3.0T superconducting magnetic resonance scanner and Toshiba Aquilion ONE 320 slice CT scanner. Non ionic contrast medium Ultravist 300 (Bayer healthcare Co. Ltd, country medicine accurate H10970164) was injected via elbow vein by high pressure injector and 19G needle, the injection speed was 5 ml/s, the dose was 40 ml. Basal ganglia was chosen by CT scan to carry on the CTP examination. Scanning parameters were as follows, 80 Kv, 209 mAs, 512×512 of matrix, 12mm of layer thickness, scanning was began 4 second delay, the total scan time was 40 s (2 layers a second, 40 dynamic images). Parameter acquisition scanning data and images were processed by Toshiba Vitrea2 work station, the superior sagittal sinuses of the same level were selected as the output vein in order to obtain the perfusion images including cerebral blood flow (CBF), cerebral blood volume (CBV), and time to peak (TTP). The interest region was drawn on both sides of the middle cerebral artery distribution area, CBF, CBV and TTP of interest region were obtained. Reference region was selected to calculate relative perfusion value. Parameter values of affected side was compared with corresponding healthy side, the ratio was calculated, rCBF, rCBV and rTTP relative perfusion values were calculated. 4. Patients in all groups were given standard treatment, patients in treatment group were given oral Dl-3-butylphthalide soft capsules besides standard treatment, 3 times a day,0.2 g a time, a month was a treatment course.

1.3 Statistical processing Statistical method

All data was processed by SPSS13.0 statistical software, Normal distribution data was processed by t test, the result was indicated by $\bar{\chi} \pm s$, comparison of proportions was processed by χ^2 test, significant level was $\alpha = 0.05$.

2. Results

2.1 Comparison of general clinical data in two groups

Table 1: general clinical data in two groups

	Treatment group n=21	control group n=24
Male(%)	14（66.7%）	17（70.8%）
Age(y)	55±4.46	57±5.32
Middle school and above	8（38.1%）	11（45.8%）
Smoking(%)	9（42.6%）	10（41.7%）
alcoholism(%)	6（28.6%）	7（33.3%）
hypertension(%)	14（67.7%）	13（54.2%）
diabetes(%)	4（19.0%）	6（25.0%）
Cholesterol（mmol/L）	6.45± 0.33	6.81± 1.53
Triglyceride（mmol/L）	2.40± 1.33	2.62± 0.75
Low density lipoprotein（mmol/L）	3.64± 1.67	3.35±1.25
Infarct volume(cm3)	15.4±6.68#	13.50±4.36

Compared with the control group, $P < 0.05$.

2.2 Comparison of serum hs-CRP and Hcy concentration in two groups

The difference of serum hs-CRP and Hcy concentration in treatment and control group was significant statistically ($P<0.05$).

Table 2: The difference of serum hs-CRP and Hcy concentration in treatment and control group

Group	n		Hcy（umol/L）	hs-CRP(mg/L)
control group	24	before treatment	28.3±3.16	6.13 ±3.72
		after treatment	19.5±4.33*	4.58 ±2.40*
treatment group	21	before treatment	26.7± 4.25	6.28±2.93
		after treatment	13.5± 3.31*#	3.35±1.72*#

Compared with the control group, $P < 0.05$, compared with the same group before treatment, *$P<0.05$

2.3 Comparison of cerebral perfusion imaging relative value of infarction center region and penumbra region in two groups (Table 3, 4), the difference was significant statistically (P<0.05). Illustrate representative patients from the treatment group (Figure 1 and 2).

Table 3: Comparison of cerebral perfusion imaging relative value of infarction center region in two groups

Group	n		rCBF	rCBV	rTTP
control group	24	before treatment	0.63±0.16	0.45 ±0.73	1.05 ±0.73
		after treatment	0.54±0.32	0.58 ±0.52	1.15 ±0.42
treatment group	21	before treatment	0.71± 0.25	0.42±0.34	1.03 ±0.24
		after treatment	1.18± 0.20*#	0.32±1.83	1.32 ±0.33

Compared with the control group, P < 0.05, compared with the same group before treatment, *P<0.05

Table 4: Comparison of cerebral perfusion imaging relative value of infarction penumbra region in two groups

Group	n		rCBF	rCBV	rTTP
control group	24	before treatment	2.36±1.16	1.75 ±2.23	1.25 ±1.73
		after treatment	2.45±2.32	1.08 ±2.52	1.35 ±1.13
treatment group	21	before treatment	2.70± 1.25	1.29±1.94	1.05 ±0.73
		after treatment	3.35± 2.20*#	2.32±0.83*#	0.96 ±0.83

Compared with the control group, P < 0.05, compared with the same group before treatment, *P<0.05

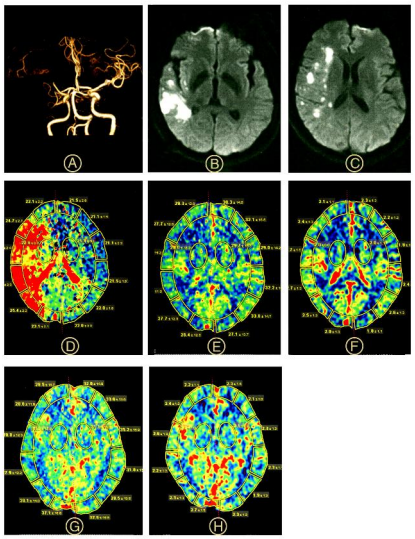

Figure1. Case 1, male, aged 53, Slurred speech, paralysis of the right limbs for 14 hours
(A)M1 segment of the right middle cerebral artery was occluding. (B and C)DWI showed a right temporal lobe infarction. CTP showed TTP(D) was obviously abnormal. After treatment, rCBF(G) and rCBV(H) were improved than rCBF(E) and rCBV(F) before treatment.

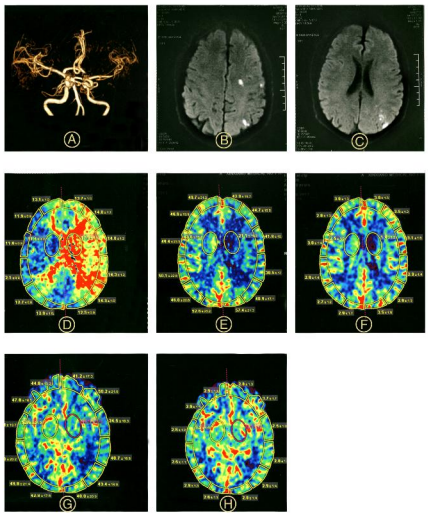

Figure 2: Case 2, male, aged 41, left limbs activity problems for 8 hours,
(A) The left middle cerebral artery was stegnotic. (B and C) DWI showed multiple infarction focus in left temporal parietal. CTP showed TTP(D) was obviously abnormal. After treatment, rCBF(G) and rCBV(H) were improved than rCBF(E) and rCBV(F) before treatment.

2.4 NIHSS and MMSE score before and after treatment in two groups and the score after treatment in control group (table 5) the difference was significant statistically (P<0.05).

Table 5: NIHSS and MMSE score before and after treatment in two groups and the score after treatment in control group

Group	n		NIHSS	MMSE
control group	24	before treatment	9.82±6.16	11.05 ±3.73
		after treatment	5.56±4.32*	20.68±2.50*
treatment group	21	before treatment	8.71± 5.25	11.29±2.94
		after treatment	3.34± 3.20*#	24.32±1.83*#

Compared with the control group, $P < 0.05$, compared with the same group before treatment, *$P<0.05$

3. Discussion

High Hcy stimulates the proliferation of vascular smooth muscle cells, destroys coagulation and fibrinolysis system balance by causing vascular endothelial cell injury and dysfunction, it makes the body in the prethrombotic state and eventually leads to the higher risk of cardiovascular and cerebrovascular diseases by affecting lipid metabolism. Hcy not only damages endothelial cells of great vessels such as carotid artery, but also damages brain perforating small vessels, and eventually lead to different types of cerebral infarctions. Eikelboom et al[4] found the correlation between high Hcy hyperlipidemia and large artery disease was the strongest, the next was small artery disease. Tan et al[5] found Plasma Hcy of large artery disease was higher than that of small artery disease in patients with acute cerebral infarction younger than 50. Conclusion of foreign research[7-8] showed high hcy not only had close relationship with serum in large artery disease, but it also had a close relationship with progressive stroke. The domestic research thought the incidence of high Hcy in young people was higher, therefore, prevention and treatment of high Hcy in young people were particularly important.

Leys D et al[5] observed cognitive dysfunction was more common than stroke recurrence after stroke, and dementia affected survival after stroke, the ratio was 30%. More seriously, new dementia ratio increased from 7% to 48% between 1 to 25 years after the stroke. Patients with ischemic stroke are younger in recent years, cognitive dysfunction is more and more common in clinical practice. Clinical research in recent years found plasma Hcy was an independent risk factor of cognitive function impairment for it was closely related to cognitive function impairment[6]. The level had a negative correlation with cognitive function, the cognitive impairment progress was faster when the level of Hcy was higher. High Hcy promoted atherosclerosis, and atherosclerosis had a direct effect on cognitive dysfunction. In addition, high Hcy spured the generation hydrogen peroxide and oxygen free radical, increased oxidative damage of endothelial cells and neurons. Some studies found the increase of plasma Hcy levels could cause damage to the DNA repair function in hippocampal neurons, and enhanced the toxicity of beta amyloid protein in hippocampal neurons, led to its gradual apoptosis, caused the impairment of memory and general cognitive ability, and eventually led to the occurrence of VD. Animal studies showed that the relationship between elevation of Hcy level and cognitive dysfunction was in the form of visual spatial skills, memory, non verbal memory, information processing speed and cognition[8].

Plenty of Studies showed that Dl-3-butylphthalide could block multiple pathogenic links in ischemic brain damage, increase the cerebral blood flow and rebuild the microcirculation in ischemic region, it could regulate cerebral energy metabolism under the condition of cerebral ischemia and hypoxia, reduce the apoptosis of brain cells, it could stimulate the recovery of neuronal function cognitive function after cerebral ischemia[9]. It had obvious therapeutic effect on ischemic cerebral infarction[10]. This experiment found Serum Hcy, hs-CRP levels in treatment group were lower than control group significantly ($P < 0.05$), the NIHSS score improved significantly compared with control group ($P < 0.05$). This illustrated Dl-3-butylphthalide improved symptoms of neurological deficit, inhibited the inflammation reaction in atherosclerosis, maybe the mechanism of action was improving the injury of vascular endothelial cell and protecting neuronal function. General cognitive function score improved significantly in treatment group one month after treatment ($P < 0.05$). Foreign researches showed that 44% to74% patients had cognitive impairment 6 months after stroke[11-13]. Meta analysis of ischemic stroke in 18-50 year old patients showed that 50% patients had long-term cognitive impairment, memory, attention and speed of information processing were the most common defects after 11 years of follow up [14]. The difference of cognitive function improvement degree was not significant one month after stroke, whether the difference would be more significant with time was worthy to research in the future.

Cerebral CT perfusion technique could be used to distinguish the infarction center and surrounding penumbra, the concept of penumbra was from MRI in medical imaging, No matching area of MRI perfusion weighted and diffusion weighted in hyperacute stroke was composed of low perfusion area around the infarction center, in this danger region, neurons survived for only a few hours, large number of nerve cells would be necrosis gradually beyond the therapeutic time window. Therefore, restoring the reperfusion injury salvage penumbra was the most important in the treatment of acute cerebral infarction. Reperfusion could achieve the goal of treatment by carrying the drug into the lesion area, most patients with cerebral ischemia reperfusion were healthy in the local. MurPhy et al [15] determined the penumbra and infarct core area by using different CBF and CBV threshold, many scholars[16,17~19] studied the different superiority of the application of CTP in acute cerebral infarction and ischemic diseases.

Bivard et al[20] found brain CTP parameter differences of the lesion side and uninjured side was significant, CBF and CBV had the higher specificity to determine infarction and had the more accurate judgment to determine the position of the center of cerebral infarction. This study observed the parameters before and after treatment of unilateral middle cerebral artery disease in patients with acute ischemic stroke, studied the improvement of cerebral hemodynamics. The related parameters of cerebral perfusion improved significantly in central and penumbra region after treatment in 21 patients using Dl-3-butylphthalide, rCBF increased significantly in infarction area, rCBF and rCBV increased significantly in central and penumbra region, the improvement was significant. This showed reperfusion occurred in infarction tissue after treatment of Dl-3-butylphthalide, maybe the significant reduce of neural function defect and advanced intelligent disorder after treatment was due to the change of pharmacological action.

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