Clinical Efficacy and Safety of Joint Butylphthalide and Human Albumin Treatment of PTCI

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Abstract: Objective: To observe the clinical efficacy and safety of butylphthalide joint human albumin in the treatment of the progress of type in acute cerebral infarction(PTCI). Methods: 120 patients with PTCI in Department of Neurology of Shuyang People's Hospital were used to observe the efficacy. These patients were all treated by routine medicine including anti-platelet, statins, edaravone, ginkgo leaf extract and dipyridamole after admission. According to whether used butylphthalide and(or) human albumin in the treatment of PTCI, the patients were divided into A group 30 cases, B group 45 cases, and C group 45 cases.Patients of group C were given conventional treatment. Group B were given conventional treatment and human albumin injection(5 g, ivgtt, qd, 3 days in a course); Group A were treated with butylphthalide (first, with butylphthalide and sodium chloride injection 100 ml, ivgtt, for 7 d, then with butylphthalide soft capsules 0.2 g, tid, for 21 d), human albumin(5 g, ivgtt, qd, for 3 d) and routine medicine. The change of NIHSS score, Barthel Index, and mRS of three groups respectively during progress,1 week, 2 weeks and 90 days after progress were observed and analyzed. Results: NIHSS score, Barthel Index, and mRS of group A, group B and group C all showed no statistically significant (all $p > 0.05$) on 1 week after treatment; NIHSS score and mRS of group A were both lower than group B and group C on 2 weeks and 90 days after treatment, and both of them showed statistically significant ($p < 0.05$); Barthel Index of group A was higher than group B and group C on 90 days after treatment,it showed statistically significant ($p < 0.05$); The total effective rate of group A(96.7%) > group B(88.9%) > group C(77.8%),showed statistically significant ($p < 0.05$). Conclusions: Butylphthalide joint human albumin treatment of PTCI has good therapeutic effect and safety, it is useful to clinical promotion and further research.

Keywords: Butylphthalide; Human albumin; PTCI

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1. Introduction

Progressive type of cerebral infarction (PTCI) is a cerebral infarction, which is progressive aggravation of neurological impairment within 6 hours to 1 weeks in patients with cerebral infarction, or the progression of the disease is still after active treatment. PTCI accounts for about 20% to 40% of all ischemic cerebrovascular patients, and the morbidity and mortality are significantly higher than those of stable cerebral infarction, which seriously affects the prognosis of patients with cerebral infarction. Application of butylphthalide injection (Shijiazhuang Pharmaceutical Group dl-3-butylphthalide Pharmaceutical Co. Ltd.) combined with human serum albumin (Wuhan Biological Products Research Institute Co., Ltd.) on the treatment of PTCI in our department to achieve good results.

2. Data and Methods

2.1 General Information

The cases were from 120 pataients with PTCI in neurology department of Shuyang People's Hospital of Jiangsu Province from January 2014 to January 2017. The general clinical data of the patients were age, sex, admission to infarct progression time, the risk factors cerebrovascular such as hypertension, diabetes, smoking and hyperlipidemia, and the blood pressure, blood glucose and blood lipids at admission. The patients were divided into three groups, there were 14 males and 16 females in group A, 20 males and 25 females in group B, 25 males and 20 females in group C.

2.2 The Set of Standard

(1) Between the ages of 18-80; (2) the onset time is with-

in 4.5-48 hours; (3) the diagnostic criteria of all patients were consistent with the standard of PTCI[1]; (4) able to cooperate with the NIHSS score checker; (5) understand and agree with this study.

The exclusion criteria include these: (1) The patients with arterial thrombolysis, embolectomy or fibrinolysis; (2) the patients with cardiac insufficiency; (3) the patients with severe hepatorenal insufficiency, malnutrition and electrolyte disturbances; (4) refusal to cooperate with the NIHSS score checker.

2.3 Treatment Method

All patients were immediately given aspirin enteric-coated tablets 300 mg or clopidogrel hydrogen sulfate tablets 300 mg (aspirin enteric-coated tablets 100 mg, qn + clopidogrel sulfate tablets 75 mg, qd were given the next day and later), atorvastatin calcium (40 mg, qn), alprostadil, edaravone, ginkgo dipyridamole, with regulating blood sugar, blood pressure, rehabilitation and other conventional treatment, and the total course of treatment is 14 days.

Group A was included in 30 patients (14 males and 16 females): given butylphthalide (sodium butyryl phthalate 100 ml, intravenous drip 2 times / day for 1 week, after change to butyl phthalate soft capsules 0.2, 3 times/ Day for 21 days) + human serum albumin (5 g, intravenous drip, 1 times / day for 3 days) + conventional therapy; Group B was included in 45 patients (20 males and 25 females): given human serum albumin (5 g, intravenous drip, 1 time / day for 3 days) + conventional therapy; Group C was included in 45 patients (25 males and 20 females): given conventional therapy.

2.4 Observation Index

The neurological deficits were scored using the National Institutes of Health Stroke Scale (NIHSS), the daily living ability was assessed using the Barthel Index (BI), and the degree of disability and the total effective rate for 90 days of pataints was assessed with Modified Rankin Scale (MRS) at the progress of cerebral infarction, 1 week, 2 weeks, and 90 days after treatment.

2.5 Criteria of Curative Effect

According to the criteria of clinical neurological deficit score in patients with stroke assessment(1995)[2]. Essentially recovered: functional defect score decreased by 46% to 90%; ignificant progress: functional defect score decreased by 18% to 45%; no change: functional defect score decreased by about 17%; deterioration: functional defect score decreased or increased by more than 18% or died. Total effective rate = (basic recovery + significant progress + progress) / total number of cases × 100%.

2.6 Statistical Method

SPSS24.0 statistical software was used used for statistical analysis of all data. The count data were represented in frequency or rate, and χ^2 tests were used between groups; the measurement data were expressed by mean standard deviation (x + s), and the three groups were compared by variance analysis and after two two comparison. The difference of $P < 0.05$ was statistically significant.

3. Conclusion

3.1 Baseline Data of Three Groups of Patients

As shown in Table 1, there was no significant difference in the baseline data (age, sex, time of admission to infarct progression, history of hypertension, history of diabetes mellitus, hyperlipidemia, smoking history and blood pressure, blood glucose and blood lipids) between the three groups, and no statistically significant .

3.2 Comparison of the Scores Between the 1 Week of Treatment and the Progression of the Same Group

There was no significant difference in NIHSS（8.93 ± 3.12，9.69 ± 2.88，9.51 ± 3.29）、BI（34.00 ± 24.93，30.56 ± 19.69，33.89 ± 22.51）、mRS (3.83 ± 1.12,4.09 ± 0.93,3.91 ± 1.14) between these after 1 week of treatment {NIHSS(9.50 ± 3.18, 10.02 ± 2.95, 9.51 ± 3.29); BI（31.00 ± 24.40, 28.44 ± 20.00, 32.33 ± 21.60); mRS(3.97 ± 1.10，4.13 ± 0.94, 3.93 ±1.10)} of patients in Group A, Group B and Group C, indicating that the improvement of neurological deficit symptoms was not obvious in the three groups after 1 week of treatment.

3.3 Comparison of the Scores Between the 2 Weeks and 90 Days of Treatment and the Progression of the Same Group

The scores of NIHSS, BI and mRS of each group were improved, and there were significant differences ($P < 0.05$) (see Table 2), which indicated that the neurologic impairment are improved after 2 weeks and 90 of treatment.

3.4 Comparison of Scores in Different Groups over the Same Period

After treatment for 2 weeks and 90 days, the NIHSS score and mRS score of group A were lower than those of group B and group C ($P < 0.05$). After 90 days of treatment, BI of group A was significantly higher than that of group B and group C ($P < 0.05$) (see Table 2), indicating that the improvement of neurological impairment in group A was better than that in group B and group C after 2 weeks and 90 days of treatment.

3.5 The Total Effective Rate of the Three Groups was Compared after 90 Days of Treatment

The total effective rate of group A (96.7%) > that of group B (88.9%) > that of group C (77.8%), there was statistical difference (2 = 67.601, P < 0.05) (see Table 3).

3.6 Adverse Reaction

There was no definite adverse reactions occurred in the three groups.

Table 1. Comparison of general baseline data between the three groups

Baseline Data	Group A	Group B	Group C	Test Value	P
Age	64.93±9.03	64.47±8.41	64.71±8.01	0.028a	0.072
Sex(Male/Female)	14/16	20/25	25/20	1.211b	0.546
Admission to infarction progression time (hour)	27.10±6.11	24.91±7.17	24.42±6.92	1.487a	0.23
Hypertension(%)	23(76.7)	35(77.8)	37(82.2)	0.421b	0.81
Diabetes(%)	5(16.7)	13(28.9)	13(28.9)	1.754b 1.754b	0.416 0.416
Smoke(%)	9(30.0)	13(28.9)	15(33.3)	0.221b 0.221b	0.895 0.895
Hyperlipidemia(%)	13(43.3)	21(46.7)	20(44.4)	0.407b 0.221b	0.816 0.816
Systolic pressure (mmHg) Diastolic pressure(mmHg)	141.63±9.84 77.53±9.91	143.0±8.88 78.80±9.17	144.0±9.46 76.33±9.22	0.577a 0.736a	0.563 0.481
Blood sugar(mmol/l)	6.10±1.09	6.20±1.16	6.32±1.20	0.33a	0.718
LDL(mmol/l)	2.68±0.70	2.66±0.70	2.63±0.69	0.056a	0.945
CHOL(mmol/l)	5.16±0.50	5.23±0.54	5.16±0.54	0.228a	0.797
TG(mmol/l)	2.22±0.61	2.23±0.62	2.13±0.59	0.36a	0.699

** [a] is the variance analysis F value; [b] is chi-square test χ^2 value; 1 mmHg = 0.133 kpa; LDL: low density lipoprotein; CHOL: total cholesterol; TG: triglyceride*

Table 2. The NIHSS, BI and mRS scores were compared between the 3 groups after treatment

Group and time	Number	NIHSS	BI	mRS
Group A	30			
Progress time		9.50±3.18	31.00±24.40	3.97±1.10
1 week		8.93±3.12	34.00±24.93	3.83±1.12
2 weeks		5.27±2.32*1	62.83±20.95*1	2.43±0.86*1
90 days		2.57±1.91*1	89.83±12.96*1	1.17±0.79*1
Group B		45		
Progress time		10.02±2.95	28.44±20.00	4.13±0.94
1 week		9.69±2.88	30.56±19.69	4.09±0.93
2 weeks		6.76±2.60*1*2	54.56±20.58*1	2.87±0.94*1
90 days		4.22±2.34*1*2	78.56±17.57*1*2	1.82±0.94*1*2
Group C	45			
Progress time		9.51±3.29	32.33±21.60	3.93±1.10
1 week		9.47±3.35	33.89±22.51	3.91±1.14
2 weeks		8.69±3.40*2	39.22±22.21*2	3.62±1.15*2
90 days		7.24±3.22*1*2	51.11±23.21*1*2	2.93±1.10*1*2

** Compared with the progress in this group, [*1]p < 0.05; Compare with the group A at the same time, [*2]p < 0.05*

Table 3. The total effective rate of the 3 groups was compared after 90 days treatment

Group	Total	Recovered	Significant progress	Progress	Unchanged	Total effective rate	χ^2	*p*
Group A	30	6(20%)	23(76.7%)	0(0%)	1(3.3%)	96.7%		
Group B	45	3(6.7)	29(64.4%)	11(24.4%)	2(4.4%)	88.9%	67.601	*<0.05*
Group C	45	0(0%)	4(8.9%)	31(68.9%)	10(22.2%)	77.8%		

4. Conclusion

PTCI is a cerebral infarction, which is progressive aggravation of neurological impairment within 6 hours to 1 weeks in patients with cerebral infarction, or the progression of the disease is still after active treatment. According to the deterioration of neurological impairment in patients with different time, PTCI can be divided into two types, namely early-onset and late-onset. Davalos etc.[3] It proposed that the Scandinavian Stroke Scale (SSS), awareness score or exercise score was reduced by 2 points in 24 hours or a 3-point was reduced in the language score could be judged as early-onset PTCI, which these ratings were resuced in 24 hours to 1 week was classified as late-onset. The early-onset PCI is more common in clinical practice, Davalos etc.[4] It found that the deterioration of neurological function is the result of multi-factor and multiple mechanisms of interaction in the early stage of cerebral infarction. The cerebral ischemia injury excitotoxin hypothesis suggests that when brain perfusion is reduced, glutamate and glycine transporters can be accumulated in the ischemic region or its surrounding area, which excites specific receptors as excitatory amino acids, leading to sodium ions and calcium ions into cells, triggering a series of biochemical and structural changes, for example mitochondrial is injured, microfilament protein is hydrolyzed, membrane phospholipid destruction, oxygen free radical formation and cell death, thereby aggravating and promoting the damage of ischemic brain tissue. Its mutilation rate and fatality rate are very high, which seriously endangers human health. Thrombolytic therapy is the most effective treatment for acute ischemic stroke, the treatment direction is to open the occlusion of blood vessels, save the ischemic penumbra, PTCI super-thrombolysis window time, it is difficult to clear the pathogenesis in the early stage, and the clinical treatment is difficult, there is no normative clinical treatment standards, so to explore a good treatment strategy is particularly important.

Butylphthalide is a kind of new medicine for the treatment of acute stroke in China. The experimental study of related animals shows that[5-10], butylphthalide is a multi-target anti-ischemic medicine, which can repairs the mitochondrial function, inhibits oxygen free radicals, improves the ability of antioxidant enzymes, reduces the infarct size, improves the degree of neurological impairment, increases regional cerebral blood flow, improves microcirculation and energy metabolism depletion of cerebral ischemia, reduces the cerebral edema caused by cerebral ischemia and play a role in antiplatelet agglomeration. At present, Liying Cui etc.[11] have conducted a multi-center, randomized, double-blind, double-opioid and aspirin-controlled study of dl-3-n-butylphthalide soft capsules for acute ischemic stroke. The study showed that the curative effect of butyphthalide was better than that of aspirin in acute ischemia Stroke treatment on day 11 and day 21, which is evidence of intolerance or inability to use aspirin and confirms the therapeutic status of butyphthalide in acute ischemic cerebrovascular disease. Therefore, many Chinese domestic scholars have also carried out the experiment of butylphthalide in the treatment of acute PTCI[12-15], and achieved good results.

Albumin is an important component of human plasma and plays a major role in regulating plasma colloid osmotic pressure. Human serum albumin is mainly used in hypoproteinemia, ascites due to cirrhosis, burns and so on, by increasing the blood osmotic osmotic pressure, albumin can reduce the brain edema and infarct volume. Guohua Liang etc.[16] confirmed its efficacy and safety in treatment of PTCI in the study of PTCI in 130 cases, and found that human serum albumin can effectively reduces blood viscosity, thereby improving the neurological impairment and the prognosishe of patients with PTCI.

This study found that the combination of butyphthalide and albumin in the treatment of PTCI did not show a significant advantage after 1 week of treatment, and showed significant effects at 2 weeks and 90 days after treatment, its NIHSS and mRS were significantly lower than these of single albumin and conventional treatment group, and its BI and ADL was significantly higher than these of single albumin and conventional treatment group, said that the combination of the two drugs can be better improves the symptoms of neurological impairment in patients with PTCI, improves the prognosis, and confirms the value of its clinical treatment.

There was fewer samples were included in this study, and further expand the sample size was needed to obtain more reliable results to provide further evidence for the treatment of patients with PTCI.

References

[1] The Fourth National Conference on cerebrovascular diseases. Diagnostic points of various cerebrovascular diseases[J]. Chinese Journal of Neurology, 1996,29(6):381-3. (in Chinese)

[2] Scoring standard of clinical neurological deficit in stroke patients (1995)[J]. Chinese Journal of Neurology, 1996,06:62-64. (in Chinese)

[3] DaValos A, 1'oni D, 1weiIls F, et al. Neurological deterioration in acute ischemic stroke: potential predictors and

associated factors in the European cooperatiVe acute stroke study(ECASS)I[J]. Stroke, l999,3.0:2631-2636.

[4] Dá valos A, Castillo J. Potential mechanisms of worsening[J]. Cerebrovasc Dis, 1997,7(suppl 5):19-24.

[5] Jie xiong, Yipu Feng. The protective effect of butylphthallde against mitochondrial injury during cerebral ischemia[J]. Acta Pharmaceutica Sinica, 2000,35(6):408-412. (in Chinese)

[6] Xiaoying Zheng, Wei Kong, Shumin Zhao, et al. Effects of 3-n-butylphthalide pretreatment on microvascular architecture and free radical metabolism in hippocampus induced by cerebral ischemia/reperfusion[J]. Tianjin Medical Journal,2015,43(8):867-870. (in Chinese)

[7] Ruxun Huang, Changxin Li, Liyun Chen, et al.. Effects of dl-3n-butyphthalide in the treatment of rat cerebral infarction with middle cerebral artery occlusion[J]. Chinese Journal of New Drugs, 2005,14(8):985-988. (in Chinese)

[8] Ping Zhang. Effects of butylphthalide on HGF expression, cognitive function and cerebral perfusion in patients with acute ischemic stroke[D]. Zhengzhou University, 2016. (in Chinese)

[9] Hairu Ji, Lingwei Kong, Wei Kong, et al. Effects of pretreatment with NBP on brain edema and blood brain barrier in rats during cerebral ischemia reperfusion injury[J]. Journal of Apoplexy and Nervous Diseases, 2014,31(8):698-700. (in Chinese)

[10] Haoliang Xu, Yipu Feng. Effects of 3-n-butylphthalide on thrombosis formation and platelet function in rats[J]. Acta Pharmaceutica Sinica, 2001,36(5):329-333. (in Chinese)

[11] Liying Cui, Shunwei Li, Weiwei Zhang, et al. Effects of dl-3-butylphthalide soft capsules on treatment of acute ischemic stroke: multi-center, randomized, double-blind, double-dummy and aspirin-control study[J]. Chinese Journal of Neurology, 2008,41(11):727-730. (in Chinese)

[12] Xuelan Zhang, Weijing Duan, Yanning Zhao, et al. Observation of curative effect of butylphthalide injection in treatment of progressive cerebral infarction[J]. Journal of Hebei Medical University, 2015,36(5):565-567. (in Chinese)

[13] Huimin Wang, Jianshe Li, Jingjing Li. Efficacy of Butylphthalide and Sodium Chloride Injection in the treatment of anterior circulation progressive cerebral infarction[J]. Chinese Journal of Practical Nervous Diseases, 2016,19(16):133. (in Chinese)

[14] Hanwei Jia, Lei Jiang. Observation of curative effect of Butylphthalide and Sodium Chloride Injection in treatment of progressive cerebral infarction[J]. Chinese Journal of Practical Nervous Diseases, 2016,19(22):48-49. (in Chinese)

[15] Shuqin Zhao, Zhenhao Zhang, Fang Gu. Observation of curative effect of butylphthalide on progressive cerebral infarction[J]. Journal of Apoplexy and Nervous Diseases, 2011,28(6):550-551. (in Chinese)

[16] Guohua Liang, Baoyu Lai, Feng Chen, et al. Clinical efficacy of human albumin in the treatment of progressive cerebral infarction,and its affecting factors[J]. Journal of Bengbu Medical College, 2016,41(8):1061-1063,1067. (in Chinese)