Int J Clin Exp Med 2017;10(2):3757-3761
www.ijcem.com /ISSN:1940-5901/IJCEM0026624

Original Article

Clinical application of butylphthalide in massive cerebral infarction treatment

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Received February 24, 2016; Accepted August 17, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Purpose: This study aims to investigate the effect of butylphthalide on the prognosis of acute massive cerebral infarction (MCI). Methods: A total of 92 MCI patients, who received inpatient treatment in the Department of Neurology, Harrison International Peace Hospital from February 2011 to December 2013, were enrolled into this study. As a controlled study, patients were randomly divided into two groups: control group (n=46) and treatment group (n=46). Patients in the control group were administered with an intravenous drip of edaravone, while patients in the treatment group were given edaravone combined with butylphthalide capsules. Furthermore, patients in the two groups underwent continuous administration for two weeks as a course of treatment. Improvement of symptoms in the two groups was assessed based on the National Institutes of Health Stroke Scale (NIHSS). The effect of butylphthalide on collateral circulation in the ischemic infarct area was assessed according to the collateral vessel grading standard of susceptibility-weighted imaging (SWI), and these results were analyzed. Results: Symptoms and signs of patients in both the control and treatment groups improved to some extent. Improvement in patients in the treatment group was significantly better than patients in the control group (P<0.05). NIHSS scores of patients in the treatment group were better than that in the control group (P<0.05). Furthermore, SWI collateral vessel display grades of patients in both the control and treatment groups were upgraded, but the number of upgraded cases in treatment group was significantly larger than that in the control group (P<0.05). No obvious adverse reaction occurred in the two groups during the treatment. Conclusion: Butylphthalide exhibited good efficacy in the treatment of MCI, which could effectively improve nerve function defect and promote the re-formation of collateral circulation in the infarct area.

Keywords: Massive cerebral infarction, prognosis, butylphthalide, susceptibility-weighted imaging

Introduction

Cerebral infarction is the “number one killer” to human health. Its mortality rate has remained high and seriously affects the quality of life of patients [1]. It also is a potentially useful neurovascular protective agent, used in combination with thrombolytic agents to treat >15 million patients devastated by stroke worldwide annually. Additional clinical studies are necessary to verify the efficacy of edaravone when used in combination with a thrombolytic agent. Edaravone has neuroprotective effects [2]. Its efficacy in the treatment for cerebral infarction is well-known, and it has been used in many clinical practices. Butylphthalide, an anti-cerebral ischemia drug developed in recent years, can effectively improve regional blood flow in the brain. Zhang PL, etc [3] investigated the effect of dl-3n-butylphthalide (NBP) on the protection of cerebral tissue and possible mechanism in ischemia-reperfusion injury, and to find out whether NBP therapy can extend the reperfusion window in an experimental stroke model in rats. This possible mechanism maybe related to the VEGF expression and may extend the reperfusion window for subsequent salvage of cerebral ischemia by reperfusion. Many studies have indicated its positive effect on the prognosis of cerebral infarction [4-9]. In our clinical practices, MCI patients were treated with butylphthalide capsules combined with edaravone treatment, and SWI technology was applied to monitor the blood supply of collateral circulation in the cerebral infarct region; in which satisfactory results have been achieved. These results are reported as follows.

Table 1. Comparison of efficacy between two groups [n (%)]

Group	Cases	Recovery	Excellence	Effective	Invalid	Total effective rate
Control group	46	7 (15.22)	9 (19.57)	18 (39.13)	12 (26.09)	34 (73.91)
Treatment group	46	11 (23.91)	12 (26.09)	16 (34.78)	7 (15.22)	39 (84.78)*

*P<0.05, compare with control group.

Table 2. Comparison of NIHSS score before and after treatment between two groups

Group	Cases	Before treatment	After treatment
Control group	46	16.01±2.72	7.82±3.16*
Treatment group	46	15.29±3.08	5.19±2.46*,Δ

Data are shown as mean±SD. *P<0.05, compare with the group before treatment; ΔP<0.05, compare with control group.

Materials and methods

Subjects

Ninety-two MCI patients, who received inpatient treatment in Harrison International Peace Hospital from February 2011 to December 2013, were enrolled into this study. Inclusion criteria: the diagnosis of all patients was in line with the main points of cerebral infarction diagnosis, which was revised in the Fourth Academic Conference of National Cerebral Vascular Disease in China [5]; Imaging revealed that pathogenic causes in all patients were cerebral infarction of the internal carotid artery system; and the biggest infarct area was >3 cm in diameter. Patients were randomly divided into two groups: treatment group (*n*=46) and control group (*n*=46). General data of patients in these two groups were statistically analyzed, and the difference was not significant.

Methods

Patients in both groups were given anti-platelet aggregation, statin lipid-lowering and blood pressure-stabilizing Chinese patent medicines and other conventional treatments. On the basis previously mentioned, the control group was administered with an intravenous drip of edaravone (Sinopharm Guorui Pharmaceutical, National drug approval no. H20080056) at a dose of 40 mg per 200 mL (twice daily). On the basis of treatment in the control group, the treatment group was also given oral butylphthalide capsules (CSPC NBP Pharmaceutical, National drug approval no. H20050299) at 0.2 g/day (twice daily). Patients in the two groups were given continuous administration for two weeks as a course of treatment. In this study, treatment schemes for all patients in both the control and treatment groups have been approved by the ethics committee; and all patients provided signed informed consent.

Curative effect

Curative effects in all patients were evaluated based on the NIHSS [6]. Evaluation criteria: According to NIHSS scores, patients were divided into four types after treatment: cured, excellent, effective and ineffective. Cured: NIHSS scores decreased by 91%-100% and disability degree was grade 0; Excellent: NIHSS scores decreased by 45%-45% and disability degree is within grade 1-3; Effective: NIHSS scores decreased by 18%-45%; Ineffective: no improvement or deterioration in patient rating. Total effective rate = (cured + excellent + effective)/treatment cases × 100%.

Changes in micro vessels in collateral circulation in the two groups were analyzed through SWI technique, and comparison was performed. Grading standard of SWI collateral vessel display: Grade 0: no collateral vessels were displayed; Grade 1: collateral vessels cover only part of the infarct area; Grade 2: collateral vessels cover the full extent of the infarct area.

Statistical methods

All data were recorded by Epidata 3.0 and were statistically processed by SPSS17.0. Measurement data of normal distribution were treated with *t*-test, while counting data and the difference between groups were treated with *Chi*-square test. *P*<0.05 was considered statistically significant.

Results

Comparison of curative efficacy between the two groups

After two weeks of treatment, symptoms and signs of patients in both the control and treat-

Table 3. The displayed grading of collateral vessels before and after the treatment between two groups

Group	Cases	Before treatment			After treatment		
		0 level	1 level	2 level	0 level	1 level	2 level
Control group	46	33	13	0	12	31	3
Treatment group	46	35	11	0	9	31	6

Table 4. Comparison of display grading changes of collateral vessels between the treatment and control group before and after treatment

Group	The total number of cases	After treatment	
		Hierarchical increase the total number of cases	Proportion %
Control group	46	24	52.17
Treatment group	46	32	69.56$^{\Delta}$

$^{\Delta}$P<0.05, Compared with control group.

ment groups improved to some extent. Furthermore, improvement in the treatment group was significantly better than the control group (P< 0.05, **Table 1**).

Comparison of NIHSS scores of patients in the two groups before and after treatment

Before treatment, there was no significant difference in NIHSS scores between the two groups. After treatment, NIHSS scores in the treatment group were remarkably lower than those in the control group (P<0.05, **Table 2**).

Comparison of SWI display of grading of collateral vessels between the control and treatment group before and after treatment

SWI analysis revealed that before treatment, collateral vessels in the infarct area in both two groups were significantly reduced or disappeared, and there was no significant difference in collateral vessel display of grading between the two groups (**Table 3**). After treatment, the number of microvessels and upgraded cases of collateral vessel display grading increased in both the treatment and control group, but the increased percentage in the treatment group was significantly higher than in the control group (P<0, **Table 4**, Supplementary Figure 1).

Adverse reactions

There were no obvious adverse reactions in the two groups during the treatment.

Discussion

Cerebral infarction has a series of characteristics such as acute onset, high incidence and high mortality. It seriously endangers the health of human beings. Effective treatment for MCI has become one of the main subjects of clinical research at home and abroad. The pathogenesis of cerebral infarction is relatively complex, and the main cause is damage to brain blood vessels and microcirculation. This leads to cerebral ischemia, and induces swelling and death of endothelial, nerve and glial cells; thus, cerebral infarction occurs. At present, in the treatment of MCI, the basic idea is to improve blood circulation in the ischemic area, maintain mitochondrial function, and remove free radicals. Edaravone is a free radical scavenger and antioxidant [10]. It is highly soluble in fat and its function inhibits the peroxidation of brain tissues and scavenging of free radicals. Related research [11] revealed that edaravone has low molecular weight; thus, it can effectively penetrate the blood-brain barrier and directly exert on lesions. Concordantly, edaravone has been found to have neuroprotective effects in a number of animal models of disease, including stroke, spinal cord injury, traumatic brain injury, neurodegenerative diseases and brain tumors. The proven safety of edaravone following 9 years of use as a free radical scavenger suggests that it may have potential for development into an effective treatment of multiple neurologic conditions in humans [11]. Butylphthalide is a synthetic racemic drug, also known as 3-n-butylphthalide. Its pharmacological action is to increase the level of NO [12] and PGI_2 in cerebral vascular endothelial cells, inhibit the release of glutamate, increase the activity of antioxidant enzymes, and inhibit platelet aggregation. It is a new mitochondria-protecting drug that can effectively inhibit apoptosis, improve blood flow to the brain [13, 14], and improve cerebral circulation and energy metabolism [15-17], taking effect in the treatment of cerebral infarction [18-20].

The results of this study were as follows. In the treatment group, patients were given edara-

vone combined with butylphthalide capsules, receiving a total effective rate of 84.78% [21]; while in the control group, patients were given edaravone alone, obtained a total effective rate of 73.91%. The difference between these two groups was statistically significant ($P<0.05$). NIHSS scores in treatment group before and after treatment significantly changed ($P<0.05$). Differences of NIHSS scores between the treatment and control group before and after treatment were statistically significant ($P<0.05$). In comparing changes in collateral vessel display grading between the treatment and control group, more cases with upgraded displays appeared after treatment in the treatment group, which accounted for a bigger proportion of the total number ($P<0.05$).

Conclusion

Magnetic susceptibility weighted imaging (SWI) sequence of collateral vessels display classification changes suggestive of acute large area cerebral infarction, infarct area of collateral circulation can be set up quickly; butylphthalide combined with edaravone treatment can more effectively promote the reconstruction of collateral circulation and improve patients prognosis.

Disclosure of conflict of interest

None.

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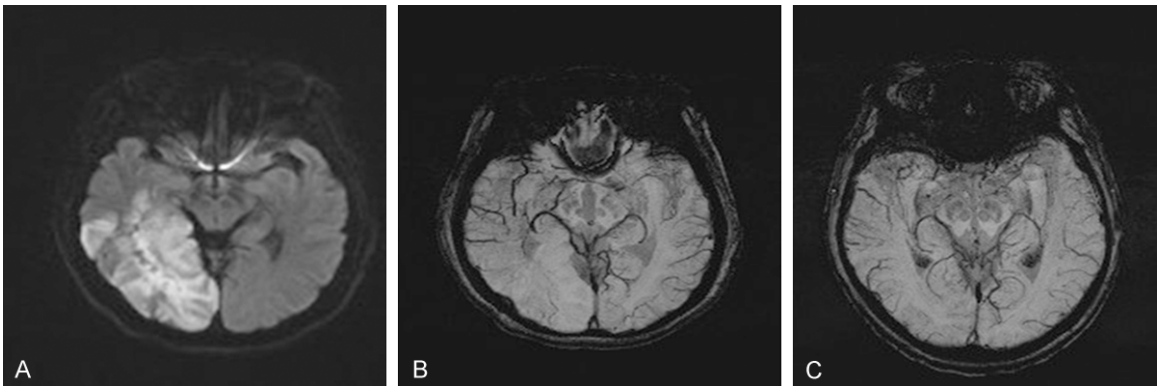

Supplementary Figure 1. The changes of SWI collateral vessels in the treatment group. A: DWI prompted the right temporal occipital Ye Xin cerebral infarction. B: The acute phase SWI sequence showed that the number of micro vessels in the infarct area was significantly decreased compared to the contralateral side. C: After 2 weeks, The number of microvessel in the infarct area was significantly increased.