Efficacy and safety comparison of DL-3-n-butylphthalide and Cerebrolysin: Effects on neurological and behavioral outcomes in acute ischemic stroke

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Abstract. Cerebrolysin and DL-3-n-butylphthalide (NBP) have each shown neuroprotective efficacy in preclinical models of acute ischemic stroke (AIS) and passed clinical trials as therapeutic drugs for AIS. The present study was a clinical trial to assess and compare the efficacy and safety of NBP and Cerebrolysin in the reduction of neurological and behavioral disability following AIS. A randomized, double-blind trial was conducted with enrolment of 60 patients within 12 h of AIS. In addition to routine treatment, patients were randomly assigned to receive a 10-day intravenous administration of NBP, Cerebrolysin or placebo. National Institutes of Health Stroke Scale (NIHSS) and Barthel Index (BI) scores were used to evaluate the efficacy of the treatment in the patients with AIS at 11 and 21 days after the initiation of therapy. Adverse events were also analyzed among the three groups. After 10 days of treatment with NBP or Cerebrolysin, the NIHSS and BI scores at day 21 showed statistical differences compared with those in the placebo group ($P<0.05$). The improvements of NIHSS and BI scores in the NBP and Cerebrolysin groups were higher than those in the placebo group at days 11 and 21 ($P<0.05$). A statistically significant difference in the improvement of 21-day NIHSS scores was observed between the two treatment groups ($P<0.05$). No significant difference was found among the three groups with regard to the rate of adverse events. Favorable outcomes and good safety were observed in the patients with moderate AIS treated with NBP or Cerebrolysin. The results indicate that NBP may be more effective than Cerebrolysin in improving short-term outcomes following AIS. This trial is registered at ClinicalTrials.gov with clinical trial identifier number NCT02149875.

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Introduction

The racemic compound DL-3-n-butylphthalide (NBP), which has multiple effects on various pathophysiological processes, is considered to be beneficial for the treatment of ischemic stroke, since it has been shown to protect neuronal cells against ischemia-induced brain damage and neurotoxic damage, improve cerebral blood flow, decrease brain edema and preserve the blood brain barrier (1-5). Cerebrolysin is a peptide-containing preparation that also exerts beneficial effects on ischemic stroke; preclinical studies have shown that Cerebrolysin substantially improves neurological outcome and promotes neurological functional recovery following ischemia by preventing cell death, the formation of free radicals, inflammation and by counteracting excitotoxicity (6-9). Clinical trials have been performed to test the efficacy and safety of NBP and Cerebrolysin in the treatment of patients with acute ischemic stroke (AIS), and encouraging results have been reported (10-13). For example, a clinical trial in China that enrolled 573 patients within 48 h of ischemic stroke reported that 90 days of treatment with NBP was able to improve outcomes at the third month following stroke, and that both intravenous and oral administrations were safe (10). In addition, a large double-blind, placebo-controlled randomized clinical trial, involving 1,071 patients from 49 participating centers, was launched in Asia between 2009 and 2011 to assess the efficacy and safety profile of Cerebrolysin in patients who had experienced an acute ischemic stroke (11,12). Following treatment with 30 ml Cerebrolysin (intravenous infusion for 10 days), the number of severely affected patients with ischemic stroke who exhibited a favorable response in neurological outcome measures was significantly more, as compared with the placebo group (11,12). However, to the best of our knowledge, there has not yet been a prospective study for the comparison of the therapeutic effects of these two drugs.

Therefore, a randomized, double-blind trial was conducted in which patients with AIS were treated with NBP or Cerebrolysin. The safety of NBP was compared with that of Cerebrolysin, and the improvements in neurological and

behavioral outcomes for each method of treatment were evaluated.

Patients and methods

Patient selection. From January 2010 to May 2010, a randomized, double-blind trial was conducted, which involved patients with AIS in the Neurology Ward of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Shanghai, China). The study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, and informed consent for participation in the study was obtained from the patients or legally acceptable surrogate or appropriate member of each patient's family. Patients included in the study suffered from AIS for the first time <12 h prior to entry into the study, and had a score of between 6 and 25 on the National Institutes of Health Stroke Scale (NIHSS). Prior to randomization, all patients were evaluated using cranial computed tomographic (CT) or magnetic resonance imaging (MRI) scanning and were followed with serial neurological examinations to confirm AIS. All the imaging studies were technically adequate and reviewed by the staff of the radiology department. Patients with lacunar infarction, cerebral hemorrhagic infarction, epilepsy or epileptic seizures, history of neurological diseases, myocardial infarction, renal and hepatic abnormalities, metabolic diseases and contraindications to antiplatelet treatments were excluded. This trial has been registered with the National Institutes of Health (ClinicalTrials.gov, identifier number: NCT02149875).

Randomization and therapeutic schedule. Patients were randomly assigned to the NBP group, Cerebrolysin group or placebo group. Patients in the three groups were given routine treatments including antithrombotic drugs, hypoglycemic agents, antilipemic agents, antihypertensive(s) and dehydration, according to guidelines for the management of ischemic stroke in the neurological intensive care unit (14). Patients in the NBP group received an intravenous infusion of 100 ml NBP (CSPC NBP Pharmaceutical Co., Ltd., Shijiazhuang, China) and sodium chloride (NaCl) injection, which contained 25 mg NBP and 0.9 g NaCl, twice daily. The treatment was administered for 10 days starting within 12 h of stroke onset. The Cerebrolysin group was treated with an intravenous infusion of 30 ml Cerebrolysin (Ever Pharma, Unterach am Attersee, Austria) per day in 100 ml normal saline for 10 days, and the infusion lasted between 50 and 70 min. The placebo group was given 100 ml saline intravenous infusion once daily for 10 days. Patients in the three groups also received 100 mg aspirin orally as standard treatment. Randomization was performed by means of computer-generated numbers through software by a third party who was not involved in patient management. The random numbers were placed in concealed envelopes.

Clinical assessment. Patients were subjected to a series of evaluations at enrollment and on days 11 and 21 from the initiation of administration of NBP, Cerebrolysin or placebo. Clinical assessments included a physical examination (including heart rate, blood pressure and oxygen concentration), laboratory tests (including urine test, complete blood count, renal function, liver function, electrolyte and blood-glucose), electrocardiogram, cranial CT or MRI, chest radiograph, the quantification of neurological deficit using the NIHSS (scores ranging from 0 to 42, with higher scores indicating increasing severity) (15), and functional and behavioral measures using the Barthel Index (BI; scores ranging from 0, indicating complete dependence on help with activities of daily living, to 100, indicating independence) (16).

Safety assessment. Safety variables such as vital signs and laboratory data of all subjects were recorded from the first day of drug administration to the last day of the observation period. Adverse events were recorded using the treatment emergent symptom scale (TESS) (17) throughout the study and categorized by body system, type of event, severity and course. Changes in the laboratory indices of the NBP and Cerebrolysin groups prior to and following treatment were analyzed. The frequencies of adverse events in these three groups were also compared.

Statistical analysis. Data were analyzed using the software package Statistical Program for Social Sciences (version 17.0; SPSS, Inc., Chicago, IL, USA) and expressed as mean ± standard deviation. The statistical analyses of efficacy followed the intention-to-treat principle, which included all randomly assigned patients. The primary end points were the outcome at day 21 assessed by NIHSS and the Barthel Index scores. Paired t-tests and one-way analysis of variance were used to assess the inter-group differences in quantitative variables, whereas the Chi-square test (χ^2) test was used for the assessment of qualitative variables. For the safety analysis, differences among groups were compared using Fisher's exact test. Missing values were substituted by last observation carried forward. $P<0.05$ was considered to indicate a statistically significant result.

Results

Baseline characteristics. During the trial period, 84 patients with ASI underwent randomization. Among these, 60 patients who received study intervention were included in the efficacy analysis. The NBP group contained 9 male and 11 female patients, whose ages ranged from 53 to 79 years. The Cerebrolysin group contained 9 males and 11 females, and their ages ranged from 54 to 85 years. The placebo group contained 10 males and 10 females, whose ages were from 52 to 87 years. Baseline demographic and clinical characteristics of the three groups are listed in Table I. Comparison of baseline characteristics among the treatment groups revealed no significant differences ($P>0.05$).

Neurological and behavioral outcomes. The post-therapy NIHSS and BI scores of the three treated groups are shown in Tables II and III, respectively. During the observation period, statistically significant trends toward decreased NIHSS scores and increased BI scores were observed in the patients in the NBP and Cerebrolysin groups ($P<0.05$).

At 21 days after the initiation of treatment, NIHSS scores in the NBP and Cerebrolysin groups were significantly

Table I. Baseline characteristics of the three treatment groups in the trial (n=60).

Characteristic	NBP (n=20)	Cerebrolysin (n=20)	Placebo (n=20)	P-value
Age (years)[a]	67.1±6.3	66.5±8.1	68.4±4.2	0.67
Gender (male/female)[b]	9/11	9/11	10/10	1.00
Time until admission (h)[a]	5.4±3.0	5.0±3.3	4.8±3.7	0.83
Time until treatment (h)[a]	7.7±5.9	7.6±3.6	5.6±3.0	0.51
Systolic blood pressure (mmHg)[a]	148.6±14.6	150.7±13.7	152.5±12.8	0.35
Diastolic blood pressure (mmHg)[a]	88.7±10.7	85.1±13.6	87.2±12.5	0.29
Thrombolysis treatment[b]	5 (25)	7 (35)	6 (30)	0.86
Previous history				
Hypertension[b]	7 (35)	6 (30)	10 (50)	0.65
Diabetes[b]	8 (40)	7 (35)	6 (30)	0.95
Coronary heart disease[b]	6 (30)	8 (40)	9 (45)	0.78
NIHSS score[a]	12.40±4.38	10.60±4.74	10.20±3.72	0.81
Barthel index score[a]	19.75±6.38	22.25±7.16	22.00±6.96	0.64

Data are presented as mean ± standard deviation or n (%). Results were compared by [a]t-test and [b]Fisher's exact test. NBP, DL-3-n-butylphthalide; NIHSS, National Institutes of Health Stroke Scale.

Table II. Comparison of NIHSS scores among the three groups pre- and post-therapy.

			Post-therapy	
Group	n	Pre-therapy	Day 11	Day 21
NBP	20	12.40±4.38	8.78±2.48	5.48±2.34[a]
Cerebrolysin	20	10.60±4.74	7.80±5.81	5.90±3.96[b]
Placebo	20	10.20±3.72	8.85±4.43	7.30±4.78

Values are expressed as mean ± standard deviation. [a]P<0.01 vs. the placebo group by ANOVA; [b]P<0.05 vs. the placebo group by ANOVA. NBP, DL-3-N-butylphthalide; ANOVA, analysis of variance.

Table III. Comparison of Barthel index scores among the three groups pre- and post-therapy.

			Post-therapy	
Group	n	Pre-therapy	Day 11	Day 21
NBP	20	19.75±6.38	35.25±10.57	54.00±14.01[a]
Cerebrolysin	20	22.25±7.16	36.00±10.81	53.75±13.10[a]
Placebo	20	22.00±6.96	31.00±8.68	43.75±15.50

Values are expressed as mean ± standard deviation. [a]P<0.05 vs. with the placebo group evaluated by analysis of variance. NBP, DL-3-n-butylphthalide.

lower than those in the placebo group (P<0.01 and P<0.05, respectively; Table II), and the BI scores of the two groups were significantly higher than those in the placebo group (P<0.05; Table III). However, the differences in the mean NIHSS and BI scores between the NBP and Cerebrolysin groups were not significant. The NIHSS and BI scores in the NBP and Cerebrolysin groups were improved with significant differences at days 11 and 21 after the initiation of treatment compared with those in the placebo group (P<0.01 in the NBP group, P<0.05 in the Cerebrolysin group; Table IV). Although no significant difference was observed between the two groups with regard to the increase of BI score, the patients treated with NBP were significantly more likely to have a favorable outcome than patients treated with Cerebrolysin, as indicated by comparison of the reduction in NIHSS scores at day 21 (P<0.05; Table IV).

Table IV. Changes in NIHSS and BI scores from baseline among the three groups.

Outcome variable	NBP (n=20)	Cerebrolysin (n=20)	Placebo (n=20)
Improved NIHSS score			
Day 11	3.63±2.74[a]	2.80±1.88[b]	1.35±1.90
Day 21	6.93±3.09[a,c]	4.70±2.15[b]	2.90±1.97
Improved BI score			
Day 11	15.50±7.93[a]	13.75±6.85[b]	9.00±5.88
Day 21	34.2±13.21[a]	31.50±14.66[b]	21.75±10.79

Values are expressed as mean ± standard deviation. [a]P<0.01 vs. the placebo group by ANOVA. [b]P<0.05 vs. the placebo group by ANOVA. [c]P<0.05 vs. the Cerebrolysin group by ANOVA. NBP, DL-3-n-butylphthalide; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel index; ANOVA, analysis of variance.

Table V. Comparison of laboratory indices of the NBP and Cerebrolysin groups prior to and following treatment.

	NBP group		Cerebrolysin group	
Laboratory test values	Pre-therapy	Day 21	Pre-therapy	Day 21
RBC ($x10^{12}$/l)	4.06±0.48	4.08±0.51	4.11±0.27	4.13±0.14
Hemoglobin (g/l)	127.43±18.42	133.21±11.16	126.64±19.31	130.42±10.36
Leukocyte ($x10^9$/l)	6.71±1.77	6.73±1.45	6.69±1.93	6.72±1.58
Platelet ($x10^9$/l)	188.63±46.27	190.30±44.16	194.12±32.18	192.46±38.17
Urine leukocyte (/ul)	14.48±6.24	12.75±7.10	16.39±3.55	13.61±5.27
Urine RBC (/ul)	7.24±2.67	5.62±3.10	5.86±3.42	4.68±4.07
Blood glucose (mmol/l)	6.24±0.87	5.65±1.06	5.67±1.03	5.27±0.76
ALT (u/l)	28.64±12.01	31.21±10.20	29.38±10.57	32.01±9.34
AST (u/l)	22.47±6.58	23.16±5.82	21.94±8.21	22.65±7.57
γ-GT(u/l)	28.58±15.06	27.83±13.59	27.04±11.46	28.35±12.41
Urea (mmol/l)	5.07±0.66	4.91±1.13	4.97±0.75	4.93±0.92
Creatinine (μmol/l)	71.90±18.03	73.16±15.28	72.37±16.51	73.09±14.72

Values are expressed as mean ± standard deviation. NBP, DL-3-n-butylphthalide; RBC, red blood cell; ALT, alanine transaminase; AST, glutamic oxalacetic transaminase; γ-GT, γ-glutamyltransferase. P>0.05 vs. pre-therapy by t-test for all day 21 results.

Safety analysis. Adverse events were assessed at each visit from day 1 to day 21. There were no significant changes in any routine laboratory testing values following treatment in the NBP and Cerebrolysin groups (P>0.05; Table V). In addition, no significant difference in mortality rate was observed among the three treatment groups (P=1.000; Table VI). The evaluation of adverse events did not show any noteworthy inter-group differences (Table VI). Therefore, there is no indication of a safety risk associated with NBP or Cerebrolysin treatment.

Discussion

The morbidity of ischemic stroke is increasing year-by-year in China (18). Due to its high disability (50-70%) and mortality (5-15%) rates (18), AIS has become a major health problem. The impairment of neurological functions resulting from ASI creates a heavy mental and financial burden on the patients, their families and society (19). With the growing understanding of the pathophysiology of cerebral infarction, new approaches for its treatment, in addition to thrombolysis, have emerged. In particular, safe and effective neuroprotective drugs have been sought. Although the mechanism of neuroprotection is not entirely clear, the basic aim of this strategy is to interfere with pathological processes by blocking the ischemic cascade reaction and preventing the nerve cells from dying following ischemia (20).

NBP is the only drug known to have protective effects on mitochondria in ischemic stroke (21). The positive effects of NBP on cerebral ischemia, including improvement of microcirculation and energy metabolism, reduction of oxidative damage and neuronal apoptosis and inhibition of the inflammatory response, have been verified in experimental models and pharmacodynamic studies (1-5). Our previous studies demonstrated that NBP significantly inhibits caspase-3-mediated apoptosis, and decreases stroke-induced neuron loss and autophagic activity following cerebral ischemia in diabetic rats (22,23); and attenuates amyloid-β-induced activation of

Table VI. Adverse events recorded during 21 days of follow-up.

Adverse event	NBP (n=20)	Cerebrolysin (n=20)	Placebo (n=20)	P-value
Erythrema	1 (5)	1 (5)	1 (5)	1.00
Fever	9 (45)	5 (25)	7 (35)	0.32
Diarrhea	1 (5)	4 (20)	5 (25)	0.34
Nausea/vomiting	7 (35)	5 (40)	6 (30)	0.73
Positive fecal occult blood	0 (0)	0 (0)	1 (5)	1.00
Elevated aminotransferase	4 (20)	5 (25)	8 (40)	0.30
Elevated creatinine	5 (25)	3 (15)	7 (35)	0.69
Anemia	7 (35)	6 (30)	4 (20)	1.00
Coagulation disorder	10 (50)	6 (30)	8 (40)	0.33
Epilepsy	1 (5)	0 (0)	1 (5)	1.00
Cerebral hemorrhage	0 (0)	1 (5)	1 (5)	1.00
Cardiac failure	1 (5)	3 (15)	5 (25)	0.34
Mortality	1 (5)	0 (0)	0 (0)	1.00

Data are presented as n (%). NBP, DL-3-n-butylphthalide.

astrocytes and neuroinflammation via inhibition of the nuclear factor-κB signaling pathway (24). The administration of NBP for the clinical treatment of stroke in China was initiated in 2002. According to the results of a recent clinical trial, the efficiency of NBP in the treatment of ischemic cerebrovascular diseases is as high as 74.7%, with a low incidence of adverse reactions (10).

Cerebrolysin, a neuronal metabolic activator including various free amino acids and low molecular weight peptides, has been used to treat cerebrovascular diseases for many years. Previous studies have shown that it can improve neurological outcome by preventing cell death, free radical formation and inflammation, and by counteracting excitotoxicity and accelerating the recovery of neurological function (6-9). Clinical trials have shown that the usage of Cerebrolysin is reliable and effective with regard to the recovery of consciousness, language and hemiplegia in patients with AIS (11-13). Although the neuroprotective effects of NBP and Cerebrolysin in the treatment of patients with ischemic stroke have been generally acknowledged, to the best of our knowledge, no previous study has compared the efficiency of these two drugs in AIS. Thus, the present randomized, double-blind trial was conducted to simultaneously evaluate the ability of NBP and Cerebrolysin to improve the short-term prognosis of AIS.

In the present study, the 10-day treatment with NBP or Cerebrolysin was found to be beneficial for the recovery of neurological and behavioral outcomes of patients with AIS. This benefit was mainly observed on the disability end point as measured by the NIHSS and BI, which are widely accepted functional outcome measures. Although the sample size was relatively small, significant differences in NIHSS and BI scores at day 21 after the initiation of treatment were observed in patients who received either NBP or Cerebrolysin infusion in comparison with placebo-treated controls. It was also found that both NIHSS and BI scores in patients treated with NBP and Cerebrolysin improved significantly, compared with those in the placebo group, at 11 and 21 days after the initiation of administration. In addition, the improvement of NIHSS score in the NBP group was greater than that in the Cerebrolysin group at day 21. Therefore, NBP is indicated to be a more effective therapy for the treatment of cerebral infarction compared with Cerebrolysin.

Safety evaluations of NBP and Cerebrolysin were also conducted in the present trial. During the observation period of 21 days, the rate of serious and non-serious adverse events was similar among the study groups, so the intravenous administration appears to be relatively safe.

The present study has several limitations. Foremost is the relatively small sample size, which means that the efficacy results of this study should be interpreted with caution. Specifically, as the complications associated with severe AIS, which are strong predictors of outcome, may be difficult to balance in a relatively small sample study, only patients with moderate severity of stroke were enrolled. Furthermore, additional outcome measures, such as modified Rankin Scale and Glasgow Coma Scale scores were not analyzed in the present study, and so the results are not comprehensive.

In conclusion, the results of this study suggest that a 10-day treatment with NBP or Cerebrolysin can be applied safely and may provide beneficial effects for patients with acute ischemic stroke, particularly for cases of moderate severity. Additionally, NBP appears to be more effective than Cerebrolysin in providing an improvement of the short-term prognosis of AIS. Further trials with a larger sample size are required in order to evaluate the efficacy of long-term NBP therapy in ischemic stroke, and differences between doses should be also evaluated with regard to improvement of neurological and behavioral outcomes.

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