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Original Article

Effect of cerebrolysin in patients with ischemic stroke: A double-blind randomized control study

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Abstract. We investigated the effect of cerebrolysin compared with placebo efficacy in patients with ischemic stroke. A total of 50 patients with ischemic stroke participate in this randomized double-blind placebo-controlled study. Patients were randomly divided into two groups; main group (n=25) was treated by 30cc IV cerebrolysin daily for 5 days. Control group (n=25) administrated 30 cc IV normal saline as a placebo daily during first five days of stroke attack. Three scoring system was used in the present study: National Institutes of Health Stroke Scale (NIHSS) on admission and after five days, and Barthel and Rankin's scale after the 90 days. Data were analyzed by SPSS 16 using *t*-test. P-value less than 0.05 considered as significant level. The NIHSS score showed no significantly difference after 5 days (independent *t*-test, P = 0.195). There was a significant difference between Barthel and Rankin's scale after 90 days (P = 0.039 and P = 0.008 respectively). In conclusion, cerebrolysin prevented the development of ischemic stroke's sign and symptoms through 90 days.

Keywords: Cerebrolysin, ischemic stroke, neuroprotection

Introduction

Acute stroke leading to cause of adult disability and has poor prognosis of survival than most forms of cancer. In recent years, considerable efforts have been devoted to the development of new therapeutic strategies for acute stroke victims [1, 2].

Substantial effort has been expended to the development of neuroprotective therapies that intervene at various stages of the ischemic cascade and which potentially have a wider clinical application. Several classes of compound have been tested, including calcium channel blockers, N-methyl-D-aspartate (NMDA) antagonists, glutamate release inhibitors, anti-adhesion antibodies (anti-ICAM 1), GM-1 gangliosides, gamma-butyric acid antagonists, sodium channel blockers, glycine antagonists, free oxygen radical scavengers, and potassium channel agonists [3, 4]. Numerous neuroprotective agents have shown promising results in animal experiments. However, clinical trials have thus far failed to confirm benefits [5-8].

Cerebrolysin is a peptide preparation for IV infusion which mimics the action of neurotrophic factors. The compound is produced by a biotechnological process, a controlled hydrolysis of purified brain proteins, and consists of low-molecular-weight neuropeptides and free amino acids. Cerebrolysin has been shown to exert neurotrophic as well as neuroprotective effects in vitro and in vivo. It induces neuritis out growth and reduces apoptosis triggered by growth factor withdrawal in cultivated neurons. In animal models of stroke, intravenous cerebrolysin reduced mortality by about 50% after bilateral carotid artery occlusion in rats and reduced infarct size as well as the loss of MAP-2 immunoreactivity in a model of middle cerebral artery occlusion [9].

Ladurner et al. reported a significantly better regression of motor disturbances by the day 21 and 3 month after administration of 50 mL/day cerebrolysin [9].

Hence, the aim of present study was to investigate the efficacy of cerebrolysin management of ischemic stroke.

Materials and Methods

Ethical approval

This randomized double-blind placebo-controlled study conducted in department of neurology, Al Zahra hospital during 2014-2015. This study was submitted to and approved by the Ethical Committee for Research in Isfahan University of Medical Sciences, Isfahan, Iran and had no conflict with declaration of Helsinki. All patients signed the inform consent from.

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TABLE 1
DEMOGRAPHIC CHARACTERISTICS AND QUESTIONNAIRE SCORE OF STUDY SUBJECTS

Variable	Main group (Cerebylosin)	Control group (Placebo)
Male	11	10
Female	14	15
Age	70.96±9.1	69.84±11.8
Mean NIHSS score (admission)	10.64±2.6	11.56±2.3
Mean NIHSS score (after 5 days)	8.92±4.5	9.92±3.7
Mean Barthel score after 90 days	78.80±27.6	62.27±16.0

Inclusion criteria

Patients who referred to emergency room by diagnosis of acute ischemic stroke (within 6-24 hours after attack) in middle cerebral artery territory of both genders, more than 45 year old, and the stroke deficit of moderate degree (NIHSS score more than 7, less than 17) selected for this study. Patients were examined by a single physician on admission, after neuroimaging and confirmation of diagnosis; routine stroke management was started including anti-platelet therapy, statins and etc. According to mentioned criteria fifty patients were selected.

Exclusion criteria

Patients with ICH, SDH, EDH, SAH, cerebro-degenerative or demyelinating disease, brain tumor, previous stroke, metabolic disorders, and patients with stroke in other artery distributions and patients with lacunar infarct were excluded.

Study groups

Patients were randomly divided into two groups; first group (n = 25) treated by 30 cc IV cerebrolysin daily for 5 days. Second group (n = 25) received 30 cc IV normal saline as a placebo daily during first to five days of stroke attack.

Neurological score

Three scoring systems were used in this study: National Institutes of Health Stroke Scale (NIHSS) [10], Barthel's scale [11], and Rankin's scale [12]. Each patient examined by NIHSS scoring system on admission and after five days. The Barthel activities of daily living index and Rankin's score were checked after 90 days. The study end point is after completion of the 3 months follow up period. Also all subjects were visited every 4 weeks up to 3 months.

Statistical analysis

Data were analyzed with SPSS 16 using independent *t*-test for study groups. Differences between mean score of NIHSS on admission and after 5 days were determined using Paired t-test for each group. Pearson correlation was implemented to compare Barthel and Rankin's scales with each other. P-value less than 0.05 considered as significant level.

Results

Table 1 shows the demographic feature of subjects and the mean score of NIHSS, Barthel and Rankin's scales. Seven patients out of 50 were died (4 in cerebylosin group and 3 in control group).

The mean NIHSS's score of cerebylosin group on admission and five days after was 10.64±2.6 and 8.92±4.5 respectively (Paired *t*-test, P = 0.026). The mean NIHSS's score of placebo group on admission and five days after was 11.56±2.3 and 9.92±3.7 respectively (Paired t-test, P = 0.011). There was no statistically significant difference between the mean score of NIHSS on admission and after five days through the groups (Independent t-test, P > 0.05).

There were significant differences between study groups after 90 days by Barthel and Rankin's scales evaluation (Independent t-test, P= 0.039 and Chi-square, P= 0.027 respectively).

Pearson correlation was used to determine the correlation of Barthel and Rankin's scales with each other after 90 days. The result showed a significant correlation of these questionnaire (r = -0.928, P = 0.000).

Discussion

The authors conducted that cerebrylosin therapy can reduce cerebral infraction signs and symptoms volume after 3 months. The results of this study confirmed an improvement of activity in patients who treated with cerebrylosin.

The term "neuroprotection" is used to describe the putative effect of interventions protecting the brain from pathological damage. In ischemic stroke, the concept of neuroprotection includes inhibition of pathological molecular events leading to calcium influx, activation of free radical reactions and cell death. Knowledge of pathophysiology in acute ischemic stroke stimulated development of a number of potential neuroprotective agents [13, 14].

In a preliminary randomized controlled trial (SAINT I) with 1722 patients, NXY-059 treatment of acute ischemic stroke was associated with a small but significant reduction in the primary outcome of disability at 90 days compared with placebo, but there was no significant improvement in co-primary outcome of neurologic function or any of the secondary outcome measures [15]. In the SAINT II trial involving over 3000 patients, NXY-059 treatment compared with placebo did not result in a statistically significant reduction in the primary outcome of stroke-related disability or improvement on any of the secondary outcome measures [16]. Similarly, a pooled analysis of the SAINT I and II trials confirmed the lack of benefit for NXY-059 on all primary and secondary end points in the overall population and in the pre-specified subgroups [17].

Several methods have been introduced for the management of ischemic stroke patients such as; the use of neurotrophic factor and stem cell therapy. For this respect,

basic fibroblast growth factor (bFGF), brain derived neurotrophic factor (BDNF), insulin-like growth factor (IGF) and osteogenic protein 1 have been studied. The therapeutic potential has convincingly been shown for bFGF and osteogenic protein 1. Both factors achieved improvement of behavioral outcome and a reduction of infarct size in animal model [13, 18].

cerebrolysin is a peptide which induces neurite out growth and reduces apoptosis triggered by growth factor withdrawal in cultivated neurons. In a recent study in rats, cerebrolysin has been shown to increase the number of neuronal progenitor and to enhance neurogenesis in the dentate gyrus of adult animals which correlated with improved spatial memory performance in these animals. In other hand, on a molecular level, an inhibitory effect of cerebrolysin on calpain has been demonstrated. In animal models of stroke, intravenous cerebrolysin reduced mortality by about 50% after bilateral carotid artery and reduced infarct [9].

Ladurner et al. [9] evaluated the safety and preliminary outcome of cerebrolysin treatment in patients with acute stroke. The results of their study showed that neurotrophic treatment with cerebrolysin is safe and well tolerated by patients with acute stroke. In conclusion, cerebrolysin may be considering as a potent therapeutic approach cerebral ischemic stroke.

Conflict of Interest

The authors declare no conflicts of interest.

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