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Effects of cerebrolysin on functional recovery in patients with severe disability after traumatic brain injury: A historical cohort study

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ABSTRACT

Objective: To determine the effects of cerebrolysin on functional recovery in patients with severe disability after traumatic brain injury (TBI).
Methods: This was a retrospective cohort study being performed during a 2-year period in a level I trauma center in Southern Iran including all the adult patients (>16 years) with severe disability (GOS of 2 and 3) 1-month after trauma. We excluded those with posttraumatic seizures and those with meningitis or current infections. Some patients received cerebrolysin (n = 65) and some did not (n = 64). Cerebrolysin was administered intravenously in 10 mL dosage daily for 30 days. Patients in two study groups were matched regarding the baseline characteristics including age, gender, GCS on admission, pupil reactivity and Rotterdam score. The administered cerebrolysin dosage was 10 mL intravenously daily for 30 days. The 3- and 6-month Glasgow Outcome Scale Extended (GOSE) was recorded. The outcome scales were compared between two study groups.
Results: Overall we included 129 patients with severe disability 1-month after TBI. The baseline characteristics were comparable between groups. We found that GOSE at 3-month ($p = 0.017$) and 6-month ($p = 0.009$) was significantly higher in those receiving cerebrolysin. Cerebrolysin administration was associated with lower mortality rate, and higher good recovery after 6 month of therapy ($p = 0.024$). Cerebrolysin administration was also associated with higher favorable and lower unfavorable outcome ($p = 0.043$). Cerebrolysin was associated with higher seizure rate ($p = 0.042$).
Conclusion: Cerebrolysin administration in patients with severe disability after TBI is associated with improved functional recovery, decreased mortality rate and increased favorable outcome. Seizure is important side effect of cerebrolysin administration in TBI patients.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity among young age groups worldwide being associated with high healthcare, social and economic burden [1,2]. According to United States statistics, the cost of TBI is approximately 48.3–76.3 billion dollars annually [3]. Center for Disease Control (CDC) has reported that the incidence of TBI is 1.7 million annually with 52,000 deaths and over 250,000 hospitalizations in US alone [3]. The incidence rates are even higher in developing countries with a TBI with associated mortality rate of 37.7–48.4 per 100,000 populations per year [4,5]. The brain injury following TBI is classified as primary and secondary based on the consequence of appearance. The secondary brain insults including hypoxia and infarction, brain edema and swelling, herniation and infections following TBI is the preventable and treatable portion of the pathology [6]. The secondary insults following TBI result in apoptosis, cell death and axonal loss [7] leading to long-term cognitive and neurologic dysfunctions and deficits, impaired functional outcome and long-term disability [8,9]. Currently the management and treatment of patients with TBI are based on the evidence-based guideline mostly focusing in preventing and treating the secondary insults and rehabilitation [10,11]. To date, there is no effective pharmacological therapy available for TBI [12]. Therapies with multiple pathophysiological targets might be helpful in treating these injuries.

Several lines of evidence have suggested that administration of growth hormones and neurotrophic factors, such as brain derived

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neurotrophic factor (BDNF), glial cell derived neurotrophic factor (GDNF), nerve growth factor (NGF), insulin-like growth factor (IGF) and neurotensin are associated with improved functional recovery after neuronal tissue injuries (brain and spinal cord) [13–16]. Cerebrolysin is a low molecular neuropeptide and amino acids prepared from porcine brain tissue under specific manufacture procedures. Administration of cerebrolysin in vitro and in vivo has been shown to be associated with decreased excitotoxicity, inhibiting free radical formation, microglial activation/neuroinflammation, and calpain activation/apoptosis, and additionally, it has been demonstrated to exhibit neurotrophic activity, promote neuronal sprouting, improve cellular survival, and stimulate neurogenesis [17–19]. Previous human studies have shown that cerebrolysin is associated with improved outcome after ischemic stroke [20,21], Alzheimer's disease [22], and TBI [23–25]. Animal studies have demonstrated that cerebrolysin administration is associated with increased functional recovery after closed head injury [26] and improved cognitive function after mild TBI [27]. Although cerebrolysin therapy for TBI has been previously studied, but clinical data and the results in severe disabled patients after TBI are yet to be identified. The aim of the current study was to determine the effects of cerebrolysin on functional recovery of patients with severe disability after TBI.

2. Methods

2.1. Study population

This was a retrospective cohort study which was conducted during a 2-year period from March 2013 to March 2015 in Shahid Rajaei hospital, a large level I trauma center in Southern Iran affiliated with Shiraz University of Medical Sciences. All the patients admitted to our center during the study period were managed according to the Guidelines for the management of severe traumatic brain injury (3rd Edition) [10]. We included those patients with severe disability 1 month after TBI measured by Glasgow outcome scale (GOS). Vegetative state (GOS of 2) and severe disability (GOS of 3) were defined as severe disability and only these patients were found eligible to be included in the study. Those between 16 and 80 years of age were included and none of them had significant neurologic disability before the TBI. We excluded the patients with a preexisting or active major neurological or psychiatric disease; a history of significant alcohol or drug abuse within the previous 3 years; advanced liver, kidney, cardiac, or pulmonary disease; a terminal medical diagnosis with an expected survival of <1 year; any condition that would represent a contraindication for cerebrolysin administration, including allergy, pregnancy or lactation, current infection (meningitis, pneumonia, urinary tract infection or osteomyelitis) and fever (oral temperature > 38.5° C). We excluded all the patients with post-traumatic seizures and those with known seizure disorders prior to the injury. All the patients with cortical injuries received 7 days of prophylactic phenytoin (according the guideline for the management of severe traumatic brain injury [10]) and none were on anticonvulsant on the time of inclusion in the study.

We included only those patients with complete medical charts with 3- and 6-month follow-up data. Case and control groups were matched primarily regarding age, mechanism of injury and GOS at inclusion. Patients received cerebrolysin based on their own preference. As this is not an approved drug for TBI, we suggest this therapeutic option to the patients. We included those patients who received the drug in case group and those who did not received it were considered as controls. Cerebrolysin was administered 1 month after the primary injury and none of the patients received cerebrolysin during the acute phase of the injury. Institutional review board (IRB) and medical ethics committee of Shiraz University of Medical Sciences approved the study protocol before recruitment. As this was a retrospective analysis, no informed written consents were required.

2.2. Study protocol

All the patients admitted to our center with TBI during the study period were evaluated for eligibility after 1 month of therapy. We recorded the demographic information, clinical findings, surgical managements and the GOS after 1 month in a data gathering form. These information included age, gender, mechanism of injury, on admission GCS, injury severity score (ISS) and CT-scan findings according to Rotterdam and Marshall classification [28]. The GOS at 1 month after the initial trauma was recorded and those with GOS of 2 and 3 were further included in the study. Cerebrolysin (Cerebrolysin®, EVER Neuro Pharma GmbH., Austria) was administered intravenously in 10 mL dosage daily for 30 days. Cerebrolysin was diluted with physiological saline to a total volume of 100 mL and was infused over 20 min. The infusion was discontinued if the patients developed fever or convulsions. The cerebrolysin administration was discontinued if the patient developed seizures. In the case of post-cerebrolysin seizures, proper anticonvulsants were started. There was no blinding as the patients received the drug based on their own preference and according to the neurosurgeon prescription. All the patients were visited in an outpatient clinic and received the cerebrolysin in a nursing facility.

2.3. Follow-up and outcome measures

We recorded the 3- and 6-month follow up data. The Glasgow outcome scale extended (GOSE) was evaluated by a neurosurgeon in each visit and was recorded into the data gathering form. Each patient was followed for 6 months and the final GOSE was recorded accordingly.

2.4. Statistical analysis

All the recorded data were entered into a computer database and was further analyzed with statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 16.0. Data are presented as mean ± SD and proportions as appropriate. The proportions were compared using chi-square test while the parametric variables with normal distribution were compared by independent *t*-test. The parametric variables without normal distribution were compared using Mann-Whitney *U* test. Paired *t*-test was used to compare the parametric variables within groups. We also used a multivariable logistic regression model to eliminate the effects of confounders. A two-sided p-value of less than 0.05 was considered statistically significant.

3. Results

Overall we included a total number of 129 patients with GOS of 2 and 3 one month after the TBI who received cerebrolysin (n = 65) or nothing (n = 64). The mean age of the patients was 33.3 ± 16.4 (ranging from 16 to 88) years. Among the patients there were 110 (85.3%) men and 19 (14.7%) women. Motor-vehicle accidents were the most common mechanism of injury accounted for 69 (53.4%) patients. The baseline characteristics of the patients in two study groups are summarized in Table 1. As demonstrated, there was no significant difference between two study groups regarding the baseline characteristics and all the variables were matched between the cerebrolysin and control groups.

In those who received cerebrolysin, the GOSE increased significantly from baseline to 3-month ($p < 0.001$) and from 3-month to