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# Investigation of the effect of cerebrolysin on patients with head trauma and diffuse axonal injury

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**KEYWORDS**

Brain Teauma, diffuse axonal injury, cerebrolysin, Outcome

**A B S T R A C T**

Traumatic brain injury is one of the main causes of death and disability in America and Iran and every year about of 53,000 people die in America because of this. Moderate to severe brain damage causes of death and disability in physical and cognitive activities. Cerebrolysin improves performance and accelerates regeneration of damaged nerve cells. The aim of this study was to investigate the effect of cerebrolysin in patients with head trauma and diffuse axonal injury. In a clinical trail study that perfored in Neurosurgery department of Tabriz University of Medical Scienences on patients head trauma that had diffuse axonal injury, the effect of the effect of cerebrolysin in patients with head trauma and diffuse axonal injury evaluated. Twenty five patients underwent tratment by cerebrolysin and 28 patients evaluated in control group. Mean age of patients in control group was 30.53±16.54 year and in case group was 27.84±15.24 year(P=0.542). Mean Admission day count in control group patients was 15.82±13.19 day and in control group was 23.72±21.91 day(P=0.114). Mean Admission GCS score of patients in control group was 6.78±0.91 in case group was 6.72± 0.84(P=0.788). Mean Discharge time GCS score of patients in control group was 9.57±4.96 in case group was 13.32±3.31(P=0.002). Mean Discharge time GOS score of patients in control group was 2.96±1.59 in case group was 4.08±1.11(P=0.005). Significant increase was found in GCS score of patients in both group but mean increase rate of GCS in control group was 2.78± 4.98 and in case group was 6.60±3.26 that significantly higher in case group than control group. Eight patient of control group and 2 patients of case group, died due to the severity of the trauma. Although the mortality rate in the control group was approximately four times more than the case group but the difference was not statistically significant.

## Introduction

Traumatic brain injury is among the major causes of death and disability in America and Iran as every year about 53000 individuals in America die of these injuries

(1-2). Moderate to severe traumatic brain injuries lead to death and the inability to perform physical and cognitive activities (3-5).

Cerebrolysin is a pharmaceutical composition composed of low-weight nerve stimulator peptides and amino acids. This medicine has been applied to different cases in some European and Asian countries. Very little side effects of this medicine have been reported so far. Shi et al. (1990) for the first time used this medicine to treat patients with hemorrhagic stroke (6). Cerebrolysin has also been used as an effective treatment for acute ischemic stroke (7).

This medicine increases the neurons' intake of oxygen and thus reduces the concentration of lactic acid and free radicals. In numerous studies, Cerebrolysin has also demonstrated its effectiveness for neural improvement (8-9).

Cerebrolysin leads to a considerable improvement in the cognitive and non-cognitive activities of Alzheimer patients. It also leads to the enhancement of symptoms and daily activities of patients suffering from stroke (7-10). Plosker et al. reported the effectiveness of Cerebrolysin for treatment of vascular dementia (11).

Various medicines have been administered so far to enhance the cognitive and physical performance of patients with traumatic brain injury. Due to the unique effectiveness of Cerebrolysin for this condition and this medicine is properly and safely tolerated by patients with hemorrhagic stroke (12), it is recommended to use this medicine on these patients. Hence, in the present research, it was decided to analyze the positive effect of this medicine on such patients. The objective was to determine the ameliorative effect of Cerebrolyn on basic treatment of patients with traumatic brain injury.

## Materials and Methods

In a clinical trial performed in the neurosurgery department of the Medical Sciences University of Tabriz, the effect of Cerebrolysin on patients with axonal traumatic brain injury was examined.

## Method

A total of 53 patients suffering from moderate to severe traumatic brain injury with 6-12 GCS were examined in the following two groups: experimental group (25 patients) and control group (28 patients). In this study, patients over 18 who had visited the Imam Reza Clinic and who had at most suffered from 48 hours of traumatic brain injury were consecutively studied by the project manager. The resulting random figures were divided into two groups as follows:

First group (experimental group): Patients received basic treatment as well as 10 mL of Cerebrolysin procured from Austria. This daily treatment lasted for 10 days.
The GCS of patients was recorded at the time of reception, 24 and 48 hours after admission, one week after admission, and at the time of release. GOS of patients was also recorded at the time of release.

Second group (control group): These patients received basic treatment as well as placebo. GCS of patients in the control group was also recorded at the time of reception, 24 and 48 hours after admission, one week after admission, and at the time of release. GOS of patients was also recorded at the time of release.

A comparison was performed between the ages, genders, and hospitalizations as well as levels of GCS at the time of reception, 24 and 48 hours after admission, one week after admission, and at the time of release. GOS levels of patients were also compared at the time of release.

Patients suffering from one of the following diseases or demonstrating one of the following symptoms were excluded from the study: severe renal, hepatic, pulmonary and cardiac diseases; decreased consciousness due to the intake of drugs or alcohol; history of stroke; pregnancy; life threatening repeated traumas; brain dysfunction symptoms; and epilepsy symptoms.

## Data Statistical Analysis

In order to compare quantitative data, the T-test method was used for independent groups. The chi-square test was also used to perform qualitative analyses of the data.
The Paired-Samples T-test method was also employed to draw a comparison between variations in the course of treatment. The statistical significance level for this study was determined to be 0.05. This clinical trial was registered at www.IRCT.ir as IRCT201304031288N2.

## Moral Considerations

Formal consent of patients' companies was obtained after providing them with adequate comprehensible information. The research was carried out in accordance with the Helsinki Statement and all of the duties defined in this statement were fulfilled for the examination of patients under study.

## Results and Discussion

In this study 53 patients with brain trauma suffering from axonal injuries were selected and the effect of Cerebrolysin drug was compared with placebo in these patients and the following results were obtained:

25 patients were treated with Cerebrolysin in case group and 28 patients were studied in the control group. 26 patients from case group and 23 patients in the control group were male and the remaining were female (P = 1). The mean age of the patients in the control group was 30.53±16.54 and it was 27.84±15.24 year in case group, respectively (P = 0.542).

The mean number of days of hospitalization, mean GCS of patients on admission, duration of treatments and time of clearance of patients and mean GCS of patients on when discharging in two groups are shown in table 1.

There was a significant increase in the amount of GCS of patients in both groups after the study. The amount of GCS increase was 2.78±4.98 in case group and 3.26±6.60 in control group which was significantly higher than case group.
Laboratory findings of patients in the two groups are shown in table 2. The Distribution of patients GCS in case and control groups during treatment is shown in charts 1 and 2.

8 patients in the control group and 2 patients in case group died because of the severity of the injury. Although the rate of mortality among patients in the control group was approximately four times the patients in case groups but this difference was not statistically significant (P = 0.056).

Neuroprotective content of Cerebrolysin, a therapeutic compound from a low molecular weight neuropeptide and free amino acids

from porcin origin, has been shown to has profound effects on neural toxicity, inhibition of the formation of free radicals, microglia activation, neurotrophic activity, inducing neuronal sprouts, improving cell cycle and stimulation of neurogenesis. Multi-factors approach was successful in laboratory models of ischemia, reducing infarct volume after blockage of middle artery of brain and improving neurogenesis in a dent jiros (13).

In a study by Lucas et al at the University of Otto-von-Guericke of Germany in 2014 the effect of Cerebolysin on Rat shwanoma cells they was investigated and he found that Cerebolysin cause the intensification of activity of shwanoma c ells and qunsequently the neural regeneration (13).

In a study by Shchudlo et al. at the University of Kurgan of Russia in 2013 on the evaluation of the effect of Cerebolysin on the performance and expression of neural cells they suggest that Cerebolysin leads to performance improvement and acceleration of regeneration in neural cell injuries (14).

In a study by Abdel-Salam et al. in Egypt's Cairo University in 2013 the effect of Cerebolysin on the expression of brain trauma was studied and Cerebolysin had a useful therapeutic effect in patients with traumatic brain injury (15).

In this study we also investigated therapeutic effects of Cerebolysin in patients with cerebral trauma accompanied with progressive axonal injuries and according to the results of this drug on patients it could be found that this drug is effective in accelerating the process of treatment of patients in comparison with the placebo.

In a study performed by Formichi at the department of neuro surgery of Sie Nay University of Italy in 2012 it became obvious that Cerebolysin has anti-inflammatory and anti-oxidative effects in patients with traumatic brain injury (16).

In a research by González Alcántara et al at the University of Puebla of Mexico in 2012, the effects of Cerebolysin on neurons studied and useful therapeutic effects of this drug on neuron injuries was confirmed(17). Study of Zhivolupov et al in Russia on therapeutic effects of Cerebolysin in patients with cerebral trauma they expressed that this drug has useful therapeutic effects and leads to improvement of patients (18).

Wang et al carried out a research in the neurosurgery Department of the University of Hong Kong in 2005 about evaluation of the therapeutic effects of Cerebolysin on prognosis of the patients with traumatic brain injury and found that 67% of patients had a good prognosis (GOS 3-5) in 6-month follow-up, so they suggested that according to the beneficial effects of Cerebolysin in the treatment of patients with moderate to severe brain trauma and lack of adverse effects in these patients, this drug could be used for the treatment of Patients with traumatic brain injuries (19).

In our study the mean GOS of patients at the time of discharge was 2.96±1.59 in control group and 4.08±1.11 in patients of case group and the mean of GOS was significantly higher in patients of case group (treated with Cerebolysin ) at the time of discharge compared to patients in the control group (P = 0.005).

**Table.I** Days of hospitalization, mean GCS and GOS of patients in two groups

| | Group | | P |
|---|---|---|---|
| | Case | Control | |
| Admission day count | 15.82 ± 13.20 | 23.72 ± 21.92 | 0.114 |
| Admission GCS | 6.79 ± 0.92 | 6.72 ± 0.84 | 0.788 |
| GCS 24 hour late | 6.79 ± 1.42 | 7.52 ± 0.87 | 0.030 |
| GCS 48 hour late | 6.82 ± 1.39 | 7.96 ± 2.67 | 0.053 |
| GCS 1 week hour late | 8.33 ± 3.36 | 10.20 ± 3.75 | 0.073 |
| Discharge time GCS | 9.57 ± 4.96 | 13.32 ± 3.31 | 0.002 |
| Discharge time GOS | 2.96 ± 1.60 | 4.08 ± 1.12 | 0.005 |

**Table.II** Laboratory finding of tow groups

| | Group | | P |
|---|---|---|---|
| | Case | Control | |
| BUN | 37.21 ± 18.71 | 31.36 ± 7.96 | 0.153 |
| Cr | 0.98 ± 0.27 | 0.94 ± 0.29 | 0.638 |
| $K^+$ | 4.11 ± 0.70 | 4.20 ± 0.42 | 0.574 |
| $Na^+$ | 144.14 ± 4.27 | 142.44 ± 4.69 | 0.172 |
| BS | 180.54 ± 77.13 | 204.56 ± 72.52 | 0.250 |
| Hb | 12.43 ± 3.17 | 11.73 ± 1.87 | 0.338 |
| PLT | 241.36 ± 81.23 | 220.28 ± 86.44 | 0.365 |
| WBC | 15621.43 ± 7309.52 | 16536.40 ± 5076.34 | 0.603 |

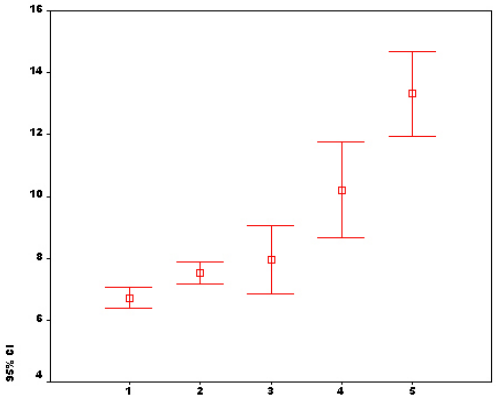


**Chart.I** Distribution of Case group patients at during of treatment

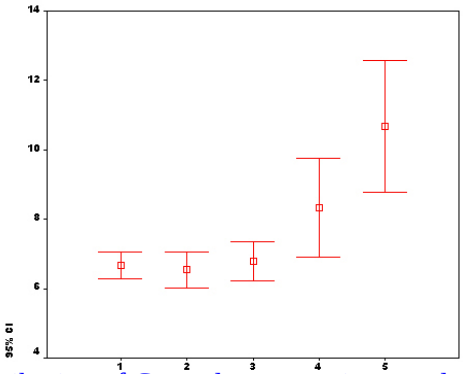


**Chart.II** Distribution of Control group patients at during of treatment

The study of Ladurner et al at the Neurology Department of Austria University of Salzburg in 2005 on the effects of Cerebolysin on ischemic stroke showed beneficial effects of this drug in such patients (20). In a study done by ALvarez et al at the University of Santa Marta de Babia of Spain in 2003 on the effects of Cerebolysin on patients with ischemic stroke they expressed that Cerebolysin is a useful, safe and effective medication for improving the prognosis of the patients with neuronal injuries (21).

Bornstein et al also studies therapeutic effects of Cerebolysin in patients with brain injuries they concluded use of Cerebolysin may lead to improving the prognosis of the patients and the acceleration of the process of treatment effectively (22).

In our survey there was a significant increase in the amount of GCS in both groups after the study and the amount of increase was 2.78±4.98 in control group and 6.60±3.26 in patients of case group which was significantly higher than those in the control group.

8 patients in the control group and 2 patients in case group died because of the severity of the injury. even though the rate of mortality among patients in the control group was about four times the patients in case groups but this difference was not statistically significant (P = 0.056).

Cerebolysin is regarded as a useful therapeutic product in the prognosis of patients with traumatic brain injury combined with progressive axonal injury improving and accelerating the process of treatment of patients in comparison with the placebo according to the results obtained from patients. In our study the mean GOS when discharging patients of case group (treated with Cerebolysin) was more than those in the control group, significantly.

## Conclusion

In our research there was a significant increase in the amount of GCS in both groups but the degree of increase of the GCS was significantly higher in case rather than control group. Although the mortality rate in patients in the control group was approximately four times the patients of case groups but this difference was not statistically significant.

In accordance with the results and the useful effect of Cerebolysin in traumatic patients it is recommended that use of this drug in patients in case of not having the prohibition. Further studies with high sa mple size are recommended.

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