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Full Length Research Paper

A double-blind, placebo-controlled and randomized trial of Cerebrolysin in patients with acute ischemic stroke in Iran

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Stroke is the third common cause of mortality and the most common neurologic disease resulting disability in the United States. Because the disability caused by this disease and its effects on the quality of life of the patients and economic burden, is an important health problem in the societies. Various treatments proposed for this disease that one of them is cerebrolysin administration. This agent stimulates cell differentiations, has direct effect of neurons' regeneration, reduce the infarct size area, reduce the apoptosis and edema and stabilize blood circulation to involved area. The aim of this study was evaluating the therapeutic effect of cerebrolysin in patients with stroke. In a randomized controlled trialed 122 patients with confirmed ischemic acute stroke enrolled to study. The patients divided to two groups, study and control group. The study group received 10 ml cerebrolysin in 100 ml saline as an infusion for 30 minutes daily during seven days and control group received only saline same by same way of the study group. All the patients evaluated at the days 1, 3, 7 and 30 for the CSS, MRS and Barthel index for treatment results. The results analyzed by t- student test and chi-square test with the SPSS software. The mean of Canadian Stroke Scale score (CSS) at the day 7 increased about 59% in study group and about 42% in the control group (p>0.05). There was not significant differences between two groups in terms of subgroup (CSS (GCS, tongue and physical functions) Barthel and MRS index (P>0.05)). This study indicates cerebrolysin has not noticeable effect in the patients with acute ischemic stroke.

Keywords: Ischemic Stroke, Cerebrolysin, Efficacy.

INTRODUCTION

Stroke is a syndrome that starts with acute neurologic problems which lasts at least for 24 hours, and it is the reflex of localized involvement of CNS and a disorder in blood circulation in the brain (Simon et al., 2009). Stroke is developed because of two problems in brain vessels which are ischemia and bleeding. About 80% of strokes are developed because of ischemia. Major causes of stroke have acute decrease of blood circulation into brain, diffuse lesions of atherosclerosis and disorders of little vessels and thrombotic or ambolic obstruction in blood suppliers artery. Diffuse lesions of atherosclerosis make disturbance with reparative mechanisms in border

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regions and the disorder of little vessels leads to infarcts cavity in deep structures of the brain. In all of these ischemia strokes, a sudden decrease of regional blood circulation is responsible for a functional disorder leading to activates cascade of pathophysiologic mechanisms that cause tissue damages. When blood circulation becomes lower than threshold, it causes damage in neurologic function instantly, but if the range of blood circulation becomes normal after short time it, this damage can be recovered (Lipsanen and Jolkkonen, 2011). The most effective known treatment till know is restoration of blood circulation that could be gotten through thrombolytic during the first hours after attack. The treatments which are used for stroke are intra-arterial or intravenous thrombolytic and anti platelets drugs (like aspirin, clopodogrel, ticlopidine and dipyridamole) and anti coagulant therapy and sometimes surgery (cerebellum hemorrhage) (Simon et al., 2009). Other treatments are suggested for patient's amelioration like injection of cerebrolysin and erythropoietin. Cerebrolysin is a hydrolyzed protein obtained from pig brain. This protein is combined from low molecular weight (LMW) peptides and amino acids and function of this protein is related to breakage of LMW peptides (Shamalov et al., 2010). Treatment with cerebrolysin during first 24-48 hours after stroke increases the role of neurogenesis in the ischemic region and ameliorates patient's function. This drug increases the rate of secretion, differentiation and migration of stem cells from supraventricular zone (SVZ) into ischemic zone and this process itself amplifies the neurogenesis of caused by cerebrolysin (Zhang et al., 2010). It can also prevent degeneration of cytoskeleton by increasing the major protein in cytoskeleton of neurons. This drug stimulates the range of cell differentiation, amplifies the function of neurons, and has direct effect on restoration of neurons (Hutter-Paier et al., 1996). This drug affects directly on neurons and by increasing the plasticity in neurons can enhance the level of learning (Schwab et al., 1998). It decrease the level of infract, inhibits the apoptosis and edema, stabilizes the perfusion and ameliorates cognitive performance. Among human studies which have been conducted, this drug increases the activity of the patients and reduces the patients need to care and support. Overall, 60/70% of patients show positive responses to this drug (www.everpharma.com.A4866.Austria.April 2009). Combined treatment with cerebrolysin and thrombolytic may be studies in future trials, restoration of blood flow with the usage of cerebrolysin relying on its neurotrophic and neuroprotective properties, may be a good therapy for ischemic stroke in future.

Ischemic stroke has a great role in incidence of mortality and disability in addition to remained physical remained disability, this disorder imposes a lot of psychic problems on patients, even affects the quality of entourage's lives. As regards studies about cerebrolysin and its effectiveness on improving stroke patients health have been done in different researches with different results and in limited studies, the effectiveness of cerebrolysin has been described brightly, but in most studies ,the beneficial effects of cerebrolysin have been shown. This research has been enrolled to ameliorate the clinical status of stroke patients with the usage of cerebrolysin.

MATERIAL AND METHODS

Patients

In this case-control clinical trial double blinded study the inclusion criteria were everyone with ischemic stroke, the age between 40-85 years and it hasn't passed more than 24 hours after stroke and the exclusion criteria were coma, hemoragic stroke, malignant hypertension (with oliguria), myocardial infarction (MI) and heart failure (CHF) MI and CHF, chronic kidney disease (CRF), liver disease, severe senile dementia and it has passed more than 24 hours after stroke.

3 scale applications were used in this study and the numbers of sample for each group were 61 individuals. Canadian stroke sale scale: It is use for assessment of stroke patients in early diagnosis and it is covering assessments of consciousness level, speech, motor function and the patient gets different scores according to his/her above abilities. Two scales are available for determination of (outcome) fate of disease. Modifued Rankin Scale: This scale is between 0-6 and 0 means the patient is independent in doing individual tasks and 6 means the patient is dead. Barthel Index: It analysis some individual tasks like walking, dressing, bathing and etc…and according to doing these abilities ,every patients gain a score. This scale is between 0-100 and 0 means the patient is dependent totally and 100 means the patient is independent completely.

In this case-control clinical trial double blinded study, 122 patients which were examined by neurologic specialist and their ischemic stroke were approved by CT scan, based on inclusion criteria and after their consent, participated in this study. The sampling method was based on Block Randomization through different subtypes of patients based of their seventy of injuries. Basic information like GCS, age and other primary variables were gotten and recorded. The eligible patients were divided randomly into two groups (The intervention group and the control group). First, before dividing patients in to two groups, the severity of injury which was caused by stroke, was measured based of CSS scale. If CSS was below 6.5, the severity of injury was considered as a severe injury, If CSS was between 7-10, the severity of injury was considered as moderate and if the severity of injury was 10 or more, the severity of injury considered as slight injury. In the next step, according to the importance of severity of injury, we tried to divide patients

Table 1. Status scale of Canadian stroke scale in case group in first day

Conscious status	Group	Number	Score mean±Standard deviation	p-value
Conscious	Intervention	55	7.90±2.18	2.55
	Control	54	8.33±1.74	
Unconscious	Intervention	6	2.88±1.64	2.72
	Control	7	1.78±1.38	

Table 2. Status scale of Canadian stroke scale in case group in third day

Conscious status	Group	number	Score mean ±Standard deviation	p-value
Conscious	Intervention	55	7.90±2.17	0.20
	Control	54	8.37±1.67	
Unconscious	Intervention	6	3.25±1.75	0.44
	Control	7	2.50±1.63	

into two groups of 61 patients which are the same based on their severity of injuries. It means that in every subgroup (slight, moderate and severe), we need 20 patients which are selected randomly through patients. Every two groups got the usual treatments for ischemic stroke like control of the blood pressure, lipid lowering drugs, regulating blood sugar drugs and physiotherapy after stabilizing vital signs. In addition this is usual treatment, the intervention group got 10cc cerebrolysin in 100cc of 0.9% normal saline (overall 110cc) through intravenous (IV) IV during 7 consecutive days. The first dose was injected to patients at last after 24 hours of onset of symptoms. For prevention of bias and for matching interventions in two groups in order to comply blinding in this study, in addition to usual treatments, the control group got just 110cc of 0.9% saline. The infusions of control group and intervention group were prepared by one of colleagues who did not have any information about analysis of patients status. Then a number was allocated to each treatment group. Patients and specialists were not informed about the mentioned encoding.

Statistical analysis

In this study, for data analysis the SPSS 16 software was used. The average index, frequency and the standard deviation index were reported. In analytical analysis, bivariant T-test and Chi-square test were used. The significant p-value was considered below 0.05.

RESULT AND DISCUSSION

The mean age of patients in case group was 70.72±8.64 and in control group was 72.21±8.23 and according to the mean age, no significant difference was shown among two group (p value=0.33). In terms of gender, 26 of patients equivalent of 57/4% were women in control patients equivalent of 54% were men and 28 of patients equivalent to 45/9% were women and no significant difference was indicated in terms of gender among two groups.

As demonstrated in Table 1, analysis of CSS scale showed that in the first day of hospitalization the mean of conscious patients among intervention group was 7.90±2.18 and the mean of conscious patients among control group was 8.33±1.74. This difference between two groups wasn't significant (p value=2.55).

As shown in Table 2, analysis of Canadian stroke scale among patients showed that in third day of hospitalization the mean among conscious patients in intervention group was 7.90 ±2.17 and the mean among conscious patients in control group was 8.37±1.67.This difference is not significant (p value=0.2). Also, in the third day of hospitalization, the mean among unconscious patients in intervention group was 3.25±1.75 and among unconscious patients in control group was 2.50±1.63. This difference was not significant too (p value=0.44).

Analysis of CSS scale in the 7th day of hospitalization showed that the mean in case group was 8.45±7.52 and the mean in the control group was 8.72±1.37 and this difference was not significant too (p value=0.32).

According to Table 3, Analysis of sub types of Canadian stroke scale in patients in seven days of hospitalization showed that the mean of conscious level in case group 3 and control group was 2.97±0.19 And there was no significant statistical in both group (p value=0.31). In terms of tongue mean was in case group 0.83±0.26 and in control group was 0.81±0.27 (p value=0.40). Also, according to Barthel index scale the mean score in case group was 71.80±3.80 and in control group was 66.55±1.55 that mean in case group is more than control group, but there was no significant in both group and according to Modified Rankin Scale (MRS) the mean score in case group was 2.80±1.45 and in control

Table 3. The abilities status of Canadian stroke scale in patient in 7th day

Characteristics of case study	Group	Score mean ±Standard deviation	p-value
Conscious	Intervention	3	0.31
	Control	2.97±0.19	
Language	Intervention	0.83±0.26	0.40
	Control	0.81±0.27	
Motor Function	Intervention	4.61±1.41	0.17
	Control	4.94±1.20	

group was 2.95±1.55 and there was no significant in two group (p value=0.51).

This study aimed to investigate the effect of cerebrolysin drug on improvement of ischemic stroke patients. The intervention group and control group did not have significant difference in terms of age and gender. The severity of injury caused by stroke was measured by CSS scale on the visit day and before taking the drug. In this term, no significant difference was shown among intervention group and control group. In the 3th day and 7th day of hospitalization, the patients were examined again and their recovery process was measured by CSS scale and in this term, no significant difference was indicated between two groups. In 2010 in Russia, a research was enrolled on 47 patients and the severity of injury which caused by stroke was measured through continuous visits by NIHSS scale there was not significant difference among two groups (Shamalov et al., 2010).

In 1390 in Iran, a study was done on 47 patients and severity of injury caused by stroke was measured through continuous visits by NIHSS scale (Aminianfar et al., 2013). They did not get any significant difference between two groups, either. So the results of these two studies are the same with our research. In this present study, after 30days the patients were reexamined and their physical abilities were measured by Barthel index and MRS scale. No significant difference was shown among intervention group and control group. Since this study analysis remained disability caused by stroke, it showed that taking cerebrolysin cannot decrease the physical disability among patients.

A study was enrolled on 47 patients in Russia in 2010 and in this study, 24 of patients were injected 50 ml drug during 10 days (Shamalov et al., 2010). They concluded that in MRI after stroke, the volume of infarct in intervention group decreased in comparison with control group but it didn't have any effect on physical function of patients.

Another study was enrolled on 36 ischemic stroke patients in 2004, indicated that taking cerebrolysin with dosage of 10 and 50 ml per day can ameliorate sensomotor disorders among patients (Skvortsova et al., 2004).

In terms of impact on physical function, in a study which was enrolled on 47 patients were gotten cerebrolysin with dosage of 50 ml per day, for 7 days, and in a research which was done in Germany on 539 patients which were gotten cerebrolysin with the dosage of 30 ml per day for 10 days, it can be said that this drug does not have any effect on physical function of patients (Aminianfar et al., 2013; Heiss et al., 2012). So the results are the same with our study.

In a study which was enrolled in Australia on 146 patients, 78 of patients were intravenous injected cerebrolysin with dosage of 50 ml per day for 21 days and then the functional ability and cognitive ability were evaluated (Ladurner et al., 2005). This study indicated that this drug has no effect on physical abilities of the patients, but it can improve the cognitive function of patients. But in our study, the cognitive ability showed no significant difference between control group and intervention group. It is possible that this difference arises for the higher dosage of the drug and also for the longer period of treatment with crebrolysin in Australia.

In a study which was enrolled in Italia in 2010 on 156 patients, 52 patients were injected cerebrolysin with dosage of 30 ml per day for 21 days (Jianu et al., 2010). This research indicated that this drug can improve tongue's relapse of aphasia patients after stroke, but it has no effect on physical function of patients and this indication is as our result in our research. But in this study it was no significant difference between case group and control group from the point of tongue's relapse. May

be it was for higher dosage of the drug and also the longer period of treatment in Italia.

In another study on 180 ischemic stroke patients, 40 patients were injected 50 ml cerebrolysin per day for 3 weeks. The come out of patients were assessed by Barolin's Scale. The results showed that the patients which took the drug, showed significant improvements in their motor function and also in their activities and social communication in comparison with control group (Koppi and Barolin, 1998).

Among the participating patients in this study, one death has been reported among intervention group, but no death has been reported among intervention group. So from this point of view, it is no significant difference between two groups. This result is similar the studies which was done in Russian (Shamalov et al., 2010) and Australia (Ladurner et al., 2005), but it is different from the results of the study which was enrolled in Germany (Heiss et al., 2012). Among participating patients in this study, two cases of patients in control group faced to stroke recurrence and both of them were men. But no stroke recurrence was seen among intervention group. This result cannot be compared with the results of other studies, because the stroke recurrence wasn't assessed in other studies.

CONCLUSION

Cerebrolysin drug in the area of cognitive function, Tongue and physical performance was not helpful. So it may be concluded in patients with stroke was not effective. Therefore it suggests that broader studies with more sample number and higher dosage should be done in order to assessment the results with more analysis.

REFERENCE

Aminianfar M, Salehi H, Saidi A, Ranjbar naeeni, Rastgo F (2013). The Cerebrolysin efficacy in acute ischemic stroke. Ann. Mil. Health Sci. Res. 10(4):293-299.

Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z (2012). Cerebrolysin in patients with acute ischemice stroke in Asia. Am. Stroke Assoc. j. 43(3):630-636.

Hutter-Paier B, Frühwirth M, Grygar E, Windisch M (1996). Cerebrolysin protects neurons from ischemia – induced loss of microtubule – associated protein. J. Neurol. transm. 47:276.

Jianu DC, Muresanu DF, Bajenaru O, Popescu BO, Deme SM, Moessler H, Meinzingen SZ, Petrica L (2010). Cerebrolysin adjuant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artry. .J. Med. Life. 3(3):297-307.

Koppi S, Barolin G (1998). The use of Cerebrolysin in the treatment of ischemic stroke. Neurol. Psychiat. J. 10:30-34.

Ladurner G, Kalvach P, Moessler H (2005). Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomized controlled trial. J. Neural. Transm. 112(3):415-428.

Lipsanen A, Jolkkonen J (2011). Experimental approaches to study functional recovery following cerebral ischemia. Cell. Mol. Life Sci. 68(18): 3007-3017.

Schwab M, Antonow-Schlorke I, Zwiener U, Bauer R (1998). Brain-drived peptides reduse the size of cerebral infarction and loos of MAP2 immunoreactivity after focal ischemia in rats, Ageing and Dementia. J. Neural. Transmis. 53:299-313.

Shamalov NA, Stakhovskaia LV, Burenchev DV, Kichuk IV, Tvorogova TV, Botsina AIu, Smychkov AS, Kerbikov OB, Moessler H, Novak P, Skvortsova VI (2010). Effects of cerebrolysin 50 ml/day on brain lesion morphometry in patients with ischemic stroke. Neurol. psychiat. j. 12(2):270-276.

Simon RP, Greenberg DA, Aminoff MJ (2009). Clinical b Neurology. 7th ed. MC Graw-Hill companies, Inc. pp. 292-328.

Skvortsova VI, Stakhovskaia LV, Gubskiĭ LV, Shamalov NA, Tikhonova IV, Smychkov AS (2004). A randomized double – blind placebo – controlled study of the safety and efficacy of cerebrolysin in thetreatment of acute ischaemic stroke. Neurol. psychiat. j. 11:53-59.

www.everpharma.com.A4866.Austria.April 2009

Zhang C, Chopp M, Cui Y, Wang L, Zhang R, Zhang L, Lu M, Szalad A, Doppler E, Hitzl M, Zhang ZG (2010). Cerebrolysin enhances neurogenesis in the ischemic brain and improves functional outcome after stroke. J. Neuroci. Res. 18(15):3275-281.