Thai J Neurol Surg 2023;1(1):1-11.

Research Article

Clinical Outcome and Safety of Cerebrolysin® For Neurological Recovery after Traumatic Brain Injury and Stroke

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Abstract

Background: Traumatic brain injury and stroke lead to a brain dysfunction and complex neurological sequelae despite aggressive surgical intervention and secondary brain injury prevention. However, alternative neuromodulation therapies can be a potential modality. Cerebrolysin is the drug which contains peptides derived from the brain of a pig that has potential neuroprotective properties and may help to protect and repair brain cells.

Objective: To compare the efficacy and safety of Cerebrolysin with usual care.

Methods: Randomized single blind study from December 2016 to May 2022. 68 Subjects including all the adult patients with severe disability (GOS of 2 and 3) after trauma or stroke. Patients were classified to receive cerebrolysin (n=32) and usual care (n=36). Cerebrolysin was administered intravenously in 30 mL dosage daily for 21 days. The 6-month NIHSS, Barthel Index and modified Rankin Scale were recorded. The outcome scales, safety and complications were compared between two study groups.

Results: Baseline characteristics were comparable between two groups. We found that NIHSS and modified Rankin Scale were significantly lower in those receiving cerebrolysin [6.40 ± 2.13 vs 10.02 ± 3.75 (p = 0.013) and 2.34 ± 0.11 vs 3.2 ± 0.46 (p=0.048)] and Barthel Index was significantly higher in those receiving cerebrolysin [77.23 ± 11.71 vs 68.82 ± 9.63 (p = 0.025)]. Cerebrolysin administration was associated with lower mortality rate, and no significant in seizure, cardiovascular complication, recurrent ischemic stroke and intracerebral hemorrhage.

Conclusion: Cerebrolysin administration is associated with improved functional neurorecovery and increased favorable outcome.

Keywords: Cerebrolysin, Functional neurorecovery, Severe Disability, Traumatic brain injury

บทคัดย่อ

การศึกษาผลลัพธ์ของการรักษาทางคลินิกและความปลอดภัยในการใช้ยาเซเรโบรไลซินในผู้ป่วยที่ได้รับบาดเจ็บที่สมองจากอุบัติเหตุและผู้ป่วยโรคหลอดเลือดสมอง

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ที่มาและความสำคัญ: การบาดเจ็บที่สมองจากอุบัติเหตุและโรคหลอดเลือดสมองนำมาสู่การสูญเสียการทำงานของสมองและภาวะแทรกซ้อนทางระบบประสาทที่ตามมาหลายอย่างแม้ว่าจะได้ทำการผ่าตัดรักษาแล้วและให้การดูแลเพื่อป้องกันการบาดเจ็บของสมองแบบทุติยภูมิอย่างไรก็ตามการรักษาด้วยยากระตุ้นและปรับเปลี่ยนการทำงานของเซลล์ประสาทเป็นทางเลือกหนึ่งของการรักษาผู้ป่วยดังกล่าว ยาเซเรโบรไลซินเป็นยาที่สกัดมาจากสมองของสุกรซึ่งมีประสิทธิภาพในการปกป้องและช่วยซ่อมแซมเซลล์สมองที่ถูกทำลาย

วัตถุประสงค์: เพื่อเปรียบเทียบผลลัพธ์ของการรักษาทางคลินิกและความปลอดภัยของกลุ่มผู้ป่วยที่ได้รับยาเซเรโบรไลซินกับการรักษาตามปกติ

วิธีการศึกษา: เป็นการศึกษาแบบการสุ่มผู้ป่วยที่ทำการศึกษาแบบ single blind ตั้งแต่เดือนธันวาคม 2559 ถึงเดือนพฤษภาคม 2565 ได้ผู้ป่วยบาดเจ็บที่สมองจากอุบัติเหตุและโรคหลอดเลือดสมองทำการศึกษาทั้งหมด 68 ราย จำแนกเป็นผู้ป่วยที่ได้รับยาเซเรโบรไลซิน จำนวน 32 รายและผู้ป่วยที่ได้รับการรักษาตามปกติจำนวน 36 ราย โดยผู้ป่วยที่ได้รับยาเซเรโบรไลซินจะได้รับยาเซเรโบรไลซินในขนาด 30 มิลลิลิตรวันละครั้งต่อเนื่องจำนวน 21 วัน และประเมินผลลัพธ์ของการรักษาทางคลินิกโดยการใช้คะแนน NIHSS, Barthel Index และ modified Rankin Scale ที่ระยะเวลา 6 เดือน

ผลการศึกษา: ข้อมูลพื้นฐานผู้ป่วยที่ทำการศึกษาทั้งสองกลุ่มสามารถทำการเปรียบเทียบกันได้เนื่องจากไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ ในผู้ป่วยที่ได้รับยาเซเรโบรไลซินพบว่ามีระดับคะแนน NIHSS และ modified Rankin Scale น้อยกว่ากลุ่มผู้ป่วยที่ได้รับการรักษาตามปกติอย่างมีนัยสำคัญทางสถิติ [6.40 ± 2.13 vs 10.02 ± 3.75 (p=0.013) และ 2.34 ± 0.11 vs 3.2 ± 0.46 (p = 0.048)] และผู้ป่วยที่ได้รับยาเซเรโบรไลซินพบว่ามีระดับคะแนน Barthel Index สูงกว่ากลุ่มผู้ป่วยที่ได้รับการรักษาตามปกติอย่างมีนัยสำคัญทางสถิติ [77.23 ± 11.71 vs 68.82 ± 9.63 (p = 0.025)] ซึ่งมีความสำคัญกับผลลัพธ์ของการรักษาทางคลินิกที่ดี ผู้ป่วยที่ได้รับยาเซเรโบรไลซินมีอัตราการเสียชีวิตที่น้อยกว่า และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในอาการชัก, ภาวะแทรกซ้อนทางระบบหัวใจและระบบไหลเวียนโลหิต และ การเกิดซ้ำของโรคหลอดเลือดสมองทั้งในกลุ่มสมองขาดเลือดและเลือดคั่งในสมอง

บทสรุป: การใช้ยาเซเรโบรไลซินช่วยให้มีผลลัพธ์ของการรักษาทางคลินิกที่ดีในผู้ป่วยบาดเจ็บที่สมองจากอุบัติเหตุและโรคหลอดเลือดสมอง

Keywords: ยาเซเรโบรไลซิน, ผลลัพธ์ของการรักษาทางคลินิกที่ดี, บาดเจ็บที่สมองจากอุบัติเหตุ, โรคหลอดเลือดสมอง

Introduction

Traumatic brain injury and stroke can lead to hypoxic–ischemic encephalopathy (HIE)[1], a brain dysfunction due to oxygen deprivation with a complex neurological sequela. The pathophysiology of HIE is not entirely understood, with surgical intervention and secondary brain injury prevention being the standard treatment with only limited value. However, alternative neuroprotective therapies can be a potential treatment modality. Cerebrolysin[2] is the drug which contains peptides derived from the brain of a pig that has potential neuroprotective properties. Some of the proteins in Cerebrolysin are found naturally in the human brain and may help to protect and repair brain cells. It is widely used in the treatment of acute ischemic stroke and used in neurological practice for recovery of stroke patients and treatment of dementia[3]. Despite the evidence-basis[4] and some experimental studies[5], the distinct mechanisms of pharmacological action of this drug was active peptide fragments of nerve growth factor, enkephalins, orexin, halanin. The results of current clinical and experimental studies[6-7] of cerebrolysin have been compared. The activity of above-mentioned neuropeptides explain experimental and clinical details of all known effects (neurotrophic, neuroprotective and immunomodulating) of cerebrolysin in ischemic and neurodegenerative CNS injuries[8-14]. Cerebrolysin has up to 6 month treatment window post-ischemic insult. TBI is one of the risk factors in developing cognitive impairment at a later stage and induces breakdown of the blood-brain barrier (BBB) to serum proteins into the brain and leads to extravasation of plasma amyloid beta peptide (AβP) into the brain fluid compartments causing brain pathology. In this study, we used Cerebrolysin (Ever NeuroPharma, Austria) is a neurotrophic nerve growth factors and active peptide fragments in exploring its effects on alterations in key excitatory (Glutamate, Aspartate) and inhibitory (GABA, Glycine) amino acids in the CNS in relation brain pathology in dose and time-dependent manner. In severe traumatic brain injury (TBI) patients with nonoperative lesions are known to have a poorer prognosis. Recent and ongoing clinical studies5 have been exploring the utility of Cerebrolysin in improving patient outcomes among TBI patients. Compared to the control group, a significantly higher proportion of patients who received Cerebrolysin treatment achieved a favourable outcome at Day 21 post-TBI. The mean length of hospital stay was approximately seven days shorter in the Cerebrolysin group. Neurotrophic nerve growth factors are the most important endogenous molecules involved in brain protection and recovery[22]. The objective of this study was to compare the clinical safety and efficacy of Cerebrolysin with usual care in patients after traumatic brain injury and both acute ischemic and hemorrhagic stroke.

Materials and Methods

Randomized interventional prospective cohort study from December 2016 to May 2022. 68 Subjects including all the adult patients with severe disability (GOS of 2 and 3) after trauma or stroke. Randomization and treatment with the trial medication initiated within 12 hours after trauma or stroke onset. Signed informed consent was obtained from the patient or the patient's legally accepted representative. For randomization which patients received cerebrolysin or usual care, we used block of four

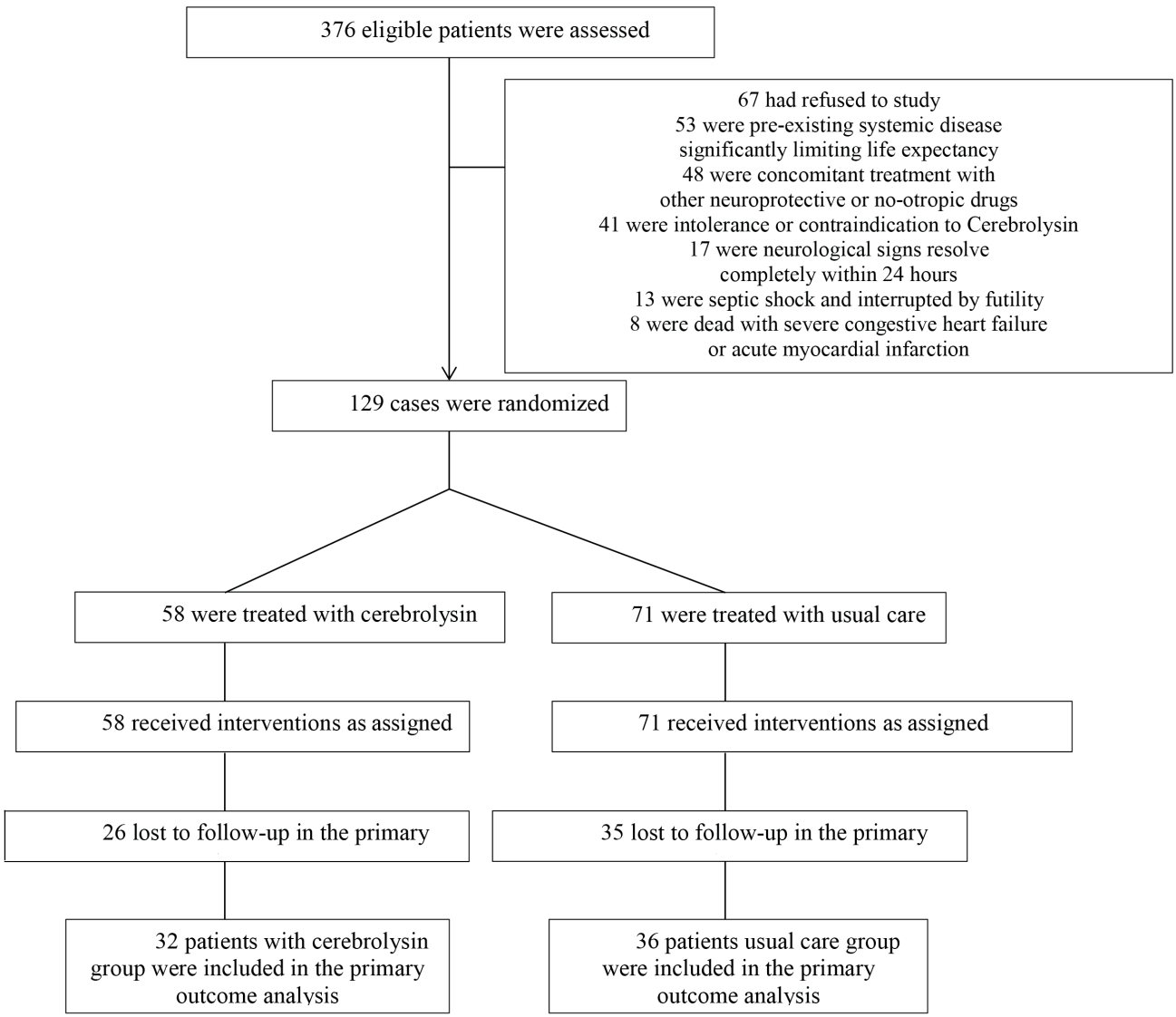

Figure 1 Flow chart of patient enrollment and analysis in this study

method by randomize 1:1 ratio by variables block size and used computer-generated sequence and allocation, single blind by opaque envelopes (concealed with opaque envelopes), patients were classified to receive cerebrolysin (n = 32) and usual care (n = 36). Cerebrolysin was administered intravenously in 30 mL dosage daily for 21 days. The 6-month NIHSS, Barthel Index and modified Rankin Scale were recorded. The outcome scales, safety and complications were compared between two study groups. with approval by the institutional ethics committee. Consecutive patients with age > 18 years having focal neurological deficits presenting with magnetic resonance imaging (MRI) brain or computed tomography (CT) head suggestive of

MCA territory AIS presenting within 24 hour of symptom onset, National Institute of Health Stroke Scale (NIHSS) score of >4 and with a modified Rankin Scale (mRS) score of 0 or 1 before the stroke were included in this study. Patients with hemorrhagic stroke, brainstem and cerebellar strokes, transient ischemic attacks, brain tumor, demyelinating dis-

eases, inflammatory diseases, craniotomies, traumatic brain injuries, hepatic failure, congestive heart failure, acute myocardial infarction, pregnancy and lactation, systemic malignancy, acute or chronic renal failure, and known allergy to above group of drugs/ tetracycline group of drugs were excluded from the study.Primary study endpoints were 6 month in an a priori-ordered sequence of hypotheses (fixed sequence of multidimensional endpoints). A follow-up assessment was performed at this period. The study duration for each patient was scheduled for 6 month. The study was performed in the Phramongkutklao hospital, with a planned total of 68 participating. Enrollment criteria were designed to recruit patients after TBI, hemorrhagic and ischemic stroke.

Baseline characteristics between two groups of patients

Table 1 Baseline characteristics comparison between two patient groups.

Variables	Cerebrolysin (n=32)	Usual care (n=36)	*p*-value
Male, n (%)	14 (43.8)	16 (44)	1.0
Age (yr)	70 ± 12	62 ± 15	0.16
BMI (kg/m2)	22.7 ± 3.4	22.0 ± 2.1	0.58
Coexisting diseases, n (%)			
HT	13 (40.6)	16 (44.4)	0.480
DLP	8 (25)	10 (27.8)	0.751
DM	8 (25)	10 (27.8)	0.751
CKD	2 (6.3)	3 (8.3)	0.65
chronic liver disease	2 (6.3)	3 (8.3)	0.65
CAD	2 (6.3)	1 (2.8)	0.106
Smoking	8 (25)	10 (27.8)	0.751
Alcohol	2 (6.3)	3 (8.3)	0.65
Thrombolysis treatment	2 (6.3)	3 (8.3)	0.65
ASPECTS score (median)	5	6	0.63
NIHSS score	13.1 ± 4.59	14.15 ± 5.30	0.8
APACHE II Score	12.7 ± 1.95	12.65 ± 2.23	0.940
Time until admission (hr)	11.59 ± 3.25	11.81 ± 3.301	0.381
Time until treatment (hr)	13.1 ± 4.10	13.30 ± 4.95	0.741
Dominant lobe	16 (50)	18 (50)	1
BI score	31 ± 2.93	37.5 ± 2.25	0.56
mRS score	3.75 ± 0.29	4.5 ± 0.27	0.15
Survival at hospital admission	16 (80)	13 (65)	0.480
Pulmonary complication	2 (10)	1 (5)	0.231
Seizure complication	11 (34.4)	13 (36.1)	0.598
Cardiovascular complication	7 (21.9)	9 (25)	0.559
Recurrent ischemic stroke	2 (6.3)	3 (8.3)	0.64
Recurrent intracerebral hemorrhage	1 (5)	3 (8.3)	0.3
Means days in neuro intensive care unit	5	6	0.63

Value presented as mean ± SD. or n (%). *P*-value corresponds to Independent-t test and Fisher's exact test. Abbreviations: ASPECTS, Alberta Stroke Program Early CT score; BI, Barthel Index; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

Baseline characteristics between two groups of patients

Table 2 Baseline characteristics comparison between two patient groups in specific condition.

Variables	Cerebrolysin (n=32)	Usual care (n=36)	*p*-value
Acute hemispheric ischemic stroke	11 (34.4)	14 (38.9)	0.592
– Right MCA or ICA infarction	7 (21.9)	9 (25)	0.447
– Left MCA or ICA infarction	4 (12.5)	5 (13.9)	0.584
Acute hemorrhagic stroke	13 (40.6)	15 (41.7)	0.139
– Right Basal ganglion	4 (12.5)	5 (13.9)	0.584
– Left Basal ganglion	2 (6.25)	3 (8.3)	0.630
– Right Thalamic	1 (3.1)	1 (2.8)	1.000
– Left Thalamic	1 (3.1)	1 (2.8)	1.000
– Right cerebellar	1 (3.1)	1 (2.8)	1.000
– Left cerebellar	1 (3.1)	1 (2.8)	1.000
– Lobar	2 (6.25)	1 (2.8)	0.980
– Brainstem	1 (3.1)	2 (5.6)	0.849
Traumatic Brain injury	8 (25)	7 (19.4)	0.965
– Acute subdural hematoma	3 (9.4)	4 (11.1)	0.776
– Acute Epidural hematoma	2 (6.25)	1 (2.8)	0.106
– Traumatic intracerebral hemorrhage anywhere	1 (3.1)	1 (2.8)	1.000
– Others traumatic brain injury	2(6.25)	1 (2.8)	0.106

Value presented as n (%). *P*-value corresponds to Independent-t test and Fisher's exact test. Abbreviations: ICA, Internal carotid artery; MCA, Middle cerebral artery; Others traumatic brain injury, Diffuse axonal injury, Traumatic subarachnoid hemorrhage, Combination of Traumatic intracerebral hemorrhage

Participants

From December 2016 to May 2022. 68 Subjects including all the adult patients with severe disability (GOS of 2 and 3) after trauma or stroke. Patients were classified to receive cerebrolysin (n=32) and usual care (n=36). Cerebrolysin was administered intravenously in 30 mL dosage daily for 21 days. The 6-month NIHSS, Barthel Index and modified Rankin Scale were recorded. The outcome scales, safety and complications were compared between two study groups.

Standard medical therapy

All patients were admitted to a stroke unit or intensive care unit in the department of Neurology and Neurosurgery. The patient's head was kept elevated by 30°. All patients were kept in a mild fluid restriction state with 1,800 ml of daily fluid in the first week. Intravenous antihypertensive agents were administered when blood pressure was higher than 220/120 mmHg. Body temperature was kept below 38°C and blood glucose level was maintained at less than 180 mg/dl. Endotracheal intubation was

Table 3 Comparison of outcome assessment pre- and post-therapy between two patient groups at 6 month follow-up.

Variables	Cerebrolysin (n=32)	Usual care (n=36)	*p*-value
Pre-NIHSS score	13.1 ± 4.59	14.15 ± 5.30	0.8
Post-NIHSS score	6.40 ± 2.13	10.02 ± 3.75	0.013
Pre-BI score	31 ± 2.93	37.5 ± 2.25	0.56
Post-BI score	77.23 ± 11.71	68.82 ± 9.63	0.025
Pre-mRS score	3.75 ± 0.29	4.5 ± 0.27	0.15
Post-mRS score	2.34 ± 0.11	3.2 ± 0.46	0.048
Survival after hospital discharge at 6 month	19 (59.4)	10 (27.8)	<0.001
Seizure complication at admission	11 (34.4)	13 (36.1)	0.598
Seizure complication after discharge	15 (46.9)	18 (50)	0.291
Cardiovascular complication at admission	7 (21.9)	9 (25)	0.559
Cardiovascular complication after discharge	8 (25)	10 (27.8)	0.751
Recurrent ischemic stroke	2 (6.3)	3 (8.3)	0.64
Recurrent ischemic stroke after discharge	6 (18.8)	7 (19.4)	0.754
Recurrent intracerebral hemorrhage	1 (5)	3 (8.3)	0.3
Recurrent intracerebral hemorrhage after discharge	2 (6.3)	4 (11.1)	0.45

Value presented as mean ± SD. or n (%). *P*-value corresponds to ANOVA. Abbreviations: ANOVA, analysis of variance; BI, Barthel Index; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation

performed to maintain adequate tissue oxygenation in patients with clinical deterioration or signs of respiratory insufficiency. Hyperventilation was used only in an emergency with the target level of $PaCO_2$ of 30–35 mmHg. Osmotherapy with Mannitol or glycerol launched when there was an evidence of mass effect. Mannitol was administered with the dosage of 0.25–0.5 g/kg body weight bolus. During osmotherapy, blood osmolarity was maintained at approximately 300–320 mOsm/l. Oxygenation, blood pressure, glucose were sustained at appropriate level. Early enteral nutrition was given. Pneumonia and deep venous thrombosis were monitored and well treated.

Outcome assessment

The clinical assessment to record the functional outcome was done at discharge, 3 and 6 months. Barthel index (BI) and mRS were employed to assess the functional outcome. The mRS score and BI were recorded at admission, 3 and 6 months. The hospital mortality and its causes were also included. Outcome was assessed with mRS at 3 and 6 months follow-up. It was dichotomized into good outcome (mRS 0 to 3) and poor outcome (mRS 4 to 6).

Hemodynamic monitoring

Radial arterial catheter and central venous catheter was linked to a bedside monitor on one side and to a specific transducer (Philips Intellivue Philips MX600, USA) for blood pressure and central venous pressure (CVP) monitoring. If patients have unstable hemodynamics value of cardiac output (CO)

and Stroke volume (SV) were estimated from pulse contour analysis (EV1000 clinical platform, Edwards advanced hemodynamic monitoring tools for an integrated Edwards Critical Care System, USA).

Statistical analysis

Student's unpaired t -test was used to compare continuous variables expressed as mean ± standard deviation. Chi-squared test was used to compare categorical variables expressed as frequency with percentage. Analysis of variance tests and multiple comparison tests were used for comparison of NIHSS, mRS, and BI scores among individual NPA and placebo group. Mann–Whitney U tests were used to determine a significant change in mRS score at 3 and 6 months. Kruskal–Wallis tests were used to determine the existence of statistically significant differences among different groups with change in mRS score at 3 and 6 months. p-value ≤ 0.05 was considered as statistically significant. The statistical analyses were conducted using SPSS 23 software.

Ethics approval and consent to participate

Institutional Review Board Royal Thai Army Medical Department Ethics Committee approved this study on December 8, 2016. Research no. R102h/59 followed Council for International Organization of Medical Science (CIOMS) Guidelines 2012 and Good Clinical Practice of International Conference on Harmonization statement no.IRBRTA1731/2559.

Result

68 patients with severe disability 6-month. The baseline characteristics were comparable between two groups. We found that NIHSS and modified Rankin Scale were significantly lower in those receiving cerebrolysin [6.40 ± 2.13 vs 10.02 ± 3.75 (p = 0.013) and 2.34 ± 0.11 vs 3.2 ± 0.46 (p = 0.048)] and Barthel Index was significantly higher in those receiving cerebrolysin [77.23 ± 11.71 vs 68.82 ± 9.63 (p = 0.025)]. Cerebrolysin administration was associated with lower mortality rate, and no significant in seizure, cardiovascular complication, recurrent ischemic stroke and intracerebral hemorrhage.

Discussion

In this study we found that in patients with severe disability after 6-month follow-up. NIHSS and modified Rankin Scale were significantly lower and Barthel Index was significantly higher in cerebrolysin group. Cerebrolysin administration was associated with lower mortality rate, and no significant in seizure, cardiovascular complication, recurrent ischemic stroke and intracerebral hemorrhage similar with CAPTAIN studies[8,9], that Cerebrolysin was the only agent that was associated with a significant improvement of neurological outcome after stroke and for adults with mild traumatic brain injury (MTBI) frequently results in impairments of cognitive functions which would lead to psychological consequences in the future. Cerebrolysin can significantly improve cognitive function that could explain by inhibited cleaved caspase-3, conversion of LC3-II, down-regulation of Bcl-2 and amelioration of secondary brain damage and functional recovery after cerebral infarction[11] and this study correspond to MCI (mild cognitive impairment) that suggests the impact of cerebrolysin on the pathogenesis of MCI[12] that Cerebrolysin accelerated recovery and prevented acute neuronal damage. Previous clinical trials support

therapeutic effects in stroke patients[13] when clinical was longer than 24 hours[17] causes significant morbidity including physical dependence, cognitive decline, depression, and seizures. The treatment of AIS includes neuroprotective drugs (NPDs)[18-21] act directly on the neuron, prevent disruption of the blood brain barrier (BBB) and loss of microvascular integrity that triggers extracellular and intracellular proteolytic cascades had ability to reduce tissue damage and help in improving functional outcomes and quality of life of patients.For Traumatic brain injury, the effectiveness of cerebrolysin on Glasgow outcome score (GOS) showed favorable GOS[15-16]. The pharmacological modulation of cerebrolysin in the ischemic cascade include glutamate release and glutamate receptor activation, excitotoxicity, calcium influx into cells, mitochondrial dysfunction, and activation of intracellular enzymes, free radical production, nitric oxide production, apoptosis, and inflammation can promote neuroprotection. In our study, The objective of our study was to determine the effectiveness of cerebrolysin in changing the functional outcome at 6 months of patients with AIS involving MCA territory showed beneficial effect in treated group with significant improvement in NIHSS score, BI score, and mRS score. The mean time between stroke onset and cerebrolysin administration was within 12 hours. In the previous studies[23,24], it was from 5 to 24 hours. There was decrease in NIHSS score and improvement in BI score and improved the functional outcome. Cerebrolys in acute stroke treatment in Asia trial showed that had an improvement in the NIHSS on day 90 compared with placebo. and in AIS showed significant improvement of 21-day NIHSS scores with cerebrolysin. The small sample size was the limitation of our study. It was a single-blinded study wherein the investigators were aware about the neuroprotective agents received by the patients and the outcome was assessed by the investigators themselves with a possibility of research bias. A randomized control trial with a bigger sample size is required to strengthen the results of this study.

Limitation

This study has some limitations. First, the benefit of surgery in motor and aphasia recovery is progressive and sustained until 1 year. Results of the present study suggests that 6 months outcome assessment may be insufficient to understand the true benefit and at least 1 year follow-up should be recommended for measuring its functional benefit. Second, our study was conducted in single center. Finally, many exclusion criteria so many patients were excluded. In this study, performance and emotional state outcome measures were applied. This approach may be complemented in the future by measures that evaluate subjective health related quality of life, such as the QOLIBRI instruments (Quality of life after brain injury), in order to facilitate treatment effectiveness measurement from the patient's perspective.

Future direction

Although small sample size was the limitation of our study. The outcome was assessed by the investigators themselves with a possibility of research bias. A randomized control trial with a bigger sample size is required to strengthen the results of this study.

Conclusion

Cerebrolysin administration in patients with

severe traumatic brain injury and stroke is associated with improved functional neurorecovery, and decreased mortality rate.

Conflict of interests

No potential conflict of interest relevant to this article was reported.

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