EFFECT OF CEREBROPROTEIN HYDROLYSATE WITH CITICOLINE VERSUS CITICOLINE ALONE IN THE INITIAL MANAGEMENT OF HEAD INJURY AND ITS CLINICAL OUTCOME "A PROSPECTIVE RANDOMISED COMPARATIVE STUDY"

Varadaraju D. N[1], Ananthakishan[2]

[1]Assistant Professor, Department of Neurosurgery, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru.
[2]Professor, Department of Neurosurgery, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru.

ABSTRACT

BACKGROUND

Traumatic brain injury is an important cause of morbidity. It also represents the most frequent reason for neurological illness after headache. Compared with other types of brain insult, traumatic brain injury produces more diffuse injury causing more cognitive and neuropsychiatric disturbances. Various drugs have been used in an attempt to improve the clinical outcome, citicoline and Cerebrolysin hydrolysate have been used to improve the clinical outcome in traumatic brain injury. The evidence thus far has been conflicting with reports in favour and against the use of these drugs in the clinical benefit of the patients with traumatic brain injury. We attempt to determine the benefits and advantages of using these drugs in the management of traumatic brain injury.

MATERIALS AND METHODS

This is a prospective study comprising 60 patients of head injury admitted in the Department of Neurosurgery at Vydehi Institute of Medical Sciences and Research Centre, Bangalore. The purpose of the current study is to evaluate the effect of cerebroprotein hydrolysate with citicoline compared to citicoline alone in the initial management of head injury and its clinical outcome and to assess the improvement.

RESULTS

Sixty patients with head injury were recruited and divided into group A and group B randomly. The mean age was 43.5 years with 43 male patients and 17 female patients. The GCS at admission of 27 patients was mild head injury and of 33 patients was moderate head injury. Group A had 13 patients with mild head injury and 17 patients with moderate head injury. Group B had 14 patients with mild and 16 patients with moderate head injury at the time of admission. The GCS was assessed at 1 week and 3 weeks. On assessing the patients at 1 week, group A had 14 patients with mild head injury and 16 patients with moderate head injury, whereas group B had 14 patients with mild and 16 patients with moderate head injury. The extended Glasgow Outcome Scale (GOSE) was assessed after 6 months in which group A had fifteen patients with a GOSE score of 8, 10 patients with a score of 7 and 2 patients with a score of 6. Whereas, the group B had 10 patients with a GOSE score of 8, 12 patients with a score of 7 and 4 patients had a score of 6.

CONCLUSION

The results suggest a beneficial effect of Cerebrolysin infusion in patients with mild or moderate head injury during the acute phase. This magnitude in terms of GOS improvement certainly is valuable to the patients and further studies to evaluate the role of Cerebrolysin is warranted.

KEYWORDS

Traumatic Head Injury, Citicoline, Cerebrolysin.

HOW TO CITE THIS ARTICLE: Varadaraju DN, Ananthakishan. Effect of cerebroprotein hydrolysate with citicoline versus citicoline alone in the initial management of head injury and its clinical outcome "a prospective randomised comparative study." J. Evid. Based Med. Healthc. 2017; 4(47), 2835-2837. DOI: 10.18410/jebmh/2017/562

BACKGROUND

Traumatic brain injury is an important cause of morbidity. It also represents the most frequent reason for neurological illness after headache compared with other types of brain insult, traumatic brain injury produces more diffuse injury causing more cognitive and neuropsychiatric disturbances.[1]

Traumatic brain injuries are divided into two main categories, primary, which occur at the moment of trauma and secondary one that develops after the initial injury. The secondary injury causes excessive synthesis of nitric oxide and oxidative stress, microglia activation, local inflammatory disturbances of microcirculation and blood brain barrier dysfunction. The above-mentioned processes are the most recently acknowledged delayed mechanism of cell death, which leads to neuronal necrosis, neuronal apoptosis,

Financial or Other, Competing Interest: None.
Submission 01-06-2017, Peer Review 05-06-2017,
Acceptance 08-06-2017, Published 09-06-2017.
Corresponding Author:
Dr. Varadaraju D. N.,
 # 534, 'E' Block, Brigade Golden Triangle,
Huskur, Old Madras Road, Bangalore-560049.
E-mail: varada_82@yahoo.co.in
DOI: 10.18410/jebmh/2017/562

hygroma formation, disturbance in morphofunctional nerve pathway. Therefore, minimising the secondary damage cascade could result in maximising post injury favourable evolution/recovery including more rapid and consistent neurorehabilitative outcome.[2]

Various drugs have been used in an attempt to improve the clinical outcome.

Cerebrolysin is a peptide preparation produced by biotechnologically standardised enzymatic breakdown of purified porcine brain proteins. It consists of approximately 15% peptide with a molecular weight not exceeding 10 kD and 85% amino acids based on total nitrogen. The solution is free of proteins, lipids and antigenic properties.[3]

Unique neurotrophic activity that results in pleiotropic effects that provides for efficient neurogenesis, neuronal survival, neuromodulatory effect, neuronal plasticity, neuronal repair and neuroimmunotrophic actions.

Cerebroprotein hydrolysate has been shown to counteract the negative effect of the elevated FGF-2 on neurogenesis and neuronal maturation.[4]

Cerebroprotein hydrolysate augmented proliferation, differentiation and migration of adult SVZ neural progenitor cells, thus significantly increased the number of neural progenitor cells and neuroblasts to contribute to neurogenesis.

It counteracts, destructive effects of glutamate and reversibly inhibits calpain and hence prevents ion-induced neurodegeneration, decreases brain demand for oxygen, increased resistance to hypoxia-ischaemia and significantly decreases lactate level.[5]

Expression of the blood brain barrier-GLUT-1 gene is augmented in brain with brain-derived neurotrophic factor and cerebroprotein increases GLUT-1 expression (responsible for >90% of glucose transport), promotes production of GAP - 43 (growth associated protein), which helps in sprouting of axons and dendrites in CNS.

MATERIALS AND METHODS

This is a prospective study comprising 60 patients of head injury admitted in the Department of Neurosurgery at Vydehi Institute of Medical Sciences and Research Centre, Bangalore. The purpose of the current study is to evaluate the effect of cerebroprotein hydrolysate with citicoline compared to citicoline alone in the initial management of head injury and its clinical outcome and to assess the improvement.

The data was collected in prescribed proforma, which contained particulars of the patient, clinical history, examination findings, diagnosis and treatment.

The inclusion criteria being patients admitted with head injury (age 15-69 years) willing to give informed consent or their formal primary caregiver who would sign the informed consent.

Exclusion criteria being patients' refusal, patients needing immediate surgery for defined causes like EDH, SDH, parenchymal contusions and haematoma, patients below 14 and above 70 years, patients with psychiatric illness on treatment, patients with polytrauma, patients with severe liver and renal disease, pregnancy, lactation and known epileptic patient on treatment.

Patients' assessment includes GCS at admission, 1 week and 3 weeks and extended Glasgow outcome scale at 6 months.

60 patients were randomly divided into 2 groups in which 30 cases were given cerebroprotein hydrolysate with citicoline (group A) and 30 cases were given citicoline only (group B).

Group A - Inj. Cerebrolysin 60 mg twice daily for 10 days + citicoline 2 g stat followed by 500 mg twice daily continued for 3 months.

Group B- citicoline 2g stat followed by 500 mg IV/p.o. twice daily continued for 3 months.

Ethics- Ethical committee clearance was taken for the treatment of the patients.

Statistical Analysis- The results of two groups were compared and analysed by using Fisher's exact test. A 'P' value of <0.05 will be considered as statistically significant.

RESULTS

Sixty patients with head injury were recruited and divided into group A and group B randomly. The mean age was 43.5 years with 43 male patients and 17 female patients. The GCS at admission of 27 patients was mild head injury and of 33 patients was moderate head injury. Group A had 13 patients with mild head injury and 17 patients with moderate head injury. Group B had 14 patients with mild and 16 patients with moderate head injury at the time of admission. The GCS was assessed at 1 week and 3 weeks. On assessing the patients at 1 week, group A had 14 patients with mild head injury and 16 patients with moderate head injury. Whereas group B had 14 patients with mild and 16 patients with moderate head injury.

When the same was assessed at 3 weeks, 3 patients from group A and 4 from group B were lost to follow up. On assessment at 3rd week, group A patients had 16 patients with mild and 11 patients with moderate head injury, whereas group B patients had 12 patients with mild and 14 patients with moderate head injury.

The extended Glasgow Outcome Scale (GOSE) was assessed after 6 months in which group A had 15 patients with a GOSE score of 8, 10 patients with a score of 7 and 2 patients with a score of 6. Whereas, the group B had 10 patients with a GOSE score of 8, 12 patients with a score of 7 and 4 patients had a score of 6.

None of the patients from either of the groups had any drug reactions.

1.	**Dead**	**D**
2.	Vegetative state	VS
3.	Lower severe disability	SD-
4.	Upper severe disability	SD+
5.	Lower moderate disability	MD-
6.	Upper moderate disability	MD+
7.	Lower good recovery	GR-
8.	Upper good recovery	GR+

Table 1. Extended Glasgow Outcome Scale

DISCUSSION

Various studies have demonstrated that an important part of the recovery after traumatic brain injury occurs in the first 6 months after the injury. A functional recovery is essential for the patient to return to society. Most of the mild and moderate head injury patients studied had cognitive and physical deficits, which hindered their eventual recovery.[6] The neurotrophic effects of Cerebrolysin are theoretically beneficial to traumatic brain injury patients in particular when considering the cognitive function. With these data in mind, we performed this study to observe and record its clinical effect. The results were encouraging with more patients attaining good outcome at 6 months in the Cerebrolysin group as compared to the citicoline group.

Study conducted by Lombardi VR et al reported cerebroprotein down regulates the microglial activation and controls the expression of IL-1 beta.[7] Citicoline cytidine diphosphate choline is a naturally occurring, water soluble biological compound that is an essential intermediate for the synthesis of phosphatidylcholine, a major constituent of the gray matter of brain tissue. Citicoline promotes brain metabolism by enhancing the synthesis of acetylcholine and restoring phospholipid content in the brain.[8] Citicoline is approved for treatment in cases of head trauma, stroke and neurodegenerative disease in Japan and Europe. Citicoline improves the clinical outcome following an ischaemic stroke as evinced by the reduction in size of lesions caused by ischaemic strokes after supplementation.

No significant side effects were noted. The safety profile in head injury patients is confirmed with the current series.[9]

In our series, the outcome with the Cerebrolysin with citicoline group had a better recovery than the patients in the citicoline only group. Group A had a statistically significant outcome as compared to Group B with a p value of 0.03 when assessed at the 6th month follow up based on extended Glasgow outcome scale.

CONCLUSION

The results suggest a beneficial effect of Cerebrolysin infusion in patients with mild or moderate head injury during the acute phase. This magnitude in terms of GOS improvement certainly is valuable to the patients and further studies to evaluate the role of Cerebrolysin is warranted.

REFERENCES

[1] Wong GK, Zhu XL, Poon WS. Beneficial effect of Cerebrolysin on moderate and severe head injury patients: result of a cohort study. Acta Neurochir Suppl 2005;95:59-60.

[2] Wilson J, Pettigrew L, Teasdale G. Emotional and cognitive consequences of head injury in relation with Glasgow outcome scale. J Neurol Neurosurg Psychiatry 2000;69(2):204-209.

[3] Alvarez XA, Sampedro C, Figueroa J, et al. Reductions in qEEG slowing over 1 year and after treatment with Cerebrolysin in patients with moderate-severe traumatic brain injury. J Neural Transm 2008;115(5):683-692.

[4] König P, Waanders R, Witzmann A. Cerebrolysin in TBI: a pilot study of a neurotropic and neurogenic agent in the treatment of acute traumatic brain injury. Journal Für Neurologie Neurochirurgie Und Psychiatrie 2006;7(3):12-20.

[5] Onose G, Mureşanu DF, Ciurea AV, et al. Neuroprotective and consequent neurorehabilitative clinical outcomes, in patients treated with the pleiotropic drug Cerebrolysin. J Med Life 2009;2(4):350-360.

[6] Zhang C, Chopp M, Cui Y, et al. Cerebrolysin enhances neurogenesis in the ischemic brain and improves functional outcome after stroke. J Neurosci Res 2010;88(15):3275-3281.

[7] Lombardi VR, Windisch M, García M, et al. Effects of cerebrolysin on in vitro primary microglial and astrocyte rat cell cultures. Methods Find Exp Clin Pharmacol 1999;21(5):331-338.

[8] Boado RJ, Wu D, Windisch M. In vivo upregulation of the blood-brain barrier GLUT1 glucose transporter by brain-derived peptides. Neurosci Res 1999;34(4):217-224.

[9] Zafonte RD, Bagiella E, Ansel BM, et al. Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). JAMA 2012;308(19):1993-2000.