Research Article

The Effect of Two Different Doses Regimens of Cerebrolysin on the Outcome of Traumatic Brain Injuries in Intensive Care

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Abstract
Objective: To evaluate the efficacy and safety of two different doses regimen of intravenous Cerebrolysin © (١٠ ml or ٣٠ ml) on the outcome after traumatic brain injuries and to investigate the role of S ١٠٠ β protein as early prognostic markers of outcome after acute traumatic brain injuries.
Methods: ٤٠ patients admitted to ICU with moderate TBI and fulfill the inclusion criteria included in this prospectively randomized double blind study.The patients divided to equal groups group (I) received ١٠ ml of Cerebrolysin and group (II) received ٣٠ ml of Cerebrolysin. Neurological evaluation done by using (GCS), GOS and (APACHE) II score. Blood sampling on admission day collected to detect S١٠٠ β protein on admission, day ٣ and day ٥. **Results*:*** the beneficial effect of Cerebrolysin infusion in patients with moderate TBI during the acute phase, and is more beneficial with Patients receiving high dose of Cerebrolysin © (٣٠ ml) than the patients receiving low dose (١٠ ml). With significant difference between the two groups in the GCS, GOS, Serum level of S ١٠٠ B.
Conclusion: cerebeolysin is safe and tolerated in a dose ٣٠ ml and had a good long term outcome as detected by GOS. These results confirmed by the serum level of S ١٠٠ β which was decreased more in this group.
Key words: S١٠٠ β protein, Cerebrolysin, Moderate TBI.

Introduction
Traumatic brain injury (TBI) defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force[١]. Moderate TBI is ١٥ per ١٠٠.٠٠٠ populations. The highest risk of TBI peaks among the individuals aged ١٥-٣٠ years. Motor vehicle accidents are the leading cause of TBI (approximately ٥٠٪)[٢]. Cerebrolysin© is a neuropeptide derived synthetic preparation produced by breakdown of lipid-free animal neuroprotiens. It regulates the neuronal energy metabolism and is supposed to afford brain protection by its neurotrophic stimulation[٣]. Cerebrolysin© passes through the blood-brain barrier. Up to eight hours after iv administration of Cerebrolysin© neurotophic activity can be detected in the human long-lasting effects even after a single iv administration[٤].

S١٠٠ β, a calcium-binding protein found in high concentrations in astroglia and Schwann cells, is an acknowledged marker of traumatic brain injury (TBI). Increased levels of S١٠٠ β have been reported in minor head trauma as well as moderate and severe TBI[٥]. The use of the neurochemical serum marker, S١٠٠ β, provides valuable information concerning nervous tissue injury, its release into the circulation is associated with secretion by reactive astrocytes and functional disturbances of membrane integrity[٦]. S١٠٠ β is viewed as the most promising biomarker for brain damage.[٧]

Patients and Methods
After obtaining approval of the local ethics committee of El-Minia university hospital and written informed consent were obtained from first degree relative of the patients prior to entry into the study, ٤٤ patients (according to sample size) of either sex, aged between ٢٠-٥٠ years old, with acute TBI admitted to ICU within ٢٤ hours after injury with moderate TBI (GCS ٩-١٢), were enrolled in this prospective rando-mized controlled double blind study. This study been carried out at the intensive care unit (ICU), of Minya University Hospital, between January ٢٠١٢ to May ٢٠١٣.

Patients were excluded if they met the following criteria:Severe renal, liver, lung or cardio-vascular disease, drug or alcohol abuse, concomitant stroke, Pregnancy or lactation, life-threatening multiple trauma. Primary resustation was performed in the form of: maintenance of patient airway, peripheral venous canulation, fluid resustation and drugs therapy.

The randomization was computer based (sealed envelope). The key of the solution was opened at the end of the study. The patients were divided into two equal groups. Each group included ٢٠ patients, Group (I) patients received the solution ١ (cerebrolysin ١٠ ml) by intravenous infusion, the total volume infused ٢٠٠ ml of (٠.٩ saline and solution ١) over ٢٠-minute-periods once daily plus the conventional therapy, during the period of stay in the (ICU), group (II) patients received the solution ٢ (cerebrolysin ٣٠ ml) the total volume infused ٢٠٠ ml of (٠.٩ saline and solution ٢) over ٢٠-minute-periods once daily plus the conventional therapy, during the period of stay in the intensive care unit (ICU).

General assessments: Examine the patients from head to toes. Examine if the patients have congested neck veins, the absence or presence of associated injuries,

Neurological assessments: Severity of the brain injury was assessed by usinghe most widely used methods of initial early assessment is GCS introduced by[٨], long term assessment done by Glasgow outcome scale (GOS)[٩], three months and six months after TBI. Acute Physiology and Chronic Health Evaluation (APACHE) II score[١٠], was done to the patients within the first ٢٤ hours from admission to predict the prognosis of the patients.

Radiological evaluation: Plain X ray on body skeleton, abdominal ultrasound and CT brain at admission and follow ups.

Laboratory investigation:

Routine ICU investigation: CBC, blood urea and serum creatinine, liver function test, blood sugar(random blood glucose).

Specific investigation: for detection of S ١٠٠ β protein (by ELISA). Two ml of venous blood taken from the patients. The separated serum was divided in ٢ eppendorf tubes, one used for routine chemistry and the other one was kept frozen at – ٢٠°c for assay of S ١٠٠ β protein by ELISA (Enzyme-linked immunosorbent assay).

Statistical analysis

Data were collected from patients on admission and during ICU stay. P-value considered significant when it < ٠.٠٥, mean and stander deviation were calculated. Mann-Whitney-U test to compare between The mean values between the two groups for serum level of S١٠٠ beta, GCS, GOS, APACHE II score and The admission value and the following values in the same group for S ١٠٠ β, GCS , GOS.

Results

There was a significant improvement in GCS starting from ٤٨ hours after admission in group I and ٣٦ hours after admission in group II. comparison between the two groups showed significant difference with p value <٠.٠٠١as shown in fig (١).

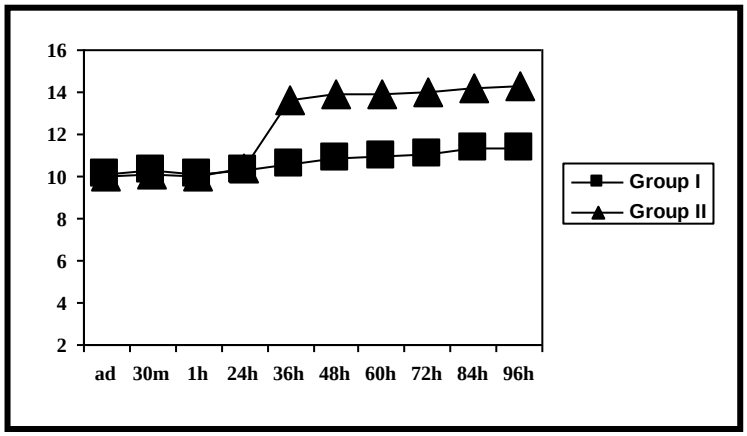

Fig. (١): Changes of GCS in the study groups.

As regards GOS after follow up for ٦ months, our results reveled that, there was no patient got sever disability (score ٣) in both groups. Thirteen cases had moderate disability (score ٤) in group I while only three cases had moderate disability in group II. Seven cases had good recovery (score ٥) in group I while seventeen cases had good recovery in group II. Comparison between the two groups showed highly significant difference at GOS after ٣ months and GOS after ٦ months with p value <٠.٠٠١.

The concentration of the S ١٠٠ ß protein was decreased from admission day (١١٠.٢٥ ± ٥٩.٩٢ pg/ml) to day ٣ (٨٢.١ ± ٤٤.٧ pg/ml) and day ٥ (٥٢.٨ ± ٢٤.٢٣ pg/ml) in group I but was markedly decreased in group II from admi-ssion day (١٢٨.٨ ± ٥٥.٧٥ pg/ml) to day ٣ (٥٦.٥ ± ٢٩.٢٥ pg/ml) and day ٥ (٢٥.٩ ± ٨.٣٧ pg/ml). There was significant difference between the two groups at day ٣ with (P value <٠.٠٥) and at day ٥ with (P value <٠.٠٠١).as shown in table (١) and fig (٢).

Table (١): Change in the level of serum S ١٠٠ ß (pg/ml) (Mean ±SD)

Time	Group I	Group II	P value (GI Versus GII)
Admission (Day ١)	١١٠.٢٥ ± ٥٩.٩٢	١٢٨.٨ ± ٥٥.٧٥	NS
Day ٣)	٨٢.١ ± ٤٤.٧ *	٥٦.٥ ± ٢٩.٢٥ *	#
Day ٥)	٥٢.٨ ± ٢٤.٢٣ *	٢٥.٩ ± ٨.٣٧ *	*

NS: non-significant (P-value > ٠.٠٥ is NS).

: P-value = <٠.٠٥

- : P-value = <٠.٠٠١

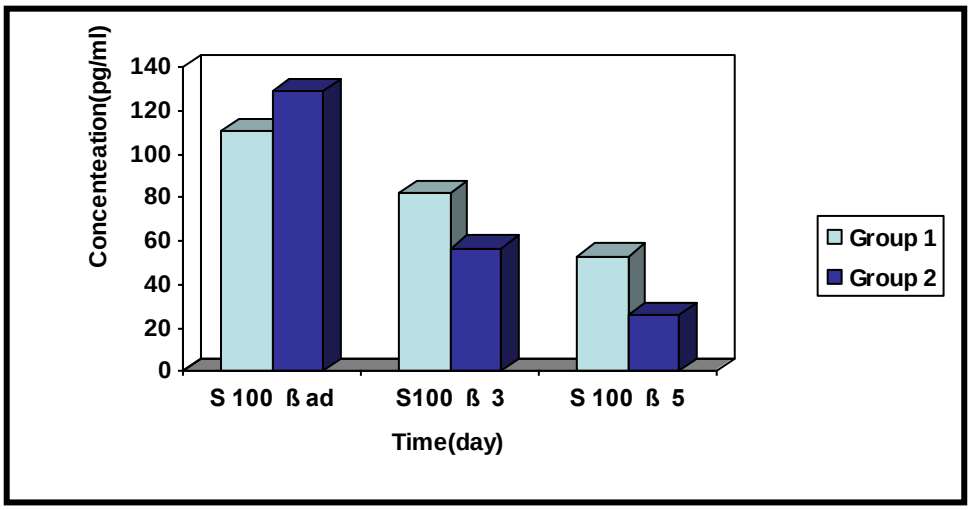

Fig (٢): Changes of serum S ١٠٠ ß (pg/ml) in both groups

Correlation between Glasgow coma scale and S ١٠٠ ß (pg/ml).

Spearman's rho correlation test was done between GCS and level of S ١٠٠ ß and demonstrate a significant negative correlation between them in both groups as shown in table ٢, figure ٣.

Table (٢): Correlation between GCS and S ١٠٠ ß on admission, day ٣ and day ٥

	Group I		Group II	
	r	P value	r	P value
Admission	-٠.٧٩٢	<٠.٠٠١	-٠.٧٣٣	<٠.٠٠١
Day ٣	-٠.٤٥٧	<٠.٠٥	-٠.٧١٩	<٠.٠٠١
Day ٥	-٠.٥٩٧	<٠.٠٥	-٠.٥٣٦	<٠.٠٥

Discussion

TBI is one of the most common causes of death after cardiovascular diseases and cancer Men are approximately twice as likely to sustain TBI as women[٢].

Numerous studies of patients with severe traumatic brain injury (TBI) have shown an association between serum levels of S١٠٠B and outcome.

The use of the neurochemical serum marker, S١٠٠ β, provides valuable information concerning nervous tissue injury, its release into the circulation is associated with secretion by reactive astrocytes and functional disturbances of membrane integrity[٦].

The primary goal of this study was to evaluate the efficacy and safety of two different doses

regimen of intravenous Cerebrolysin © (as a neuroprotective agent) on the outcome after moderate traumatic brain injuries in intensive care unit and to compare the effect of two doses of Cerebrolysin © (١٠ ml or ٣٠ ml/day) used in traumatic brain injured patients. The secondary goal was to evaluate the role s ١٠٠ β as early progonostic marker in TBI.

In the present study, we found that, cerebeolysin © when taking in the acute phase of TBI can result in clinical and significant improvement in functional outcome of patients as measured by

GOS which were better in patients received high dose of cerebeolysin © (٣٠ ml), group II. This study also demonstrated that cerebeolysin © injection either in ١٠ ml or ٣٠ ml daily is safe and well tolerated.[١١], in their study which aimed to identify the factors predicting outcome following TBI they measured it at ٣ months as a midterm outcome. Six-month GOS scoring is considered an acceptable time period for assessment in head-injured patients, allowing enough time for recovery from the neurologic injury and minimizing losses to follow up[١٢].

According to all previous studies, in our study, we assessed the long term outcome by using the Glasgow outcome scale at, ٣ months and ٦ months after TBI. As regards GOS categories there were no patient in the two groups get score ١ (death) or score ٢ (vegetative state). All patients get score ranged between ٣-٥. On day ٥ there were great decline in the serum level of S ١٠٠ B in group II and the decline in the serum level of S ١٠٠ β much less in group I who receive ١٠ ml of cerebrolycin.

Conclusion

Our study demonstrated that, the beneficial effect of Cerebrolysin infusion in patients with moderate TBI during the acute phase, and is more beneficial with patients receiving high dose of Cerebrolysin © (٣٠ ml) than the patients receiving low dose (١٠ ml). With significant difference between the two groups in the GCS, GOS, Serum level of S ١٠٠ B.

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