ROLE OF NEUROPROTECTIVE AGENT-CEREBROLYSIN IN TRAUMATIC BRAIN INJURY

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Abstract: *Traumatic Brain Injury is a major cause of chronic disabilities like Behavioural problems, Mood cognition, Particularly Memory, Attention and Executive functional commonly impaired by TBI. In TBI patients, over the long-term, this imbalance between EDA and DM may leads to neurodegenerative process characterized by a chronic neuro inflammatory process that can continue for years after the injury. The molecular alterations have direct effects on local circuits and large scale networks by generating heterogenic phenotypes in which cognitive impairment plays an important role. Such impaired cognitive and functional outcomes following TBI can be improved via administration of Neuroprotective agents. Cerebrolysin is a neuropeptide with potential Neuroregenerative entities.*

Key Words: *Traumatic Brain Injury, Cerebrolysin, Glasgow Coma Scale.*

1. INTRODUCTION:

Traumatic Brain Injury (TBI), a form of acquired brain injury, occurs when a sudden trauma causes damage to the brain which is a leading cause of disability under the age of 40s. TBI can result when the head suddenly and violently hits an object, or when an object pierces the skull and enters brain tissue which leads to behavioural problems, mood, cognition, particularly memory, attention, and executive function are commonly impaired by TBI.

Cerebrolysin is a low molecular neuropeptide with neuroregenerative properties, which is prepared from the extract of the porcine brain tissue with specific laboratory and manufacturing considerations. In vitro and in vivo studies have demonstrated several beneficial effects of Cerebrolysin, including decreased excitotoxicity.[1,2]

The highest incidence of TBI is among young(15-25yrs old) and old(75yrs and older) individuals, and it is the first cause of injury related to death and disability in children and young adults; it accounts for hospitalization of approximately 100 cases per 100,000 population /year and for an annual death rate of 18deaths /100000population ,which is even greater in low income countries. Furthermore, it enhances the risk of death for atleast 7yrs after hospitalization and causes long term disabilities more than 1% of the population.[3]

Different types of Scales used in Brain Injury Patients some of them are Advocacy Activity Scale (AAS), Cognitive Log (Cog-Log), Coma Recovery Scale-Revised (CRS-R), Extended Glasgow Outcome Scale (GOS-E), in our study we used Glasscow Coma Scale (GCS). The Glasgow Coma Scale (GCS) is used to measure the depth of coma. The GCS rates three aspects of functioning: Eye Opening, Movement and Verbal Response. Individuals in deep coma score very low on all these aspects of functioning, while those less severely injured or recovering from coma score higher. A GCS score of 3 indicates the deepest level of coma, describing a person who is totally unresponsive. A score of 9 or more indicates that the person is no longer in coma, but is not fully alert. The highest score (4) refers to a person who is fully conscious. It has widespread acceptance because of highly accurate characterization of patients and its high level of inter-observer reliability.

2. PATHOPHYSIOLOGY:

Neurochemical changes associated with TBI:

Normal transmission of signals involves neurotransmitter-mediated activation of receptors and subsequent controlled ionic changes in the postsynaptic membranes of neurotransmitter-releasing cells. Ionic changes across the bilipid membrane are meticulously regulated by energy-dependent sodium-potassium (Na+-K+) ATPase pumps, which maintain the membrane potential between −40 and −70 Mv[5]. TBI induces transient cell membrane disruptions that lead to redistribution of ions and neurotransmitters, altering the membrane potential. During the acute phase (≤1 hour) after TBI, there is a massive release of glutamate from presynaptic terminals, which disrupts ionic equilibrium on postsynaptic membranes. The amount of potassium (K+) released increases with injury severity, as measured by microdialysis [6].More severe injuries produced greater increases (4.3- to 5.9-fold) in [K+] that were tetrodotoxin-resistant. Administration of kynurenic acid, an antagonist of excitatory amino acids, attenuated the [K+] increase in a

dose-dependent manner, suggesting that the K+ surge is dependent on excitatory neurotransmitters. In order for brain cells to fire again, ionic equilibrium must be re-established, which requires ATP (cellular energy).

In addition to rising [K+], calcium (Ca2+) accumulation is also commonly observed after TBI. Accumulation of intracellular Ca2+ activates mitochondrial Ca2+ uptake. Ca2+ overloading of the mitochondria has been shown to induce oxidative stress and to impair mitochondrial function [7].

NEUROTROPHIC FACTOR-LIKE MECHANISMS OF NEUROPROTECTION AND NEUROREGENERATION

Cerebrolysin exerts its effects simultaneously on two physiologically related but functionally independent therapeutic levels: Neuroprotection and Neuroregeneration. These multimodal effects are triggered by immediate and delayed/long-term acting mechanisms. The immediate response arises from interactions with the cellular signaling networks immediately, or soon after, Cerebrolysin is administered. The delayed response, on the other hand, arises from stimulation of Neuroregenerative processes within the nervous tissue. As mentioned earlier, the modulation of the endogenous response to an insult is a feature of NTFs2, and therefore a unique characteristic that differentiates Cerebrolysin from other therapies which are currently employed. This Pleiotropic Neuroprotective Effect which leads to improved neuronal survival consists of several elements. Anti-apoptotic activity offers protection against the progress of the neuro-degenerative cascade which is triggered by chronic or acute insults. The modulation of inflammatory response, as well as the decrease in the amount of free radicals produced in the diseased tissue, are effects which prove important for scaling down the extent of intracellular damage linked with pathological process.

3. LITERATURE REVIEW:

Effects of Cerebrolysin on functional outcome of patients with traumatic brain injury: a systematic review and meta-analysis"

Author name: Fariborz Ghaffarpasand, et.al,

This study has concluded that Intravenous Cerebrolysin administration has been associated with improved functional recovery after TBI as measured by mRS and GOS. The various grades of TBI (mild, moderate, and severe) seem to benefit from Cerebrolysin therapy after the injury with regard to the functional outcome indices. Intravenous could be recommended for treatment of patients with different grades of TBI with level II of evidence. More randomized clinical trials are recommended to elucidate the issue.

Effect of Cerebroprotein in Hydrolysate In management of Mild And Moderate Traumatic Brain Injury-An Institutional Study

Author name: Dr. Duttaluru Seshadri Sheka et.al,

Their results suggest a beneficial effect of Cerebroprotein Hydrolysate infusion in patients with mild and moderate traumatic brain injury. It is safe, can be well tolerated and is associated with improved functional recovery.

Beneficial effect of cerebrolysin on moderate and severe head injury patients: result of a cohort study

Author name: Wong GK, el.al,

Aim of this study was to investigate whether addition of Cerebrolysin to the initial treatment regimen of moderate and severe head injury patients would improve their outcome. It is concluded that the use of Cerebrolysin as part of the initial management of moderate and severe head injury is safe and well tolerated. The results suggest that Cerebrolysin is beneficial in regard to the outcome in these patients, especially in elderly patients**.**

Efficacy of cerebrolysin in the treatment of traumatic brain injuries

Author name: M Khalaf, et.al,

The study concludes that the use of cerebrolysin as part of the initial management of head trauma is effective in improving the clinical status of patients with TBI after 20 days**.**

New Directions in Research and Therapies in Traumatic Brain Injury

Author name: Johannes Thome et.al,

This study has concluded that Cerebrolysin significantly improved Glasgow Outcome Scores (GOS) and respiratory distress (RDS) in patients with moderate or severe TBI at 10 and 30 days compared with controls. This and other experimental treatments have potential in TBI but, in developing such therapies, the design of clinical trials should closely reflect the reality biological processes underlying natural recovery from brain injury.

4. MATERIALS & METHOD:

This prospective & Retrospective Observational study was done to evaluate the role of Cerebrolysin in TBI patients. A total of 60 patients satisfied inclusion and exclusion of study all of them were informed regarding the study and required information was collected from the patient case sheet and the patients.

5. DISCUSSION:

In our study population, we found that maximum patients (n=41) were administered with Cerebrolysin twice daily and for 10 patients it was administered only once daily and the drug was administered thrice daily for 9 patients. Maximum efficacy is seen in 52 patients with frequency of 86.66%. There is no minimum efficacy due to LAMA (n=4) and death (n=4).Out of 60 patients, surgical treatment was performed for 26 patients with frequency of 43.33% and surgery is not performed for 34 patients with frequency of 56.66%.During our study four patients expired and the reasons for mortality were Hypoxia (n=1), Aspiration (n=1) and Cardiac Arrest (n=2) but not due to administration of Cerebrolysin. Among 60 study population, GCS of 52 patients was 15 at the time of discharge.4 cases were LAMA (Left Against Medical Advice). It can be concluded that the use of Cerebrolysin as part of the initial management of moderate and severe head injury is proved to improve GCS and it is safe and well tolerated. The results suggest that Cerebrolysin is beneficial in regard to the outcome in Traumatic Brain patient

6. ANALYSIS:

The data was analyzed based on information obtained from case sheets like Age wise, Gender wise, Drug discontinuation, Drug interactions, Inappropriate prescription

7. RESULTS:

The study “Role of Cerebrolysin in Traumatic Brain Injury” was conducted at Renee Hospital. A total number of 60 patients were admitted in the hospital with Traumatic Brain Injury treated with Cerebrolysin.

DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

GENDER	NO OF PATIENTS	PERCENTAGE (%)
MALE	51	85
FEMALE	9	15

Table.4 Gender wise distribution of patients.

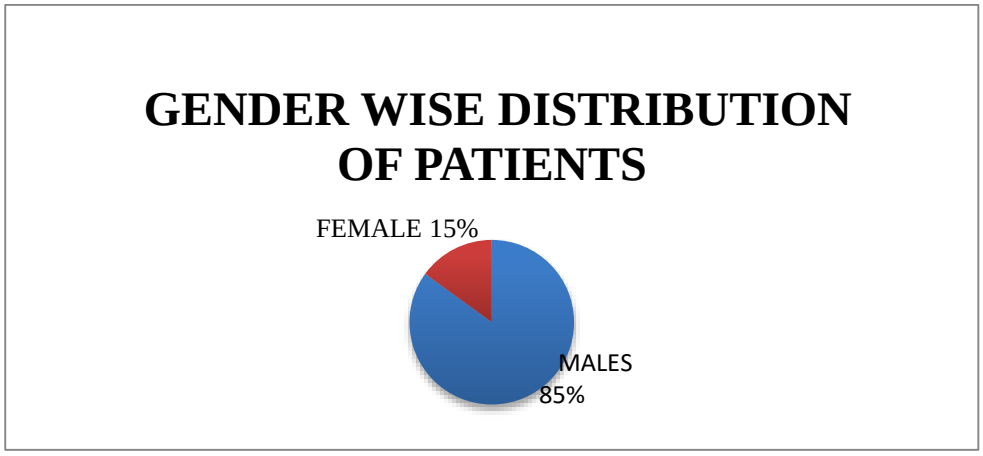

Figure: 6 Gender wise distribution of patients.

This graphical presentation shows distribution of study population according to gender. In the study population maximum were males (51) and females (9) with the frequency of 85% and 15% respectively.

DISTRIBUTION ACCORDING TO AGECRITERIA

AGE (Yr)	NO OF PATIENTS	PERCENTAGE (%)
10 -20	3	5
21-30	14	23.33

31-40	12	20
41-50	14	23.33
51-60	9	15
61-70	7	11.66
71-80	1	1.6

Table 5: Distribution of patients according to Age.

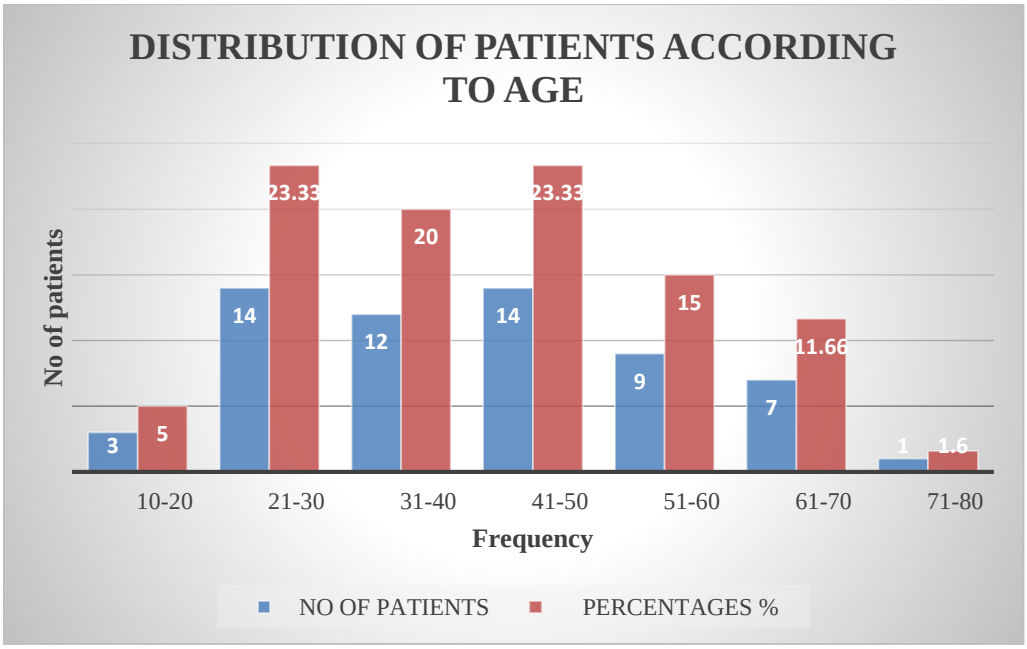

Figure:7 Distribution of patients according to Age.

Age-wise distribution of total study population showed that a maximum number of study cases fall in the age group of 21-30yrs and 41-50yrs. Among 60 study population, 12 patients were between 31-40yrs, 9 patients were between 51-60yrs, 7 patients were between 61-70yr, 3 patients were between 10-20yrs. A lower prevalence is between 71-80yrs of age group.

DISTRIBUTION OF PATIENTS BASED ON PAST MEDICAL HISTORY

COMORBIDITIES	NO OF PATIENTS	PERCENTAGE (%)
Renal Calculi	1	1.66
Diabetes Mellitus(DM)	3	5
Hypertension(HTN)	3	5
DM+HTN	5	8.33
Obstructive Sleep Apnoea	1	1.66
HTN+Cerebro Vascular Accident (CVA)	1	1.66
HTN+DM+Parkinson Disease + Chronic Kidney Disease (on peritoneal dialysis)	1	1.66
Absence of Disease	45	75

Table: 6 Distribution of patients based on past medical history.

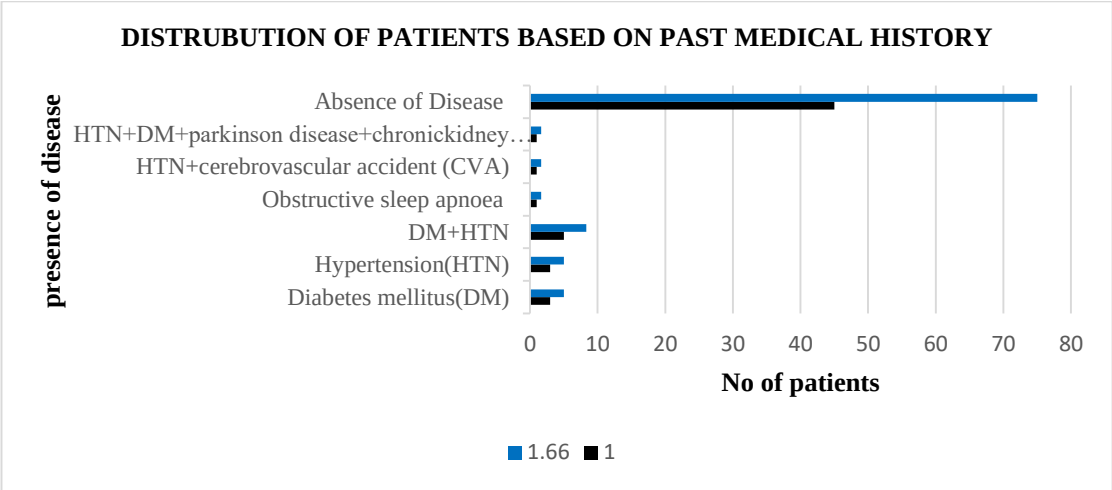

Figure :8 Past medical history versus number of patients.

The above graph represents Distribution of patients based on past medical history. out of 60patients, 15 patients were having various co-morbidities like Diabetes mellitus (n=3) with frequency of 5% ,Hypertension(n=3)with frequency of 5%,both Diabetes and hypertension(n=5)with frequency of 8.33%, Renal calculi, Obstructive sleep apnoea ,HTN+CVA, HTN+DM+Parkinson disease+chronic kidney disease(on peritoneal dialysis) with frequency of 1.66% respectively.

DISTRIBUTION OF PATIENTS ACCORDINGTOTHEIR GCS AT ADMISSION.

GCS AT ADMISSION	NO OF PATIENTS	PERCENTAGE (%)
3	3	5
4	2	3.33
5	2	3.33
6	2	3.33
7	2	3.33
8	5	8.33
9	4	6.66
10	4	6.66
11	5	8.33
12	7	11.66
13	8	13.33
14	8	13.33
15	8	13.33

Table 7: Distribution of patients according their GCS at admission.

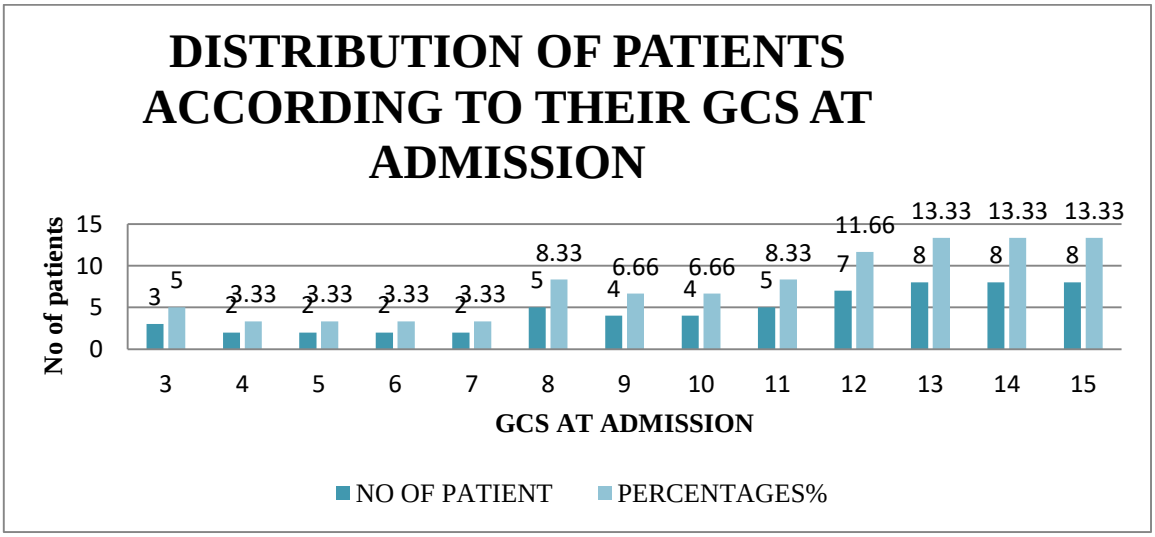

Figure 9: Distributiom of patients according to their admitted GCS.

In our study population, maximum number of patients had GCS of 13 (n=8), 14(n=8), and 15(n=8) at admission with frequency of 13.33%, 7 patients had GCS of 12 with the frequency of 11.66%, GCS of 8 (n=5) and 11(n=5) with the frequency of 8.33%, GCS of 9 (n=4) and 10 (n=4)with the frequency of 6.66%, GCS of 3 (n=3) with the frequency of 5%, GCS of 4 (n=2), 5 (n=2), 6 (n=2), 7 (n=2) with the frequency of 3.33%.

DISTRIBUTION OF PATIENTS BASED ON TIME INTERVAL BETWEEN INJURY AND ADMINISTRATION OF CEREBROLYSIN

TIME INTERVAL BETWEEN INJURY AND ADMINISTRATION OF CEREBROLYSIN(hours)	NO OF PATIENTS	PERCENTAGE %
0-5	20	33.33
6-10	5	8.33
11-15	6	10
16-20	2	3.33
21-25	26	43.33
26-30	-	
31-35	-	
36-40	1	1.66

Table 8: Distribution of patients based on time interval between injury and administration of cerebrolysin.

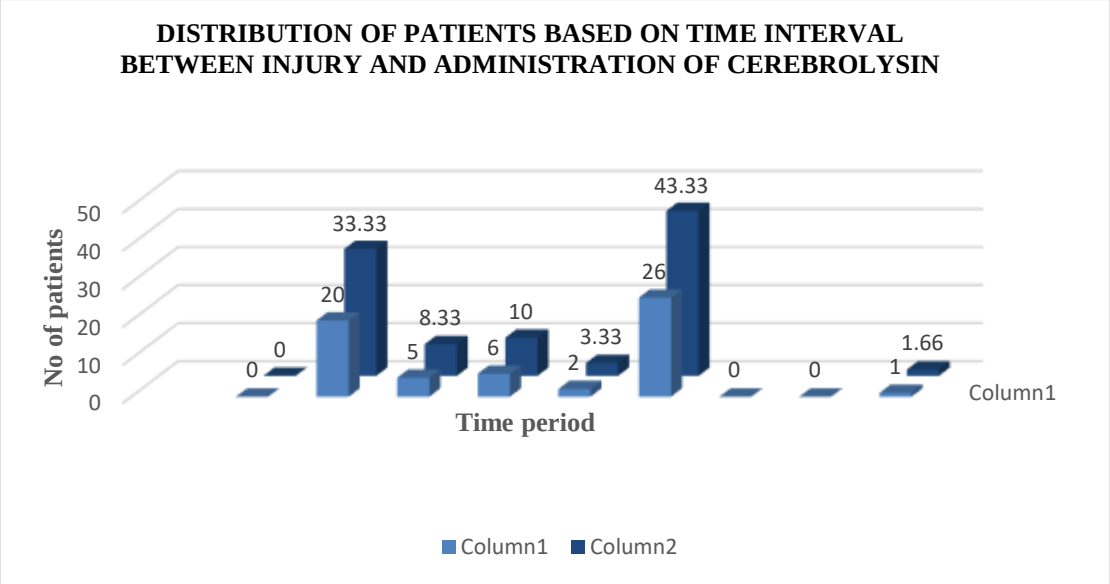

Figure:10 Distribution of patients based on time interval between injury and administration of cerebrolysin.

In our study population the time interval between brain injury and administration of cerebrolysin was 26-30hrs (n=26) with frequency of 43.33%, 20 patients (n=20) were administerd cerebrolysin with in 5hrs after injury with frequency of 33.33%, 6 patients were administerd cerebrolysin in between 6-10hrs after the injury with frequency of 8.33%,2 patients were administerd cerebrolysin in between 16-20hrs after the injury with frequency of 3.33%.

DISTRIBUTION OF PATIENTS BASED ON DOSE OF CEREBROLYSIN:

DOSE OF CEREBROLYSIN IN mg/ml (215.2mg/ml)	NO OF PATIENTS	PERCENTAGE (%)
1 ampule(215.2)	20	33.33
2 ampule(430.4)	30	50
3ampule(645.6)	10	16.66

Table 9: Distribution of patients based on dose of cerebrolysin

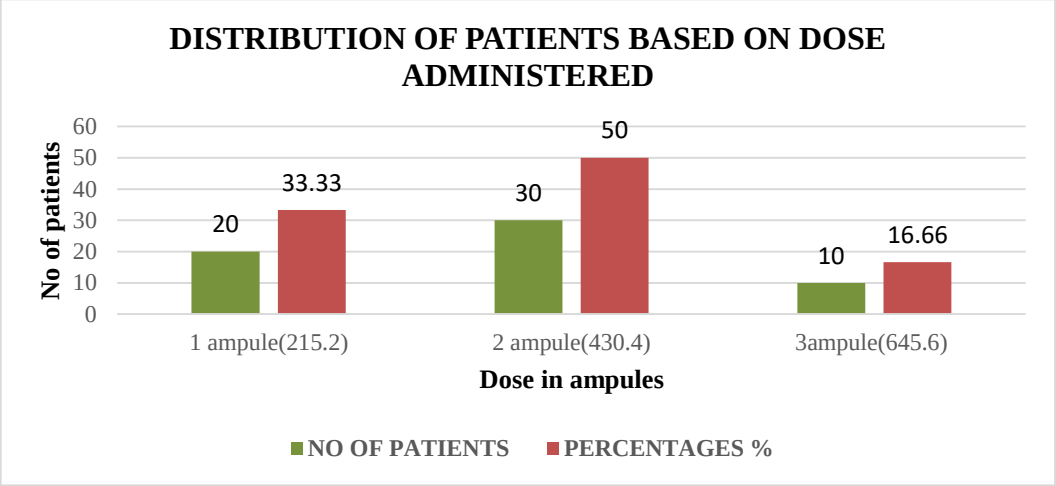

Figure: 11 Dose of Cerebrolysin (in ampules) versus number of patients

In our study population, most of the patients were administerd 2 ampules (430.4mg/ml) of cerebrolysin in 30 number of patients with frequency of 50%.20 patients were administerd 1 ampule (215.2mg/ml) of cerebrolysin with a frequency of 33.33% and 10 patients were administerd 3 ampules (645.6mg/ml) of cerebrolysin with frequency of 16.66%.

DISTRIBUTION OF PATIENTS BASED ON FREQUENCY OF CEREBROLYSIN ADMINISTERED:

FREQUENCY	NO OF PATIENTS	PERCENTAGE (%)
ONCE (OD)	10	16.66
TWICE (BD)	41	68.33
THRICE(TID)	9	15

Table 10: Distribution of patients according to frequency of cerebrolysin administerd

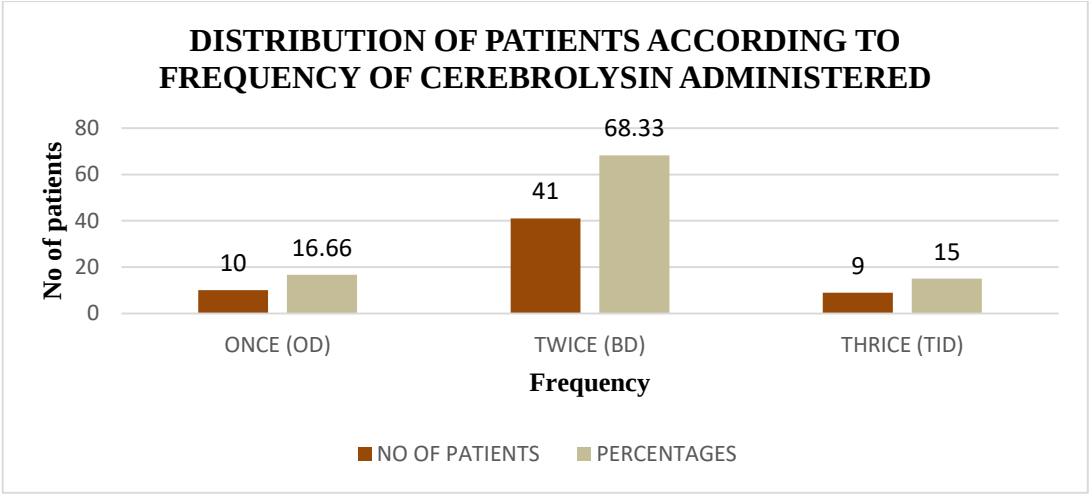

Figure:12 Distribution of patients according to frequency of cerebrolysin administration.

In our study population, we found that maximum patients (n=41) were administered with cerebrolysin twice daily and for 10 patients it was administered only once daily and the drug was administered thrice daily for 9 patients.

DISTRIBUTION OF PATIENTS BASED ON EFFICACY OF CEREBROLYSIN:

EFFICACY	NO OF PATIENTS	PERCENTAGES %
Minimum	-	-
Maximum	52	86.66

Table 11: Distribution of patients based on efficacy.

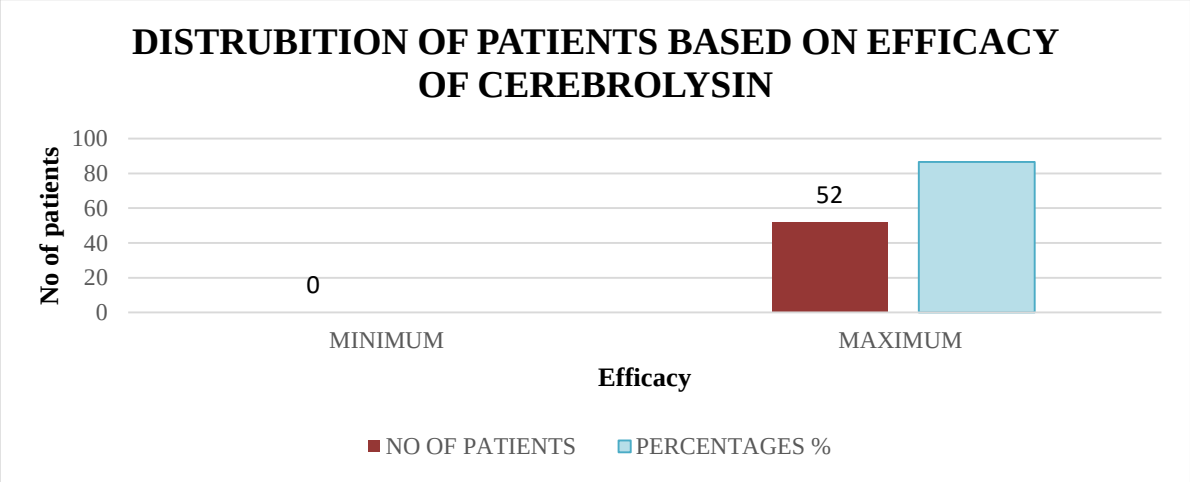

Figure:13 Distribution of patients based on efficacy of cerebrolysin.

In our study population, maximum efficacy is seen in 52 patients with frequency of 86.66%. There is no minimum efficacy due to LAMA (n=4) and death (n=4).

DISTRIBUTION OF PATIENTS BASED ON SURGICAL TREATMENT

SURGICAL TREATMENT	NO OF PATIENTS (N=60)	PERCENTAGE (%)
SURGERY PERFORMED	26	43.33
SURGERY NOT PERFORMED	34	56.66

Table 12: Distribution of patients based on surgical treatment

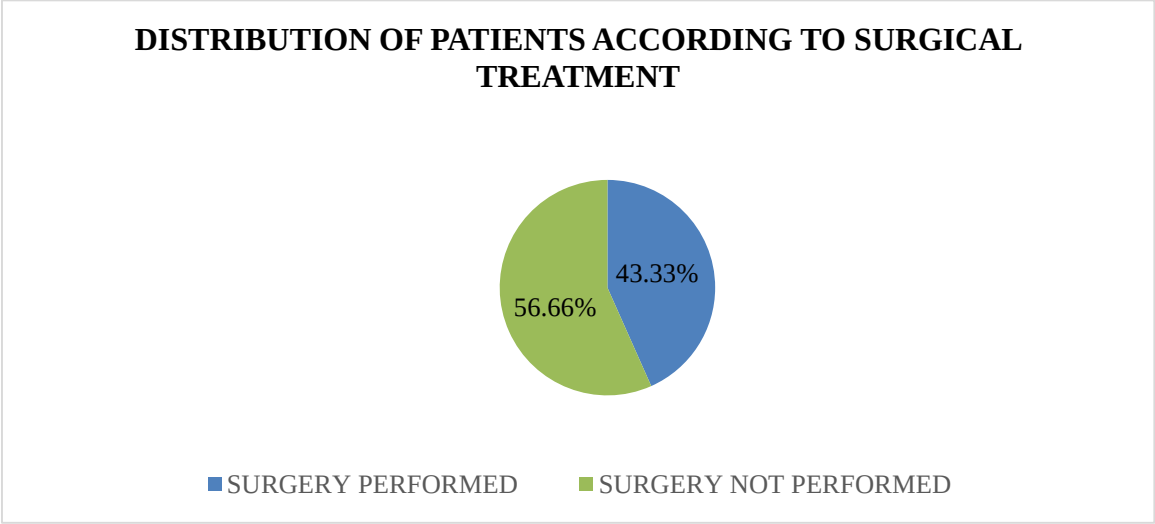

Figure:14 Distribution of patients based on surgical treatment

Above pie diagram represents distribution of patients based on surgical treatment. Out of 60 patients, surgical treatment was performed for 26 patients with frequency of 43.33% and surgery is not performed for 34 patients with frequency of 56.66%.

DISTRIBUTION OF PATIENTS BASED ON REASONS FOR MORTALITY

REASONS FOR MORTALITY	NO OF PATIENTS	PERCENTAGE (%)
Aspiration	1	1.66
Hypoxia	1	1.66
Cardiac arrest	2	3.33

Table 13 : Distribution of patients according to their reasons for mortality

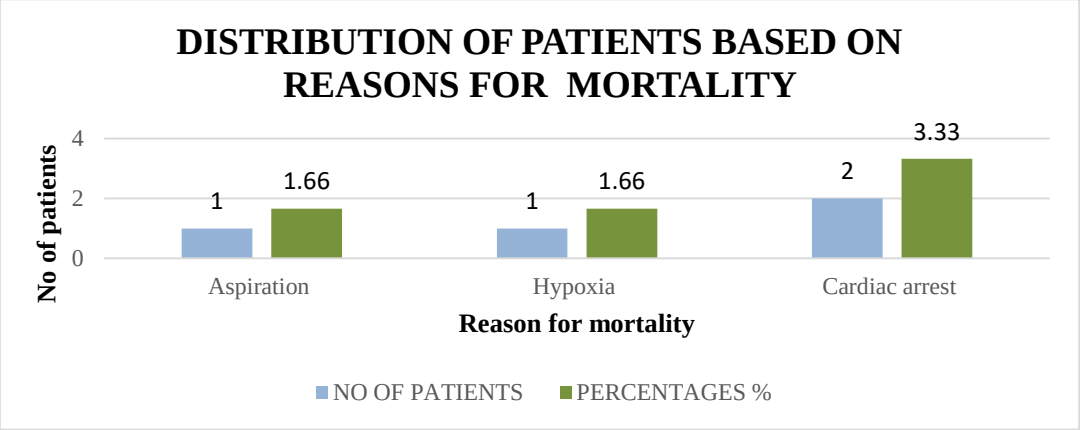

Figure:15 This graph depicts reasons for mortality during cerebrolysin treatment.

This graphical presentation represents, distribution of patients based on reasons of mortality. Four patients expired due to hypoxia (n=1), aspiration (n=1) and cardiac arrest (n=2) but not due to administration of cerebrolysin.

DISTRIBUTION OF PATIENTS BASED ON GCS AT DISCHARGE

GCS AT DISCHARGE (15)	NO. OF PATIENTS (N=60)	PERCENTAGE %
15	52	86.66%

Table 14: Distribution of patients according to their discharge GCS.

Among 60 study population, GCS of 52 patients was 15 at the time of discharge. 4 cases were expired due to various reasons like hypoxia (n=1), aspiration (n=1), cardiac arrest (n=2). 4 cases were LAMA (left against medical advice).

8. CONCLUSION:

Cerebrolysin is a neuroprotective agent. In the present study we analysed the Role of Cerebrolysin in Traumatic Brain Injury patients. Cerebrolysin is a peptide preparation for IV infusion which mimics the action of neurotrophic factors. Cerebrolysin has been shown to exert neurotrophic as well as neuroprotective effect in vitro and vivo.

Intravenous Cerebrolysin administration has been associated with drastic changes in GCS after the TBI. It also improved functional recovery after TBI as measured by GCS.The results of our current study also confirm the efficacy of the Cerebrolysin therapy in improving the functional outcome of patients with various grades of TBI(moderate and severe). Cerebrolysin administration in patients with severe disability after TBI is associated with improved GCS and functional recovery, decreased mortality rate and increased favourable outcome. It can be concluded that the use of Cerebrolysin as part of the initial management of moderate and severe head injury is proved to improve GCS and it is safe and well tolerated. The results suggest that Cerebrolysin is beneficial in regard to the outcome in Traumatic brain patients. We suggest the health care professionals to implement the use of Cerebrolysin in TBI patients as it results in greater outcome in their GCS as a cognitive functional outcome.

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