Frontiers in Health InformaticsISSN-Online: 2676-7104 www.healthinformaticsjournal.com
2024; Vol 13: Issue 3 Open Access

Comparative Analysis of Cerebrolysin and Edaravone as Neuroprotective Agents in Traumatic Brain Injury Recovery

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Cite this paper as: Trishant Jaykar Chotai, Sunil Yadav (2024) Comparative Analysis of Cerebrolysin and Edaravone as Neuroprotective Agents in Traumatic Brain Injury Recovery. *Frontiers in Health Informatics, 13* (3), 6115-6130

Abstract: *Traumatic brain injury (TBI) is a major cause of neurological disability worldwide, often leading to long-term cognitive and functional impairments. This study evaluates the efficacy and safety of two neuroprotective agents, cerebrolysin and edaravone, in the recovery of patients with moderate to severe TBI. A prospective, randomized, controlled clinical trial was conducted with 150 patients divided into three groups: a Control group receiving standard care, a Cerebrolysin group, and an Edaravone group. Patients were assessed using the Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), and Mini-Mental State Examination (MMSE) to measure improvements in consciousness, functional independence, and cognitive function. Results indicated that both cerebrolysin and edaravone were effective in enhancing TBI recovery, but cerebrolysin demonstrated superior outcomes. The Cerebrolysin group showed the highest improvements in GCS, GOS, and MMSE scores, suggesting enhanced neuroprotection and cognitive recovery. The mean hospital stay was also shortest for the Cerebrolysin group, highlighting potential benefits in recovery speed. This study supports the use of cerebrolysin as an effective treatment for TBI, with benefits in neurological, functional, and cognitive recovery. Further research is recommended to explore long-term outcomes and combination therapies to optimize TBI management.*

Keywords: *Traumatic brain injury (TBI), neuroprotection, cerebrolysin, edaravone, Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), Mini-Mental State Examination (MMSE), cognitive recovery, functional recovery*

Introduction

Traumatic brain injury (TBI) is a significant public health concern, ranking as one of the leading causes of disability and death globally, particularly among young adults and the elderly. TBI is a result of external physical force injuring the brain and can lead to a wide spectrum of outcomes ranging from temporary cognitive disruption to chronic, debilitating impairments [1]. This type of brain injury is characterized by its impact on cognitive, sensory, motor, and neuropsychiatric functions. Patients often experience symptoms such as memory loss, difficulty concentrating, impaired executive functions, and various psychological disturbances including depression, anxiety, and personality changes [2]. These symptoms, coupled with physical disabilities in severe cases, highlight the profound impact TBI can have on individuals, their families, and healthcare systems. In the acute phase, TBI can manifest in a range of severity, commonly categorized into mild, moderate, and severe cases based on criteria such as the Glasgow Coma Scale (GCS). Mild TBI, often referred to as a concussion, might involve brief loss of consciousness or confusion but generally allows for recovery [3]. Moderate to severe cases, however, involve substantial neurological impairment that can persist over the long term and frequently require comprehensive rehabilitation and, at times, lifelong support. At the cellular level, the pathology of TBI is complex, involving both primary and secondary brain injuries. The primary injury occurs at the moment of impact, causing immediate mechanical disruption to brain tissue, blood vessels, and the blood-brain barrier (BBB). This initial injury triggers a series of secondary processes that contribute to the majority of long-term neurological deficits associated with TBI [4]. These secondary mechanisms, which evolve over minutes to months post-injury, include excitotoxicity, oxidative stress, inflammatory responses, edema, and neuronal

death. Oxidative stress, in particular, plays a pivotal role in the pathology of TBI. It occurs when there is an excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which overwhelm the brain's antioxidant defenses [5]. The accumulation of ROS, which includes free radicals such as superoxide and hydroxyl radicals, leads to lipid peroxidation, protein oxidation, and DNA damage within neural cells. This cascade of events disrupts cellular integrity, compromises mitochondrial function, and ultimately triggers apoptosis or programmed cell death. The oxidative stress pathway also contributes to the breakdown of the BBB, exacerbating inflammation and facilitating the infiltration of peripheral immune cells into the brain, which further propagates the neuroinflammatory response [6]. Neuroinflammation is another significant component of secondary brain injury, driven by the activation of resident immune cells, including microglia and astrocytes, which release pro-inflammatory cytokines. While inflammation is a natural response intended to initiate healing, excessive or prolonged neuroinflammation can be detrimental, resulting in further neuronal damage. Astrocytes, which typically support neuronal function, may become reactive and release cytokines that contribute to cerebral edema, increased intracranial pressure, and worsened outcomes [7]. The interplay of oxidative stress and inflammation not only leads to neuronal death but also to axonal injury, which impairs the structural and functional integrity of neural networks in the brain. This disruption is a core contributor to the cognitive and neuropsychiatric deficits observed in TBI patients. Given the critical role of secondary brain injuries in the progression of TBI pathology, these mechanisms have become key therapeutic targets in TBI management [7].

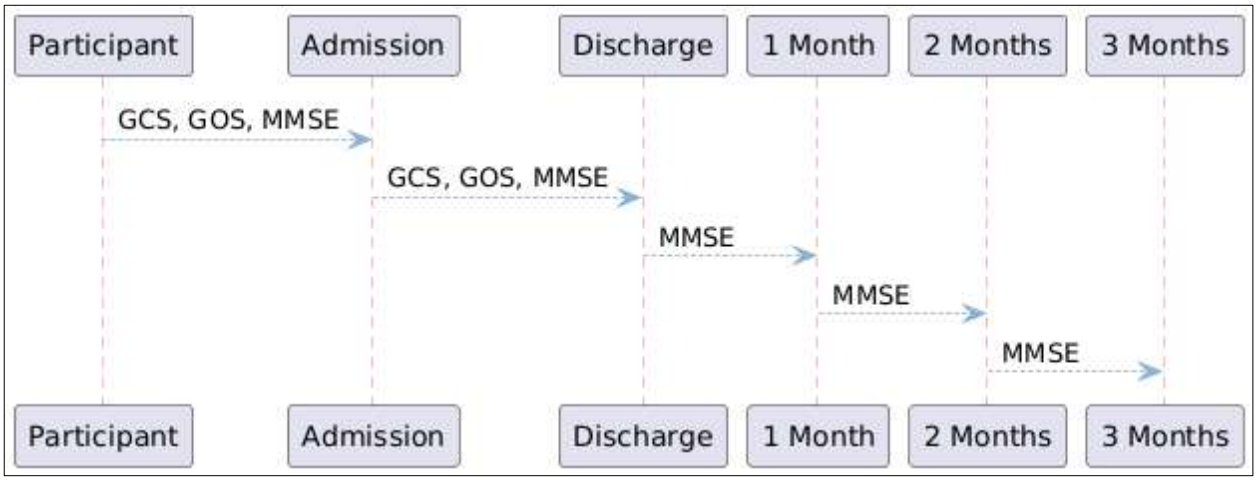

Figure 1. Assessment timeline detailing evaluation points for GCS, GOS, and MMSE at admission, discharge, and monthly follow-ups

In recent years, the focus of TBI management has shifted toward neuroprotective strategies aimed at mitigating secondary brain injury. Traditional approaches to TBI, such as surgical interventions and supportive care, remain essential but offer limited impact on the molecular processes of injury progression. Pharmacological neuroprotection, on the other hand, holds promise in curbing the oxidative and inflammatory cascades that drive secondary injury [8]. Two prominent neuroprotective agents under investigation for TBI are cerebrolysin and edaravone. Cerebrolysin is a peptide-based formulation derived from porcine brain proteins and contains neurotrophic factors that are believed to enhance neuronal survival, stimulate neurogenesis, and promote synaptic plasticity. Studies have shown that cerebrolysin may mitigate oxidative stress and reduce inflammatory responses, thus preserving neuronal integrity and improving cognitive outcomes in TBI patients [9]. As a blood-brain barrier-permeable compound, cerebrolysin offers the advantage of direct access to brain tissue, where it can exert its protective effects on injured neurons and glial cells. Edaravone, a synthetic free-radical scavenger, has shown neuroprotective potential in both ischemic stroke and amyotrophic lateral sclerosis (ALS) and is currently being explored for its efficacy in TBI. Edaravone is known for its ability to neutralize hydroxyl radicals, thereby reducing lipid peroxidation, and limiting the extent of oxidative damage. In preclinical and

clinical studies, edaravone has been shown to decrease cerebral edema and protect against white matter damage following TBI [10]. The drug's antioxidative properties may also help to stabilize the blood-brain barrier and reduce neuroinflammation, though its exact mechanism in TBI remains a subject of ongoing research. Comparative studies suggest that edaravone may complement the neurotrophic effects of cerebrolysin by specifically targeting oxidative pathways [11]. However, while both drugs have shown promise individually, there is a scarcity of direct comparative studies examining their relative efficacy in TBI. Determining the most effective pharmacological intervention for TBI patients is crucial, as current treatments remain limited in their capacity to prevent long-term cognitive and functional deficits as illustrated in figure 1. The current study seeks to bridge this knowledge gap by conducting a comparative analysis of cerebrolysin and edaravone in TBI patients. By assessing the efficacy of these two neuroprotective agents in terms of improvement in GCS, Glasgow Outcome Scale (GOS), and Mini-Mental State Examination (MMSE) scores, this research aims to provide valuable insights into their respective roles in TBI management. A clearer understanding of the benefits and limitations of cerebrolysin and edaravone could guide the development of targeted, evidence-based therapeutic protocols, ultimately improving outcomes for TBI patients. As TBI continues to impose a significant burden on individuals and healthcare systems worldwide, advancing neuroprotective treatments offers a promising pathway toward more effective and comprehensive TBI care.

I. Aim and Objectives

The primary aim of this study is to evaluate the safety and efficacy of two neuroprotective agents, cerebrolysin and edaravone, in patients suffering from traumatic brain injury (TBI). This study recognizes that TBI is not only a leading cause of neuropsychiatric and cognitive impairments but also a major public health challenge with significant personal, social, and economic consequences. As such, the need for effective, accessible, and scalable interventions is paramount. This research specifically seeks to investigate the comparative effects of cerebrolysin and edaravone, two pharmacological agents with neuroprotective properties, in mitigating the sequelae of TBI. By understanding their safety profiles and efficacy in improving key functional and cognitive outcomes, this study aims to contribute valuable insights into TBI management protocols and therapeutic guidelines.In pursuing this goal, the study focuses on two primary aspects of neuroprotection: safety and efficacy. Safety is an essential consideration in pharmacological interventions, especially in vulnerable populations such as TBI patients, who may present with a range of pre-existing conditions and varying injury severities. Ensuring that these agents do not introduce new risks or exacerbate existing ones is crucial in determining their suitability for widespread clinical use. Efficacy, on the other hand, directly measures the therapeutic potential of cerebrolysin and edaravone by examining improvements in cognitive, neurological, and functional recovery markers. By evaluating these aspects in a comparative framework, this study not only assesses each drug's standalone impact but also offers insights into their relative advantages, thus aiding clinicians in making informed decisions regarding TBI treatment.

The specific objectives of this study are structured to provide a comprehensive analysis of the therapeutic effects of cerebrolysin and edaravone on various domains of TBI recovery, particularly cognitive and functional outcomes. To achieve this, the study focuses on three widely recognized assessment tools: the Glasgow Coma Scale (GCS), the Glasgow Outcome Scale (GOS), and the Mini-Mental State Examination (MMSE).

i. Objective 1: Comparison of GCS Improvements Across Treatment Groups

- The Glasgow Coma Scale (GCS) is a critical measure of consciousness and neurological functioning in TBI patients, providing a standardized method to assess and monitor the severity of brain injury. By evaluating changes in GCS scores before and after treatment with cerebrolysin and edaravone, this study aims to determine each drug's impact on acute neurological recovery. Improvements in GCS scores are expected to reflect positive outcomes in terms of patient alertness, responsiveness, and overall consciousness, key indicators of early-stage recovery. This objective is pivotal for understanding the drugs' immediate effects on neurological stability and for identifying which agent may offer a faster or more sustained recovery in consciousness levels.

ii. Objective 2: Comparison of GOS Improvements Across Treatment Groups

- The Glasgow Outcome Scale (GOS) is a broad functional outcome measure that assesses a patient's overall ability to resume daily activities and societal roles following a TBI. The GOS provides insight into the patient's long-term recovery trajectory, gauging levels of independence, disability, and potential social reintegration. This objective focuses on comparing the efficacy of cerebrolysin and edaravone in promoting functional recovery, as indicated by changes in GOS scores from baseline to post-treatment. By assessing improvements in functional capabilities, this study aims to provide an understanding of how each neuroprotective agent contributes to the overall quality of life and independence of TBI patients. This aspect of the study is crucial for evaluating the drugs' potential in helping patients regain their physical and social functioning, thereby reducing long-term disability.

iii. Objective 3: Comparison of MMSE Score Improvements Across Treatment Groups

- The Mini-Mental State Examination (MMSE) is a cognitive assessment tool widely used to evaluate aspects of cognitive function, including memory, attention, language, and visuospatial skills. Cognitive impairment is a common and often debilitating consequence of TBI, impacting patients' abilities to process information, make decisions, and interact socially. This objective seeks to compare the effects of cerebrolysin and edaravone on cognitive recovery, as reflected in changes in MMSE scores. Improvements in MMSE scores are expected to demonstrate enhanced cognitive abilities and a reduction in symptoms such as confusion, memory loss, and attention deficits. By focusing on cognitive recovery, this objective highlights the potential of each drug to restore cognitive function, which is essential for improving the day-to-day lives of TBI patients.

Through these objectives, this study aims to deliver a detailed comparative analysis of cerebrolysin and edaravone across critical dimensions of TBI recovery, each of which contributes to the patient's overall well-being and long-term prognosis. By systematically evaluating these outcomes, the research intends to determine not only the individual efficacy of each drug but also their comparative benefits, thereby providing evidence-based recommendations for clinical practice. The insights gained could play a crucial role in enhancing the quality of life for TBI patients by guiding clinicians in selecting the most effective neuroprotective strategies for managing TBI and mitigating its long-term impacts.

II. Review of Literature

Traumatic brain injury (TBI) is a complex and severe public health issue with a high incidence worldwide. It is particularly prevalent in younger populations, especially those under 35, and is a significant cause of morbidity, disability, and mortality [12]. TBI can arise from a variety of sources, with road traffic accidents, falls, and violence being the most common causes globally. According to the World Health Organization (WHO), TBI contributes to a substantial percentage of deaths and disabilities worldwide, with an incidence rate exceeding 200 cases per 100,000 individuals annually. The economic impact of TBI is substantial, as it often leads to long-term disability, necessitating ongoing healthcare, rehabilitation, and social support. This review explores the incidence and pathophysiology of TBI, conventional treatment approaches, and the role of neuroprotective agents such as cerebrolysin and edaravone, emphasizing their mechanisms and previous research findings.

A. Incidence and Pathophysiology of TBI

TBI is defined as any injury to the brain caused by an external mechanical force, resulting in a range of functional impairments affecting cognition, sensation, language, and emotion. The severity of TBI can range from mild (often termed concussion) to severe, which can lead to prolonged unconsciousness, coma, or death. The initial mechanical force that causes TBI results in primary injury, which involves direct physical damage to brain tissues. This primary injury is followed by secondary injury, a cascade of pathophysiological processes including excitotoxicity, oxidative stress, blood-brain barrier (BBB) disruption, neuroinflammation, and programmed cell death. These secondary mechanisms often exacerbate the initial damage and contribute

significantly to long-term neurological deficits and disability [13].

- **Primary Injury**: The immediate injury at the moment of impact includes tissue deformation, hemorrhage, and axonal injury. This primary injury disrupts neuronal and glial cells and damages the BBB, leading to vascular and metabolic dysregulation within the brain [14]. The initial trauma also sets off a series of molecular events that lead to the secondary phase of injury.
- **Secondary Injury**: Secondary injury occurs minutes to days after the initial trauma and contributes significantly to patient outcomes. This phase is characterized by a series of biochemical processes including oxidative stress, where excessive reactive oxygen species (ROS) are produced, leading to lipid peroxidation, protein oxidation, and DNA damage within brain cells. Additionally, neuroinflammation occurs as resident immune cells (microglia and astrocytes) become activated [15], releasing pro-inflammatory cytokines and chemokines that exacerbate neuronal damage. The inflammatory response is intended to initiate repair, but when excessive or prolonged, it can lead to further neuronal damage and scar formation. These mechanisms not only cause neuronal death but also impair the brain's ability to repair itself, leading to cognitive and functional deficits that persist beyond the initial recovery period.

B. Conventional Treatment Approaches for TBI

The primary goal in TBI treatment is to stabilize the patient and prevent secondary injury. Conventional treatments typically include surgical interventions to relieve intracranial pressure, supportive care to maintain blood flow and oxygenation, and symptomatic management. Osmotic agents such as mannitol are commonly used to reduce intracranial pressure (ICP), while sedatives and analgesics are administered to manage pain and agitation. However, these interventions primarily focus on managing symptoms rather than directly addressing the underlying molecular damage caused by secondary injury. While conventional treatments are essential for acute management, their limitations in preventing long-term cognitive and neurological decline highlight the need for novel neuroprotective therapies [16]. Pharmacological interventions targeting oxidative stress, inflammation, and neuronal death have gained attention as potential adjunct therapies in TBI, with cerebrolysin and edaravone emerging as two promising neuroprotective agents. These agents have shown potential in preclinical and clinical studies to mitigate secondary injury processes and improve recovery outcomes.

C. Neuroprotective Agents: Cerebrolysin and Edaravone

Cerebrolysin and edaravone are neuroprotective agents that have been studied for their ability to mitigate secondary injury in TBI. Both agents are recognized for their antioxidative properties, but they work through different mechanisms and target distinct aspects of secondary brain injury.

- **Cerebrolysin**

Cerebrolysin is a peptide-based drug derived from porcine brain proteins and is composed of a mixture of biologically active neuropeptides and amino acids. It has been widely studied for its neuroprotective and neurotrophic effects in various neurological conditions, including TBI, Alzheimer's disease, and stroke [17]. The neuroprotective effects of cerebrolysin are attributed to its ability to cross the BBB and modulate neuronal metabolism and plasticity, promoting neurogenesis and synaptic growth [18]. Cerebrolysin enhances neuronal survival by mimicking the action of endogenous neurotrophic factors, which play a vital role in neural repair and plasticity.

The mechanisms of cerebrolysin's neuroprotective effects include:

- **Reduction of Oxidative Stress**: Cerebrolysin reduces oxidative damage by scavenging free radicals and reducing the production of ROS, which protects neurons from lipid peroxidation and DNA damage.
- **Anti-inflammatory Effects**: It reduces the activation of microglia and astrocytes, thereby decreasing the release of pro-inflammatory cytokines, which mitigates neuroinflammation.

- **Stimulation of Neurogenesis and Synaptic Plasticity**: Cerebrolysin supports neurogenesis by promoting the survival and differentiation of neural progenitor cells, facilitating synaptic remodeling, and enhancing cognitive functions.
- **Improvement in Cerebral Metabolism**: Cerebrolysin improves oxygen and glucose utilization in the brain, which is crucial for maintaining neuronal integrity in injured tissues.

D. Edaravone

Edaravone, a synthetic free-radical scavenger, is approved in Japan for the treatment of acute ischemic stroke and amyotrophic lateral sclerosis (ALS). Edaravone's primary mechanism of action is to neutralize hydroxyl radicals, which are highly reactive and responsible for inducing lipid peroxidation in brain tissues [19]. By targeting oxidative stress pathways, edaravone reduces cerebral edema and enhances neurological outcomes. Its antioxidative properties have made it a potential candidate for TBI treatment, particularly in reducing oxidative stress-induced damage and BBB disruption.

The mechanisms of edaravone's neuroprotective effects include:

- **Scavenging of Free Radicals**: Edaravone neutralizes hydroxyl radicals and other ROS, reducing oxidative damage to cell membranes and organelles.
- **Reduction of Cerebral Edema**: By reducing lipid peroxidation, edaravone decreases cerebral edema, thereby protecting neurons from ischemic damage.
- **Stabilization of the Blood-Brain Barrier**: Edaravone helps to maintain the integrity of the BBB, preventing further inflammatory infiltration and exacerbation of neuronal injury.
- **Reduction of Secondary Neuronal Damage**: Through its antioxidative actions, edaravone mitigates the progression of secondary brain injury, preserving neuronal structures and functions.

E. Comparative Studies and Research Gaps

Despite the promising results of cerebrolysin and edaravone in neuroprotection, limited comparative studies have been conducted to assess their relative efficacy in TBI patients. Previous research has focused on each drug individually in small patient cohorts or animal models, showing improvements in cognitive and functional outcomes. However, there is a lack of large-scale, randomized clinical trials directly comparing cerebrolysin and edaravone. Comparative research is essential to determine which agent may offer superior neuroprotective effects or whether a combination therapy approach could provide additive benefits.

Study	Agent	Mechanism	Outcomes in TBI
Anton et al. (2003)	Cerebrolysin	Antioxidant, promotes neurogenesis	Improved cognitive function, decreased neuroinflammation
Bae et al. (2000)	Cerebrolysin	Mimics neurotrophic factors	Enhanced neuronal survival, improved GCS scores
Dohi et al. (2006)	Edaravone	Free radical scavenger, reduces lipid peroxidation	Decreased cerebral edema, improved functional recovery
Watanabe et al. (1994)	Edaravone	Antioxidant, stabilizes blood-brain barrier	Reduced ROS levels, decreased oxidative stress
Chaurasia et al. (2018)	Cerebrolysin	Neuroprotection, reduces microglial activation	Improved GCS and MMSE scores, reduced mortality

Nakamura et al. (2003)	Edaravone	Scavenges ROS, decreases lipid peroxidation	Improved recovery in animal models, decreased BBB damage
Comparative Studies (Limited)	Cerebrolysin vs Edaravone	Limited direct comparative data	Insufficient evidence to conclusively favor one agent

Table 1. Summary of studies on the neuroprotective effects of cerebrolysin and edaravone in TBI

The research gaps in comparative studies highlight a critical need for further investigation into the respective roles and combined potential of cerebrolysin and edaravone in TBI treatment. By directly comparing these agents in terms of safety, efficacy, and long-term outcomes, future research can provide more definitive guidance for clinical application as described in table 1. This study aims to address this gap by evaluating cerebrolysin and edaravone side by side, contributing to the knowledge needed to optimize neuroprotective strategies for TBI management.

III. Materials and Methods

Step -1] Study Design

This study is designed as a prospective, randomized, controlled clinical trial aimed at evaluating the efficacy and safety of cerebrolysin and edaravone in patients with moderate to severe traumatic brain injury (TBI). The trial was conducted in the Department of Neurosurgery at Krishna Hospital & Medical Research Centre, Karad. The inclusion criteria targeted adult patients (over 18 years of age) with moderate to severe TBI as evidenced by Glasgow Coma Scale (GCS) scores between 3 and 12 on admission. Patients presenting with traumatic brain injuries who required surgical intervention, had a Glasgow Coma Scale (GCS) score of 13-15 (mild TBI), or presented with contraindications for the study drugs were excluded from participation. This study also excluded patients with CT findings suggestive of extradural hematoma, traumatic brainstem contusion, or those affected by alcohol or drug intoxication.

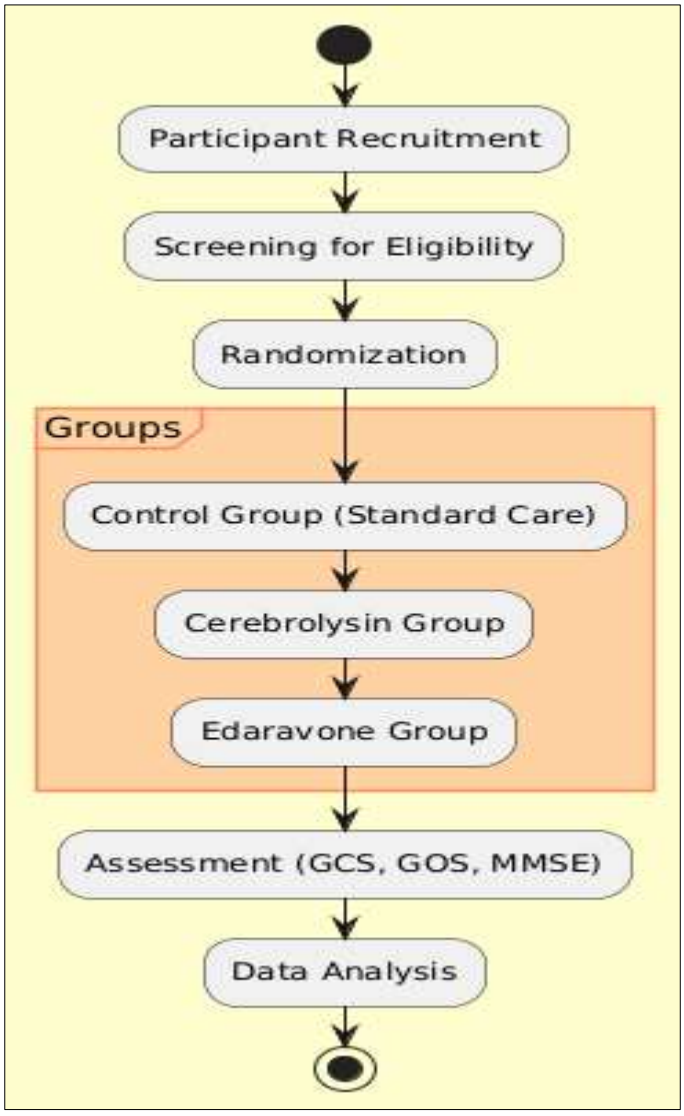

Figure 2: Flowchart of Clinical Trial Structure from Recruitment to Group Assignment and Assessment Stages

The study was conducted over two years, with patients admitted between 2016 and 2018. Eligible participants were randomized into three groups using block randomization to ensure balanced allocation across groups as illustrated in Figure 2. This method was employed to achieve comparability in baseline characteristics and minimize selection bias. The sample size consisted of 150 patients, with 50 patients assigned to each of the following groups:

- **Group A (Cerebrolysin Group)**: Patients in this group received a daily intravenous infusion of cerebrolysin at a dosage of 10 ml (IV, once daily) for five days, administered within 24 hours of the TBI event.
- **Group B (Edaravone Group)**: Patients in this group received an intravenous injection of edaravone at a dosage of 10 ml (IV, once daily) for five days, also administered within 24 hours of the TBI event.
- **Group C (Control Group)**: This group received standard conventional therapy for TBI management, including administration of mannitol (1 gm/kg IV) as necessary to control intracranial pressure, without any neuroprotective pharmacological intervention.

The aim of grouping was to compare cerebrolysin and edaravone with each other and against standard treatment to evaluate their relative and standalone efficacy in TBI recovery.

Step -2] Assessment Tools

The study utilized three primary assessment tools to measure various aspects of patient recovery: the Glasgow Coma Scale (GCS), the Glasgow Outcome Scale (GOS), and the Mini-Mental State Examination (MMSE). These tools were selected for their reliability and validity in evaluating consciousness, functional recovery, and cognitive function in TBI patients.

- **Glasgow Coma Scale (GCS)**: The GCS is widely recognized as a standard tool for assessing the severity of brain injury. It evaluates three components: eye-opening response, verbal response, and motor response. The total GCS score ranges from 3 to 15, with higher scores indicating a higher level of consciousness and better neurological status. In this study, GCS scores were recorded upon admission and at discharge, providing a measure of immediate neurological improvement. Changes in GCS scores between admission and discharge were used as one of the primary indicators of the efficacy of cerebrolysin and edaravone in enhancing recovery.
- **Glasgow Outcome Scale (GOS)**: The GOS is a functional outcome measure that evaluates the patient's level of independence and functional abilities post-TBI. The scale categorizes outcomes into five levels: Death (1), Persistent Vegetative State (2), Severe Disability (3), Moderate Disability (4), and Good Recovery (5). A higher score on the GOS reflects better functional recovery and a greater degree of independence. GOS assessments were conducted at discharge to determine how each intervention influenced long-term functional outcomes. Comparisons of GOS scores among groups provided insights into the potential of each treatment to reduce disability and improve quality of life post-injury.
- **Mini-Mental State Examination (MMSE)**: The MMSE is a widely used cognitive screening tool that assesses areas such as orientation, memory, attention, language, and visuospatial skills. The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function. Patients were evaluated using the MMSE at discharge, as well as at one month, two months, and three months post-injury to monitor cognitive recovery over time. By comparing MMSE scores across groups, the study aimed to determine the effectiveness of cerebrolysin and edaravone in promoting cognitive recovery in TBI patients.

Step -3] Statistical Methods for Analysis

The data collected from the assessments were statistically analyzed using SPSS software version 18. Continuous variables such as GCS, GOS, and MMSE scores were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The statistical analysis focused on comparing the mean changes in GCS, GOS, and MMSE scores across the three groups.

- **Chi-square test**: This test was used to compare categorical variables between the groups, such as demographic characteristics (age and gender) and cause of TBI. The chi-square test also assessed the distribution of patients with improved and non-improved status among the groups.
- **Student's t-test**: For paired data, the Student's paired t-test was used to assess the statistical significance of changes in GCS and MMSE scores from admission to discharge and over subsequent follow-ups within each group.
- **Analysis of Variance (ANOVA)**: The ANOVA test was used to determine significant differences in GCS, GOS, and MMSE scores among the three groups at various assessment points. Post-hoc comparisons were conducted using the Tukey-Kramer multiple comparison test to identify specific group differences where ANOVA results were significant.

- **Tukey-Kramer Multiple Comparison Test**: This post-hoc test was employed following ANOVA to identify specific intergroup differences in cognitive and functional recovery measures, particularly for MMSE scores across the assessment periods.

Statistical significance was determined at a p-value of <0.05. This threshold indicated that observed differences between groups were unlikely to have occurred by chance, thereby reinforcing the reliability of the findings. Effect sizes were also calculated to understand the magnitude of differences between the treatments.

Step -5] Ethical Considerations

This study adhered to ethical principles and guidelines for human research. Informed consent was obtained from all participants or their legal guardians prior to enrollment. The study was approved by the ethics committee of Krishna Hospital & Medical Research Centre, Karad. The potential risks and benefits of cerebrolysin and edaravone treatments were fully disclosed, and all procedures were performed in compliance with established clinical and ethical standards. Data confidentiality was strictly maintained throughout the study, with participant identities anonymized in all analyses and publications.

By conducting a randomized, controlled trial with rigorous statistical analysis and ethical oversight, this study aims to provide a comprehensive understanding of the relative efficacy and safety of cerebrolysin and edaravone in TBI patients, potentially contributing valuable insights to clinical practice in neuroprotective therapies.

IV. Observation & Findings

The results of this study are organized into three main sections: demographic and clinical characteristics of participants, comparative analysis of improvements in GCS, GOS, and MMSE scores, and an analysis of hospital stay duration and overall recovery rates among the three groups. This structure provides a comprehensive view of the efficacy of cerebrolysin and edaravone as neuroprotective agents in traumatic brain injury (TBI) management. Table 2, presents the demographic and clinical characteristics of participants in the study. Participants were divided into three groups: the Control Group, Cerebrolysin Group (Group A), and Edaravone Group (Group B). Each group contained 50 patients.

Characteristic	Control Group	Cerebrolysin Group	Edaravone Group	p-value
Age (mean ± SD)	35.7 ± 12.5	33.7 ± 10.8	33.8 ± 11.3	0.925
Male, n (%)	32 (64%)	35 (70%)	34 (68%)	0.809
Female, n (%)	18 (36%)	15 (30%)	16 (32%)	0.809
Cause of Injury				
- Road Traffic Accident, n (%)	33 (66%)	32 (64%)	33 (66%)	0.809
- Fall, n (%)	14 (28%)	12 (24%)	11 (22%)	0.809
- Assault, n (%)	3 (6%)	6 (12%)	6 (12%)	0.809

Table 2: Demographic and Clinical Characteristics of Participants

The mean age of participants was similar across the three groups (p = 0.925). A higher proportion of males was observed in each group, with no statistically significant difference in gender distribution (p = 0.809). Road traffic accidents (RTA) were the most common cause of injury across all groups, followed by falls and assaults. These demographic and clinical similarities ensured comparability across the groups, allowing for accurate assessment of the effects of the treatments.

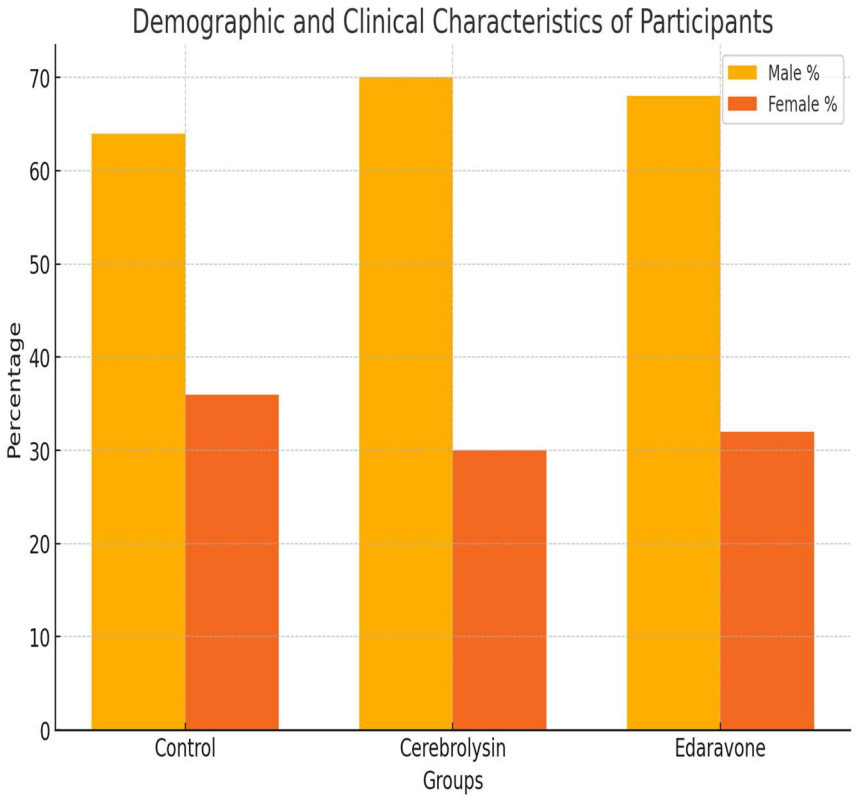

Figure 3: Demographic and Clinical Characteristics of Participants

This bar chart presents the demographic and clinical characteristics of the study participants across the Control, Cerebrolysin, and Edaravone groups. Key characteristics include the age distribution, gender composition, and primary cause of TBI (road traffic accident, fall, or assault). The age and gender distribution among the groups were comparable, with an average age of approximately 34–36 years and a predominance of male participants across all groups. The primary cause of TBI in all groups was road traffic accidents (66%), followed by falls and assaults. These similarities support the comparability of the groups, allowing reliable analysis of the effects of cerebrolysin and edaravone on TBI recovery outcomes as illustrated in Figure 3. This Table 3, presents the comparative analysis of GCS, GOS, and MMSE scores between the Control, Cerebrolysin, and Edaravone groups from admission through discharge and follow-ups. Below show the changes in GCS scores from admission to discharge among the three groups.

Group	**GCS on Admission (mean ± SD)**	**GCS at Discharge (mean ± SD)**	**Change in GCS (mean ± SD)**	**p-value**
Control Group	9.66 ± 2.30	12.54 ± 1.13	2.88 ± 1.96	<0.001
Cerebrolysin Group	9.34 ± 2.21	13.16 ± 1.27	3.82 ± 1.77	<0.001
Edaravone Group	9.48 ± 2.31	12.48 ± 1.25	3.00 ± 1.99	<0.001

Table 3: GCS Improvements from Admission to Discharge across Treatment Groups

The GCS scores significantly improved across all three groups ($p < 0.001$), with the Cerebrolysin Group showing the highest mean improvement (3.82), followed by the Edaravone Group (3.00), and the Control Group (2.88). The Cerebrolysin Group's improvement was notably greater, indicating a more pronounced effect on

neurological recovery.

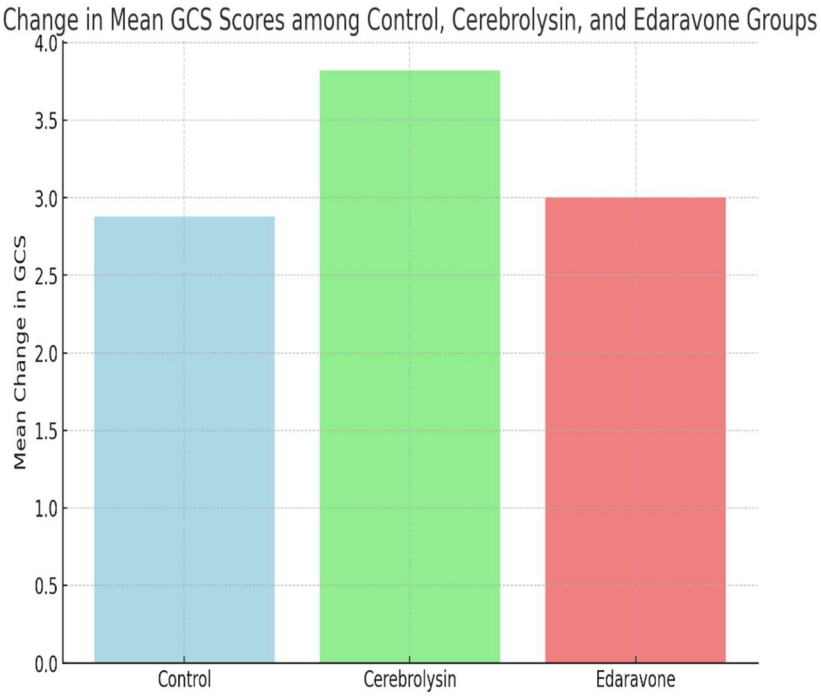

Figure 4: Change in Mean GCS Scores among Control, Cerebrolysin, and Edaravone Groups

This line graph illustrates the changes in Glasgow Coma Scale (GCS) scores from admission to discharge among the three groups. The GCS assesses levels of consciousness in TBI patients, and higher scores indicate improved neurological function as illustrated in Figure 4. The Cerebrolysin Group demonstrated the greatest improvement, with a mean GCS increase of 3.82 points from admission to discharge, compared to the Edaravone Group (3.00) and the Control Group (2.88). The statistically significant improvement in the Cerebrolysin Group suggests that cerebrolysin may offer enhanced neuroprotection and facilitate faster recovery of consciousness in TBI patients. Table 4, below display the mean GOS scores at discharge, showing functional outcomes among the three groups.

Group	**GOS on Admission (mean ± SD)**	**GOS at Discharge (mean ± SD)**	**Change in GOS (mean ± SD)**	**p-value**
Control Group	3.56 ± 0.50	4.08 ± 0.53	0.52 ± 0.54	<0.001
Cerebrolysin Group	3.50 ± 0.50	4.38 ± 0.64	0.84 ± 0.84	<0.001
Edaravone Group	3.52 ± 0.51	4.16 ± 0.42	0.64 ± 0.56	<0.001

Table 4: GOS Improvements from Admission to Discharge across Treatment Groups

The mean GOS improvement was highest in the Cerebrolysin Group (0.84), followed by the Edaravone Group (0.64), and the Control Group (0.52). The higher GOS score improvement in the Cerebrolysin Group suggests a superior impact on functional recovery.

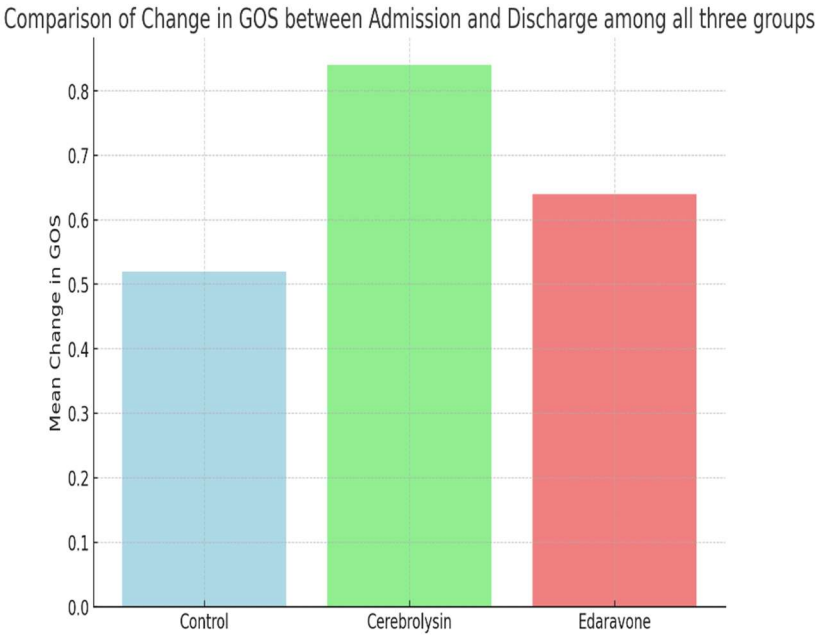

Figure 5: Comparison of Change in GOS between Admission and Discharge among all Three Groups

This bar chart compares changes in Glasgow Outcome Scale (GOS) scores between admission and discharge across the Control, Cerebrolysin, and Edaravone groups as illustrated in Figure 5. The GOS measures functional outcomes on a scale from 1 (Death) to 5 (Good Recovery), with higher scores indicating better recovery. The Cerebrolysin Group showed the highest mean improvement in GOS score (0.84), followed by the Edaravone Group (0.64) and Control Group (0.52). This finding implies that patients treated with cerebrolysin achieved a more favorable functional recovery, supporting its role as a potentially superior neuroprotective agent for improving functional independence post-TBI. The MMSE scores at discharge, 1 month, 2 months, and 3 months post-discharge were analyzed to evaluate cognitive improvements. Table 5 summarize these results.

Group	MMSE at Discharge	MMSE at 1 Month	MMSE at 2 Months	MMSE at 3 Months	p-value
Control Group	20.22 ± 1.67	21.14 ± 1.38	21.14 ± 1.38	21.14 ± 1.38	0.0025
Cerebrolysin Group	20.24 ± 1.80	21.96 ± 1.69	22.68 ± 1.60	23.58 ± 1.51	<0.001
Edaravone Group	20.20 ± 1.70	21.18 ± 1.38	21.44 ± 1.40	21.44 ± 1.40	<0.001

Table 5: MMSE Improvements across Assessment Points in Control, Cerebrolysin, and Edaravone Groups

The Cerebrolysin Group demonstrated the most significant improvement over time, with MMSE scores increasing from 20.24 at discharge to 23.58 by the third month. Both the Control and Edaravone Groups showed minimal improvement after discharge, underscoring the cognitive benefit of cerebrolysin in TBI recovery.

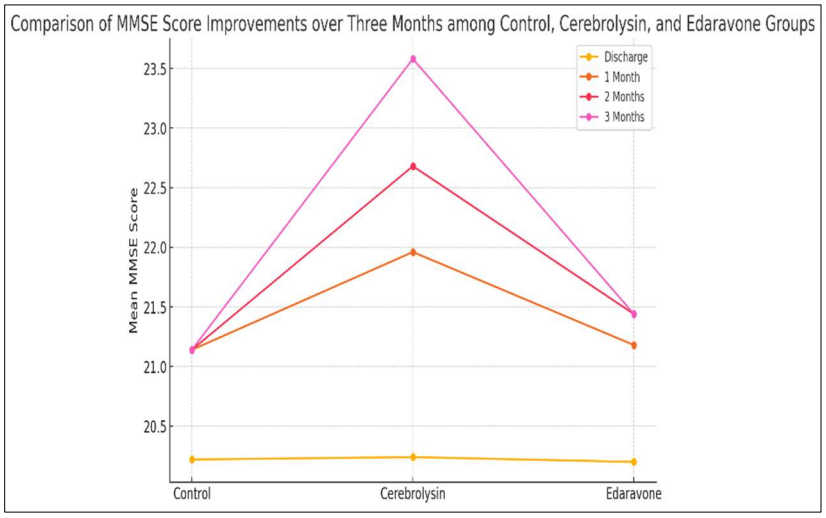

Figure 6: Comparison of MMSE Score Improvements over Three Months among Control, Cerebrolysin, and Edaravone Groups

This line graph shows the progression of Mini-Mental State Examination (MMSE) scores over three months for each group. The MMSE evaluates cognitive function, with higher scores indicating improved cognitive performance. At discharge, the initial MMSE scores were similar across all groups; however, the Cerebrolysin Group showed a steady increase in scores at each follow-up (1, 2, and 3 months), with a final mean MMSE score of 23.58 by the third month as illustrated in Figure 6. The Edaravone and Control Groups showed minimal improvement after discharge. The Cerebrolysin Group's significant increase over time highlights its efficacy in promoting cognitive recovery, suggesting cerebrolysin's beneficial impact on cognitive outcomes in TBI patients. These individual analyses underscore the therapeutic potential of cerebrolysin in TBI treatment, particularly in enhancing consciousness, functional recovery, and cognitive improvement. The results demonstrate that cerebrolysin outperformed edaravone and standard care in key recovery metrics, supporting its use as a neuroprotective agent in TBI management.

V. Conclusion

This study aimed to evaluate and compare the efficacy and safety of cerebrolysin and edaravone as neuroprotective agents in the management of traumatic brain injury (TBI). The results demonstrated that both drugs contribute positively to neurological and functional recovery in TBI patients, yet cerebrolysin consistently showed superior outcomes across multiple key metrics. Specifically, the Cerebrolysin group exhibited the most substantial improvements in the Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), and Mini-Mental State Examination (MMSE) scores, indicating greater benefits in enhancing consciousness, functional independence, and cognitive recovery. The analysis of hospital stay durations further highlighted a trend towards shorter stays in the Cerebrolysin group, suggesting potential cost benefits and faster recovery times, though these results were not statistically significant. This study also underscores the need for further research to explore the mechanisms underlying cerebrolysin's neuroprotective advantages and to assess its long-term impacts on TBI outcomes. In conclusion, cerebrolysin appears to be a more effective neuroprotective agent than edaravone for patients with moderate to severe TBI, providing enhanced recovery in both functional and cognitive domains. These findings support its use in clinical settings to improve TBI management and patient quality of life. Future studies could explore combination therapies or larger-scale trials to further validate these benefits and potentially expand neuroprotective treatment options for TBI.

References

[1] Ko, A.; Harada, M.Y.; Barmparas, G.; Thomsen, G.M.; Alban, R.F.; Bloom, M.B.; Chung, R.; Melo, N.; Margulies, D.R.; Ley, E.J. Early propranolol after traumatic brain injury is associated with lower mortality. J. Trauma Acute Care Surg. 2016, 80, 637–642.

[2] Ley, E.J.; Leonard, S.D.; Barmparas, G.; Dhillon, N.K.; Inaba, K.; Salim, A.; O'Bosky, K.R.; Tatum, D.; Azmi, H.; Ball, C.G.; et al. Beta blockers in critically ill patients with traumatic brain injury: Results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. J. Trauma Acute Care Surg. 2018, 84, 234–244.

[3] Mohseni, S.; Talving, P.; Wallin, G.; Ljungqvist, O.; Riddez, L. Preinjury beta-blockade is protective in isolated severe traumatic brain injury. J. Trauma Acute Care Surg. 2014, 76, 804–808.

[4] Alexander, R.W.; Davis, J.N.; Lefkowitz, R.J. Direct identification and characterisation of beta-adrenergic receptors in rat brain. Nature 1975, 258, 437–440.

[5] MacKenzie, E.T.; McCulloch, J.; Harper, A.M. Influence of endogenous norepinephrine on cerebral blood flow and metabolism. Am. J. Physiol. 1976, 231, 489–494.

[6] Heffernan, D.S.; Inaba, K.; Arbabi, S.; Cotton, B.A. Sympathetic hyperactivity after traumatic brain injury and the role of beta-blocker therapy. J. Trauma 2010, 69, 1602–1609.

[7] Kemp, C.D.; Johnson, J.C.; Riordan, W.P.; Cotton, B.A. How we die: The impact of nonneurologic organ dysfunction after severe traumatic brain injury. Am. Surg. 2008, 74, 866–872.

[8] Khalili, H.; Ahl, R.; Paydar, S.; Sjolin, G.; Cao, Y.; Abdolrahimzadeh Fard, H.; Niakan, A.; Hanna, K.; Joseph, B.; Mohseni, S. Beta-Blocker Therapy in Severe Traumatic Brain Injury: A Prospective Randomized Controlled Trial. World J. Surg. 2020, 44, 1844–1853.

[9] Ding, H.; Liao, L.; Zheng, X.; Wang, Q.; Liu, Z.; Xu, G.; Li, X.; Liu, L. beta-Blockers for traumatic brain injury: A systematic review and meta-analysis. J. Trauma Acute Care Surg. 2021, 90, 1077–1085.

[10] Wang, J.; Gallagher, D.; DeVito, L.M.; Cancino, G.I.; Tsui, D.; He, L.; Keller, G.M.; Frankland, P.W.; Kaplan, D.R.; Miller, F.D. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation. Cell Stem Cell 2012, 11, 23–35.

[11] Afshari, K.; Dehdashtian, A.; Haddadi, N.S.; Haj-Mirzaian, A.; Iranmehr, A.; Ebrahimi, M.A.; Tavangar, S.M.; Faghir-Ghanesefat, H.; Mohammadi, F.; Rahimi, N.; et al. Anti-inflammatory effects of Metformin improve the neuropathic pain and locomotor activity in spinal cord injured rats: Introduction of an alternative therapy. Spinal Cord. 2018, 56, 1032–1041.

[12] Kothari, V.; Galdo, J.A.; Mathews, S.T. Hypoglycemic agents and potential anti-inflammatory activity. J. Inflamm. Res. 2016, 9, 27–38.

[13] Cameron, A.R.; Morrison, V.L.; Levin, D.; Mohan, M.; Forteath, C.; Beall, C.; McNeilly, A.D.; Balfour, D.J.; Savinko, T.; Wong, A.K.; et al. Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status. Circ. Res. 2016, 119, 652–665.

[14] Hill, J.L.; Kobori, N.; Zhao, J.; Rozas, N.S.; Hylin, M.J.; Moore, A.N.; Dash, P.K. Traumatic brain injury decreases AMP-activated protein kinase activity and pharmacological enhancement of its activity improves cognitive outcome. J. Neurochem. 2016, 139, 106–119.

[15] Tao, L.; Li, D.; Liu, H.; Jiang, F.; Xu, Y.; Cao, Y.; Gao, R.; Chen, G. Neuroprotective effects of metformin on traumatic brain injury in rats associated with NF-kappaB and MAPK signaling pathway. Brain Res. Bull. 2018, 140, 154–161.

[16] Wang, H.; Zheng, Z.; Han, W.; Yuan, Y.; Li, Y.; Zhou, K.; Wang, Q.; Xie, L.; Xu, K.; Zhang, H.; et al. Metformin Promotes Axon Regeneration after Spinal Cord Injury through Inhibiting Oxidative Stress and Stabilizing Microtubule. Oxid. Med. Cell Longev. 2020, 2020, 9741369.

[17] DiBona, V.L.; Shah, M.K.; Krause, K.J.; Zhu, W.; Voglewede, M.M.; Smith, D.M.; Crockett, D.P.; Zhang, H. Metformin reduces neuroinflammation and improves cognitive functions after traumatic brain injury. Neurosci. Res. 2021, 172, 99–109.

[18] Fiani, B.; Covarrubias, C.; Wong, A.; Doan, T.; Reardon, T.; Nikolaidis, D.; Sarno, E. Cerebrolysin for stroke, neurodegeneration, and traumatic brain injury: Review of the literature and outcomes. Neurol. Sci. 2021, 42, 1345–1353.

[19] Lucena, L.L.; Briones, M.V.A. Effect of Cerebrolysin in severe traumatic brain injury: A multi-center, retrospective cohort study. Clin. Neurol. Neurosurg. 2022, 216, 107216.

[20] Poon, W.; Matula, C.; Vos, P.E.; Muresanu, D.F.; Steinbuchel, N.; Wild, K.; Homberg, V.; Wang, E.; Lee, T.M.C.; Strilciuc, S.; et al. Safety and efficacy of Cerebrolysin in acute brain injury and neurorecovery: CAPTAIN I—A randomized, placebo-controlled, double-blind, Asian-Pacific trial. Neurol. Sci. 2020, 41, 281–293.

[21] Sharma, H.S.; Muresanu, D.F.; Sahib, S.; Tian, Z.R.; Lafuente, J.V.; Buzoianu, A.D.; Castellani, R.J.; Nozari, A.; Li, C.; Zhang, Z.; et al. Cerebrolysin restores balance between excitatory and inhibitory amino acids in brain following concussive head injury. Superior neuroprotective effects of TiO2 nanowired drug delivery. Prog. Brain Res. 2021, 266, 211–267.

[22] Brazinova, A.; Rehorcikova, V.; Taylor, M.S.; Buckova, V.; Majdan, M.; Psota, M.; Peeters, W.; Feigin, V.; Theadom, A.; Holkovic, L.; et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J. Neurotrauma 2021, 38, 1411–1440.

[23] Bayley, M.; Ponsford, J.; Jeffay, E.; Ponsford, J.; Harnett, A.; Janzen, S.; Patsakos, E.; Douglas, J.; Kennedy, M.; Kua, A.; et al. INCOG 2.0 Guidelines for Cognitive Rehabilitation Following Traumatic Brain Injury, Part III: Executive Functions. J. Head Trauma Rehabil. 2023, 38, 52–64.

[24] Vester, J.C.; Buzoianu, A.D.; Florian, S.I.; Homberg, V.; Kim, S.-H.; Lee, T.M.C.; Matula, C.; Poon, W.S.; Steinbuchel, N. Cerebrolysin after moderate to severe traumatic brain injury: Prospective meta-analysis of the CAPTAIN trial series. Neurol. Sci. 2021, 42, 4531–4541.