*Review Article*

Neuroprotection strategies in traumatic brain injury: Studying the effectiveness of different clinical approaches

Barbara Buccilli[1,2] , Albert Alan[2,3,4], Baha'Aljeradat[2,5], Akmal Shahzad[2,6], Yasser F. Almealawy[2,7] ,
Nathan Simbarashe Chisvo[2,8], Michelle Ennabe[2,9], Martin Weinand[3,4]

[1]Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, [2]Global Neurosurgical Alliance, United States, [3]College of Medicine, The University of Arizona College of Medicine - Tucson, [4]Department of Neurosurgery, University of Arizona, Tucson, Arizona, Unite States, [5]Department of Neurosurgery, The University of Jordan School of Medicine, Amman, Jordan, [6]Department of Medicine, Aga Khan University, Karachi, Pakistan, [7]Department of Neurosurgery, University of Kufa College of Medicine, Kufa, Iraq, [8]Department of Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom, [9]Departmenty of College of Medicine, The University of Arizona College of Medicine, Phoenix, Arizona, United States.

E-mail: Barbara Buccilli - doctor.b.buccilli@gmail.com; *Albert Alan - albertalan@arizona.edu; Baha' Ghandi Aljeradat - bha0171190@ju.edu.jo;
Akmal Shahzad - akmal.shahzad@scholar.aku.edu; Yasser F. Almealawy - almealawyyasser@gmail.com; Nathan Simbarashe Chisvo - nathan_chisvo@outlook.com;
Michelle Ennabe - mennabe@email.arizona.edu; Martin Weinand - mweinand@arizona.edu
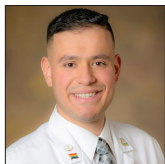
*Corresponding author:
Albert Alan,
Department of Neurosurgery,
University of Arizona, Tucson,
Arizona, United States.

albertalan@arizona.edu

ABSTRACT

Background: This review delves into clinical strategies aimed at addressing the complexities of traumatic brain injury (TBI), specifically focusing on pharmaceutical interventions and stem cell therapies as potential avenues for enhancing TBI outcomes.

Methods: A thorough review of clinical strategies for TBI management, encompassing pharmaceutical and non-pharmaceutical interventions, was performed. PubMed, MEDLINE and clinical trial databases were searched to identify relevant studies and clinical trials. Inclusion criteria consisted of studies involving pharmaceutical agents and other clinical approaches (i.e., stem cell therapies) targeting neuroinflammation, excitotoxicity, oxidative stress, and neurodegeneration in TBI. Data from clinical trials and ongoing research initiatives were analyzed to assess the current status and potential of these clinical approaches.

Results: Many trials have been conducted to face the challenge that is TBI. These interventions are designed to target critical aspects of secondary brain injury, encompassing neuroinflammation, excitotoxicity, oxidative stress, and neurodegeneration. Despite this, there is no panacea or definitive remedy for this condition. Combining therapies in a patient-tailored approach seems to be our best chance to improve these patients' outcomes, but systematic protocols are needed.

Conclusion: Clinical strategies represent dynamic and continually evolving pathways in TBI management. This review provides an extensive overview of the existing landscape of clinical approaches and promising new studies and outlines their influence on patient outcomes. By highlighting challenges and presenting opportunities, it contributes to the ongoing mission to advance clinical care for individuals impacted by TBI.

Keywords: Excitotoxicity, Neurodegeneration, Neuroinflammation, Oxidative stress, Traumatic brain injury

INTRODUCTION

Background and significance of TBI-related neuroprotection

Traumatic brain injury (TBI) is regarded as one of the primary causes of hospitalization, disability, and death in people of all ages.[14] The most common causes of TBI are falls, motor vehicle accidents, and fights.[36]

The mechanical damage is followed by local inflammation, predominantly led by microglia.[38] There are two types of TBI-related injury: in the primary injury, the neural tissue is mechanically harmed, causing hemorrhages, contusions, cerebral blood flow (CBF) compromise, blood–brain barrier (BBB) disruption, and metabolic abnormalities.[61] Within minutes after the initial trauma, we can observe a series of complex processes. Importantly, these processes continue over long lengths of time after the original damage, from days to months and, in some circumstances, even years. In the end, neuroinflammation and neurodegeneration bring neurological deficits.[27,81] The existence of these persisting secondary damage processes [Figure 1], though, also extends the therapeutic window.[30,45]

The rationale behind early intervention is to halt or attenuate these damaging processes before they escalate further. By doing so, early interventions have the potential to yield greater benefits in terms of preserving neural tissue, minimizing neuroinflammation, and averting excessive neuronal cell death. While the benefits of early interventions are well-established, it is important to note that the therapeutic window does not abruptly close as time progresses. Some interventions can still be efficacious when introduced later in the recovery process. This is particularly relevant in cases where the secondary injury processes persist over an extended period. Late-stage interventions may focus on facilitating neural repair, enhancing cognitive rehabilitation, or addressing chronic neurological deficits.

TBI's social and financial implications are presently attracting an increasing amount of attention.[35,89] Recent statistics show that there were almost 27 million new TBI diagnoses in 2016 and that over the previous 26 years, the frequency of TBI has grown by 8.4%.[35] Despite that, due to a lack of knowledge regarding the diverse nature and complexity of TBI, years of extensive study have so far had a modest influence on therapeutic results.

Overview of TBI epidemiology and impact on the brain

Age and gender both affect the incidence of TBI. It can occur in children as young as 0 years old, teenagers as old as 15–19, and adults. The incidence is higher in men than women.[18] According to different studies, there are 100–750 cases/100,000 individuals.[7,8,20,40,62,66] According to the Glasgow coma scale [Figure 2], we can classify TBI as: mild (13–15), moderate (9–12), or severe (3–8).[33,90]

Mild TBI (mTBI), the most prevalent kind of TBI (representing 70% of cases), has good survival rates, but up to 5 million Americans live with persistent TBI-related disabilities, including social, motor and cognitive dysfunctions, mood disorders, sleep disturbances, and personality changes.[13,18,19,27] Severe or recurrent TBI

dramatically increases the risk of neurodegeneration, dementia, stroke, and epilepsy.[105]

The primary injury in TBI can lead to focal and diffuse brain damage, which often coexist in moderate-to-severe cases.[61] However, diffuse axonal injury (DAI), which accounts for around 70% of TBI cases, is the most prevalent injury pattern.[86] The damage alters the axonal cytoskeleton and disrupts axonal transport.[76]

The secondary damage is frequently delayed and protracted, and multiple variables, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axon degeneration, and apoptosis, play a role in it.[72]

24 h post-TBI, the BBB shows signs of malfunctioning, allowing circulating leukocytes to infiltrate the damaged brain parenchyma and release proinflammatory cytokines such as Interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNFα), and complement factors.[5,25,46] Neurological impairments, increased BBB permeability, and sustained overexpression of cytokines are all linked. TNF interacts strongly with the Fas ligand because it is a member of the Fas superfamily, and this interaction activates caspases, whose activity leads to apoptosis.[59] Following trauma, chemokines, including MIP-, MCP-1, and IL-8 (CXCL8), are greatly increased, working in concert to attract leukocytes to the lesion site further.[5,22,25,39,59] Astrogliosis is facilitated by persistent and delayed neuroinflammation, which also attracts macrophages and promotes the activation of local microglia.[39,59] Years after TBI, survivors can continue to exhibit a collection of macrophages and active microglia, which is indicative of phagocytosis and chronic inflammation.

A patient might experience accelerated neurodegeneration and the onset of chronic traumatic encephalopathy following a single or recurrent TBI. This has been seen in athletes and military personnel exposed to frequent head trauma and concussions.[24,54,55]

An investigation into the connection between TBI and neurodegenerative conditions found an association linking TBI and Alzheimer's. The findings showed that TBI causes tau protein to be acetylated, a mechanism connected to Alzheimer's. In animal's memory, problems were linked to this acetylation, demonstrating the long-term effects of TBI.[83]

Scope and objectives of the review

The purpose of this review is to extensively examine and assess various clinical strategies for neuroprotection in the context of TBI. It is crucial to comprehend how different neuroprotective methods and treatments can be effective in reducing the impact of TBI and enhancing
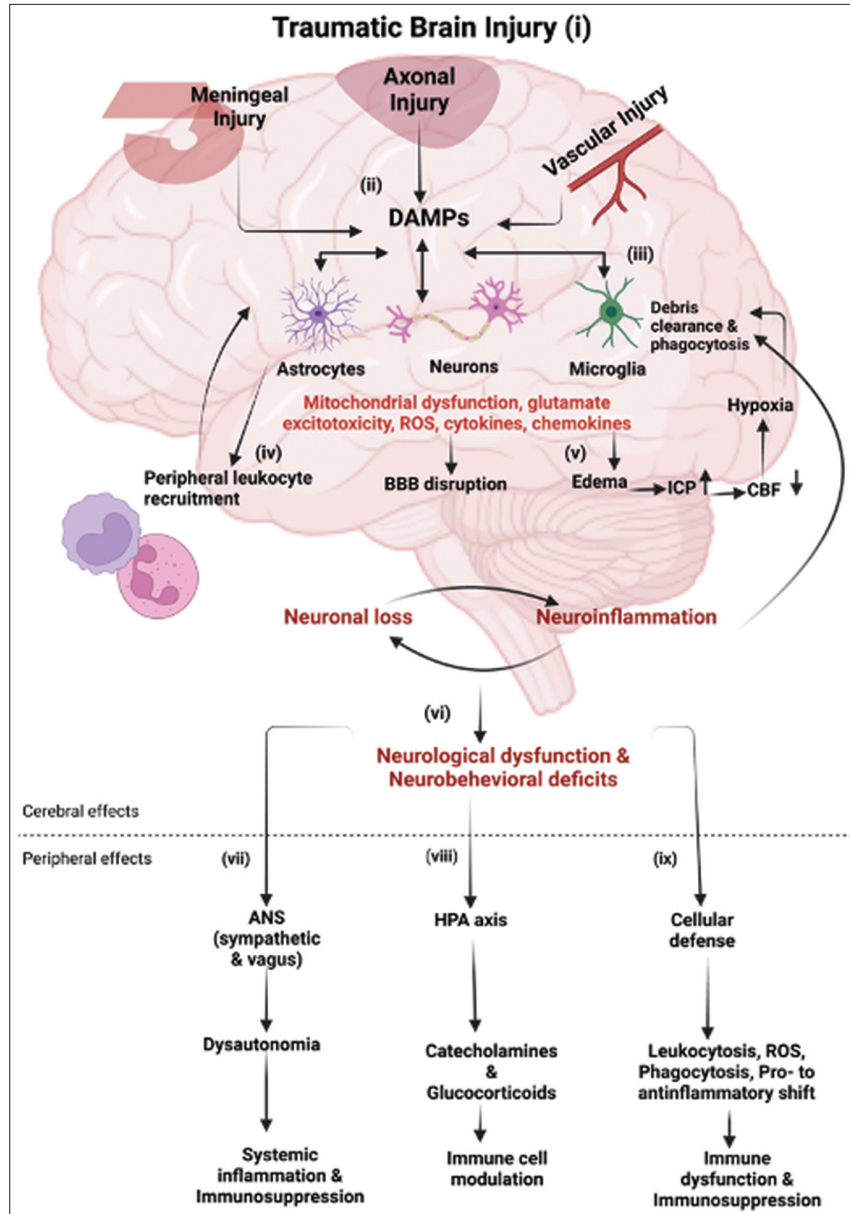
Figure 1: Immune response following traumatic brain injury (TBI): (i-ii) following TBI, the primary mechanical injury can include meningeal contusion, axonal shearing, and cerebrovascular injury, culminating in meningeal and neuronal cell death, as well as microglial and astrocytic activation. (iii) Such neuronal injury and glial engagement generate chemokines, cytokines, and reactive oxygen species, along with the release of damage-associated molecular patterns (DAMPs), setting off an inflammatory response. (iv) In the presence of DAMPs, phagocytic microglia engage in debris clearance and synthesize neurotrophic agents. Sustained stimulation of these pathways induces subsequent injury through leukocyte recruitment, which initially aids in the removal of tissue debris. (v) Subsequently, it contributes to the progression of inflammation and disruption of the blood–brain barrier (BBB). The cytotoxic edema and compromised BBB integrity bring to an elevation of the intracranial pressure, leading to decreased cerebral blood flow, thereby intensifying hypoxia and disrupting the cerebral energy supply. Consequently, this cascade drives further neuronal depletion, propelling a self-perpetuating cycle of neuroinflammation and neurodegeneration. (vi) These progressive pathological modifications culminate in neurological dysfunction and deficits in motor, cognitive, and emotional functions. TBI also induces alterations in the autonomic nervous system (ANS), which monitors and regulates DAMPs, consequently eliciting both cerebral and peripheral immune responses. (vii) Activation of the sympathetic ANS culminates in the peripheral discharge of catecholamines (epinephrine and norepinephrine), which suppress the systemic immune responses of macrophages through the cholinergic anti-inflammatory pathway (CAO), thereby mitigating systemic inflammation. (viii) Furthermore, the release of catecholamines and glucocorticoids through the hypothalamic-pituitary-adrenal axis governs the functional behavior of systemic immune cells after TBI. (ix) The cellular immune response to traumatic brain injury involves an increase in leukocytosis and ROS generation, progresses through phagocytosis, and shifts from pro-inflammatory to anti-inflammatory states, potentially leading to immune dysfunction and immunosuppression. Abbreviations: ICP (increased intracranial pressure), CBF (cerebral blood flow), HPA (hypothalamic-pituitary-adrenal), ROS (reactive oxygen species). Image created with BioRender.com.
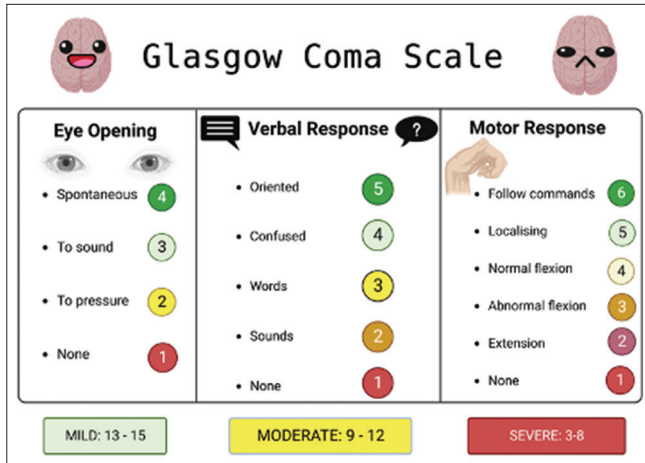
Figure 2: This figure illustrates the Glasgow coma scale (GCS), a vital neurological assessment tool, as it pertains to traumatic brain injury (TBI). The GCS quantifies the patient's level of consciousness based on eye, verbal, and motor responses, aiding clinicians in gauging TBI severity and guiding treatment decisions. Created with BioRender.com.

patient outcomes. This review intends to cover a broad spectrum of neuroprotective approaches, encompassing pharmaceutical treatments, natural compounds, as well as cellular and molecular methods. Through a thorough examination of existing literature and clinical trials, the review aims to provide a comprehensive overview of the strengths and weaknesses of each neuroprotective strategy and its potential for practical application in clinical settings. In essence, the goals of this review are to offer valuable insights to healthcare professionals, researchers, and policymakers regarding evidence-based neuroprotection techniques that show promise in mitigating the consequences of TBI and promoting improved patient recovery and quality of life.

METHODOLOGY

Inclusion and exclusion criteria for article selection

Inclusion and exclusion criteria play a crucial role in ensuring that the articles selected for this review are relevant and meet the objectives of the study. The following are the inclusion and exclusion criteria established for article selection. We included articles that directly address neuroprotection strategies in the context of TBI and focus on the prevention, reduction, or mitigation of brain injury after a TBI event. Articles published within the past 20 years have been given priority to ensure that the review reflects current research and developments in the field. Both preclinical and clinical studies have been included. This encompasses animal studies, *in vitro* experiments, as well as randomized controlled trials (RCTs), cohort studies,case–control studies, and systematic reviews.

Only articles written in English have been included for ease of comprehension and analysis, and articles accessible through academic databases, online journals, and reputable sources have been prioritized to ensure reliability and credibility.

We excluded articles not directly related to neuroprotection in the context of TBI. This includes studies focused solely on other brain disorders or general neurological conditions. Gray literature, conference abstracts, editorials, opinions, and non-peer-reviewed articles have been excluded due to potential limitations in the rigor and credibility of the information presented, and articles not written in English have been excluded to avoid translation-related inaccuracies. In case of duplicate publications, only the most comprehensive and recent version has been included to avoid redundancy.

By adhering to these inclusion and exclusion criteria, the review aims to maintain a high standard of academic rigor, relevance, and reliability. The selected articles will contribute to a comprehensive and evidence-based analysis of neuroprotection strategies in the context of TBI, enabling a meaningful synthesis of findings and implications for clinical practice and future research.

Search strategy and databases used

We identified relevant keywords and phrases related to the topic, including "traumatic brain injury," "TBI," "neuroprotection," "neuroprotective agents," "interventions," "clinical trials," and "brain injury outcome." We then combined these keywords using Boolean operators (AND, OR) to formulate effective search strings. For example, we used: (Traumatic brain injury OR TBI) AND (neuroprotection OR neuroprotective agents), (neuroprotection OR neuroprotective interventions) AND (brain injury outcome OR clinical trials), and (TBI, Neuroprotection, Outcomes evaluation, biomarkers, Imaging techniques, Challenges, "Brain Injuries, Traumatic"[Mesh], "Neuroprotection"[Mesh], "Outcome Assessment, Health Care"[Mesh], "Biomarkers"[Mesh], and "Diagnostic Imaging"[Mesh]). We incorporated synonyms, alternate spellings, and related terms to capture a wider range of relevant articles. Our search spanned the following databases: PubMed, Embase/MEDLINE, and Scopus.

To ensure a thorough search, the reference lists of relevant review articles and included studies have been manually checked for potentially relevant articles that may not have appeared in the initial database search.

By employing this comprehensive search strategy and using reputable databases, the review aims to gather a diverse and extensive collection of literature on neuroprotection strategies in TBI, enabling a robust analysis and synthesis of the available evidence.

PHARMACEUTICAL INTERVENTIONS

A recent study developed bioactive nanofibrous dural substitutes that release insulin-like growth factor 1 (IGF-1). These substitutes significantly enhanced neural cell survival post-TBI.[102] Furthermore, the study indicated a reduction in inflammation and apoptosis in the brain tissue, suggesting a protective role of the IGF-1-releasing dural substitutes.[102] Building on this, another study showed that animals treated with exosomes postinjury exhibited faster neurological recovery.[104] Specifically, the exosome-treated animals demonstrated improved motor function, reduced brain lesion sizes, and enhanced synaptic plasticity, indicating the potential of exosomes in promoting neural repair.[104]

A pediatric preclinical study on the effects of LM22A-4, a TrkB agonist, revealed that treated animals displayed improved anxiety-related behavior.[21] In addition, there was a notable reduction in myelin deficits, suggesting that LM22A-4 could aid in the repair of damaged neural pathways in pediatric TBI cases.[21] However, the PROTECT III and SYNAPSE studies, two important phase-III clinical trials, found that early administration of progesterone did not yield any benefits in terms of neurological recovery for TBI patients. A detailed analysis showed no significant difference in the Glasgow Outcome Scale (GOS) scores between the treated and placebo groups, indicating that progesterone might not be as effective as previously thought.[58]

Another approach combined ketamine and perampanel to study their effects on TBI-induced behavioral changes in mice.[2] The results were encouraging, with treated mice showing improved spatial memory and reduced aggressive behaviors in the Morris water maze test. Moreover, there was a notable decrease in inflammatory markers in the brain tissue of treated mice.[2] Similarly, another study used advanced imaging techniques to evaluate the effects of low-intensity transcranial ultrasound stimulation and Baicalin intervention in rats with TBI.[67] The detailed outcomes revealed that the combined treatment resulted in reduced brain edema, improved BBB integrity, and enhanced neural connectivity, suggesting its potential as a therapeutic strategy.[67]

Numerous studies have explored the potential neuroprotective properties of erythropoietin (EPO) in the context of TBI. EPO's mechanism of action involves binding to the EPO receptor, which leads to downstream signaling activation. This includes JAK-2 phosphorylation, initiating pathways such as PI3-K/Akt, Ras/MAPK, and JAK2-STAT, which are pivotal for EPO's antiapoptotic and trophic effects. In addition, EPO has been shown to mitigate excitotoxicity, oxidative stress, and inflammation. It enhances neuronal viability under stress conditions and reduces glutamate toxicity, primarily through calcium-dependent mechanisms.

Furthermore, EPO potentially improves cerebral perfusion and vascular integrity and stimulates angiogenesis through the VEGF pathway. It also plays a role in neurogenesis following TBI. EPO's hematopoietic side effects have prompted the development of EPO analogs with neuroprotective potential. Clinical trials have yielded mixed results, with some suggesting neuroprotective effects while others remain inconclusive. Further research is needed to establish EPO's definitive role in TBI treatment.[44,64,70,82,99,107,110,111]

Progesterone is another drug with neuroprotective capabilities which uses a series of intracellular pathways to achieve its effect. One study shows how EGFR activation mitigates BBB cell connexin loss in brain injury, stabilizing BBB structure, decreasing permeability, and reducing brain tissue edema. ERK, a MAPK family member encoded by the MAPK1 gene, operates through the Ras/Raf/MEK/ERK1/2 pathway.[70] ERK/MAPK pathway activation contributes to neuronal injury and apoptosis, causing brain tissue damage. ERK/MAPK disinhibition through PD98059 effectively mitigates brain edema and neurological damage in a rat TBI model.[101]

Progesterone treatment in TBI influences steroid hormone receptor activity, RNA polymerase II transcription factor activity, receptor signaling protein tyrosine kinase activity, MAP kinase, and related protein kinase activity. KEGG analysis reveals core targets of progesterone treatment regulating apoptosis and signaling transduction. These targets enrich PI3K/Akt, Ras, and MAPK pathways, indicating multi-pathway, multi-target effects for TBI treatment.[91]

The MAPK pathway, a prominent KEGG finding, employs a 3-stage enzymatic cascade (MAP3K/MAP2K/MAPK) to activate downstream transcription factors for signal transduction. JNK, a MAPK family component, participates in extracellular stimulus-induced activities such as apoptosis, metabolism, and DNA repair. In TBI, downregulated JNK3 expression aids nerve function recovery and reduces edema and nerve cell apoptosis through TNFα, IL-1α, IL-1β, and IL-6 downregulation.[1,9]

P38 MAPK, a vital serine/threonine protein kinase, influences neural tissue pathophysiology. This pathway responds to oxidative stress and inflammation, initially inducing neurotoxicity and later inhibiting inflammation through an anti-apoptotic effect. P38 MAPK regulates apoptosis-related protein expression and enhances BBB permeability.[10]

Ras signaling, a classical MAPK pathway, operates through the Ras/Raf/MEK/ERK1/2 route. Inhibiting ERK/MAPK reduces neuronal injury, apoptosis, brain edema, and neurological damage. EGFR interaction with ligands like EGF activates Ras signaling, protecting against ischemic stroke and inflammation while promoting neuroprotection through IL-20 and reduced excitatory amino acid release.

Thus, progesterone's influence on MAPK and Ras pathways mitigates secondary TBI effects and neuronal apoptosis and enhances neurological function.[42]

Numerous investigations have demonstrated the neuroprotective attributes of progesterone in both animal models and clinical trials of TBI, with no reports of severe adverse effects associated with treatment.[6] Specifically, in animal models of TBI, progesterone has been linked to a reduction in secondary injuries following the initial trauma, manifested as a decrease in cerebral edema and the prevention of secondary neuronal degeneration.[74] These mechanisms contribute to the amelioration of behavioral deficits resulting from TBI. In addition, two independent Phase II clinical trials have reported positive effects of progesterone on both mortality rates and the GOS scores in TBI patients.[106,108]

However, the outcomes of two randomized, double-masked, and multicenter Phase III RCTs have indicated no significant differences between placebo- and progesterone-treated groups concerning mortality rates and functional outcomes at the 6-month post-TBI mark.[106,108] Furthermore, a comprehensive meta-analysis conducted in 2016 found that progesterone did not significantly reduce mortality rates or improve neurological outcomes in severe TBI patients.[47] Intriguingly, while certain studies, such as the one conducted by Santarsieri *et al.*,[79] administering medroxyprogesterone through nasogastric tubing, have shown limited clinical benefits, other meta-analyses have suggested that progesterone provided neuroprotection exclusively when administered intramuscularly. The variation in efficacy between intravenous and intramuscular administration remains unclear, necessitating a careful examination of the delivery route across clinical trials.[4]

Another study included seven RCTs that were also featured in the meta-analysis. While these trials spanned follow-up periods ranging from 30 days to 6 months, they did not conduct stratified analyses based on follow-up duration, overlooking potential time-dependent effects of progesterone. The researcher's investigation assessed the efficacy of progesterone in severe TBI patients at both short-term (within three months postinjury) and long-term (at six months postinjury) endpoints. Remarkably, progesterone administration correlated with a reduced mortality rate and higher GOS scores within the first three months following injury; however, no significant advantages were observed at the 6-month mark. It is important to note that interpreting the long-term effects of progesterone should be approached with caution due to the influence of numerous confounding factors.[65]

In summary, progesterone administration enhances clinical outcomes in severe TBI patients within three months following injury, although discernible long-term benefits at the 6-month postinjury interval are less evident. Further, investigations are warranted to thoroughly explore inter-study variations and inform the design of future clinical trials.

N-acetylcysteine (NAC) is a compound known for its antioxidant properties and its potential as a neuroprotective agent.[17,78] From a biochemical perspective, NAC serves as a provider of cysteine, a crucial component in synthesizing the intracellular antioxidant glutathione (GSH). This ability allows NAC to enhance the availability of cysteine for the replenishment of GSH when the body is under oxidative stress.[23] NAC can directly function as an antioxidant through its thiol group. NAC is highly hydrophilic, with a low log value of −5.4, suggesting that it has limited ability to traverse the intact BBB passively.[41] In clinical applications, NAC has been established as an effective therapy for preventing liver damage from acetaminophen/paracetamol overdose.[23,103] Moreover, it has been explored in clinical trials for various neurological conditions, including autism, major depression, neonatal asphyxia, and neurodegenerative diseases. Notably, NAC has exhibited promising results in mitigating the consequences of mTBI, likely through its antioxidative properties in the brain.[32,41]

N-acetyl cysteine has demonstrated significant neuroprotective effects in animal models, particularly in mitigating secondary neuronal injury following TBI. Studies in rats have confirmed the beneficial antioxidant effects of NAC when administered after brain injury.[8,15,109] NAC functions by elevating the levels of GSH, a molecule composed of L-glutamic acid, L-cysteine, and glycine, within the brain. By providing a source of cysteine, a precursor to GSH, NAC can counteract the damage caused by reactive oxygen species within the mitochondria of the substantia nigra in Parkinson's disease.[8] Furthermore, NAC has shown the ability to reduce the deposition of tau and beta-amyloid and act as an anti-inflammatory agent in treating Alzheimer's disease by upregulating GSH. This demonstrates its effectiveness in addressing TBI and managing subsequent neurodegenerative conditions associated with TBI in rat models.[52]

A double-masked and placebo-controlled clinical trial was conducted to assess the efficacy of NAC in patients with mTBI caused by blasts. The treatment group received 2 g of NAC twice daily for the first four days, followed by 1.5 g of NAC twice daily for the next three days. After seven days of treatment, patients were evaluated for symptoms such as dizziness, headache, hearing loss, memory loss, sleep disturbances, and neurocognitive dysfunction. Significant improvements ($P < 0.01$) in these symptoms were observed in patients who received NAC within 24 hours of injury, and the treatment group had an 86% chance of recovery. These findings suggest the need for further investigation into the long-term effects of NAC treatment in TBI.[32]

In addition, in 2017, Clark *et al.* conducted a randomized, double-masked, and placebo-controlled Phase I study in children aged 2–18 who were admitted to a Pediatric Intensive Care Unit after severe TBI.[11] The study revealed no adverse effects, including undesirable physiological changes, and did not observe alterations in contemporary brain injury biomarkers related to administering the drug combination. These results support the potential for progressing to a Phase II/III trial to explore the efficacy of NAC treatment in severe TBI.

TARGETING INFLAMMATION AND OXIDATIVE STRESS

The impact of inflammation and oxidative stress in TBI

According to normal physiology, both intracellular and extracellular processes contribute to and lead to secondary injury. Inflammatory and oxidative responses following TBI can be disruptive. Proinflammatory factors such as tumor necrosis factor and IL -6, along with reactive species such as superoxide and peroxynitrite, are found in high concentrations in injured brain tissue. All these factors can contribute to increased inflammation, leading to damage to neuronal tissue and DNA, particularly due to reactive species. However, this also promotes apoptosis of the affected cells.[16,26,29,84] Therefore, treatments targeting these processes can play an important role in neuroprotection.

Anti-inflammatory and antioxidant therapies explored

NMDA-receptor antagonists

Elevated concentrations of glutamate exceeding 100 μM are implicated in neuronal destruction and cell death.[49,97] Numerous clinical trials involving NMDA receptor antagonists such as aptiganel, dextromethorphan, dizocilpine, eliprodil, gavestinel, licostinel, and selfotel were initiated, but some were discontinued prematurely or failed to demonstrate their efficacy in stroke or TBI trials. Other trials suggested potential neurotoxic effects linked to this class of drugs.[34,69]

Glutamate agonists

Microglia, astrocytes, and neurons exhibit high glutamate receptor expression. Glutamate agonists have been observed to inhibit caspase-dependent apoptosis and mitigate microglial inhibition of NADPH oxidase. The mGluR5 agonist (RS)-2-chloro-5-hydroxyphenylglycine (CHPG) has demonstrated neuroprotective and anti-apoptotic properties in neuronal and microglial cultures. In summary, early treatment with glutamate agonists in laboratory settings has shown promising neuroprotective effects post-TBI.[45]

Calcium-channel antagonists

The blockade of neural calcium channels holds the potential to mitigate glutamate excitotoxicity, reduce neurotransmitter release, and disrupt the apoptosis cascade. Calcium channel blockers such as nicardipine and nimodipine have been suggested to play a neuroprotective role and mitigate vasospasm in subarachnoid hemorrhage.[49,53]

Immune system modulation

The immunosuppressant Cyclosporine-A reduces T-cell-mediated immunity and is used in organ transplant recipients. It inhibits calcineurin and cyclophilin-A, suppressing mitochondrial pore formation and potentially curbing the apoptotic cascade.[88] Higher doses of cyclosporine seem associated with improved outcomes. A controlled trial involving 100 patients with GCS <10 and radiological evidence of DAI found that while cyclosporine had no adverse effects post-TBI, it did not improve outcomes or mortality.[3] Other studies showed little impact on lymphocyte count or infection rates following administration in TBI patients.[12,28]

Challenges and potential for clinical translation

On the frontier of data-driven research, Lipponen *et al.* developed a unique pipeline for TBI treatment discovery using transcriptomics data.[43] The outcomes of their approach identified several potential drug candidates that could modulate the inflammatory response post-TBI, offering a new avenue for TBI treatment.[43]

A recent study focused on the role of NADPH oxidase 2 (NOX2) in TBI. The outcomes showed that GSK2795039 reduced NOX2 expression and activity in a TBI mouse model. In addition, treated mice displayed improved cognitive functions, suggesting that targeting NOX2 could be a potential therapeutic strategy.[100]

Therapeutic hypothermia and brain cooling

Hypothermia was first described in the Edwin Smith Papyrus, an ancient Egyptian treatise on medicine and surgery written over 5000 years ago.[98] Clinical studies focusing on hypothermia in TBI have centered around multifactorial mechanistic approaches, as demonstrated in basic science studies. Hypothermia effectively manages elevated intracranial pressure (ICP) and mitigates secondary brain injury.[77,112] Moreover, hypothermia acts to prevent secondary brain injury by improving neuroinflammation, ischemia-perfusion injury, and excitotoxic, oxidative, and cytokine-induced alterations. In addition, hypothermia protects the BBB and reduces cerebral metabolism, curbs energy expenditure and oxygen consumption.[93]

CELLULAR AND MOLECULAR APPROACHES

Cell-based therapies and gene therapies for TBI neuroprotection

A recent study aimed to evaluate the effects of administering a single dose of exosomes early after injury over seven days in a swine model of TBI and hemorrhagic shock. At the end of the seven days postinjury, levels of markers related to inflammation, apoptosis, and neural plasticity were analyzed.[104] Animals treated with exosomes showed improved neurologic outcomes, with lower severity scores and faster recovery within the first four days. By the 7th day, exosome-treated animals had smaller brain lesion sizes. Inflammatory markers were reduced, while brain-derived neurotrophic factor levels were increased. BAX and NF-κB levels were also lower.

A recent study delved into the impact of intramuscular IGF-1 gene therapy.[31] The outcomes showed a significant reduction of reactive gliosis in treated animals. Furthermore, functional outcomes, such as motor coordination and spatial memory, were notably improved in the treated group, suggesting the potential of gene therapy in TBI treatment.[31] Another study evaluated the therapeutic effectiveness of mouse multipotent adult progenitor cells (mMAPCs) against mouse mesenchymal stem cells. The outcomes revealed that mMAPCs-treated animals showed reduced demyelination and enhanced remyelination, suggesting a superior therapeutic profile of mMAPCs.[85]

Another study explored stem cell therapy combined with genetic modifications. The outcomes showed that rats treated with mesenchymal stem cells overexpressing IL-10 had reduced autophagy response, suggesting enhanced neural protection.[51]

CLINICAL IMPLICATIONS AND CHALLENGES

Translating neuroprotection strategies to clinical practice

Facilitating the transition of experimental neuroprotection methods into practical clinical applications represents a pivotal step in advancing TBI care. This phase demands meticulous planning and comprehensive evaluation to integrate these strategies seamlessly into established clinical protocols. The employment of neuroprotection techniques requires the establishment of standardized guidelines and procedures that harmonize with current therapeutic approaches. Extensive clinical trials and real-world investigations are imperative to ascertain the safety, efficacy, and feasibility of these therapies and bridge the divide between laboratory research and clinical practice. Collaboration among neurologists, neurosurgeons, rehabilitation specialists, and other medical experts is essential, fostering a coordinated approach that optimizes patient care and capitalizes on the potential benefits of neuroprotection methods.

Challenges in implementation and personalized approaches

The effective implementation of neuroprotection techniques encounters several challenges despite their considerable potential. Patient variability, injury severity, and individual responses to treatment underscore the importance of tailored strategies for each TBI case. Overcoming logistical hurdles, securing funding, and educating healthcare professionals are essential steps for integrating neuroprotection methods across diverse clinical settings. The adoption of innovative interventions demands a delicate balance between the need for swift deployment of effective therapies and the thorough evaluation required for their safe and successful application. The development of adaptable and scalable procedures that consider the complex interplay of clinical, logistical, and patient-related factors is pivotal in surmounting these obstacles.

ICP and cerebral perfusion pressure (CPP) shed light on the dynamics of CBF. However, using probes like $PbtO_2$, which measures extracellular oxygen tension, metabolic events can actually be measured.[37,48,95] Oxygen diffusion affects the equilibrium of supply and usage.[57,75] Due to edema and microvascular collapse, diffusion problems can easily develop in pericontusional tissue, lowering oxygen tension.[57]

Defining optimal $PbtO_2$ target values is complex.[68] Low oxygen levels, between 15 mm Hg and 20 mm Hg, are associated with poor outcomes.[57,80,94] By adjusting arterial pressure, oxygen tension, or both, $PbtO_2$ can be restored.[56,87] These strategies appear to have a higher chance of success than those that only rely on ICP and CPP. However, the low number of studies reduces the strength of these findings.[60]

Metabolic crisis can be recognized by a high lactate: pyruvate ratio, which also serves as a standalone predictor of death.[92] A better lactate: Pyruvate ratio could be a sign that the treatment is working. Investigations have been done into how different therapies, such as hyperoxia and hypertonic lactate, affect how the brain uses energy. Low $PbtO_2$ may normally be raised by normobaric hyperoxia, which is commonly induced by raising the inspired oxygen; however, conflicting effects of microdialysis have been recorded.[50,73] Nevertheless, results of imaging studies indicate that this intervention may enhance cerebral oxygen metabolism[63] and reverse pericontusional cytotoxic edema.[96] In individuals with a pathologic lactate: Pyruvate ratio, efforts to enhance brain glucose metabolism using hypertonic lactate infusions clearly have a positive impact.[71] These early findings must be verified.

The idea of employing advanced multimodal monitoring to guide the treatment of elderly patients is appealing, but there exists a notable gap in our understanding of this domain. This

knowledge deficit can be attributed in part to the elevated risks linked with invasive intracranial monitoring in older individuals. Many of these patients are on anticoagulant and antiplatelet medications, which heighten the potential for complications. Furthermore, due to the possibility of a less-than-optimal outcome, there is a reduced inclination toward intensive monitoring and treatment in this demographic.

Ethical considerations

Integrating neuroprotection techniques into TBI treatment demands careful ethical considerations. This involves risk assessment, informed consent, and addressing cost and access issues for equitable treatment. Patient, caregiver, and family perspectives are vital. Engaging with TBI patients' experiences guides ethical decision-making and enhances the practicality of neuroprotection techniques. A comprehensive framework balancing beneficence, autonomy, and justice emerges through the convergence of ethics and patient insights.

CONCLUSION

This comprehensive review delves into various neuroprotective strategies for TBI. These interventions work through intricate molecular pathways, affecting processes such as apoptosis, inflammation, oxidative stress, and excitotoxicity. Clinical trials have produced mixed results, influenced by factors such as administration methods, dosages, and follow-up durations.

TBI management proved to be extremely complex since no single intervention is a panacea for this multifaceted condition. Instead, a holistic approach considering patient-specific factors, timing, and a combination of therapies is crucial for improving outcomes. Ongoing efforts to standardize protocols and refine patient selection criteria offer the promise of more reliable future treatments. Despite challenges, the pursuit of neuroprotective strategies in TBI offers hope for better patient outcomes. The evolving landscape of TBI research holds the potential for continued progress in understanding and managing this critical public health concern.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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