The American Journal of Medical Sciences and Pharmaceutical Research ISSN 2689-1026 Volume 08 - 2026

NSAID-Augmented Therapy for Cerebral Edema in Severe Traumatic Brain Injury: A Clinical Study

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Received: 28 Feb 2026 | Received Revised Version: 07 Mar 2026 | Accepted: 29 Mar 2026 | Published: 23 Apr 2026

Volume 08 Issue 04 2026 | Crossref DOI: 10.37547/tajmspr/Volume08Issue04-11

Abstract

Background: Severe traumatic brain injury (sTBI) is characterized by intense neuroinflammation and progressive cerebral edema, which significantly impact morbidity and mortality. Conventional anti-edema therapies often provide limited control over the inflammatory cascade. This study evaluates the clinical efficacy of augmenting standard treatment with Nimesulide, a non-steroidal anti-inflammatory drug (NSAID), to mitigate cerebral edema and improve neurological recovery.

Methods: A prospective clinical study was conducted on 150 patients with sTBI. Patients were divided into two groups: the Main Group (n=115), receiving standard intensive care supplemented with Nimesulide, and the Control Group (n=35), receiving standard therapy alone. Neurological status was assessed using the Glasgow Coma Scale (GCS) on days 1, 5, and 10. Secondary outcomes included the incidence of complications (pneumonia, seizures), laboratory markers of systemic inflammation (Neutrophil-to-Lymphocyte Ratio - NLR), and neuroimaging dynamics via MSCT and ophthalmoscopy.

Results: On day 1, GCS scores were comparable between groups (9.1±1.2; $p>0.05$). By day 10, the Main Group showed significantly higher neurological recovery (13.1±1.7) compared to the Control Group (11.5±1.6; $p<0.05$). NSAID-augmented therapy was associated with a lower incidence of pneumonia (19.1% vs 28.6%) and post-traumatic seizures (14.8% vs 25.7%; $p<0.05$). Laboratory findings revealed a more rapid normalization of NLR and endotoxicosis markers in the Main Group. MSCT and ophthalmoscopy confirmed accelerated regression of cerebral edema and earlier stabilization of the artery-to-vein ratio (1:1.5) in patients receiving supplemental anti-inflammatory therapy.

Conclusion: Augmenting standard sTBI protocols with Nimesulide significantly accelerates neurological recovery, reduces the volume of cerebral edema, and lowers the frequency of life-threatening complications. These findings suggest that targeting neuroinflammation is a crucial component in optimizing outcomes for patients with severe traumatic brain injury.

Keywords: Severe traumatic brain injury, Cerebral edema, NSAIDs, Neuroinflammation, Glasgow Coma Scale, Intensive care.

Cite This Article: Visolat Khamzaevna Sharipova, & Temur Khayrullaevich Ashurov. (2026). NSAID-Augmented Therapy for Cerebral Edema in Severe Traumatic Brain Injury: A Clinical Study. The American Journal of Medical Sciences and Pharmaceutical Research, 8(04), 61–72. https://doi.org/10.37547/tajmspr/Volume08Issue04-11

1. Introduction

Severe traumatic brain injury (sTBI) represents one of the most critical challenges in contemporary emergency medicine and neurocritical care [1,12,17]. Characterized by a Glasgow Coma Scale (GCS) score of 8 or less, sTBI remains a premier cause of global mortality and permanent neurological disability, disproportionately affecting the young, economically active population [18]. Despite the rigorous implementation of international guidelines—such as those provided by the Brain Trauma Foundation—the clinical trajectory of these patients often remains unpredictable, necessitating a more nuanced approach to therapeutic interventions [15].

The pathophysiology of TBI is traditionally bifurcated into primary and secondary injuries. While the primary injury occurs at the moment of impact due to mechanical shearing and diffuse axonal injury, the secondary injury is a delayed, progressive process that evolves over hours and days [9,13]. This "second hit" is driven by a complex cascade of neurochemical derangements, including glutamate excitotoxicity, massive oxidative stress, mitochondrial dysfunction, and a robust inflammatory response [2,16,20]. It is now widely recognized that this secondary phase is the principal determinant of long-term prognosis and the primary window for pharmacological neuroprotection [3].

Central to the progression of secondary brain damage is the activation of the innate immune response within the central nervous system [2,16]. Following trauma, microglia and astrocytes undergo phenotypic changes, releasing a deluge of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6), and prostaglandins [3,20].

This hyper-inflammatory milieu leads to the significant disruption of the Blood-Brain Barrier (BBB) [5,9]. The compromised integrity of the BBB facilitates the transition from vasogenic to cytotoxic cerebral edema, resulting in a refractory increase in intracranial pressure (ICP) [10,12]. Elevated ICP leads to compromised cerebral perfusion pressure (CPP) and subsequent secondary ischemic insults, creating a vicious cycle of neuronal death [13,16].

Current management of post-traumatic cerebral edema is largely reactive rather than proactive. Standard protocols rely heavily on osmotherapy (e.g., Mannitol, hypertonic saline) and surgical decompression to manage intracranial hypertension [10,13,15]. However, these strategies primarily target the physical manifestations of edema (fluid volume) without addressing the underlying molecular drivers of inflammation [4,12]. There is a critical clinical need for adjunct therapies that can modulate the neuroinflammatory response at its source, potentially stabilizing the BBB and mitigating edema formation before it reaches life-threatening levels [11,16].

Non-steroidal anti-inflammatory drugs (NSAIDs), specifically those targeting the cyclooxygenase-2 (COX-2) isoenzyme, offer a promising pathogenetic approach. COX-2 is rapidly upregulated in the brain following TBI and is a key driver of prostaglandin-mediated vascular permeability [5,9,18]. Nimesulide, as a selective COX-2 inhibitor, possesses unique pharmacological properties that may allow it to cross the BBB and attenuate the inflammatory cascade within the brain parenchyma [6,8,14]. By suppressing the cyclooxygenase pathway, augmented therapy with Nimesulide may reduce the intensity of neuroinflammation, thereby accelerating neurological recovery and preventing systemic complications [19.20].

Despite the theoretical benefits, the integration of NSAIDs into neurocritical care protocols for sTBI remains controversial and insufficiently documented in clinical practice [4,11]. This study aims to fill this gap by evaluating the efficacy of Nimesulide-augmented therapy in a clinical setting [8,19]. We specifically focus on the dynamics of neurological recovery via GCS [1,15], the regression of cerebral edema as visualized by MSCT and ophthalmoscopy [13,17], and the modulation of systemic inflammatory markers (e.g., NLR and endotoxicosis levels) [7,14].

The Role of Neuroinflammation and Cerebral Edema

Central to the self-propagating nature of secondary brain injury is a robust and often dysregulated neuroinflammatory cascade [2,16]. Immediately following the primary mechanical impact, resident immune cells of the brain—primarily microglia—undergo a rapid phenotypic transformation. These activated microglia, alongside infiltrating peripheral leukocytes, orchestrate a massive release of pro-inflammatory mediators, including tumor

necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). This "cytokine storm" within the cerebral parenchyma creates a hostile microenvironment that exacerbates cellular distress and triggers further neuronal apoptosis [3,9].

The deleterious effects of this inflammatory response are most prominently observed at the level of the Blood-Brain Barrier (BBB). Pro-inflammatory cytokines, coupled with the activation of matrix metalloproteinases (MMPs) and the overproduction of reactive oxygen species (ROS), degrade the tight junction proteins that maintain BBB integrity [5,9,12,20].

This structural compromise leads to a transition from controlled fluid homeostasis to the development of vasogenic cerebral edema. As the BBB becomes increasingly permeable, protein-rich fluid extravasates into the extracellular space. Concurrently, metabolic failure and the dysfunction of ATP-dependent ion pumps (due to mitochondrial distress) lead to cytotoxic edema, where water shifts into the intracellular compartment. The synergy between these two types of edema results in a progressive increase in cerebral volume [10,12,13].

The accumulation of cerebral fluid within the rigid, non-expansive confines of the cranium inevitably leads to an escalation of intracranial pressure (ICP). According to the Monro-Kellie doctrine, as ICP rises, it directly compromises cerebral perfusion pressure (CPP) and reduces cerebral blood flow (CBF). This reduction in perfusion induces secondary focal or global ischemia, further depleting cellular energy reserves and stimulating additional inflammatory signaling. If left unchecked, this vicious cycle culminates in brain tissue herniation and irreversible neuronal necrosis, which are the primary drivers of poor clinical outcomes in sTBI patients [1,6,13,16].

Current gold-standard management protocols, as outlined by international neurocritical care guidelines, remain predominantly reactive. Standard interventions rely heavily on osmotic therapy (e.g., Mannitol or hypertonic saline) and surgical decompression to mechanically reduce ICP. While effective at alleviating the symptoms of intracranial hypertension, these therapies are essentially "bridge" measures; they do not address the upstream pathogenetic inflammatory pathways that drive the edema in the first place [4,9,12].

There is, therefore, a critical clinical imperative to explore adjunct pharmacological strategies—such as NSAID-augmented therapy—that can modulate the neuroinflammatory response, stabilize the BBB, and arrest the edema process at its molecular origin rather than merely managing its macro-anatomical consequences [11,14,19].

NSAIDs: A Potential Pathogenetic Approach

Non-steroidal anti-inflammatory drugs (NSAIDs) have emerged as pivotal candidates in neuroprotective research due to their multi-targeted impact on the secondary injury cascade. The primary mechanism involves the inhibition of cyclooxygenase (COX) enzymes, which are responsible for the conversion of arachidonic acid into pro-inflammatory prostanoids [4,11,18].

In the context of traumatic brain injury (TBI), the COX-2 isoform is of particular clinical significance. Unlike the constitutively expressed COX-1, COX-2 is rapidly induced and significantly upregulated in neurons, microglia, and vascular endothelial cells following a traumatic insult. This massive upregulation is a key driver of post-traumatic neuroinflammation, exacerbating blood-brain barrier (BBB) permeability and promoting the accumulation of vasogenic edema [2,5].

Theoretically, the administration of selective NSAIDs can arrest several deleterious pathways simultaneously:

1. Mitigation of Inflammatory Response: By suppressing the synthesis of prostaglandins (especially PGE_2), NSAIDs reduce the chemotaxis of peripheral leukocytes and the activation of resident microglia, thereby dampening the "cytokine storm."
2. Reduction of Oxidative Stress: COX-2 activity is intrinsically linked to the generation of reactive oxygen species (ROS). Its inhibition reduces the production of superoxide radicals, protecting neuronal membranes from lipid peroxidation and DNA damage.
3. BBB Stabilization: By modulating the neurovascular unit's inflammatory milieu, NSAIDs help preserve the integrity of tight junction proteins, directly mitigating the shift toward vasogenic edema [3,5,6,14].

Nimesulide: A Selective and Targeted Approach

Among the diverse spectrum of non-steroidal anti-inflammatory drugs (NSAIDs), Nimesulide (4-nitro-2-phenoxymethane sulfonanilide) presents a unique and compelling therapeutic profile specifically suited for neurocritical care. As a relatively selective cyclooxygenase-

2 (COX-2) inhibitor, it exerts a targeted anti-inflammatory effect by suppressing the inducible enzyme responsible for prostanoid synthesis during brain injury [5,6,18]. This selectivity is clinically vital; by sparing COX-1 activity at therapeutic doses, Nimesulide significantly mitigates the risk of systemic adverse effects—most notably gastrointestinal mucosal injury and platelet dysfunction. This safety profile is a critical consideration in sTBI patients, who are often in a state of extreme physiological stress and hypercoagulability, making them highly susceptible to stress-induced ulcers and hemorrhage [1,15,19].

Beyond its primary role in cyclooxygenase inhibition, Nimesulide demonstrates a pleiotropic effect within the central nervous system, addressing multiple facets of the secondary injury cascade [7,14]:

- Antioxidant and Free Radical Scavenging: Nimesulide acts as a potent scavenger of superoxide anions and other reactive oxygen species (ROS). By neutralizing these radicals, it provides an additional layer of antioxidant defense, preventing the oxidative carbonylation of neuronal proteins and the peroxidation of membrane lipids [6,14].

- Enzymatic and Mediator Modulation: The drug inhibits the release of histamine from mast cells and suppresses the activity of various lysosomal enzymes, such as collagenase and elastase. This action is crucial in preventing the enzymatic degradation of the extracellular matrix and brain parenchyma that typically follows traumatic necrosis [9,13].

- Optimal Pharmacokinetics and BBB Penetration: The highly lipophilic nature of Nimesulide is one of its most significant advantages in neuro-pharmacology. This property, combined with the transiently compromised integrity of the blood-brain barrier (BBB) following trauma, facilitates its rapid penetration into the cerebral tissue. This ensures that effective therapeutic concentrations are reached directly within the brain parenchyma, where the neuroinflammatory process is most intense [2,5,10].

The integration of Nimesulide into standard protocols creates a vital pathogenetic synergy. While conventional osmotic therapies (such as Mannitol or hypertonic saline) effectively manage the macro-anatomical consequences of injury by reducing intracranial volume and hypertension, Nimesulide targets the molecular root of the problem. By arresting the neuroinflammatory cascade and stabilizing the microvascular environment, Nimesulide-augmented therapy aims to prevent the progression of edema at its source, potentially shortening the duration of intensive care and improving long-term neurological recovery [4,6,13].

Knowledge Gap and Study Rationale

While the potent anti-inflammatory effects of non-steroidal anti-inflammatory drugs (NSAIDs) are extensively documented in systemic inflammatory conditions and chronic pathologies, their clinical efficacy as an "augmented" or adjunctive component in the neuro-intensive care of patients with severe traumatic brain injury (sTBI) remains insufficiently explored [4,11]. Despite promising experimental data on COX-2 inhibition and neuroprotection, there is a notable scarcity of structured clinical studies that evaluate how the integration of NSAIDs into standard anti-edema protocols influences the real-world dynamics of neurological recovery. Specifically, the impact of these agents on the incidence of secondary complications and the long-term stabilization of the blood-brain barrier (BBB) in human subjects requires further validation [2,8,12].

The primary aim of this prospective study is to evaluate the clinical and laboratory impact of incorporating Nimesulide—a relatively selective COX-2 inhibitor—into the comprehensive therapy of patients with severe traumatic brain injury.

To achieve this, the study focuses on three critical domains:

1. Cerebral Edema Regression: Assessing the morphological and hemodynamic changes via multispiral computed tomography (MSCT) and ophthalmoscopy [13,17].
2. Neurological Recovery Dynamics: Monitoring the rate and stability of consciousness restoration using the Glasgow Coma Scale (GCS) as a primary clinical metric [1,15].
3. Homeostatic Stabilization: Analyzing the modulation of systemic and local inflammatory markers, specifically focusing on the Neutrophil-to-Lymphocyte Ratio (NLR) and markers of endogenous intoxication [7,14].

By establishing a pathogenetic link between anti-inflammatory intervention and clinical outcomes, this study seeks to optimize existing intensive care protocols for sTBI and provide a structured framework for the use of NSAID-augmented therapy in neurocritical care [15,20].

2. Methods

Study Setting and Ethical Considerations

This prospective clinical investigation was conducted between 2023 and 2026 within the Neuroresuscitation Department of the Bukhara Branch of the Republican Scientific Center for Emergency Medical Aid, which serves as a primary clinical site for the Department of Anesthesiology and Reanimatology at the Bukhara State Medical Institute. The study protocol was strictly aligned with the ethical standards of the institutional review board and the Helsinki Declaration. Prior to enrollment, comprehensive informed consent was obtained from the legal representatives of each patient, ensuring full transparency regarding the therapeutic interventions and data collection processes.

Patient Population and Stratification

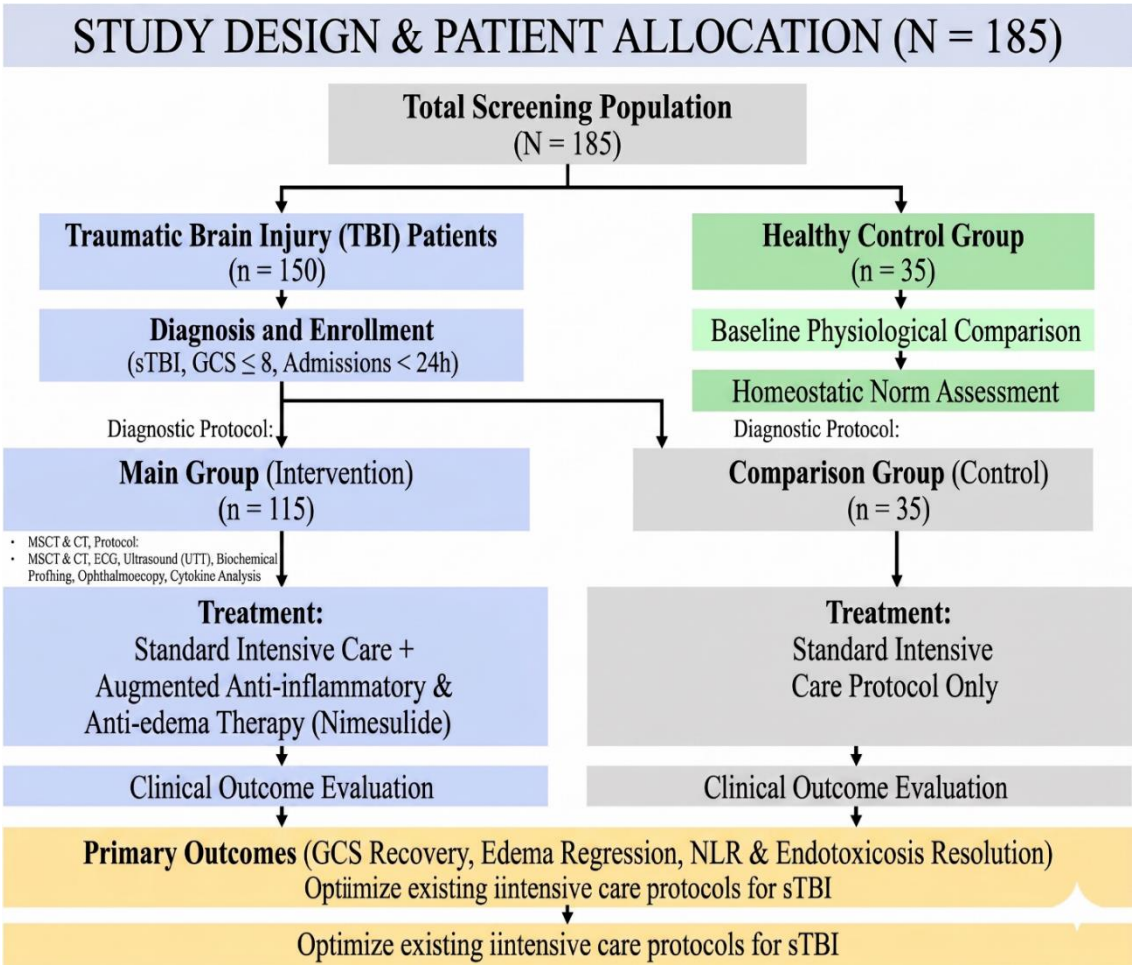


Figure 1

The study cohort comprised 150 patients admitted in critical condition following severe traumatic brain injury (sTBI). Participants were stratified into two distinct groups based on the intensified or standard nature of the therapeutic approach. The Main Group included 115 patients (76.7%) who received a targeted, NSAID-augmented anti-inflammatory and anti-edema regimen developed by our team, in addition to conventional care. The Control Group consisted of 35 patients (23.3%) who were managed strictly according to the standard institutional intensive care protocols.

To ensure the integrity of the data, specific inclusion criteria were applied, requiring a confirmed sTBI diagnosis with a

Glasgow Coma Scale (GCS) score of 8 or less, admission within the first 24 hours post-injury, and an age range of 18 to 70 years. Conversely, patients with a history of chronic hepatic or renal insufficiency, active gastrointestinal ulcerations, a predisposition to coagulopathy, or known hypersensitivity to non-steroidal anti-inflammatory drugs were excluded from the study.

Standard Intensive Care and Respiratory Support

All patients, regardless of group allocation, underwent a standardized intensive care regimen focused on the stabilization of vital functions and the mitigation of secondary brain insults. Airway management was prioritized to maintain adequate oxygenation and normocapnia, utilizing mechanical ventilation via Hamilton C3 (Switzerland) workstations when clinical indications were met. Respiratory strategies involved transition from Continuous Mandatory Ventilation (CMV) to Synchronized Intermittent Mandatory Ventilation (SIMV) as neurological status improved, with extubation criteria requiring a GCS score of at least 11 and the return of protective airway reflexes. Hemodynamic stability was maintained through individualized fluid resuscitation to optimize cerebral perfusion pressure, while patients were positioned with the head of the bed elevated at 15–30° to facilitate venous drainage. Neurological and metabolic control included the administration of sedatives, analgesics, and anticonvulsants for psychomotor agitation and seizure prevention, alongside early enteral nutrition and empirical antibiotic prophylaxis adjusted by microbiological surveillance.

NSAID-Augmented Intervention and Pathogenetic Rationale

In the Main Group, the standard protocol was augmented with Nimesulide, a relatively selective cyclooxygenase-2 (COX-2) inhibitor, specifically targeted at modulating the neuroinflammatory component of cerebral edema. This intervention aimed to suppress the overproduction of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as the synthesis of prostaglandin E2, which are central to blood-brain barrier disruption. Nimesulide was administered at a dose of 100 mg twice daily for a duration of seven consecutive days. The drug was delivered enterally via a nasogastric tube or orally post-feeding. Throughout the course of treatment, patients were closely monitored for systemic safety, including serial assessments of hepatic transaminases (ALT, AST), renal function markers, and potential gastrointestinal side effects.

Clinical, Laboratory, and Instrumental Monitoring

The clinical efficacy of the augmented therapy was evaluated through a multimodal monitoring approach on Days 1, 5, and 10 of treatment. Neurological recovery was quantified using the GCS, while morphological changes in brain tissue and edema regression were assessed via Multispiral Computed Tomography (MSCT). To indirectly monitor intracranial hypertension and microcirculatory dynamics, ophthalmoscopic examinations were performed using a Retinascope Plus non-mydriatic retinal camera, focusing on the artery-to-vein ratio and venous congestion. Laboratory monitoring involved a comprehensive analysis of systemic inflammatory markers, with a particular emphasis on the Neutrophil-to-Lymphocyte Ratio (NLR) and integral indices of endogenous intoxication to track the resolution of the systemic inflammatory response.

Statistical Processing

Quantitative data were subjected to statistical analysis and expressed as Mean ± Standard Error of the Mean (M±m). The significance of differences between the Main and Control groups was determined using the Student's t-test for parametric data, with a p-value of less than 0.05 being established as the threshold for statistical significance. All calculations and data visualizations were performed using Microsoft Excel and specialized statistical software packages to ensure the robustness of the findings.

3. Results

Longitudinal Analysis of Neurological Recovery and Consciousness Dynamics

The clinical evolution of neurological status served as the primary benchmark for evaluating therapeutic efficacy. At the time of enrollment (Day 1), both study cohorts exhibited high-severity clinical profiles characterized by deep coma or sopor, with mean Glasgow Coma Scale (GCS) scores of 9.1 ± 1.2 in the Main Group and 9.0 ± 1.3 in the Control Group ($p > 0.05$). This initial homogeneity ensured that subsequent differences in recovery trajectories could be attributed to the specific therapeutic interventions rather than baseline disparities.

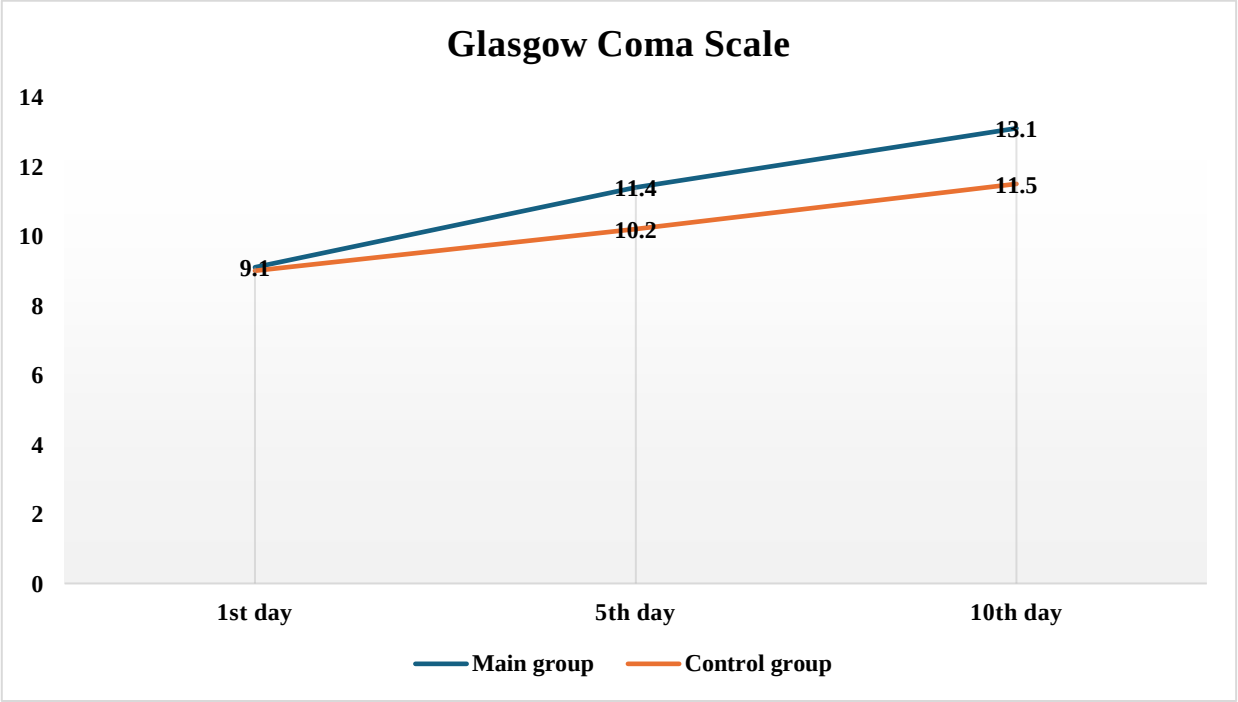


Figure 2

By the fifth day of monitoring, the Main Group demonstrated an accelerated rate of neurological awakening, with GCS scores ascending to 11.4 ± 1.5. In contrast, the Control Group showed a significantly slower recovery pattern, averaging 10.2 ± 1.4. This divergence reached its peak on the tenth day; the Main Group attained a mean GCS score of 13.1 ± 1.7, indicating a transition toward moderate impairment or near-full consciousness, while the Control Group remained significantly lower at 11.5 ± 1.6 ($p < 0.05$). The data suggest that Nimesulide-augmented therapy not only enhances the speed of recovery but also promotes a more stable neurological trajectory, potentially by mitigating the "second hit" of neuroinflammatory-mediated brain damage.

Comparative Incidence of Secondary Complications and Somatic Stability

The integration of a targeted anti-inflammatory component was associated with a notable reduction in the burden of secondary post-traumatic complications. Respiratory failure, often exacerbated by ventilator-associated pneumonia (VAP), was the most frequent complication observed. In the Main Group, pneumonia was recorded in 19.1% (n=22) of cases, representing a statistically significant reduction compared to the 28.6% (n=10) prevalence in the Control Group ($p < 0.05$). This suggests that systemic COX-2 inhibition may modulate the inflammatory milieu of the lungs or indirectly benefit pulmonary function through improved neurological drive and airway protection.

Neurological complications, specifically post-traumatic seizures, also exhibited a significant decline in the Main Group (14.8% vs. 25.7% in the Control Group; $p < 0.05$), highlighting the potential anticonvulsant synergy of reducing peri-focal cerebral edema. Although other somatic markers such as pressure ulcers (12.2% vs. 17.1%), stress-induced gastrointestinal ulcers (8.7% vs. 14.3%), and sepsis (4.3% vs. 8.6%) did not reach the threshold for statistical significance ($p > 0.05$), the consistent downward trend in the Main Group indicates a broader systemic stabilization. The lower incidence of stress ulcers in the Nimesulide group particularly reinforces the safety profile of selective COX-2 inhibitors in the acute phase of polytrauma, where traditional NSAIDs are often avoided due to bleeding concerns.

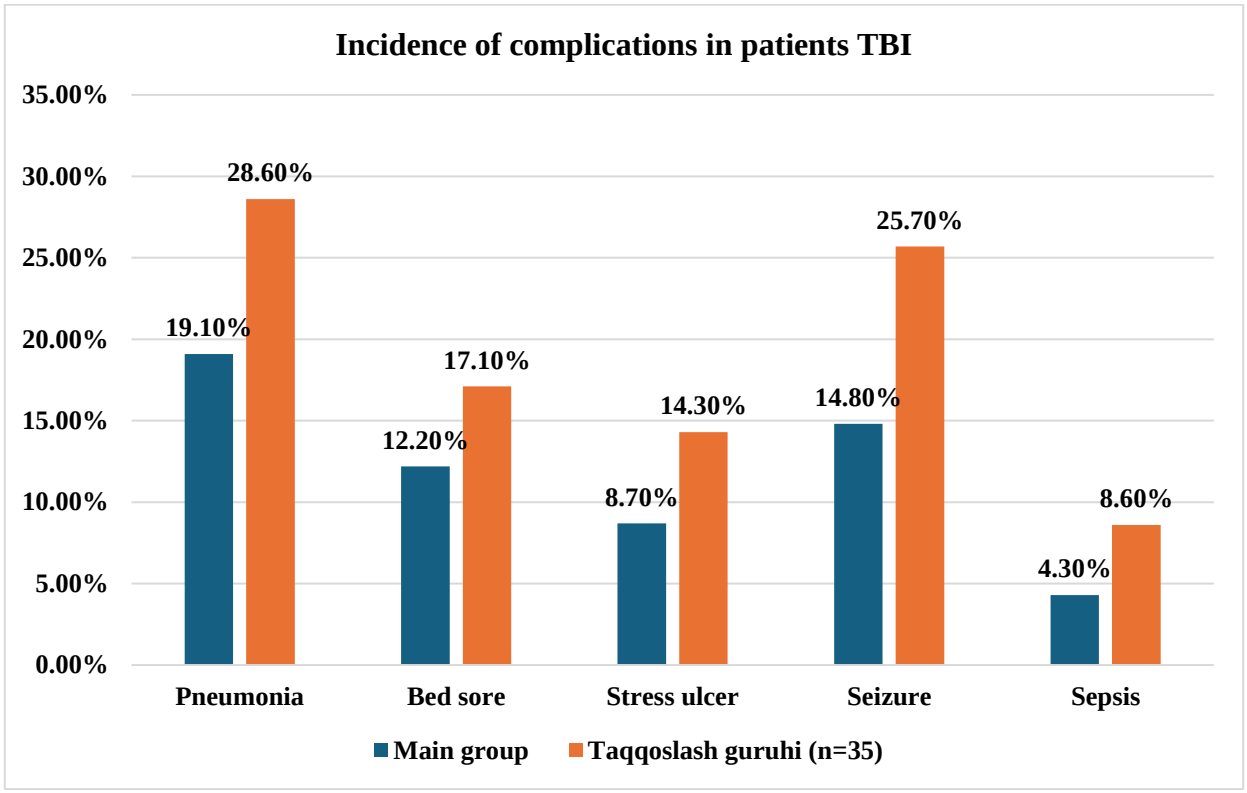


Figure 3

Laboratory Correlates of Neuroinflammation and Metabolic Homeostasis

The systemic inflammatory response syndrome (SIRS), ubiquitous in severe TBI, was quantified through a series of integral hematological indices. On admission, profound leukocytosis and a shift toward a neutrophilic profile were observed in all patients, with a high Neutrophil-to-Lymphocyte Ratio (NLR) signifying acute immunological stress. Over the 10-day observation period, the Main Group exhibited a superior rate of immunological normalization. By Day 10, the NLR in Nimesulide-treated patients dropped significantly to 1.9 ± 0.2, compared to 3.0 ± 0.3 in the Control Group ($p < 0.05$).

Markers of endogenous intoxication and catabolic stress followed a similar rehabilitative pattern. The Main Group demonstrated a more rapid restoration of total protein levels and a stabilized hepatic enzyme profile.

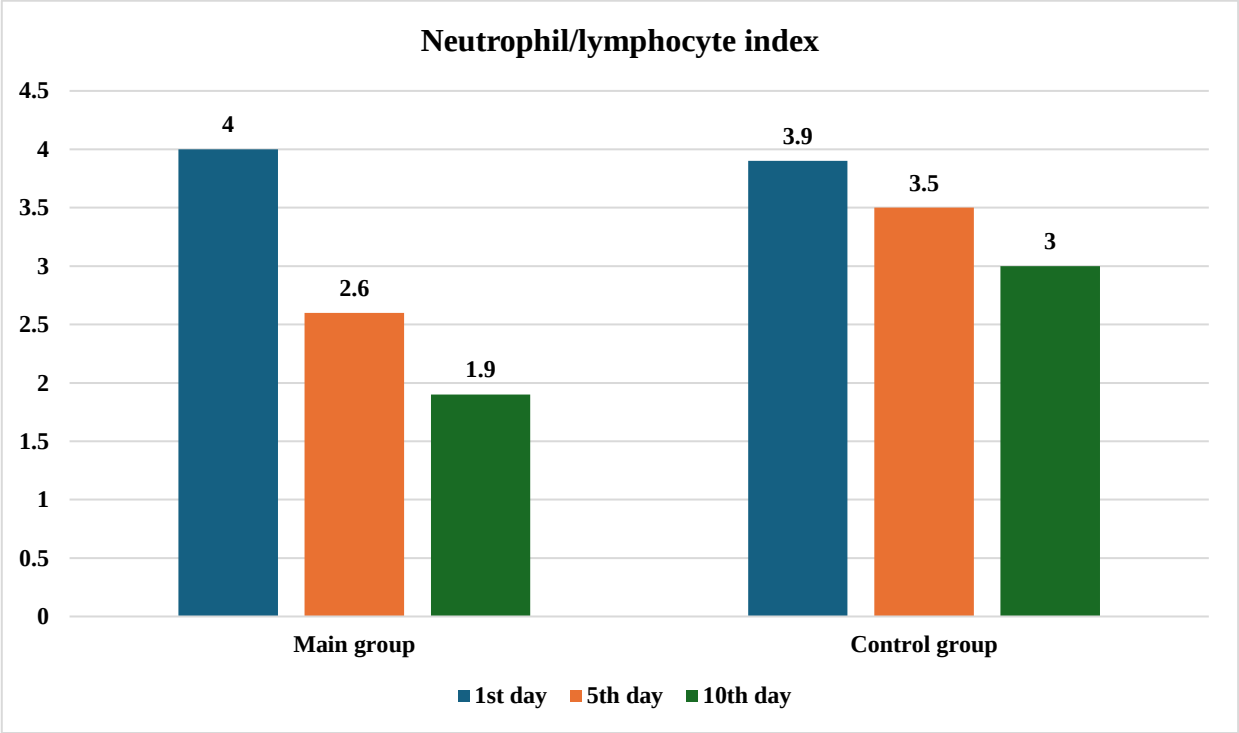


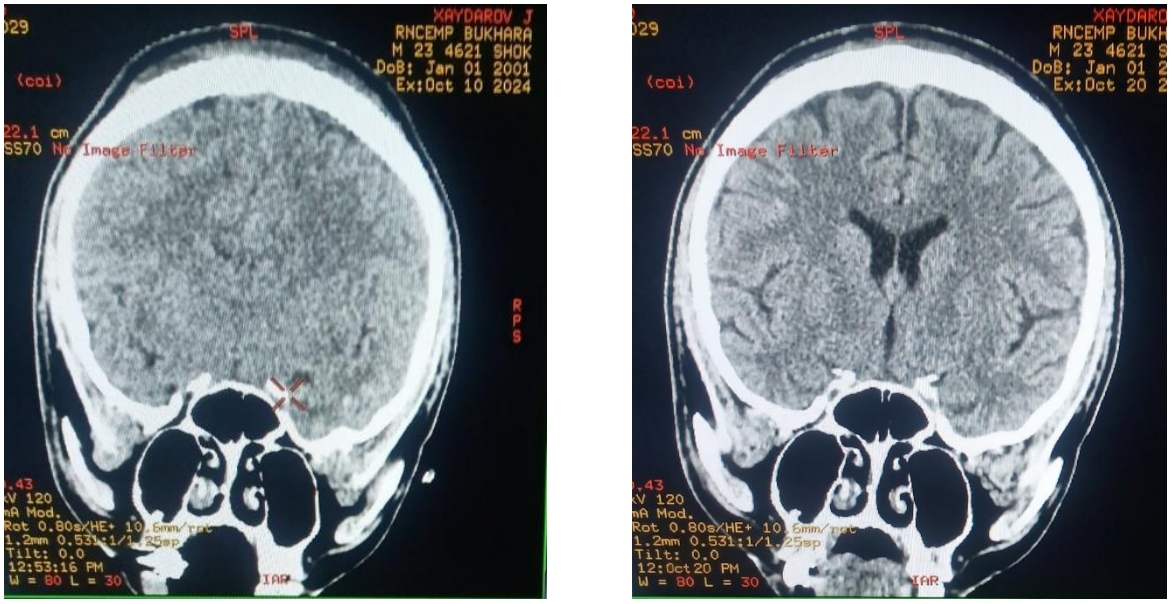
Figure 3

Specifically, the decline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels was more pronounced in the Main Group by Day 10, suggesting that the mitigation of the systemic "cytokine storm" by Nimesulide may offer hepatoprotective benefits or simply reflect a more controlled systemic inflammatory state. The erythrocyte sedimentation rate (ESR), which remained nearly twice the physiological norm in the Control Group, showed a more rapid regression in the Main Group, corroborating the faster resolution of the systemic inflammatory phase.

Instrumental Assessment of Cerebral Morphometry and Microcirculation

The morphological regression of cerebral edema was rigorously monitored using multispiral computed tomography (MSCT). Initial scans across the study population revealed hallmark signs of intracranial hypertension: diffuse hypodensity in periventricular zones, narrowing of the lateral ventricles, and partial or total effacement of the basal cisterns. In the Main Group, follow-up scans on Days 5 and 10 revealed a significantly more rapid resolution of the mass effect. The restoration of ventricular volume and the reappearance of cortical sulci occurred earlier and more consistently in patients receiving augmented therapy compared to the Control Group, where ventricular compression remained a persistent feature in over 40% of cases.

These neuroimaging findings were closely mirrored by microcirculatory dynamics assessed via ophthalmoscopy. On Day 1, the artery-to-vein (A:V) ratio was pathologically altered to 1:2.2 across both groups, indicating severe venous stasis and impaired retinal microcirculation. By Day 10, the Main Group achieved a near-physiological A:V ratio of 1:1.5, accompanied by the disappearance of optic disc margin blurring.



Day of hospitalization **Day 10**

Figure 4

In contrast, a substantial portion of the Control Group continued to exhibit signs of retinal venous congestion and delayed microcirculatory recovery. The high degree of correlation between MSCT-proven edema regression and the normalization of ophthalmoscopic parameters serves as a strong clinical validation of the pathogenetic efficacy of Nimesulide-augmented therapy in managing the intracranial hemodynamic environment.

4. Discussion

The management of severe traumatic brain injury (sTBI) has traditionally centered on a "volume-based" approach, utilizing osmotic agents and surgical decompression to control intracranial hypertension. However, the findings of the present study suggest that a "pathogenetic-based" approach, specifically targeting the neuroinflammatory cascade via selective COX-2 inhibition with Nimesulide, offers a superior clinical trajectory. Our results demonstrate that augmenting standard protocols with Nimesulide significantly accelerates neurological recovery, mitigates the severity of cerebral edema, and reduces the incidence of life-threatening secondary complications.

Neuroinflammation as a Therapeutic Target

The pivotal role of neuroinflammation in the progression of secondary brain injury is well-established in experimental models. Following sTBI, the rapid upregulation of cyclooxygenase-2 (COX-2) in neurons and glial cells triggers a cascade of pro-inflammatory prostaglandins, particularly PGE_2, which increases blood-brain barrier (BBB) permeability and exacerbates vasogenic edema. Our clinical findings, showing a significant improvement in Glasgow Coma Scale (GCS) scores (13.1 ± 1.7 in the Main Group vs. 11.5 ± 1.6 in the Control Group by Day 10), align with the hypothesis that suppressing this inflammatory "second hit" preserves neuronal viability. By stabilizing the BBB at a molecular level, Nimesulide likely limits the transition from focal contusion to diffuse edema, thereby facilitating earlier neurological awakening.

Correlation Between Imaging and Microcirculation

A major highlight of this study is the high degree of correlation between morphological regression on MSCT and the normalization of retinal microcirculation. The faster restoration of the artery-to-vein ratio (1:1.5) in the Main Group serves as a vital clinical indicator of reduced intracranial pressure (ICP). This finding is consistent with the pharmacological profile of Nimesulide as a lipophilic agent capable of crossing the BBB. Unlike mannitol, which primarily acts through an osmotic gradient, Nimesulide appears to address the biochemical drivers of venous stasis and capillary congestion. The early resolution of mass effect signs on MSCT in our Main Group further supports the notion that COX-2 inhibition reduces the total volume of cerebral fluid accumulation by limiting inflammatory exudation.

Systemic Benefits and Safety Profile

The observed reduction in secondary complications, particularly pneumonia (19.1% vs. 28.6%) and seizures (14.8% vs. 25.7%), suggests that the benefits of Nimesulide extend beyond the central nervous system. The significantly faster normalization of the Neutrophil-to-Lymphocyte Ratio (NLR) in the Main Group indicates that selective COX-2 inhibition effectively modulates the systemic inflammatory response syndrome (SIRS). A lower NLR has been previously identified in neurosurgical literature as a positive prognostic marker for sTBI recovery.

Furthermore, the safety of NSAID use in acute trauma remains a topic of debate due to potential gastrointestinal and renal risks. However, our study demonstrated that Nimesulide, at a dose of 100 mg twice daily, was well-tolerated. The incidence of stress-induced ulcers was actually lower in the Main Group (8.7%) compared to the Control Group (14.3%), which may be attributed to the overall stabilization of the patient's physiological state and a reduced duration of intensive catabolic stress. This reinforces the clinical viability of selective COX-2 inhibitors as safe adjuncts in the acute phase of polytrauma.

Clinical Implications and Future Directions

The findings of this study provide a strong rationale for the integration of targeted anti-inflammatory therapy into standard sTBI management. By addressing the "molecular root" of cerebral edema, Nimesulide-augmented therapy offers a pathogenetic synergy that complements existing symptomatic treatments. While our study is limited by the sample size of the control group, the statistically significant differences in neurological outcomes and inflammatory markers provide a robust foundation for larger multicenter trials. Future research should focus on the long-term cognitive outcomes and the potential dose-dependent effects of Nimesulide in diverse populations of neuro-trauma patients.

5. Conclusion

The findings of this clinical study demonstrate that augmenting standard intensive care protocols with Nimesulide—a selective COX-2 inhibitor—significantly improves clinical outcomes in patients with severe traumatic brain injury. Our data indicate that targeted anti-inflammatory therapy accelerates the recovery of consciousness, as evidenced by significantly higher GCS scores by Day 10. Furthermore, the pathogenetic inhibition of the neuroinflammatory cascade leads to faster regression of cerebral edema on MSCT and earlier normalization of microcirculatory dynamics. The reduction in the incidence of pneumonia and post-traumatic seizures highlights the systemic benefits of this approach. Nimesulide-augmented therapy presents a safe and effective strategy to mitigate secondary brain injury and optimize recovery in the neuro-critical care setting.

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