Cervical Sympathetic Block as a Modulator of Secondary Injury Mechanisms in Traumatic Brain Injury

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ABSTRACT

Introduction:

Traumatic brain injury (TBI) follows a biphasic clinical course in which an initial mechanical insult is followed by a prolonged secondary injury cascade that drives ongoing neurological deterioration. Secondary injury processes include neuroinflammation, blood–brain barrier (BBB) disruption, mitochondrial dysfunction, oxidative stress, maladaptive gene regulation, and neuronal apoptosis. Current TBI management strategies primarily address intracranial pressure, cerebral perfusion, and oxygenation but do not directly target these downstream biological mechanisms. Cervical sympathetic blockade (CSB) involves administration of local anesthetic to the cervical sympathetic ganglia, typically at the C6 level or at combined C6/C4 levels, resulting in transient interruption of sympathetic outflow. The cervical sympathetic system has functional connections to immune organs, including the thymus, spleen, and bone marrow, suggesting a role in immune modulation. Emerging preclinical and clinical evidence indicates that CSB may attenuate secondary injury mechanisms after TBI. This review synthesizes available evidence to evaluate the therapeutic potential of CSB in TBI and to delineate its mechanistic effects on secondary injury pathways.

Materials and Methods:

We conducted a comprehensive narrative review of preclinical and clinical studies examining the effects of CSB in TBI and related neurological conditions. Literature searches were performed using PubMed and Google Scholar, supplemented by citation tracking of relevant studies. Included evidence encompassed randomized controlled trials, prospective cohort studies, retrospective case series, and mechanistic animal models. Outcomes of interest included clinical symptom burden, inflammatory cytokines, BBB integrity markers, mitochondrial and oxidative stress measures, gene expression profiles, and apoptotic signaling. Evidence from related conditions such as subarachnoid hemorrhage, migraine, and postoperative cognitive dysfunction was incorporated to inform mechanistic interpretation.

Results:

Available clinical studies, though limited in size, demonstrate rapid and sustained reductions in TBI-related symptom burden following CSB. Randomized controlled trials show that CSB significantly reduces pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), as well as neuronal injury markers such as S100β and neuron-specific enolase, likely mediated by downregulation of nuclear factor kappa-B (NF-κB) signaling. Observational studies corroborate reductions in inflammatory biomarkers and markers of BBB disruption. Preclinical models demonstrate that CSB mitigates mitochondrial oxidative stress through enhancement of antioxidant defenses and suppression of Reactive Oxygen Species Modulator 1 (Romo1) expression. Additional studies show that CSB shifts the Bax/Bcl-2 ratio toward an anti-apoptotic profile, promoting neuronal survival. Clinical data from subarachnoid hemorrhage and surgical populations further support improved cognitive and functional outcomes accompanied by reduced inflammatory signaling.

Conclusions:

CSB targets multiple convergent mechanisms of secondary brain injury that are not addressed by current standard TBI management, including neuroinflammation, oxidative stress, mitochondrial dysfunction, dysregulated gene expression, and apoptosis. Clinical improvements following CSB are accompanied by measurable biological changes, supporting a mechanistically grounded therapeutic effect. Limitations of the current evidence include small sample sizes, heterogeneous populations, and reliance on surrogate biomarkers. Larger, well-controlled trials are needed to define efficacy, optimize patient selection, and assess long-term neurological outcomes. CSB represents a promising, mechanism-driven intervention with potential relevance for both civilian and military TBI populations.

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INTRODUCTION

Traumatic brain injury (TBI) remains a leading cause of long-term neurological morbidity worldwide. While the initial primary injury results from direct mechanical forces applied to the brain, subsequent neurological deterioration is driven by secondary injury mechanisms that evolve over hours to months following the inciting event.[1,2] These processes include neuroinflammation, mitochondrial dysfunction, oxidative stress, maladaptive gene regulation, and subsequent neuronal apoptosis. Traditionally, clinical management of TBI has focused on defending cerebral perfusion pressure, controlling intracranial pressure, and optimizing oxygen delivery.[3] While these strategies reduce mortality, there are currently no widely adopted therapies that directly target the underlying mechanisms of secondary injury progression.

The sympathetic nervous system may serve as a critical convergence point for this multifaceted cascade. Through reciprocal connections with the thymus, bone marrow, and spleen, the cervical sympathetic ganglia (CSG) act as a central hub modulating systemic immune responses that are central to secondary injury progression.[4,5] Thus, the sympathetic chain represents a specific, high-leverage target for the treatment of TBI.

Stellate ganglion block (SGB) and cervical sympathetic blockade (CSB) involve a clinical blockade of CSG with a local anesthetic, thus interrupting central afferent and efferent sympathetic signaling.[6,7] Originally developed for the treatment of pain syndromes, SGB/CSB has since been applied to a broader range of vasomotor,[8] stress-related,[9,10] and immunological conditions.[5,11,12] Emerging evidence further suggests that these techniques may mitigate secondary injury following TBI. The purpose of this review is to synthesize preclinical and clinical evidence to evaluate the therapeutic potential of SGB/CSB in TBI and explore its underlying biological mechanisms.

METHODS

Scope and Review Design

We conducted an integrative narrative review of preclinical and clinical studies evaluating CSB and SGB in TBI, with a focus on the biological mechanisms implicated in secondary brain injury. The scope of this review included both direct evidence from TBI populations and complementary mechanistic evidence from related neurological and systemic conditions in which sympathetic blockade has been studied.

This review was designed as a mechanistic synthesis rather than a quantitative efficacy analysis. Accordingly, it integrates findings across clinical outcomes, biomarker studies, and experimental models to examine how CSB/SGB may influence immune activation, oxidative stress, mitochondrial dysfunction, gene regulation, and apoptotic signaling pathways relevant to secondary injury progression.

Literature Search Strategy

Structured literature searches were performed using PubMed and Google Scholar from database inception through January 2026. Search terms included combinations of "TBI," "SGB," "CSB," "sympathetic blockade," "neuroinflammation," "oxidative stress," "mitochondrial dysfunction," and "apoptosis." Citation chaining was performed by manually reviewing reference lists of key articles to identify additional relevant studies.

Study Screening and Selection

Titles and abstracts were screened for relevance to one or more of the following criteria: (1) TBI or secondary brain injury mechanisms, and (2) effects of SGB or CSB on clinical outcomes or biological pathways relevant to TBI. Full-text articles were reviewed if they met either criterion.

Eligible studies included randomized controlled trials, prospective cohort studies, retrospective case series, mechanistic animal studies, and relevant narrative or mechanistic reviews. In addition to studies directly involving TBI, selected investigations in subarachnoid hemorrhage, migraine, and postoperative cognitive decline were included to provide complementary mechanistic insight where direct TBI data were limited.

Methodologic Considerations

With the primary objective of this review being mechanistic synthesis rather than quantitative effect estimation, formal risk-of-bias assessment and meta-analytic techniques were not performed. Instead, evidence was synthesized qualitatively, with emphasis placed on biological plausibility, consistency across study types, and alignment between clinical observations and mechanistic findings.

MECHANISTIC SYNTHESIS OF CSB IN SECONDARY TBI INJURY

Overview of SGB and CSB

The cervical sympathetic ganglia (CSG) project sympathetic fibers to the ipsilateral brain, head, neck, upper extremity, and upper part of the thorax. Studies have shown a direct connection from the CSG to the thymus, bone marrow, and spleen.[1,2] Clinical blockade of the CSG with a local anesthetic is called SGB when performed at the C7 vertebral level. This procedure has been used for nearly a century to treat painful conditions. A more effective version of the SGB, called CSB, is where the stellate ganglion and superior cervical ganglion are anesthetized.[6,7] Stellate ganglion fibers ascend to the brain via the vertebral artery where the superior cervical ganglion sympathetic fibers ascend via the internal carotid.[13] A greater reduction in sympathetic outflow explains the more intense clinical effect of the dual block. Recently, the indications for SGB/CSB have greatly expanded, including menopausal hot flashes,[8]

post-traumatic stress disorder (PTSD),[9,10] immune-related disorders,[5,11,12] prevention of post-operative cognitive decline (POCD),[14] and TBI.[7,13,15-17]

Overview of TBI Pathophysiology and Secondary Injury Processes

TBI is known to have a biphasic clinical course. While the initial primary injury is typically caused by direct insult to the brain, clinically significant neurological deterioration is subsequently driven by a cascade of biochemical, molecular, and cellular events, termed secondary injury. These processes evolve over hours to even months or years after the initial insult.[1,2] Evidence suggests that neuroinflammation, blood-brain barrier (BBB) disruption, mitochondrial damage, oxidative stress, and subsequent neuronal apoptosis are key drivers for progressive tissue damage.[18,19,20-24]

The neuroinflammatory cascade begins when injured cells release damage-associated molecular patterns (DAMPs). These molecules activate microglia (resident macrophages of the central nervous system) and peripheral macrophages that gain access to the central nervous system via a damaged BBB.[2,18,24] This engages nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling in immune cells and the rapid secretion of tumor necrosis factor-alpha (TNF-α) and Interluekin-1β (IL-1β). These cytokines reinforce NF-κB activation and sustain microglial/macrophage activity. Additionally, TNF-α and IL-1β drive production of Interleukin-6 (IL-6), thus promoting systemic acute-phase responses and exacerbated BBB damage (Figure 1).[2,18,24-26] Further transcriptomic studies in mouse models of TBI show that genes characteristic of microglial and innate immune cell activation, such as Trem2, Tyrobp, C1qa, Aif1, Grn, and Cx3cr1, are upregulated following injury.[27] This indicates that inflammation is accompanied by early shifts in gene networks.

TNF-α/IL-1β also impair mitochondrial electron transport, disrupt inner membranes, and destabilize metabolism.[28-30] This leads to excessive reactive oxygen species (ROS) production. It is further believed that an injury triggers Reactive Oxygen Species Modulator 1 (Romo1) gene activation, which encodes a mitochondrial inner membrane protein critical for generating ROS.[31-33] Together, mitochondrial dysfunction and ROS production favor apoptosis (Figure 1).

Treatment with SGB/CSB directly modulates the immune system, gene expression, mitochondrial function, oxidative stress, and neuronal apoptosis. We believe the above mechanisms are responsible for SGB/CSB's effects on TBI, and that a transient increase in cerebral blood flow, a commonly postulated mechanism for SGB/CSB's effects,[34-36] does not fully describe the lasting outcomes achieved by this treatment. The data below summarizes evidence of SGB/CSB's impact on the various mechanisms that contribute to secondary injury in TBI.

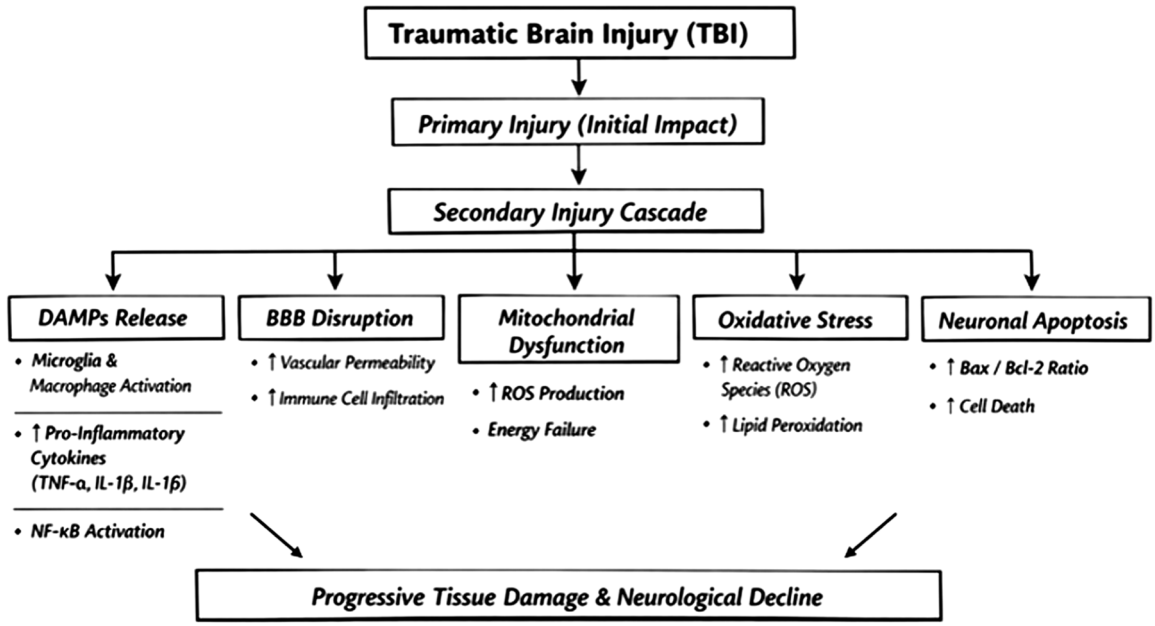

Figure 1. Traumatic brain injury initiates a primary mechanical insult followed by a secondary injury cascade characterized by damage-associated molecular pattern release, blood-brain barrier disruption, mitochondrial dysfunction, oxidative stress, and neuronal apoptosis, which together drive progressive tissue damage and neurological decline. These processes are mediated by microglial and macrophage activation, increased pro-inflammatory cytokine signaling, reactive oxygen species generation, and activation of apoptotic pathways.
Abbreviations: Bax, Bcl-2–associated X protein; Bcl-2, B-cell lymphoma-2; IL-1β, interleukin-1 beta; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-alpha;

Clinical Impact of SGB/CSB on TBI Symptoms

Several retrospective studies reported subjective improvements in TBI symptoms following bilateral, two-level CSB. In the initial cohorts, participants carried diagnoses of PTSD with co-occurring TBI.[6,36] Symptom change was assessed using the Neurobehavioral Symptom Inventory (NSI), with TBI-specific sub-scores derived by excluding PTSD-related items. In these studies, CSB was associated with a mean reduction of 53% in total NSI scores at one month in a cohort of $n = 22$ patients[36] and a 49.5% mean reduction in TBI sub-scores at one month in a cohort of $n = 20$ patients.[6]

A subsequent cohort study of $n = 41$ individuals with chronic TBI symptoms demonstrated sustained improvement, with mean reductions of 48.4% in total NSI scores and 43.1% in TBI-specific sub-scores at three months following CSB.[17] Collectively, these findings suggest that CSB may confer both rapid and durable reductions in TBI-related neurobehavioral symptoms, with effects that appear to extend beyond improvements attributable solely to PTSD symptom reduction.

Additional support is provided by a case series involving $n = 6$ Canadian Special Operations Forces personnel with co-occurring PTSD and blast-related TBI, in which combined treatment with subanesthetic ketamine and CSB was evaluated. At two weeks post-intervention, participants demonstrated a mean 87% reduction in total NSI scores, suggesting a potential synergistic effect between CSB and ketamine on neurobehavioral symptom burden.[16]

This section is restricted to studies directly investigating clinical outcomes in TBI. Table 1 summarizes the available clinical studies evaluating SGB/CSB in TBI, including block technique, laterality, confirmation of successful blockade, clinical or biomarker responses, and reported adverse events. Further reports examining CSB's impact on biologic mechanisms and clinical outcomes in subarachnoid hemorrhage and other non-traumatic cerebrovascular conditions are addressed in subsequent sections.

Impact of SGB on the Immune System, Neuroinflammation, and Gene Expression in TBI

Primary (thymus and bone marrow) and secondary immune organs (spleen, lymph nodes, mucosa-associated lymphoid tissue) receive substantial sympathetic innervation, with norepinephrine (NE) as the main neurotransmitter.[4,5] The above is likely involved in immune modulation by SGB/CSB.

Several of the clinical studies summarized in Table 1 also reported measurable changes in inflammatory and gene expression biomarkers, which provide some mechanistic context for the observed clinical effects. Dr Yang and colleagues conducted a randomized controlled study on $n = 50$ patients hospitalized for TBI, as determined by the Glasgow Coma Scale (GCS) on admission. Patients were enrolled within 24 hours of the initial injury, had closed-head injuries, and none required craniotomy. After receiving SGB every other day for one consecutive week, the treatment group had a significant decrease in the level of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) as compared to the non-SGB-treated group. The likely mechanism of action was a significant downregulation of the NF-κB transcription factor (Figure 2).[37] Similarly, Dr Kostadinov et al. conducted a prospective observational study on the effects of SGB treatment in $n = 20$ patients with moderate-to-severe TBI, determined by GCS on admission. This group reported that SGB not only lowered IL-6 but also S100 calcium-binding protein B (S100b), a marker of astroglia activation and BBB disruption. Importantly, they observed a selective decrease in NF-κB p65 expression in lymphocytes post-treatment, further evidence that SGB attenuates neuroinflammation through transcriptional modulation (Figure 2).[38]

These reductions in inflammatory markers are clinically meaningful and may correlate with patient outcomes. In a randomized trial of $n = 102$ patients undergoing surgical clipping for subarachnoid hemorrhage (SAH), SGB administered every other day significantly reduced pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and neuronal injury markers (Neuron Specific Enolase, S100b) at 1–7 days postoperatively. Importantly, those treated with SGB had improved recovery scores at 6 months.[39]

Other researchers have attempted to use these markers as prognostic indicators in TBI. In one study of $n = 138$ patients with severe TBI, elevated cerebral spinal fluid (CSF) S100b was correlated with higher acute mortality and worse long-term functional outcomes at 6 months.[40] For IL-6, findings are mixed. One prospective cohort of $n = 88$ adults demonstrated that elevated IL-6 levels were associated with greater acute injury severity and unfavorable 6-month outcomes.[41] In a preclinical mouse model, blockade of IL-6 with neutralizing antibodies corrected TBI-induced motor deficits,[42] consistent with clinical studies showing that SGB reduces IL-6 in parallel with symptom improvement. The broader literature, however, emphasizes that the predictive power of IL-6 alone is modest and that confounding variables such as timing and sampling site may produce inconsistent results.[43-45] While inflammatory biomarkers remain imperfect predictors, these studies demonstrate that reductions in IL-6, S100b, and related mediators mirror observed clinical improvement. This supports the potential for SGB/CSB to translate immunological effects, attenuating the inflammatory response, into meaningful recovery benefits after TBI.

Impact of SGB on Oxidative Stress and Mitochondrial Function in TBI

TBI induces structural and functional disruptions to mitochondria that contribute to downstream oxidative damage and decreased energy production. In preclinical models,

Table 1. Summary of available clinical studies evaluating stellate ganglion block/cervical sympathetic block in traumatic brain injury.

Study (year)	Condition treated	*N*	Intervention	Laterality and frequency	Technique	Evidence of successful block	Clinical/biomarker response	Adverse events
Yang et al. (2015)	Acute TBI	50	SGB	Unilateral[a] repeated every other day × 1 week	Landmark-guided	Horner's sign recorded	↓ IL-6, TNF-α, IL-1β; ↓ NF-κB	Not reported
Kostadinov et al. (2025)	Moderate–severe TBI	20	SGB	Unilateral[b]	Ultrasound-guided	****	↓ IL-6, ↓ S100b	Not reported
Mulvaney et al. (2024)	Chronic TBI	23	Bilateral CSB	Single session	Ultrasound-guided	Horner's sign	↓ NSI symptom scores ∼50%	None serious reported
Mulvaney et al. (2025)	Chronic TBI	41	Bilateral CSB	Single session	Ultrasound-guided	Horner's sign	Sustained symptom reduction at 3 months	None serious reported
Zhang et al. (2021)	SAH (early brain injury model)	102	SGB	Unilateral[c] repeated	Landmark-guided	Horner's sign	↓ IL-6, TNF-α, S100b; improved 6-mo outcomes	Not reported
Lipov et al. (2023)	PTSD + blast TBI	6	Bilateral CSB + ketamine	Single session	Ultrasound-guided	Horner's sign	↓ NSI ∼87%	Transient hoarseness

****"confirming successful SGB through ipsilateral facial color change, conjunctival hyperemia, increased temperature, and color change of the ipsilateral extremity compared with the contralateral side" (Kostadinov).

[a]Selection of the SGB side was not reported.

[b]Selection of the SGB side was guided by placement of the intracranial pressure (ICP) monitor.

[c]Selection of the SGB/CSB side was guided by the side of craniotomy, repeated on postoperative days 2, 4, and 6.

Abbreviations: CSB, cervical sympathetic blockade; IL-6, interleukin-6; IL-1β, interleukin-1beta; NSI, neurobehavioral symptoms inventory; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PTSD, post-traumatic stress disorder; SAH, subarachnoid hemorrhage; SGB, stellate ganglion blockade; TBI, traumatic brain injury; TNF-α, tumor necrosis factor alpha; S100b, S100 calcium-binding protein B.

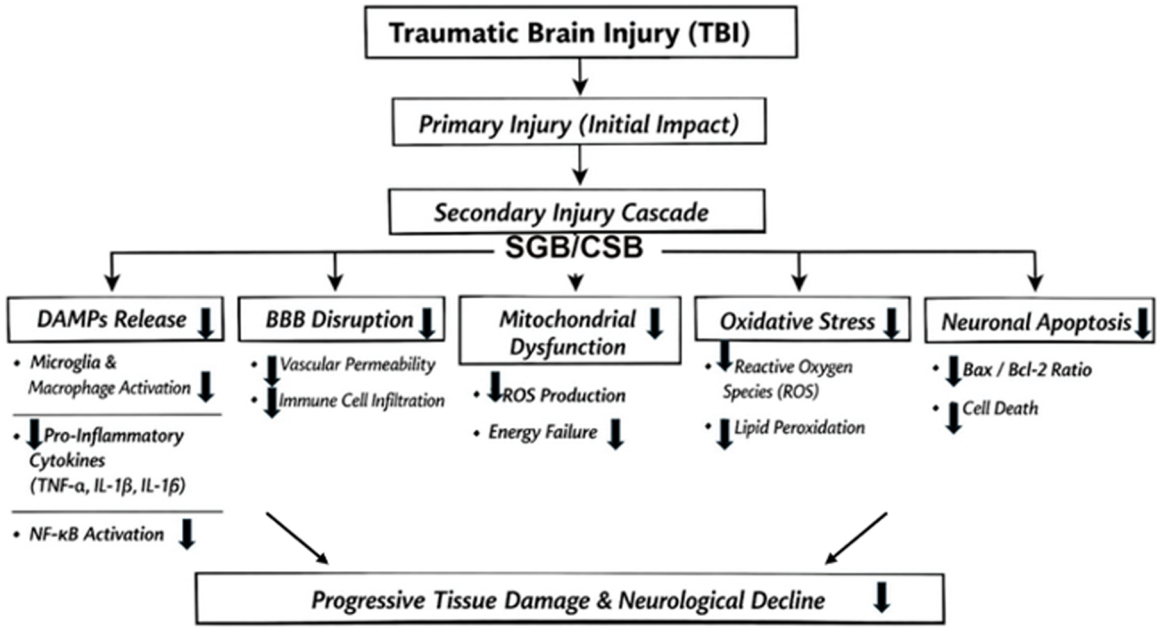

Figure 2. Following traumatic brain injury, a secondary injury cascade drives inflammation, blood–brain barrier disruption, mitochondrial dysfunction, oxidative stress, and neuronal apoptosis. Stellate ganglion block and cervical sympathetic block are hypothesized to attenuate these processes, thereby reducing progressive tissue damage and neurological decline.
Abbreviations: Bax, Bcl-2–associated X protein; Bcl-2, B-cell lymphoma-2; BBB, blood-brain barrier; DAMPs, damage-associated molecular patterns; IL-1β, interleukin-1 beta; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha

ultrastructural mitochondrial abnormalities, including swelling and inner membrane disorganization, have been documented via electron microscopy as early as 30 minutes post-injury.[46] Accompanying these changes are measurable impairments in mitochondrial energy production and calcium buffering.[47,48] This promotes mitochondrial production of ROS, largely due to impaired electron transport chain activity and the leakage of partially reduced oxygen intermediates. Normally, mitochondria contain antioxidant defense systems, including superoxide dismutase (SOD) and glutathione peroxidase that neutralize ROS. In TBI, however, these systems are quickly overwhelmed. The result is a cycle of oxidative stress that damages lipids, proteins, and DNA, thus propagating injury progression (Figure 1).[20,21]

This is reflected in Dr Paolin's study examining whether acute-phase oxidative stress markers could predict long-term clinical outcomes after TBI. Within 24 hours of admission, plasma malondialdehyde (MDA), a marker of lipid peroxidation, and SOD activity were measured and later compared with 6-month outcomes using the Glasgow Outcome Scale (GOS). Patients with poor outcomes (GOS 1–3) had significantly higher MDA, indicating increased oxidative stress. SOD levels were also increased in the poor outcome group. While one may expect that higher SOD would confer better outcomes given its role in the antioxidant defense system, this increase likely represents a compensatory response to oxidative stress that is ultimately inadequate.[49]

Data from animal and human models suggest that SGB may alleviate oxidative stress. In a randomized controlled trial of $n = 104$ elderly patients undergoing laparoscopic gastrointestinal surgery, SGB pretreatment significantly reduced perioperative IL-6 and MDA levels while increasing SOD activity. These biochemical changes were accompanied by improved postoperative cognition, as measured by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores.[14] Although these patients did not sustain direct brain trauma, SGB's ability to reduce systemic oxidative stress and inflammation is highly relevant to TBI pathology (Figure 2).

Beyond reductions in oxidative stress markers, additional mechanistic insights come from a preclinical migraine model, where the Romo1 gene was identified as a key regulator of mitochondrial ROS production. In this study, researchers used nitroglycerine to induce chronic migraines in mice. Some mice were then treated with SGB. The SGB-treated group was found to have reduced expression of Romo1, which encodes a mitochondrial protein critical for ROS production.[31] In humans, elevated Romo1 is linked to increased intracellular ROS, oxidative injury, and activation of NF-κB–driven inflammatory pathways.[32,33] Taken together, these studies indicate that SGB/CSB modulates ROS-generating pathways, mechanisms known to have a significant role in secondary injury in TBI (Figure 2).

Impact of SGB on Post-Injury Neuronal Apoptosis by Affecting Bax/Bcl2 Balance

In the injured brain, increased neuronal apoptosis is related to disruptions in the balance between Bcl-2 and Bax.[22,23,50-52] Bax is a pro-apoptotic protein that promotes mitochondrial membrane permeability and programmed cell death, whereas Bcl-2 is an anti-apoptotic protein that directly opposes the actions of Bax. The relative ratio of these proteins is therefore a critical determinant of neuronal survival. In a rat model of TBI, Dr Raghupathi demonstrated that the Bax protein concentration as compared to concentration of Bcl-2 protein increases in the post-injury period, reflecting a dynamic pro-apoptotic shift.[51] Dr Tehranian also showed that Bax-null mice subjected to controlled cortical impact exhibited significantly higher neuronal survival in hippocampal CA1 and CA3 regions compared with wild-type controls, underscoring Bax's contribution to neuronal loss.[50] Other studies of human TBI suggest that Bcl-2 upregulation post-injury is inherently neuroprotective, with increased Bcl-2 expression correlating with more favorable outcomes.[22,23]

These apoptotic pathways appear modifiable with SGB. In a rat model of induced brain injury, Dr Xu observed that SGB treatment significantly increased Bcl-2 protein expression while reducing Bax protein expression as compared to untreated controls.[52] By enhancing Bcl-2 and suppressing Bax proteins, SGB may shift the balance toward an anti-apoptotic environment (Figure 2). Dr Xu's study supports a mechanistic framework in which SGB helps defend neuronal survival following brain injury.

STUDY LIMITATIONS

Limitations of the current evidence include small sample sizes, heterogeneous populations, and reliance on surrogate biomarkers. Additionally, studies reporting positive clinical or mechanistic effects of SGB/CSB are more likely to be published than studies reporting neutral or negative findings. At present, few controlled studies specifically report null effects of sympathetic blockade in TBI, and unpublished negative studies may exist. Consequently, the available literature may overestimate treatment efficacy and have an inherent risk of potential publication bias. Furthermore, while reported adverse events following sympathetic blockade are generally infrequent and transient, serious adverse events have been reported rarely, including cases of cardiac conduction disturbance following bilateral SGB. We included adverse event data wherever possible, although this information is scarce in the existing literature as it pertains to TBI. Future prospective randomized trials and trial registries, reporting both positive and negative outcomes, will be essential to establish the true clinical effect size and overall safety profile of these therapies.

CONCLUSION

Altogether, both preclinical and clinical studies support SGB/CSB as a promising pathway for preventing secondary injury in TBI capable of attenuating multiple converging mechanisms central to injury progression. Further high-quality trials are needed to confirm these mechanisms, efficacy, safety, and refine patient selection. Deepening our understanding of these mechanisms could lead to a paradigm shift in TBI management that invites new treatment strategies, ultimately resulting in improved long-term neurological outcomes for both civilian and military populations.

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Neither author has any disclosures.

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INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

E.G.L. and J.P. contributed to the concept and research, writing and editing the final manuscript, and preparing all figures. All authors read and approved the final manuscript.

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