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Review Article

Brain Tissue Oxygenation Guided Therapy in Patients with Traumatic Brain Injury: An Umbrella Review of Systematic Review and Meta-Analysis

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Abstract

The present umbrella review aims to summarize the evidence of the efficacy and benefit of combined brain tissue oxygen monitoring and intracranial pressure (ICP) monitoring compared with ICP monitoring based therapy alone. In this study, we systematically searched five databases to retrieve systematic reviews (SRs) regarding the efficacy of ICP monitoring on patient outcomes following traumatic brain injury (TBI). This overview was prepared following the guidelines established by the Joanna Briggs Institute (JBI) for umbrella reviews. No restrictions were placed on the date, language, or country of publication. Three SRs and meta-analyses met the inclusion criteria for the study. The SRs and meta-analyses (SR-MAs) included randomized controlled trials (RCTs) and observational studies. Specifically, two SRs were rated as high quality by A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2), while one was rated as moderate quality. Two of the SR-MAs reported on the mortality outcome, with two reporting on the functional outcome and one reporting on the length of hospital stay outcome. One of the SRs indicated that using combined brain tissue oxygen monitoring led to a reduction in mortality. Two of the SRs had mixed results. Two articles found that hospital length tends to be shorter with combined therapy than with ICP monitoring-based therapy alone. Our observations suggested that brain tissue oxygen combined with ICP/cerebral perfusion pressure (CPP) guided therapy provides a favorable outcome in TBI patients than standard ICP-/CPP-guided therapy. The combined therapy has little effect on mortality rate, ICP, CPP, and length of stay.

Keywords
- brain tissue oxygen
- intracranial pressure
- monitoring
- traumatic brain injury
- outcome

Introduction

Adequate tissue perfusion and oxygenation are crucial in neurocritical care, and their impairment results in brain damage. Although the importance of perfusion and oxygenation in brain protection has been known for a long time, brain oxygen monitors were only recently included in management guidelines for severe traumatic brain injury (TBI).[1] In several past studies, the relationship between raised intracranial pressure (ICP) and poor outcome is well established in patients with

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severe TBI.[1–4] With technological advancement, ICP monitoring has evolved; however, it is resource-intensive and time-consuming. Therefore, ICP monitoring has not been routinely done in cases of severe TBI. However, with the recent updates and guidelines by the Brain Trauma Foundation, more centers have adopted the practice of ICP monitoring in severe TBI.[3] While secondary brain injury does not necessarily correlate with changes in ICP or cerebral perfusion pressure (CPP), it should be noted that proper resuscitation efforts aimed at restoring normal ICP and CPP may not always suffice in preventing brain hypoxia following TBI.[5] Still, the only randomized controlled trial (RCT) that compared the ICP-targeted management and clinical management based on physical and radiological examination failed to demonstrate the benefit of invasive ICP monitoring in reducing mortality or improving the outcome.[6] As detailed earlier, several other reasons explain how brain tissue oxygenation might be impaired in normal ICP or CPP. As brain tissue oxygen delivery is a rate-limiting step, it has been the main subject of discussion in the recent consensus meeting on the utility of multimodal neuromonitoring in TBI patients.[7] The objective of this overview is to summarize the comparative effects and benefits of a neurocritical care protocol of therapy-guided brain tissue oxygenation ($BtiO_2$) and ICP monitoring versus only ICP or CPP monitoring for the treatment of TBI.

Methods

We conducted an umbrella review to summarize the possible benefits and usefulness in a neurocritical care unit of therapy-guided $BtiO_2$ and ICP monitoring in patients with head trauma. The methodology followed the Joanna Briggs Institute (JBI) manual for evidence synthesis in its umbrella review.[8]

Inclusion Criteria

Participants

All patients with severe closed head trauma with an indication for ICP monitoring according to the Brain Trauma Foundation guidelines were included in the study.

Intervention

Invasive monitoring of ICP was done using different methods (external ventricular drainage, catheter with intraparenchymal sensors, or epidural catheters) and multimodal monitoring that included brain tissue oxygenation measure.

Comparison

Studies described therapy-guided for BtiO2 and ICP monitoring and compared with ICP or CPP alone and clinical and imaging follow-up were inlcuded.

Outcomes

Primary

Mortality was defined as the mortality rate of patients with TBI at follow-up, 1 point on the Glasgow Outcome Scale (GOS), or a modified Rankin scale (mRS) score of 6.

Secondary

Intensive care unit (ICU) stay was defined by median days of ICU stay and complications (cardiovascular, infectious, thromboembolic, ischemic, etc.).

Type of Studies

This review considered systematic reviews of prospective, retrospective, or cross-sectional and observational studies. Systematic reviews that include case reports, case series, and preclinical were excluded. Systematic reviews evaluating noninvasive measurements of ICP as diameter of the optic nerve sheath were excluded.

Search

The following databases were searched for systematic reviews: Cochrane Injuries Group Specialized Register (up to May 2022); the Cochrane Library (till May 2022); Medline (Ovid) till February 2021; Embase (Ovid); PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez; May 2022); LILACS (May 2022); Scopus (May 2022); Web of science (May 2022); and CINALH (May 2022), with Medical Subject Heading (MeSH) and descriptors in health sciences (DeCs) for the ILACS search. We adopted the following search strategy: ("intracranial pressure" OR "cerebrospinal pressure" OR "cerebrospinal fluid") AND (monitor*) AND ("Brain tissue oxygen" OR "Cerebral oxygenation" or "$BtiO_2$ monitoring" OR "$PbtO_2$") AND (traumatic brain injury OR head trauma OR Craniocerebral Trauma OR head injuries OR Brain injuries) AND (Systematic AND review) OR Meta-analysis) AND (("Animals" [Mesh]) NOT ("Humans" [Mesh] AND "Animals" [Mesh])). The detailed search strategy is shown in **The Appendix**.

Selection of Studies

Search results were entered into the Mendeley reference manager version 1.19.4 (George Manson University, Fairfax, Virginia, United States). Two reviewers independently reviewed the titles and abstracts for eligibility of the studies. Full texts were extracted and were shortlisted as per the inclusion criteria. Disagreements were resolved by consensus. The results of the search are arranged in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flowchart.[9]

Assessment of the Quality of the Included Systematic Reviews

The methodological quality of the systematic reviews of included randomized clinical trials was analyzed with the A MeaSurement Tool to Assess systematic Reviews Assess systematic Reviews (AMSTAR) tool[10] (see **Appendix**). AMSTAR is a valid, reliable, and easy-to-use tool. It consists of 11 items and has content validity to measure the methodological quality, in addition to the reliability of systematic reviews. Each of the 11 items is assigned a score of 1 if it meets the specific criterion or a score of 0 if it does not meet the criterion, is not clear, or is not applicable. The interpretation of the critical appraisal is divided into three levels: 8 to 11 points are of high quality, 4 to 7 points are of moderate quality, and 0 to 3 points are of low quality.

Risk of Bias of the Included Studies

The risk of bias in the included studies is made through the ROBIS (the risk of bias in systematic reviews) tool.[11] This tool was completed in three phases: (1) assess relevance (optional), (2) identify concerns with the review process, and (3) judge the risk of bias in the review. Signaling questions were included to help assess specific concerns about potential biases with the review. Phase I was omitted as it was not relevant to the result in the risk of bias assessment.

Results

The initial search identified 72 related articles. After removing duplicates, 50 articles underwent title and abstract screening (►**Fig. 1**). Of these 30 studies screened, 5 eligible full-text were assessed, 2 were excluded[12,13] with reasons, and 3 systematic review and meta-analysis (SR-MA) were included[14–16] in the present umbrella review.

Study Characteristics

All the included studies conducted a meta-analysis and were published in 2012, 2017, and 2022. The included SR-MA had a total of 16 studies, of which 4 were RCTs, 2 were prospective observational studies, 8 were retrospective observational studies, and 1 was a historical control study. The present overview presents a summary from 1,955 patients. Of these, 915 patients had a combined $BtiO_2$ and ICP monitoring, while 1,040 patients had only ICP monitoring. ►**Table 1** describes the study design, characteristics, conclusions, and outcome assessment of each study. Individual findings on the outcomes of the included SR-MAs are shown in ►**Table 2**.

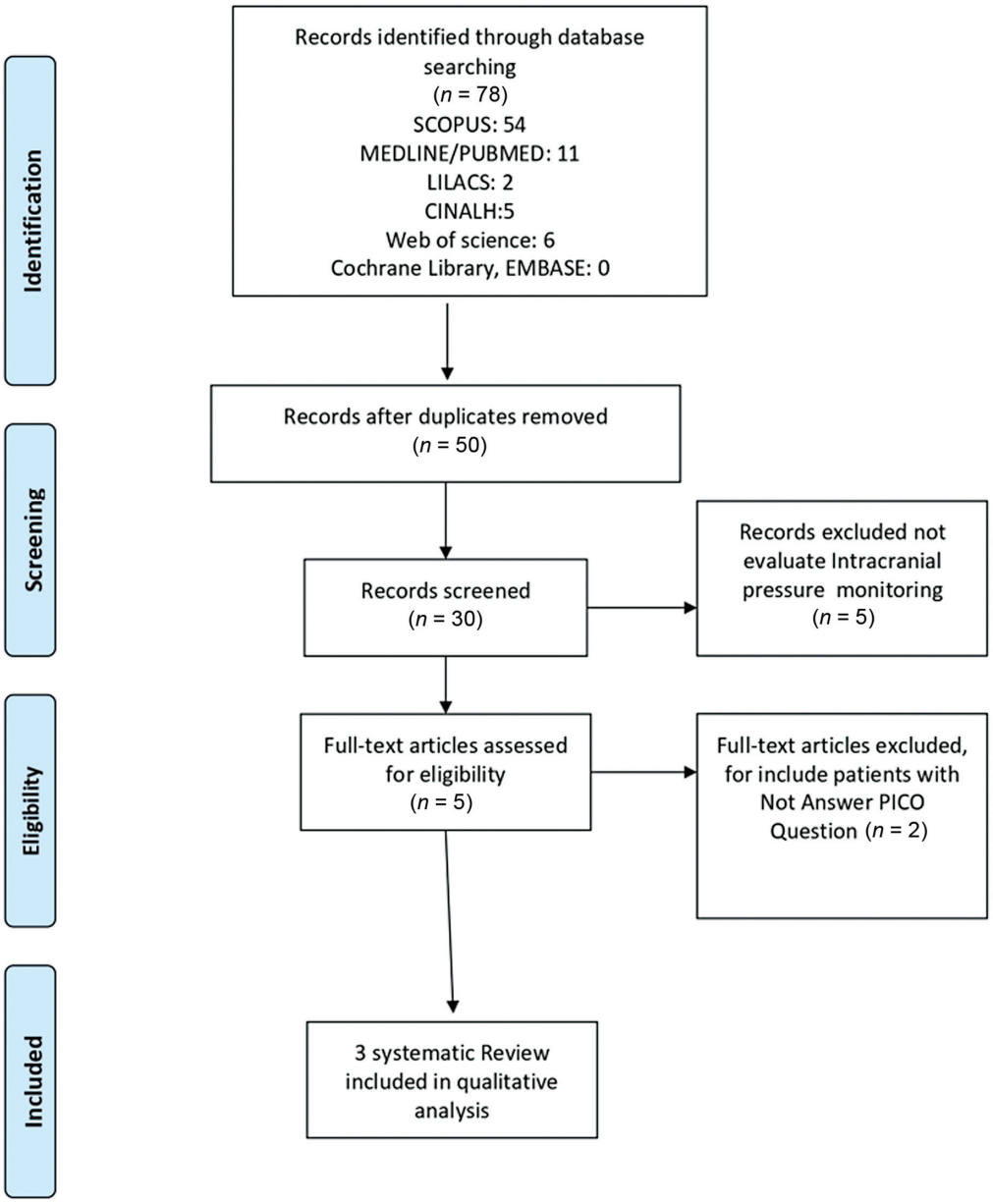

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing details of study selection.

Table 1 Characteristic of included systematic review

Study	Meta-analysis? Yes/no	Journal published in	Database search	Outcome assessed	Risk of bias and quality assessment tool	Main conclusion
Nangunoori et al[15]	Yes	Neurocritical Care	PubMed (1993–October 2010) Embase (1993–October 2010) Index Medicus (1993–October 2010)	Good outcome (Glasgow outcome scale)	Not reported	This meta-analysis did not prove that $PbtO_2$-based therapy is beneficial; they are suggestive
Xie et al[16]	Yes	World of Neurosurgery	PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science (until July 2016)	Mortality Good outcome (GOS) Length of hospital stay (LOS)	Cochrane risk of bias assessment tool and Newcastle–Ottawa Scale (NOS)	Compared with standard ICP-/CPP-guided therapy, brain tissue oxygen combined ICP-/CPP-guided therapy improved long-term outcomes without any effects on mortality, ICP/CPP, or LOS
Hays et al[14]	Yes	Journal of Clinical Neuroscience	PubMed/Medline, Embase, Cochrane Library (until February 2022)	Mortality Good outcome (GOS) Cardiovascular and respiratory events	Cochrane risk of bias assessment tool and GRADE Quality Scale	This review did not find an association between the addition of $PbtO_2$-guided management and improved neurological outcome, but found an association with increased survival

Abbreviations: CPP, cerebral perfusion pressure; ICP, intracranial pressure.

Risk of Bias

Two SR-MAs reported on the risk of bias tool used in the study as Cochrane risk of bias tool, Newcastle–Ottawa Scale, and GRADE quality scale, while one SR-MA did not mention the risk of bias assessment (►**Fig. 2**). Quality assessment of the included SR-MA is shown in ►**Tables 3** and **4**. According to the AMSTAR tool, two SR-MAs were of high quality,[14,16] while one was of moderate quality[15] (►**Table 3**). According to the ROBIS tool, there was low risk of bias in most of the domains in two SR-MAs[14,16] and unclear in one SR-MA[15] (►**Table 4**).

Mortality Rate

Two of the three included SR-MAs reported on the mortality.[14,16] One study found an association between increased survival and combined $BtiO_2$ therapy,[14] while one study did not find any association[16] and the third study suggested that there is improved survival in severe TBI patients with combined $BtiO_2$ therapy.[15] The heterogeneity of the mortality outcome was high in two studies[15,16] and low in one study.[14] The pooled analysis showed that there was no obvious differences between the two treatments in the overall mortality rate (risk ratio [RR] = 2.1; 95% confidence interval [CI]: 1.4–3.1; odds ratio [OR] = 0.76; 95% CI: 0.54–1.06; and OR: 0.54; 95% CI: 0.31–0.93).[14–16]

Favorable Outcome

The favorable outcome was assessed using the Glasgow Outcome Scale/Glasgow Outcome Scale, Extended (-GOS/GOSE) system and functional independence measure (FIM), both based on neurological function recovery. All three included SR-MAs reported on the functional outcome measured using GOS. The heterogeneity of the functional outcome was high. Included SR-MAs showed good functional outcome with the combined $BtiO_2$ therapy with good outcome (OR: 1.26 [95% CI: 1.04–1.52]) and good outcome (OR: 1.31 [95% CI: 0.89–1.93]).[14,16] We found that patients treated with $PbtO_2$ combined therapy achieved better outcomes than those treated with the standard ICP/CPP therapy.

Length of Stay

Only one included SR-MA mentioned the length of hospital stay and found that there were reduced odds of length of hospital stay with the combined therapy.[16]

Discussion

Positron emission tomography studies in severe TBI have revealed that perfusion-limited data may not be the sole mechanism for secondary brain injury and ischemia, and other means like intravascular microthrombosis, cytotoxic edema, or mitochondrial dysfunction might be responsible for brain hypoxia. Consequently, it may be necessary to incorporate newer metabolic monitors, such as microdialysis or direct $BtiO_2$, to optimize TBI management and improve outcomes.[17–20] Several systematic reviews have been published describing $BtiO_2$ monitors that compare them with other techniques.[21–25] Most studies have shown better

Table 2 Summary of systematic reviews included in this review

Study	*N*	Type of included studies	Quality of included studies	Results of outcome with heterogeneity
Nangunoori et al[15]	491 $BtiO_2$ and ICP monitoring: 312 ICP monitoring: 179	Prospective observational studies: 2 Historical control studies: 2 Total: 4	Not reported	Mortality RR: 2.1 (95% CI: 1.4–3.1); $p \leq 0.001$ Heterogeneity: high
Xie et al[16]	1,250 $BtiO_2$ and ICP monitoring: 509 ICP monitoring: 741	RCT: 1 Retrospective observational studies: 8 Total: 9	NOS score High (8–9): 2 (22.22%) Moderate (5–7): 7 (77.77%) Low (0–4): 0 (0%)	Mortality OR: 0.76 (95% CI: 0.54–1.06); $p = 0.01$; $I^2 = 60\%$ Heterogeneity: high Good outcome: OR: 1.26 (95% CI: 1.04–1.52); $p = 0.02$; $I^2 = 37\%$ Heterogeneity: low Length of hospital stay Standard mean differences: 0.13 (95% CI: 0.11–0.37); $p = 0.28$; $I^2 = 74\%$ Heterogeneity: very high
Hays et al[14]	214 $BtiO_2$ and ICP monitoring: 94 ICP monitoring: 120	RCT: 3	GRADE Quality Scale: very low 3 (100%)	Mortality OR: 0.54 (95% CI: 0.31–0.93); $p = 0.03$; $I^2 = 42\%$ Heterogeneity: low Good outcome: OR: 1.31 (95% CI: 0.89–1.93); $p = 0.17$; $I^2 = 0\%$ Heterogeneity: low Cardiovascular events: OR: 1.44 (95% CI: 0.61–3.12); $p = 0.37$; $I^2 = 10\%$ Heterogeneity: low Respiratory events: OR: 1.37 (95% CI: 0.59–3.21); $p = 0.46$; $I^2 = 15\%$ Heterogeneity: low

Abbreviations: CI: confidence interval; ICP, intracranial pressure; NOS, Newcastle–Ottawa Scale; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

outcomes and mortality reduction with the $BtiO_2$-guided therapy. However, the results were not uniform when comparing the $BtiO_2$, ICP-/CPP-guided treatment with ICP/CPP therapy. Therefore, our present overview provided important information on a summary of current evidence on the utility of $BtiO_2$ monitoring in managing severe TBI.

Severe TBI is defined clinically as a patient having post-resuscitation GCS of 8 or less. Patients with severe TBI has a high mortality rate of between 20 and 40%, and a further 20% remain severely disabled and nonfunctional, adding to the morbidity.[26] The unfavorable outcome of TBI is mainly related to brain damage at the time of impact. Primary TBI is followed by damage in secondary and tertiary brain injury. Most of the patients who have unfavorable outcomes are due to secondary brain injury that happens primarily due to impaired brain tissue and occurs in perfusion and oxygenation hours, days, and weeks after the primary insult.[2] Secondary cerebral ischemic injury has been noted in over 90% of head injury fatalities, leading to a variety of complex and potentially irreversible pathophysiologic events, including hypoxia and ischemia, as well as impaired cerebral metabolism.[13]

Therefore, closely monitoring these intracranial physiological variables is paramount to identifying secondary brain injury before it escalates and becomes irreversible. The classification of neurologic monitoring can be broadly categorized into four types, which include pressure (such as ICP for CPP estimation), blood flow (such as thermal diffusion or transcranial Doppler), electrophysiology (such as electroencephalogram), and metabolic measures (including jugular venous oximetry, cerebral microdialysis, and direct brain tissue oxygen).[13] Studies have mentioned that neuromonitoring of the intracranial physiological variables helps in early identification of secondary brain injury and thereby helps in targeting the management for optimal outcome.[13] ICP monitoring is often described as essential for this purpose, and current management guidelines for severe TBI are centered on the control of ICP and CPP.[15]

Prior studies have shown reliable evidence that impaired brain tissue oxygenation, particularly hypoxia, is associated

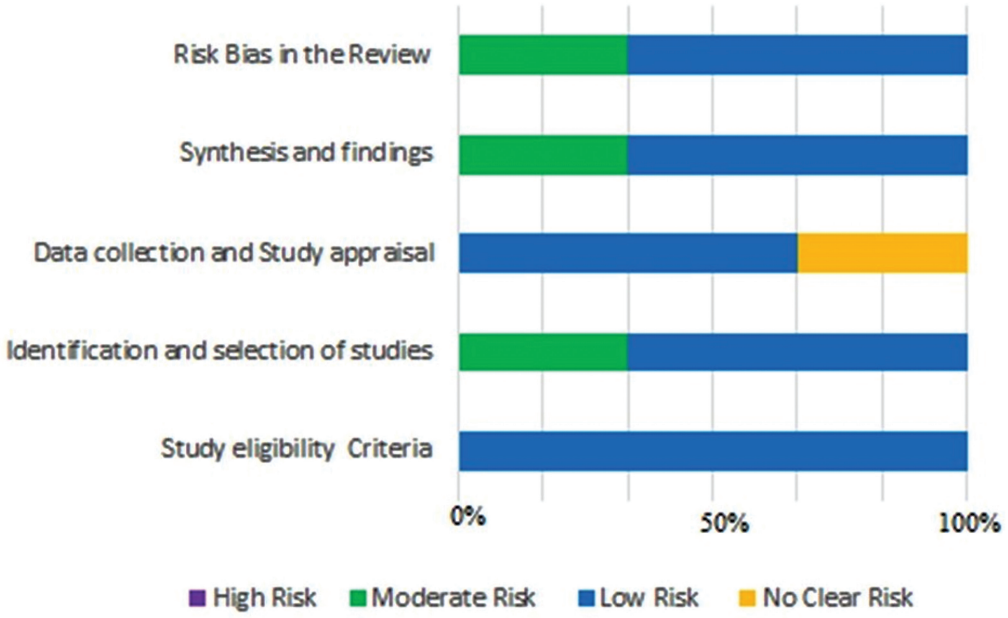

Fig. 2 Risk of bias graph: each risk of bias item presented as percentages across all included studies.

Table 3 AMSTAR tool: assessment to methodological quality on systematic review included

AMSTAR questions													
Study	1	2	3	4	5	6	7	8	9	10	11	Total	Quality of systematic review
Nangunoori et al[15]	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	6/11	Moderate
Xie et al[16]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	9/11	High
Hays et al[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11/11	High

Abbreviations: NA, not applicable; NR, not reported.

Table 4 Risk of bias assessment with Bristol University's ROBIS tool: review authors' judgments about each risk of bias item for each included systematic review

	Phase 2				Phase 3
Study	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk bias in the review
Nangunoori et al[15]	Low risk	Moderate risk	No clear risk	Low risk	Moderate risk
Xie et al[16]	Low risk	Low risk	Low risk	Moderate risk	Low risk
Hays et al[14]	Low risk	Low risk	Low risk	Low risk	Low risk

with an increased mortality risk and poor outcome following severe TBI. It has been estimated that one episode of hypoxia doubles the mortality after severe TBI.[13,27–31] The correlation between patient-centered outcomes and information obtained from a $BtiO_2$ monitor has resulted in the creation of a $BtiO_2$-based treatment approach for severe TBI that serves as an adjunct to current therapies for managing ICP and CPP. A direct $BtiO_2$ measurement of 10 to 15 mm Hg has been suggested as the critical threshold related with ischemic damage and poor patient outcome.[27,32–35] The findings suggest that suboptimal brain oxygen levels, indicated by hypoxia levels of less than 10 mm Hg, unfavorably influence clinical outcomes following severe TBI. Furthermore, the use of $BtiO_2$ probes is deemed safe in this context. The results, therefore, implicate that efforts geared toward enhancing $BtiO_2$ levels could potentially improve patient outcomes following severe TBI.[13]

However, despite the developments, current therapies have not been proven to be very successful in the clinical environment, although they are productive in the laboratory.[36–39] It is anticipated that the results of the ongoing multicenter study Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase 3 (BOOST-3) will further show the comparative

effectiveness of brain tissue oxygen and ICP monitoring versus ICP alone.[40]

Conclusion

Our results show that $BtiO_2$-based therapy combined with ICP-/CPP-based therapy results in better outcomes after severe TBI than ICP-/CPP-based therapy alone. The results of this study suggest that implementing a clinical protocol targeting both $PbtO_2$ and ICP, in conjunction with maintaining normal $PbtO_2$ levels, may potentially enhance the outcome of severe TBI patients. The combined therapy has little effect on the mortality rate, ICP, CPP, and length of stay.

Funding
None.

Conflict of Interest
None declared.

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Appendix: Search Strategy

PUBMED/MEDLINE

#1 Craniocerebral Trauma [mesh] OR Brain Edema [mesh] OR Glasgow Coma Scale [mesh] OR Glasgow Outcome Scale [mesh] OR Unconsciousness [mesh] OR Cerebrovascular Trauma [mesh] OR ((head or cranial or cerebral or brain* or intra-cranial or inter-cranial) AND (haematoma* or hematoma* or haemorrhag* or hemorrhage* or bleed* or pressure)) OR (Glasgow AND scale) OR ("diffuse axonal injury" OR "diffuse axonal injuries") or ("persistent vegetative state") OR ((unconscious* OR coma* OR concuss*) AND (injury*OR injuries OR trauma OR damage OR damaged OR wound* OR fracture*OR contusion* OR haematoma*OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR pressure))
#2 (intracranial AND pressure) OR (cerebrospinal AND pressure)
#3 (patient AND monitor*) OR (physiologic* AND monitor*)
#4 (Systematic AND review) OR Meta-analysis
#5 (("Animals" [Mesh]) NOT ("Humans" [Mesh] AND "Animals" [Mesh]))
#1 AND #2 AND #3 AND #4 NOT #5

LILACS
trauma AND head AND intracranial pressure AND (db:("LILACS") AND type_of_study:("systematic_reviews"))
EMBASE 15

1. exp Brain Injury/
2. exp Brain Edema/
3. exp Glasgow Coma Scale/
4. exp Glasgow Outcome Scale/
5. exp Rancho Los Amigos Scale/
6. exp Unconsciousness/
7. ((brain or cerebral or intracranial) adj5 (edema or edema or swell*)).ab,ti.
8. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj5 (injur* or trauma* or damag* or wound* or fracture* or contusion*)).ab,ti.
9. (Glasgow adj (coma or outcome) adj (scale* or score*)).ab,ti.
10. Rancho Los Amigos Scale.ab,ti.
11. ((unconscious* or coma* or concuss* or 'persistent vegetative state') adj3 (injur* or trauma* or damag* or wound* or fracture*)).ti,ab.
12. Diffuse axonal injur*.ab,ti.
13. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ab,ti.
14. exp Coma/
15. or/1–14
16. exp Intracranial Pressure/
17. exp Cerebrospinal Fluid Pressure/
18. (intracranial adj3 pressure).ab,ti.
19. (cerebrospinal adj5 pressure).ab,ti.
20. 16 or 17 or 18 or 19
21. exp Patient Monitoring/
22. ((physiologic* adj3 monitor*) or patient* monitor*).ab,ti.
23. 21 or 22
24. 23 and 20
25. exp Intracranial Pressure Monitoring/
26. 24 or 25
27. 26 and 15
28. exp Systematic reviews/
29. exp meta-analysis/
30. 28 or 29
31. exp animal/ not (exp human/ and exp animal/)
32. 30 not 31
33. 27 AND 30 AND 32

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("intracranial pressure" or "cerebrospinal pressure" or "cerebrospinal fluid") and (monitor*) and (traumatic brain injury OR head trauma OR Craniocerebral Trauma OR head injuries OR Brain injuries)

