Review

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Evidence-based management of adult traumatic brain injury with raised intracranial pressure in intensive critical care unit at resource-limited settings: a literature review

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Background: In underdeveloped countries, there is a greater incidence of mortality and morbidity arising from trauma, with traumatic brain injury (TBI) accounting for 50% of all trauma-related deaths. The occurrence of elevated intracranial pressure (ICP), which is a common pathophysiological phenomenon in cases of TBI, acts as a contributing factor to unfavorable outcomes. The aim of this systematic review is to analyze the existing literature regarding the management of adult TBI with raised ICP in an intensive critical care unit, despite limited resources.

Methods: This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol. Search engines such as PubMed, the Cochrane database, and Google Scholar were utilized to locate high-level evidence that would facilitate the formation of sound conclusions.

Result: A total of 11 715 articles were identified and individually assessed to determine their eligibility for inclusion or exclusion based on predetermined criteria and outcome variables. The methodological quality of each study was evaluated using recommended criteria. Ultimately, the review consisted of 51 articles.

Conclusion: Physical examination results and noninvasive assessments of the optic nerve sheath diameter (ONSD) via sonography are positively associated with elevated ICP, and are employed as diagnostic and monitoring tools for elevated ICP in resource-limited settings. Management of elevated ICP necessitates an algorithmic approach that utilizes prophylactic measures and acute intervention treatments to mitigate the risk of secondary brain injury.

Keywords: critical care, head injury, hyperosmolar therapy, hyperventilation, intracranial hypertension

Introduction

According to the report by the WHO, the burden of death and disability caused by trauma accounts for ~15% of the global population, with 12% of all deaths in low to middle-income countries being attributed to trauma, as compared to 6% in high-income countries. Traumatic brain injury (TBI), in particular, is responsible for half of all trauma-related deaths[1,2]. The prevalence of moderate to severe TBI remains a significant challenge to global health, resulting in mortality rates ranging between 36 and 42%, and unfavorable outcome rates ranging between 52 and 60%. Mild TBI accounts for ~80% of the cases, with moderate and severe TBI accounting for 10% each[3,4].

TBI is characterized by two distinct phases, namely primary injury and secondary injury. The former is caused by an external physical force applied to the head, resulting in skull fractures, hematomas, and disruption of the normal brain architecture and function. The latter, on the other hand, develops over time and

HIGHLIGHTS

- The prevalence of moderate to severe traumatic brain injury continues to pose a significant challenge to worldwide health, resulting in elevated mortality rates and unfavorable outcomes.
- Increased intracranial pressure (ICP), a common pathophysiological event in traumatic brain injury cases, is a contributing factor to the development of adverse outcomes.
- Physical examination results and noninvasive assessments of the optic nerve sheath diameter (ONSD) via sonography are positively associated with elevated ICP.
- Management of elevated ICP necessitates an algorithmic approach that utilizes prophylactic measures and acute intervention treatments to mitigate the risk of secondary brain injury.

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involves the activation of multiple molecular and cellular pathways[5]. These changes can lead to the development of cytotoxic or vasogenic brain edema and disturbed autoregulation. As a result, the volume of intracranial contents increases, which can exceed the compensatory capacities of the intracranial space and cause intracranial pressure (ICP) to rise. Factors that contribute to secondary injuries include decreased cerebral perfusion pressure (CPP), hypoxemia, hypotension and hypertension, impaired cerebral autoregulation, and both convulsive and nonconvulsive seizures[6,7].

In the context of TBI, the occurrence of intracranial hypertension (IH) is a prevalent pathophysiological event that causes compartmental compression and alteration, resulting in a reduction of CPP, which ultimately contributes to negative outcomes. Failure to treat IH can lead to further complications such as cerebral ischemia, brain herniation, and even death. The prognosis of patients afflicted with IH is often dependent on the availability of resources for critical care management.

Currently, the utilization of invasive and sophisticated ICP and CPP monitoring serves as a benchmark tool for therapeutic decision-making in neurointensive care units. These monitoring tools have the potential to minimize the factors contributing to secondary brain injury and IH. Such interventions include head-of-the-bed elevation (HBE), sedation, analgesia, cerebrospinal fluid (CSF) drainage, osmotic therapy, barbiturates, hyperventilation, and hypothermia, all of which aim to prevent additional brain damage and optimize conditions for brain recovery. However, it is important to note that these monitoring tools are not always available in areas with limited resources[8,9].

Moreover, there is a scarcity of research on the management and outcomes of TBI in low-income to middle-income countries[2]. Most TBI treatment guidelines are developed from high-income countries with ample resources and do not consider the unique challenges encountered in developing nations[10]. Consequently, applying advanced treatment guidelines in resource-limited settings is challenging. As a result, noninvasive ICP monitoring interventions have been utilized as an alternative method to enhance the quality of care and patient outcomes in such areas. Accordingly, this systematic literature review aims to develop the evidence-based management of adult TBI with raised ICP in intensive critical care units situated in resource-limited regions.

Methods and materials

Literature search strategies

A systematic search was conducted using computerized methods to search the PubMed, Google Scholar, and Cochrane databases for articles published in English since 2000. The review utilized retrospective studies, prospective observational studies, randomized control trials, systematic reviews, meta-analyses, and practical guidelines, with the incorporation of the following keywords: [(traumatic brain injury OR head trauma OR increased intracranial pressure OR intracranial hypertension) AND (diagnosis OR noninvasive monitoring OR optic nerve sheath diameters) AND (analgesics OR sedatives) AND positioning AND seizure prophylaxis AND hyperosmolar therapy AND ventilation therapies AND temperature control AND barbiturates AND glycemic control AND corticosteroids AND decompressive craniectomy]. This work was fully compliant with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) 2020 statement[11].

Scope of the guideline

The present review comprehensively examines the diagnosis, monitoring, and treatment interventions that are specifically tailored towards TBI patients exhibiting heightened ICP. However, it must be noted that the aim of this review is not to encompass all topics that are pertinent to the management of severe TBI patients in a neurointensive critical care unit. Topics that pertain to the provision of general good care for all patients, or those with trauma, have been excluded from this review.

Inclusion and exclusion criteria

The selection criteria for the review included studies that involved adult patients with nonpenetrating severe TBI, in-hospital interventional studies, studies evaluating outcomes such as mortality, neurologic function, and intermediate outcomes. The studies had to involve human subjects and be published in English since 2000. Studies that involved animal subjects, brain injury resulting from nontraumatic causes, mixed pathology without proper separation of outcomes, prehospital, or outpatient interventional studies, physiologic measures without a clear linkage to an included outcome, studies published prior to the year 2000, and those not written in English were excluded from the review.

Data extraction

The data was extracted with an adapted Excel sheet by two independent reviewers and disagreement was resolved by consensus. The extracted data includes the patient's age, country/study area, sample size, study design, year of publication, outcomes, and complications, were recorded.

Critical appraisal

The assessment of bias risk was conducted utilizing the Cochrane risk assessment tool for RCT studies and ROBIN's tool for nonrandomized studies. The ROB tool was employed to assess the methodological quality of each RCT study. The tool entails components such as selection bias (random sequence generation and allocation concealment), detection bias (blinding of outcome assessment), performance bias (blinding of personnel and participants), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (anything else, ideally prespecified). Following a comprehensive and in-depth literature appraisal, quality evaluation was carried out by classifying them into levels based on good clinical practice, GCP, WHO, 2011 (Table 1). The conclusion was deduced based on the level of evidence.

Result

A total of 11 715 articles were obtained through a comprehensive search engine query. A meticulous filtering process based on the criteria of intervention, outcome, population, and methodological quality was conducted. Ultimately, 51 studies were considered eligible to be included in the comprehensive review (Table 2). The PRISMA flow chart (Fig. 1) illustrates the systematic and rigorous study selection process.

Table 1

Levels of evidence and degree of recommendations

Level of evidences	Grading criteria	Grade of recommendation
1a	Meta-analysis, systematic review of RCTs, evidence-based guidelines	Level I: strongly recommended and directly applicable
1b	Systematic review of one RCTs	Level I : highly recommendable and directly applicable
1c	Randomized control/clinical trials	Level II A: recommended and applicable
2a	Systematic review of cohort study or individual cohort or case control studies or low quality RCT	Level II B: extrapolated evidence from other studies
3a	Nonanalytical studies like case report and case series, clinical audit, commentaries, and expert opinions	Level III: extrapolated evidence from other studies

RCT, randomized clinical trial. Source: Good clinical practice, GCP, WHO, 2011.

Discussion

Diagnosis of increased ICP

A definitive diagnosis of ICP requires the placement of an invasive monitor. However, this method is associated with complications such as hemorrhage and infection, and is not always available in all settings. In cases of elevated ICP, immediate treatment may be based on noninvasive diagnostic tests, including physical examination findings, imaging, and optic nerve sheath diameter (ONSD)[12].

The effectiveness of monitored ICP versus imaging and clinical examination-based management (referred to as ICE protocol) in the ICU was assessed in a multicenter, parallel-group trial study of 324 patients with severe TBI. Results showed no significant difference in the primary outcome measures of survival, duration and level of consciousness, functional status, and orientation at 3 months after injury, as well as functional and neuropsychological measures at 6 months after injury. The mortality rate at 6 months was also comparable between the two groups (39 vs. 41%, $P = 0.49$). However, brain-specific treatments in the ICU were significantly more common in the imaging-clinical examination group (41%) than in the pressure-monitoring group ($P = 0.002$)[13] (1c).

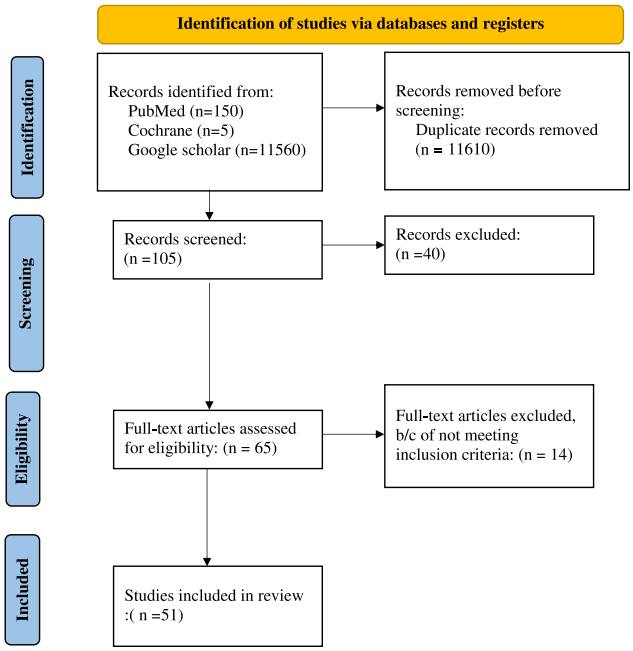

Figure 1. Flowchart for selection of studies by PRISMA flow diagram. Sources: adapted from the PRISMA 2020 statement: an updated guideline for reporting systematic reviews, 2021.

A comprehensive meta-analysis comprising 40 studies ($n = 5123$) was conducted, revealing that the presence of pupillary dilation had a sensitivity value of 28.2% (95% CI: 16.0–44.8%) and a specificity of 85.9% (74.9–92.5%) for diagnosing elevated ICP. Similarly, motor posturing had a sensitivity of 54.3% (36.6–71.0%) and specificity of 63.6% (46.5–77.8%), whereas decreased level of consciousness had a sensitivity of 75.8% (62.4–85.5%) and specificity of 39.9% (26.9–54.5%). The results of the meta-analysis suggest a correlation between pupillary dilation, motor posturing (GCS motor score ≤ 3), and decreased level of consciousness (GCS ≤ 8) with elevated ICP. However, individual findings lacked sufficient sensitivity for diagnosis[12] (1a). Based on the available evidence, we recommend the use of a combination of presence of pupillary dilation, motor posturing (GCS motor score ≤ 3), and decreased level of consciousness (GCS ≤ 8) for the diagnosis and monitoring of increased ICP in low-resource areas (level IIA).

Optic nerve sheath diameter monitoring of increased ICP

The optic nerve sheath, which is continuous with the dura mater, contains a trabeculated subarachnoid space that facilitates the flow of CSF and allows for expansion during increases in ICP[14]. A retrospective study of 204 patients (100 controls and 104 interventions) was conducted to investigate the correlation between ONSD with CT scan and increased ICP. The study revealed a statistically significant correlation with a sensitivity of 87.2% and specificity of 33.3% and a positive predictive value of 78.8%.[15] (2a). However, a blinded observational study was conducted to analyze the efficacy of optic nerve sonography (ONS) as a noninvasive diagnostic tool for detecting raised ICP. The study involved 160 patients and revealed that a cutoff value of 5.2 mm with sensitivity 81.2% (95%; CI: 69.9–89.6) and specificity 100% (95%; CI: 71.5–100) predicts raised ICP[16] (2a).

Furthermore, a monocentric observational study comprising of 100 adult patients with severe TBI demonstrated a significant correlation between ONSD and mean ICP ($r = 0.46$)[17] (2a). Similarly, a retrospective cohort study of 167 patients also showed a significant association of ONSD with increased ICP ($\beta = 0.21$, 95%; CI: 0.25–5.08) with a sensitivity of 72.2 and a specificity of 50%[18] (2a). A cross-sectional study of 100 TBI patients having suspected elevated ICP revealed that bedside sonographic measurement of ONSD reliably predicted elevated ICP in neuro-trauma patients, with a sensitivity of 93.2 and specificity of 91.1%, and a positive predictive value of 89.1 and a negative predictive value of

94.4%[19] (2a). Another prospective study analyzed 20 patients and found a statistically significant correlation between the ONSD and ICP, with a Pearson coefficient of 0.499, and a cutoff value of 6.3 mm for the ONSD predicted raised ICP with 100 sensitivity and 72.7% specificity[20] (2a).

A systematic review and meta-analysis of seven prospective studies comprising 320 patients was conducted to evaluate the diagnostic accuracy of sonographic ONSD measurement for the assessment of IH in adult patients. The findings of this analysis revealed that the accuracy ranged from 0.811 (95%; CI: 0.678–0.847) to 0.954 (95%; CI: 0.853–0.983)[21] (2a). Another meta-analysis of six studies with 352 patients was performed to validate the diagnostic accuracy of ultrasonographic (US) ONSD > 5.0 mm as a cutoff for detecting increased ICP. The pooled sensitivity of 99% (95%; CI: 96–100) and specificity of 73% (95%; CI: 65–80) for increased ICP detection were observed[22] (2a). Moreover, a meta-analysis of 10 studies comprising of 1035 patients demonstrated a significant association between ONSD on ultrasound and ICP measured through conventional monitoring with a combined AUROC value of 0.94% CI: (0.91–0.96%) for the detection of raised ICP with ONSD sonography[12] (1a). The research findings suggest that US evaluation of ONSD can serve as a simple and noninvasive method for detecting elevated ICP in neuro-trauma patients in low-resource settings. However, a consensus has not been reached regarding the appropriate threshold for ONSD measurement, and the accuracy of the method may be influenced by the expertise of the provider[12,16–19,21,22]. Based on the available evidence, the usage of optic nerve sheath diameter (ONSD > 5 mm) sonography is recommended for bedside ICP monitoring of TBI patients in low-resource settings (level II A).

General maneuvers for prevention of further ICP elevation

The primary focal points in the provision of care for patients with TBI are centered around the prevention of secondary damage that may arise from heightened ICP and the facilitation of sufficient cerebral blood flow (CBF)[9].

Analgesics and sedatives

Agitation and pain can be identified as contributing factors to the development of elevated ICP in individuals with TBI. Complications arising from the patient-ventilator dyssynchrony, such as decreased thoracic venous return leading to an increase in cerebral blood volume, elevating systemic BP, CMRO2, and brain tissue oxygen demands, have also been observed[23]. A systematic review of literature and practice recommendations involving 28 articles and 376 TBI patients revealed that the management strategy for agitation crisis is to search for an underlying factor such as pain, acute sepsis, and drug adverse effects[24](2a). Similarly, studies suggest that the optimal titration and management of sedation withdrawal should be balanced between the risks that interrupting sedation might exacerbate brain injury and the potential benefits of enhanced neurological function and reduced complications, with the aim of optimizing analgesia and minimizing sedative doses. However, treatment with a sedation interruption strategy should be avoided in all patients at risk for ICP elevation. The optimal titration and management of sedation withdrawal should also be based on the severity of acute brain injury[25,26] (3a).

A meta-analysis of four studies comparing the safety and efficacy of IV propofol and midazolam for sedation of patients with severe TBI showed no significant differences between the two sedatives. The GOS scores and mortality rates combined did not favor one sedative over the other, indicating that propofol and midazolam may have comparable efficacy and safety for the sedation of patients with severe TBI[27] (1a). In a retrospective chart review of 148 patients who primarily received etomidate, ketamine, and midazolam, it was found that receiving ketamine significantly decreased the mortality rate but increased the length of stay. The study concluded that ketamine should be used without concern for worsening outcomes in patients with elevated ICP requiring intubation[28] (2a).

Another systematic review comprising 13 RCTs with a total of 380 patients analyzed the effects of sedative agents on neurologic outcome, mortality, ICP, and CPP in critically ill adults with severe TBI. The review indicated that a long-term infusion of propofol compared to morphine was associated with a reduced need for ICP-lowering cointerventions and lower ICP on the third day. However, no significant difference was observed in ICP and CPP between propofol versus midazolam and ketamine versus sulfentanil. The review concluded that there is no convincing evidence that one sedative agent is more efficacious than another in improving patient-centered outcomes in critically ill adults with severe TBI[29] (1a).

A prospective randomized comparative study involving 120 adults with severe TBI compared the sedative effect of midazolam (administered via continuous infusion at a rate of 0.05 mg/kg/h, up to a maximal dose of 0.15 mg/kg/h), propofol (administered via continuous infusion at a rate of 0.5 mg/kg/h, up to a maximal dose of 4 mg/kg/h), and midazolam–propofol combination (dose reduced by 50%) on hemodynamic stability and subsequent ICP changes. The results showed that the midazolam–propofol combination significantly reduced ICP (19.6 ± 7.8%) compared to midazolam or propofol alone (17.3 ± 7.6 vs. 17.6 ± 6.3%), respectively. Additionally, patients who had an ICP less than 21 mmHg were significantly higher in the midazolam–propofol combination group (57.1%). The study concluded that the midazolam–propofol combination, when used at the recommended dosage, allowed for proper control of hemodynamic changes and improved CPP with a reduction in ICP[30] (2a). Based on the available evidence, we recommend a balanced sedation-analgesia management approach with a combination of midazolam–propofol continuous infusion and morphine as an essential therapeutic component of ICP therapy (level II B).

Positioning

The potential influence of patient body and head position on intracranial hemodynamics after severe brain injury has been observed. It has been found that the horizontal position can increase CPP and improve CBF. However, this position leads to elevated ICP due to brain edema. On the other hand, HBE can reduce IH due to venous return improvement and CSF distribution to the subarachnoid spinal space[31]. A quasi-experimental, prospective study of 33 patients with acute neurological conditions was conducted to compare different body and head positions. The study recorded a significant change of ICP in supine with head of bed (HOB) 45, left lateral with HOB 15, right lateral with HOB 15, and knee elevation with HOB 45. However, left lateral with HOB 30 had a significant effect on CPP. The study

concludes that there is no single optimal body position and that the lateral position should be used with caution[32] (1c). Another retrospective analysis of 115 patients with acute brain injury and acute respiratory failure treated with prone positioning showed that ICP was significantly increased during prone position (PP) compared with supine position (SP), but there was no significant difference in CPP. The analysis concluded that prone positioning significantly increases ICP but increases oxygenation[33] (2a).

A Cochrane Database of Systematic Review of three RCT studies on noninvasive physical intervention by using HBE revealed a negative and linear association between ICP and an increase in head elevation. As a result, an increase of 10 cm in the elevation of the head decreases ICP by 3.9 mmHg or (HBE at 30° position decrease by an average of 4.0 mmHg), but there is no evidence of a change in CPP after position changes at 10 min. The review concludes that the optimum angle of the HBE needs to be decided individually after an analysis of the response of ICP, CPP and CBF in each HBE position[9] (1a). Based on evidence, it is recommended that the position of TBI patients should be maintained at a 30–45° angle of the HBE, and the lateral position should be used with caution (level II A).

Seizure prophylaxis

Post-traumatic seizures (PTSs), whether occurring within 7 days postinjury (early) or after 7 days (late), are a moderately common occurrence among patients with moderate to severe TBI. This is due to the reduction of the epileptic discharge threshold caused by underlying structural and functional injuries[34]. Seizures have been observed to exacerbate IH, as they increase the cerebral metabolic rate of oxygen (CMRO2) and CBF. The Brain Trauma Foundation (BTF) has recommended early prophylaxis[35]. A prospective observational study of 522 patients failed to demonstrate any benefit of routine early seizure prophylaxis following blunt TBI[36](2a). A meta-analysis of three RCTs (750 patients) and six observational studies (3362 patients) showed that antiepileptic prophylaxis reduced the risk of early seizures by 58% compared to patients who received no treatment [risk ratio (RR) = 0.42; 95%; CI: 0.29–0.62]. A study concluded that there is a significant protective association between antiepileptic drug (mostly phenytoin) and early PTS prophylaxis[37] (1a).

In a single-center, prospective cohort analysis of 19 patients, a comparison of phenytoin (loading dose: 20 mg/kg IV over 60 min, then maintenance dose: 5 mg/kg/day IV every 12 h given over 15 min) versus levetiracetam (loading dose: 20 mg/kg IV over 60 min, then maintenance dose: 1000 mg IV every 12 h given over 15 min) for post-traumatic seizure prophylaxis after TBI found no significant difference in the GOS-E score assessed ≥ 6 months after injury (5.07 ± 1.69 vs. 5.60 ± 2.07), no difference in the incidence of early seizures or late seizures. However, patients who received phenytoin had a significantly higher rate of fever days (0.20 ± 0.22 vs. 0 ± 0). A study concluded that long-term functional outcome was not affected by treatment with phenytoin or levetiracetam[38] (2a). Similarly, a multicenter prospective study of 813 patients (LEV = 406 and PHE = 407) comparing levetiracetam (LVE) versus phenytoin (PHE) for early post-traumatic seizure prophylaxis found no significant differences in seizure rate (1.5 vs. 1.5%, $P = 0.997$) and mortality rate (5.4 vs. 3.7%, $P = 0.236$)[39] (2a).

A meta-analysis was conducted to compare the efficacy of phenytoin versus levetiracetam for seizure prophylaxis after brain injury. It included two RCTs and six observational studies, and the analysis revealed that there was no significant difference between the two drugs in preventing early seizures. The pooled OR was 1.12 (95%; CI: 0.34–3.64), and the seizure incidence at 6 months was also insignificant, with a pooled OR = 0.96 (95% CI: 0.24–3.79). Therefore, it was concluded that levetiracetam and phenytoin have equal efficacy in preventing seizures after brain injury[40] (1a). Another meta-analysis of six cohort studies compared levetiracetam versus phenytoin for seizure prophylaxis in patients with TBI, and similarly found no superiority of either drug in preventing seizures. The OR was 1.1 (95% CI: 0.55–2.20), and it was concluded that both drugs have equal efficacy in preventing seizures after TBI[41] (1a).

Conversely, a prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis was conducted with 52 patients (LEV = 34; PHT = 18). The study showed that LEV patients experienced better long-term outcomes than those on PHT. The Disability Rating Scale score was lower at 3 months and the Glasgow Outcomes Scale score was higher at 6 months ($P = 0.039$). However, there were no significant differences in seizure occurrence (LEV: 5/34 vs. PHT: 3/18) and mortality (LEV: 14/34 vs. PHT: 4/18). It was concluded that long-term outcomes improved in LEV-treated patients than in PHT-treated patients[42] (2a). On the other hand, a review about cost-minimization analysis of phenytoin versus levetiracetam for early seizure pharmacoprophylaxis after TBI found that the PHT strategy was less expensive than the LEV strategy from both the institutional and patient perspectives. Therefore, it was concluded that PHT is less expensive than LEV for routine pharmacoprophylaxis of early seizures among TBI patients[34] (2a). Based on the evidence, we recommend that phenytoin be used as the first line for early prophylaxis of post-traumatic seizures (1evel II A).

Glycemic control management

Hyperglycemia is a commonly observed consequence of TBI and is associated with unfavorable outcomes. The pathogenesis of 'stress hyperglycemia' is a result of a convoluted interplay of endogenous catecholamine, cytokines, and activation of the hypothalamic-pituitary-adrenal axis, leading to excessive cortisol secretion[43]. A retrospective study of 228 severe TBI patients who received insulin treatment showed that a blood glucose target of 90–144 mg/dl (5–8 mmol/l) during the acute stage was linked to a reduced mortality rate and decreased ICP when compared to a blood glucose target of 63–117 mg/dl (3.5–6.5 mmol/l). However, in the second week, the groups appeared to experience reverse outcomes: compared with the (5–8 mmol/l vs. 3.5–6.5 mmol/l) demonstrated a decreased incidence of ICP (15 ± 0.1 mmHg vs. 17 ± 0.1 mmHg) and reduced infectious complications. Therefore, it seems that a slightly higher blood glucose level (5–8 mmol/l) may be more beneficial during the first week, while a lower blood glucose level (3.5–6.5 mmol/l) may be more favorable during the later stages of recovery[44] (2a).

A meta-analysis of 10 RCTs, encompassing 1066 TBI patients and comparing conventional (8.4–12 mmol/l) with intensive (4.4–6.7 mmol/l) glycemic control in critically ill patients, demonstrated no association with ICU or hospital mortality. However, intensive glucose control showed a borderline significant reduction in the risk of poor neurological outcome, but markedly increased the risk of hypoglycemia[45] (1a). There is

insufficient evidence to recommend conventional or intensive glycemic control in TBI patients; however, we suggest avoiding hypoglycemia (< 4 mmol/l) and hyperglycemia (> 12 mmol/l) by employing accurate glycemia monitoring (level IIA).

Therapeutic intervention

Ventilation therapies

Hyperventilation leads to a reduction in ICP and cerebral relaxation through vasoconstriction, resulting in a decrease in cerebral blood volume. It should be noted that the reduction in CBF is more profound in the normal brain than in the injured brain since hyperventilation redistributes CBF from normal brain tissues to injured brain tissues that have luxury perfusion[46–48]. In Europe, early prophylactic hyperventilation, which targets a PaCO2 of 35 mmHg within 24 h after TBI, is practical for TBI patients. However, prolonged and overzealous prophylactic hyperventilation targeting a PaCO2 of 25 mmHg can cause more harm than good. Thus, the brain trauma foundation guideline does not recommend it[35,49] (1a).

Based on a systematic review of six studies, both hypocapnia and hypercapnia after cerebral injury are associated with poor patient outcomes[50] (2a). A prospective study of 492 patients with severe TBI revealed that patients with a PaCO2 ranging from 30 to 35 mmHg had the lowest mortality rate (16.1%). However, patients with a PaCO2 of more than 45 mmHg had the highest mortality rate (36.2%). The adjusted odds ratio (OR) for mortality of the target range compared with hypocapnea was (OR = 0.08; 95% CI: 0.01– 0.44). There were no significant differences observed in the discharge GCS, functional independence measure score, or ICU length of stay among the groups. A study concluded that the targeted ventilation is associated with lower mortality after severe TBI[51] (2a).

Based on the overall evidence, prolonged prophylactic hyperventilation targeting a PaCO2 of less than 25 mmHg during the first 24 h after injury is not recommended (level I). We adopt the recommendation from the 4th edition of the Trauma Brain Foundation guideline, which stipulates that hyperventilation should be used as a temporary measure to reduce refractory ICP elevation while ensuring the adequacy of tissue perfusion and oxygenation are simultaneously monitored (level II A).

Hyperosmolar therapy

Hyperosmolar therapy plays an essential role in pharmaceutical treatment for IH. A systematic review with meta-analysis has revealed that both hypertonic saline and mannitol successfully decrease ICP[52] (1a). The European Society of Intensive Care Medicine (ESICM) discovered that mannitol reduced ICP by 10.9 mmHg (95% CI: 8.2–13.5 mmHg), and decreased by 0.78 mmHg for every 100 mg/kg increase per dose relationship. In contrast, hypertonic saline reduced ICP by an average of 8.8 mmHg (95% CI: 6.5–11.1 mmHg). The study concluded that the use of 20% mannitol (0.25–1 g/kg) or 3% hypertonic saline solutions (2–5 ml/kg over 20 min) is effective in reducing increased ICP. A consensus recommends that a combination of neurological worsening and ICP greater than 25 mmHg acts as a trigger for starting osmotherapy to treat elevated ICP[53] (1a). A multicenter prospective cohort study of 1086 patients compared the mortality and outcomes in patients with TBI with IH (treated or not) with continuous hyperosmolar therapy, finding that patients with IH with continuous hyperosmolar therapy had a relative risk of survival at day 90 of RR = 1.43; 95% CI: 0.99–2.06, and favorable outcomes (Glasgow Outcome Scale 4–5) occurred in 45.2% of treated and in 35.8% of not treated. Additionally, a systematic review of 1304 patients from eight studies suggests that continuous hyperosmolar therapy compared with not treated is associated with a reduction of in-ICU mortality (23.6 vs. 31.2%) respectively. They conclude that the continuous hyperosmolar therapy for the treatment of post-traumatic IH was associated with improved adjusted 90-day survival[54] (2a).

A Cochrane Database of Systematic Reviews of six RCTs involving a total of 287 people, comparing HS and mannitol in patients with severe TBI found no statistically significant differences in mortality and neurological outcomes. The studies concluded that there is no evidence about the efficacy and safety of hypertonic saline versus mannitol in the management of acute TBI[55] (1a). Another meta-analysis of 10 articles discovered no clinically important differences in mortality, neurological outcomes, and ICP reduction between hypertonic saline and mannitol in the management of severe TBI. However, 3% hypertonic saline has a more sustained effect on ICP and can effectively increase CPP[56] (1a). Based on evidence, we recommend that hyperosmolar therapy (mannitol or hypertonic saline) is effective for controlling raised ICP. However, there are no evidences to recommend one is more effective than the other (level I).

Temperature control

The impact of elevated temperature on ICP is such that it increases cerebral metabolic demands and CBF. Conversely, hypothermia results in a reduction in cerebral metabolism and CBF, which ultimately lowers ICP levels as well[57]. Two randomized, multicenter clinical trials were conducted to establish the efficacy of early hypothermia induction as a primary neuroprotective strategy in patients with severe TBI. However, both trials failed to confirm its usefulness, with relative risks of 1.08 (95% CI: 0.76–1.53; $P = 0.67$) and 0.99 (95% CI: 0.82–1.19; $P = 0.94$), respectively[58,59] (1c). Moreover, a meta-analysis of a single RCT involving 41 participants found no evidence supporting the reduction of body temperature to between 35°C and 37.5°C in people with TBI with a long-term outcome. Serious adverse effects were associated with poor outcomes[60] (1b). Another meta-analysis of 23 trials that involved a total of 2796 patients investigated therapeutic hypothermia versus normothermia management in patients with TBI, and it was found that mortality rates were more significant in the therapeutic hypothermia group (RR = 1.26, 95% CI: 1.04–1.53). However, when therapeutic hypothermia was administered within 24 hours, there was lower mortality (RR = 0.83, 95% CI: 0.71–0.96), and the risk of unfavorable functional outcome following therapeutic hypothermia management was significantly reduced (RR = 0.78, 95% CI: 0.67–0.91). Notably, there was a significant increase in the risk of pneumonia (RR = 1.48, 95% CI: 1.11–1.97). Although a meta-analysis concluded that therapeutic hypothermia did not reduce but might increase the mortality rate of patients with TBI, patients with elevated IH could benefit from hypothermia in therapeutic management when initiated within 24 h instead of prophylaxis[61] (1a). Based on the available evidence, we do not recommend prophylactic or therapeutic hypothermia in patients with acute brain injury. Instead, normothermia should be maintained (level II A).

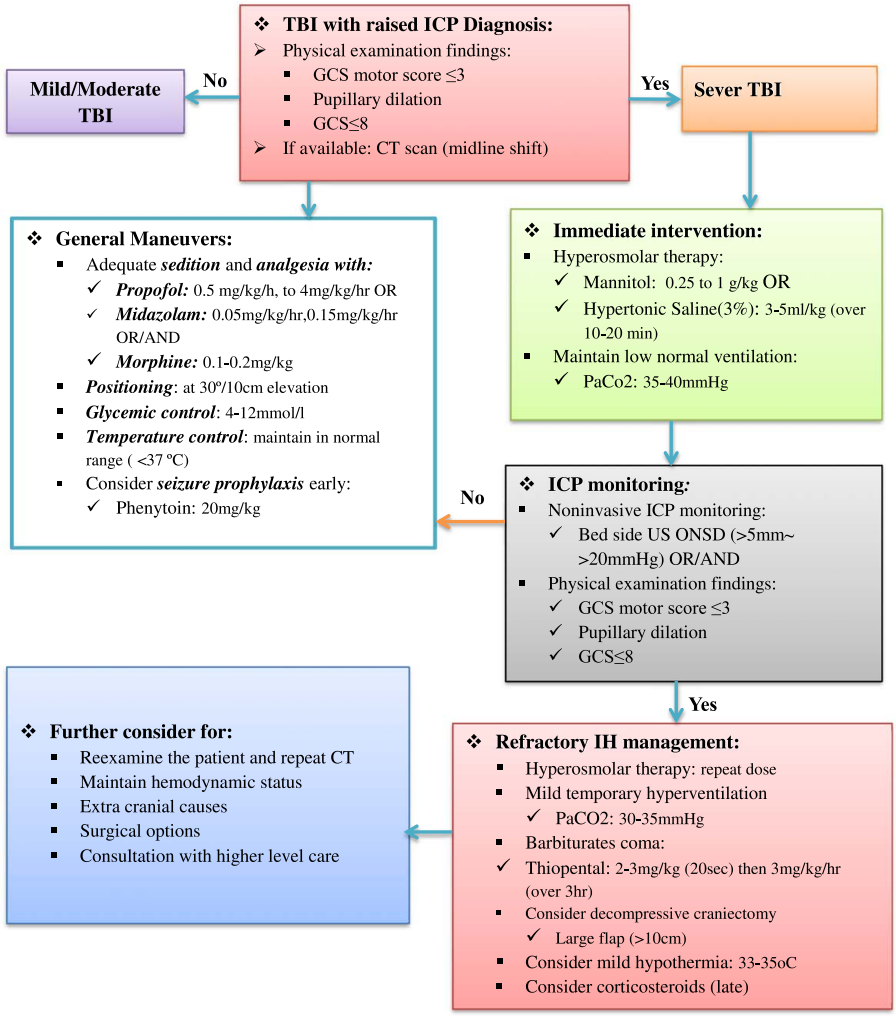

Figure 2. Management of TBI with ICP algorithm. Flow chart for diagnosis, monitoring and management of traumatic brain injury with raised ICP at resource-limited ICU.

Barbiturates

In patients with severe TBI who show refractory IH following medical and surgical intervention, high doses of barbiturates are administered. This pharmacological intervention effectively diminishes brain metabolism, curtails CBF, enhances oxygenation of the cerebral tissues, and induces burst suppression as measured by electroencephalogram[62].

The Cochrane Database of Systematic Reviews assessed the impact of barbiturates on mortality and disability in patients with acute TBI. Findings from three trials comparing barbiturates to no barbiturate use showed a pooled RR of death at 1.09 (95% CI: 0.81–1.47), a pooled RR for disability at 1.15 (95% CI: 0.81–1.64), and a decrease in mean ICP in the group treated with barbiturates. Upon comparing pentobarbital and thiopental in a trial, thiopental was found to be superior with an RR of 1.78 (95% CI: 1.03–3.08) for death, with uncontrollable ICP being observed with thiopental (RR 1.64; 95% CI: 1.03–2.60). However, there was no significant difference between the effects of pentobarbital and thiopental with respect to death or disability, as measured by the Glasgow Outcome Scale (RR 1.31; 95% CI: 0.88–1.94). Barbiturate therapy was found to be effective in reducing raised ICP, but there was no evidence of improved outcomes in acute brain injury[62] (1c). In a randomized, prospective cohort study comprising of 44 patients (22 in each group), the efficacy of pentobarbital (loading dose: 10 mg/kg over 30 min followed by a continuous perfusion of 5 mg/kg/hr for 3 h, followed by a maintenance dosage: 1 mg/kg/hr) and thiopental (loading dose: 2 mg/kg bolus over 20 s then second bolus: 3 mg/kg, followed by infusion at a rate of 3 mg/kg/hr) was compared. The pentobarbital group exhibited a significantly higher incidence of uncontrollable ICP as compared to the thiopental group (82 vs. 50%, $P = 0.03$) and thiopental was found to be five times more effective than pentobarbital in controlling refractory ICH ($P = 0.027$). However, an association with arterial hypotension was noted[63] (2a). According to the available evidence, it is recommended to utilize thiopental therapy for the management of elevated ICP that is refractory to standard medical and surgical treatment. It is crucial to ensure hemodynamic stability before and during barbiturate therapy (level II A).

Table 2

Evidences summary table

Topic and number of studies	Reference, study topic	Study design, *N*, and outcomes	Level of evidences	Results and conclusion
Physical examination two studies	*Chesnut et al. 2018*[13] Comparison of monitored ICP versus imaging and clinical examination-based management (ICE) protocol of TBI patients	Prospective randomized controlled trial total patients = 324 intervention = 167 control = 167 mortality, duration and level of consciousness, functional status, and orientation measures at 3 months after injury, and functional and neuropsychological measures at 6 months after injury	1c	Mortality: monitored ICP versus imaging and clinical examination-based management (ICE) protocol = 39 vs. 41% neuroworsening event: (22 vs. 27%). No significant difference in outcomes
	Fernando et al. 2019[12] Compare the accuracy of physical examination, computed tomography (CT), sonography of the ONSD, and transcranial Doppler pulsatility index (TCD-PI) for the diagnosis of elevated intracranial pressure (ICP) in critically ill patients	Systematic review and meta-analysis: 40 studies patients = 5123 estimates of diagnostic performance for the diagnosis of elevated ICP	1a	Physical examination signs, *pupillary dilation:* sensitivity: 28.2% specificity: 85.9% *Posturing:* sensitivity: 54.3% specificity: 63.6% *Glasgow coma scale of 8 or less:* sensitivity: 75.8% specificity: 39.9% CT findings: sensitivity: 85.9% specificity: 61.0%. Midline shift of at least 10 mm: sensitivity: 20.7% specificity: 89.2%. Absence of any one physical examination feature is not sufficient to rule out elevated ICP. Substantial midline shift could suggest elevated ICP, but the absence of shift cannot rule it out
Sonography ONSD measurement nine studies	*Robba et al. 2019*[17] Optic nerve sheath diameter ultrasonography at admission as a predictor of intracranial hypertension in traumatic brain injured patients	Prospective observational study patients: 100 correlated with the mean ICP	2a	ONSD was significantly correlated with mean ICP ($r = 0.46$, $P < 0.0001$) ONSD measured at NCCU admission can give important information about patients at risk of developing intracranial hypertension and impaired autoregulation
	Aduayi, et al. 2015[16] Comparison of mean ONSD of subjects with and without cranial CT signs of raised ICP	Prospective blinded observational study Population: 160 patients intervention: 80 control: 80. Detecting raised the intracranial pressure (ICP)	2a	A cut-off value of 5.2 mm sensitivity = 81.2% specificity = 100% optic nerve sonography can differentiate between normal and elevated ICP and may serve as a useful screening tool in resource-limited practice
	Robba et al. 2018[21] Comparative studies that evaluated the efficacy of sonographic ONSD vs. ICP measurement with invasive devices	Systematic review and meta-analysis (seven prospective studies) patients: 320 diagnostic accuracy of sonographic ONSD measurement	1b	Accuracy of ultrasonographic ONSD ranged from 0.811 to 0.954. Ultrasonographic ONSD may be a potentially useful approach for assessing IH when invasive devices are not indicated or available
	Kim et al. 2018 Ultrasonographic optic nerve sheath diameter to detect increased intracranial pressure in adults	Meta-analysis (six studies) patient: 352 ONSD > 5.0 mm for increased ICP detection in adult patients	1b	US ONSD > 5.0 mm revealed pooled: sensitivity = 99% specificity = 73%. DOR was 178. The area under the SROC curve was 0.981, indicating a good level of accuracy US ONSD > 5.0 mm used to rapidly detect IICP in adults in ED and ICU
	Al-Hassani et al. 2020[18] Association between optic nerve sheath diameter (ONSD) and intracranial pressure (ICP) in patients with mododate to rate#to#severe brain injury	Retrospective cohort study patient: 167 intension (ICH) and mortality	2a	ICP values correlated with ONSD measurement ($r = 0.21$, $P = 0.04$). cutoff value of 5.6 mm to detect ICH with: sensitivity = 72.2% specificity = 50%. ONSD is a simple noninvasive measurement on initial CT in patients with TBI that could be a surrogate for ICP monitoring

	Majeed, et al. 2019[15] A noninvasive method for the estimation of increased intracranial pressure in patients with severe traumatic brain injury using optic nerve sheath diameter measured on computed tomography	Retrospectively cohort study patients: 204 (100 control and 104 intervention) predict patients requiring an invasive ICP monitor on admission	2a	The average ONSD of the control group was 5.73 ± 0.58 mm compared to 6.76 ± 0.83 mm in the intervention group ($P < 0.0001$). Linear regression analysis demonstrated a statistically significant correlation between ONSD and opening ICP ($r = 0.40$, $P < 0.001$) and peak ICP ($r = 0.31$, $P < 0.0001$). An ONSD ≥ 6.0 mm + Marshall score ≥ 3 on initial CT head demonstrated a 92.5% sensitivity, 92.6% specificity, and 96.1% positive predictive value for developing an ICP ≥ 20 mmHg during hospitalization. Utilizing ONSD in combination with Marshall score grading is a strong predictor of elevated ICP
	Kaur et al. 2021[19] Bedside Ultrasonographic assessment of optic nerve sheath diameter as a means of detecting raised intracranial pressure in neuro-trauma patients	A cross-sectional study patients: 100 ONSD of ≥ 5.0 mm was considered as a benchmark of raised ICP	2a	The bedside sonographic measurement ONSD to detect raised ICP was sensitivity = 93.2% specificity = 91.1% when compared with CT scan. Positive predictive value of the ONSD measurement = 89.1% negative predictive value = 94.4%. Ultrasonographic assessment of ONSD is a reliable modality to detect raised ICP in neuro-trauma patients
	Sahoo et al. 2013[20] Correlation of optic nerve sheath diameter with intracranial pressure-monitoring in patients with severe traumatic brain injury	Prospective study patients: 20 The correlation between ICP and ONSD	2a	Statistically significant correlation between the ONSD and ICP; the Pearson coefficient: 0.499 ($P = 0.041$), and a cutoff value of 6.3 mm for ONSD predicted raised ICP with 100% sensitivity and 72.7% specificity. A cutoff of 6.3 mm can be used to plan therapeutic interventions when ICP monitoring is unavailable or contraindicated
	Fernando et al. 2019[12] Diagnosis of elevated intracranial pressure in critically ill adults	Systematic review and meta-analysis: 10 studies patients: 1035 estimates of diagnostic performance for the diagnosis of elevated ICP	1a	The pooled area under the ROC (AUROC) curve for ONSD sonography = 0.94 (0.91–0.96). ONSD sonography might have use, but further studies are needed
Analgesia and sedation five studies and two reviews	*Luauté et al. 2017*[24] Care management of the agitation or aggressiveness crisis in patients with TBI	A systematic review of the literature and practice recommendations (28 articles) patients = 376 agitation crisis	2a	The management strategy implies to search for an underlying factor that should be treated such as pain, acute sepsis, and drug adverse effect. This study provides a strategy for treating the agitation crisis based on scientific data and expert opinion.
	Gu et al. 2014[27] Comparison of the safety and efficacy of propofol with midazolam for sedation of patients with severe traumatic brain injury	A meta-analysis (four studies) The Glasgow Outcome Scale score, mortality, therapeutic failure, intracranial pressure, and cerebral perfusion pressure	1a	GOS scores of the combined (OR = 1.139; Z statistic = 0.242, $P = 0.809$). Mortality rate combined (OR = 0.76; Z statistic = -0.467, $P = 0.640$). No important differences between propofol and midazolam when administered to provide sedation for patients with severe traumatic brain injury
	Cornelius et al. 2018[28] Effect of sedative agent selection on morbidity, mortality and length of stay in patients with increase in intracranial pressure	A retrospective chart review patients = 148. Length of stay, morbidity and mortality		Receiving ketamine significantly lower mortality rate (E = 38.3%, K = 13.3%, M = 40.7%), but longer length of stay (E = 15.8, K = 29.5, M = 14.1) days. Ketamine should be used without concern for worsening outcomes in patient with elevated intracranial pressure requiring intubation
	Roberts, Derek J et al. 2011[29] Sedation for critically ill adults with severe traumatic brain injury	Systematic review (13 RCT) patients = 380	1a	Long-term infusion of propofol vs. morphine was associated with a reduced requirement for intracranial pressure-lowering co-interventions and a lower intracranial pressure on the third day,

Table 2

(*Continued*)

Topic and number of studies	Reference, study topic	Study design, *N*, and outcomes	Level of evidences	Results and conclusion
		Neurologic outcome, mortality, intracranial pressure, cerebral perfusion pressure, and adverse drug events		but propofol vs. midazolam and ketamine vs. sulfentanil found no difference between agents in intracranial pressure and cerebral perfusion pressure. No convincing evidence that one sedative agent is more efficacious than another for improvement of patient-centered outcomes in critically ill adults with severe traumatic brain injury
	Shabana et al. 2016[30] Outcome of sedation therapy using midazolam or propofol continuous infusion in patients with severe traumatic brain injury	A prospective randomized comparative study patients: 120 adults. Hemodynamic stability and subsequent intracranial pressure (ICP) changes	2a	ICP was significantly reduced in midazolam–propofol combination (19.6 ± 7.8%, $P = 0.0004$) compared with midazolam or propofol alone (17.3 ± 7.6% vs. 17.6 ± 6.3%, $P = 0.0006$) respectively, and patients who had an ICP less than 21 mmHg was significantly higher in midazolam–propofol combination (57.1%, $P = 0.007$). Midazolam–propofol combination in the used dosage allowed proper control of hemodynamic changes and improved cerebral perfusion pressure with reduction in ICP
Positioning: three studies	*Alarcon et al. 2017*[9] Elevation of the head during intensive care management in people with severe traumatic brain injury	Cochrane Database of Systematic Reviews (three small RCT studies) participants: 20 mortality, quality of life, disability, intracranial Pressure (ICP) after the intervention	1b	Increase of 10 cm in the elevation of the head decrease ICP by 3.9 mmHg or HBE at 30° position ICP decrease by an average of 4.0 mmHg (P value < 0.001), we are uncertain about the effects of different backrest positions in people with serious brain injury
	Ledwith et al. 2010[32] Effect of body position on cerebral oxygenation and physiologic parameters in patients with acute neurological conditions	A quasi-experimental, prospective study Patients: 33 brain tissue oxygen (PbtO2) and intracranial pressure (ICP)	1c	Significant change of ICP in supine with head of bed (HOB) 45 (decrease from (9.68 ± 5.6) to (7.48 ± 5.8),$P = 0.002$), left lateral with HOB 15 (increase from (9.92 ± 6.4) to (11.42 ± 5.1), $P = 0.026$), right lateral with HOB 15 (increase from (9.20 ± 6.0) to (12.13 ± 7.72), $P = 0.002$), and knee elevation with HOB 45 (decrease from (10.19 ± 5.8) to (8.85 ± 6.7), $P = 0.015$), but left lateral with HOB 30 had a significant effect on CPP (decrease from (91.02 ± 14.8) to (87.13 ± 16.3), $P = 0.044$). There is no single optimal body position and that the lateral position should be used with caution
	Roth et al. 2014[33] Does prone positioning increase intracranial pressure? A retrospective analysis of patients with acute brain injury and acute respiratory failure	A retrospective analysis patients = 115 values of intracranial pressure (ICP), cerebral perfusion pressure (CPP), and oxygenation	2a	ICP increased significantly during prone position (PP) compared with supine position (SP) (15.4 ± 6.2 vs. 9.5 ± 5.9 mmHg, $P < 0.0001$), and ICP > 20 mmHg were observed significantly more often during prone positioning (17.9% vs. 4%, $P < 0.0001$), but no significant difference in CPP (80.1 ± 14.1 mmHg vs. 82 ± 14.5 mmHg, $P = 0.0591$). Prone positioning significantly increase ICP, but increase oxygenation
Seizure prophylaxis: nine studies	*Wat et al. 2019*[37] Effectiveness of antiepileptic medications as prophylaxis of early seizure in patients with traumatic brain injury compared with placebo or no treatment	Systematic review and meta-analysis (three RCTs and six observational studies) patients: 750 and 3362. Early post-traumatic seizure (PTS), mortality, functional disability	1a	Pooled RR estimate across RCTs trended toward a protective effect RR = 0.58; significant protective association on six observational studies RR = 0.42; protective association between AEDs as prophylaxis of early PTS (mostly phenytoin)
	Szaflarski et al. 2010[42] Comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis	A single-center, prospective cohort analysis patients: 19	2a	LEV patients experienced better long-term outcomes than those on PHT; the Disability Rating Scale score was lower at 3 months (P = 0.042) and the Glasgow Outcomes Scale score was higher at

	Disability Rating Scale score, Glasgow Outcomes Scale score, seizure occurrence during cEEG at 6 months, mortality		6 months (P = 0.039). There were no differences between groups in seizure occurrence during cEEG (LEV 5/34 vs. PHT 3/18; P = 1.0) or at 6 months (LEV 1/20 vs. PHT 0/14; P = 1.0), mortality (LEV 14/34 vs. PHT 4/18; P = 0.227). Long-term outcomes improved in LEV-treated patients than PHT-treated patients.
Inaba, Kenji et al. 2012 Comparison of levetiracetam versus phenytoin for early post-traumatic seizure prophylaxis	A multicenter prospective study patients: 813. Seizure diagnosed clinically, occurring within 7 days of admission	2a	There were no significant differences between LEV and PHE in age [51.7 (21.3) vs. 53.6 (22.5), $P=0.205$], male (73.9 vs. 68.8%, $P=0.108$), Injury Severity Score (ISS) [20.0 (10.0) vs. 21.0 (10.6), $P=0.175$], Marshall score of 3 or greater (18.5 vs. 14.7%, $P=0.153$), or craniectomy (8.4 vs. 11.8%, $P=0.106$). There was no difference in seizure rate (1.5 vs.1.5%, $P=0.997$), adverse drug reactions (7.9 vs. 10.3%, $P=0.227$), or mortality (5.4 vs. 3.7%, $P=0.236$) LEV did not outperform PHE. Cost and need for serum monitoring should be considered in guiding the choice of prophylactic agent
Zafar et al. 2012[40] Phenytoin versus leviteracetam for seizure prophylaxis after brain injury	A meta-analysis (two RCTs and six observational studies). Early and late seizures and side effects	1a	No superiority of either drug at preventing the occurrence of early seizures with the pooled odds ratio (OR) = 1.12 (95% CI: 0.34–3.64), and seizure incidence at 6 months while comparing drug efficacy also insignificant with pooled OR = 0.96 (95% CI: 0.24–3.79). Levetiracetam and phenytoin demonstrate equal efficacy in seizure prevention after brain injury
Ardalan Golbahar-Haghighi et al. 2015[41] Comparison of levetiracetam versus phenytoin for seizure prophylaxis in patients with traumatic brain injury:	A meta-analysis (six cohort studies) seizures	1a	There is no superiority of either these two drugs at preventing of seizures based on the point estimate's odds ratio (OR) = 1.1 (95% CI: 0.55–2.20). PHT and LEV showed equal efficacy in prevention of seizures after TBI
A. Shaun Rowe et al. 2014[38,40] Long-term comparison of GOS-E scores in patients treated with phenytoin or levetiracetam for post-traumatic seizure prophylaxis after traumatic brain injury	A prospective, randomized, single-blinded comparative trial patients: 19 Glasgow Outcome Scale–Extended (GOS-E) 6 months, early seizures or late seizures, use of anticonvulsant medication	2a	There was no difference in the GOS-E score assessed $\geq$6 months after injury (5.07 ± 1.69 vs. 5.60 ± 2.07, $P=0.58$). There was no difference in early seizures ($P=0.53$) or late seizures ($P=0.53$). However, the PHT group experienced a higher rate of hospital days with recorded fever (0.20 ± 0.22 vs. 0 ± 0; $P=0.014$). Long-term functional outcome in patients who experienced a TBI was not affected by treatment with PHT or LEV; however, patients treated with PHT had a higher incidence of fever during hospitalization
Khor, D et al. 2018 Compare the incidence of early clinical seizures following TBI, between seizure prophylaxis and a not use seizure prophylaxis following TBI	Prospective observational study patients: 522 incidence of early seizures, defined as those occurring within 7 days of injury	2a	Patients with admission GCS < 9 had an overall early seizure incidence of 7.0%: 4.3% in the prophylaxis group and 14.3% in the no-prophylaxis group ($P=0.062$). Analysis of the subgroup with isolated blunt TBI showed an incidence of early seizures of 3.4% in the prophylaxis group versus 2.4% in the no-prophylaxis group ($P=0.593$). Further analyses of outcomes according to head AIS 3, 4, and 5 showed no significant difference in the seizure rate between the two groups: head AIS 3: 6.1% in the prophylaxis group versus 2.6% in the no-prophylaxis group, $P=0.329$; head AIS 4: 0 versus 2.7%, $P=0.302$; head AIS 5: 8.7 versus 4.0%, $P=0.601$.

Table 2

(*Continued*)

Topic and number of studies	Reference, study topic	Study design, *N*, and outcomes	Level of evidences	Results and conclusion
				Study failed to show any benefit of routine early seizure prophylaxis following blunt TBI
	Fredric M. Pieracci et al. 2011 A cost-minimization analysis of phenytoin versus levetiracetam for early seizure pharmacoprophylaxis after traumatic brain injury	literature review Acute care institution (cost) and patient (charges)	2a	The PHT strategy was superior to the LEV strategy from both the institutional (mean cost per patient $151.24 vs. $411.85, respectively) and patient (mean charge per patient $2,302.58 vs. $3,498.40, respectively) perspectives. Varying both baseline adverse event probabilities and frequency of laboratory testing did not alter the superiority of the PHT strategy From both institutional and patient perspectives, PHT is less expensive than LEV for routine pharmacoprophylaxis of early seizures among traumatic brain injury patients
Glycemic control: two studies	*Hermanides et al. 2018*[45] Comparing intensive with conventional glycemic control in TBI requiring admission to an ICU	Systematic review and meta-analysis (10 RCTs) patients: 1066 ICU and in-hospital mortality, poor neurological outcome, the incidence of hypoglycemia and infective complications	1a	Conventional vs. intensive control: no association with ICU or hospital mortality relative risk (RR) = 0.93 ($P = 0.64$) vs. 1.07 ($P = 0.62$) Risk of a poor neurological outcome higher with conventional control (RR = 1.10 $P = 0.047$). Severe hypoglycemia occurred less frequently with conventional control RR = 0.22 $P = 0.001$) Intensive glucose control significant reduction in the risk of poor neurological outcome, but markedly increased the risk of hypoglycemia
	Meier et al. 2008[44] Blood glucose target of 90–144 mg/dl (5–8 mmol/l) compared to a blood glucose target of 63–117 mg/dl (3.5–6.5 mmol/l)	Retrospective study patients: 228 mortality rate Intracranial pressure (ICP)	2a	In the first week (acute stage), a blood glucose target of 90–144 mg/dl (5–8 mmol/l) was associated with reduced mortality rate and decreased intracranial pressure (ICP) (12 ± 0.1 mmHg versus 14 ± 0.1 mmHg; $P < 0.001$) compared to a blood glucose target of 63–117 mg/dl (3.5–6.5 mmol/l). However, in the second week, the groups appeared to have the reverse outcomes: compared with the (5–8 mmol/l vs. 3.5–6.5 mmol/l) demonstrated a decreased incidence of ICP (15 ± 0.1 mmHg versus 17 ± 0.1 mmHg; $P < 0.001$) and reduced infectious complications. Therefore, slightly higher blood glucose (5–8 mmol/l) seems to provide benefits during the first week while lower blood glucose (3.5–6.5 mmol/l) may be more favorable during the later stages of recovery
Ventilation therapy: two studies and one guideline	*Roberts et al. 2015*[50] Effects of PaCO2 derangements on clinical outcomes after cerebral injury	A systematic review (six studies) mortality and poor neurological outcome	2a	In 13/17 (76%) studies examining hypocapnia, and 7/10 (70%) studies examining hypercapnia; the exposed group (hypercapnia or hypocapnia) was associated with poor clinical outcome. Exposure to hypocapnia and hypercapnia after cerebral injury to be associated with poor clinical outcome
	Warner KJ et al. 2007[51] The impact of prehospital ventilation on outcome after severe traumatic brain injury	A prospective study patients: 492 mortality and poor neurological outcome		Patients with a PaCO2 ranging from 30 to 35 mmHg had the lowest mortality (16.1%), but patients with a PaCO2 more than 45 mmHg had the highest mortality (36.2%), and adjusted OR for mortality of target range compared with hypocapnea was (OR = 0.08; 95% CI: 0.01– 0.44).

				This effect was even greater among patients with isolated TBI (odds ratio, 0.31; 95% CI: 0.10–0.96). Targeted prehospital ventilation is associated with lower mortality after severe TBI
Hyperosmolar therapy: three studies, one guideline, and one review	*Chen et al. 2020*[52] Comparison hypertonic saline versus other intracranial pressure-lowering agents in the management of acute traumatic brain injury	Cochrane Database of Systematic Reviews (Six trials) participant: 287. Death while in-ICU or at 6 months, severe disability, uncontrolled intracranial pressure during treatment	1a	Hypertonic saline vs. mannitol = 41.2% vs. 60% died by the end of stay in the ICU, but hypertonic saline did not reduce all-cause mortality (RR = 0.69, 95% CI: 0.34–1.39). Trial results indicated that both treatments appeared effective compared with baseline ICP, with some additional benefits for hypertonic saline immediate benefits of hypertonic saline are suggested, they do not translate into long-term benefit
	Shi et al. 2020[55] Compare the effects of 3% hypertonic saline solution and 20% mannitol solution on intracranial hypertension	Systematic and meta-analysis (10 articles) patients: 544 (270 hypertonic saline vs. 274 mannitol group) ICP and cerebral perfusion pressure (CPP), onset time, and maintenance time	1b	No significant difference in the decrease of intracranial pressure and the onset time of drug between the 2 groups after intervention (all $P > 0.05$). Statistically significant difference between the hypertonic saline group and the mannitol group in terms of duration of effect in reducing intracranial pressure (95% CI: 0.64–1.05, Z = 8.09, PP = 0.007). Both 3% hypertonic saline and mannitol can effectively reduce intracranial pressure, but 3% hypertonic saline has a more sustained effect on intracranial pressure and can effectively increase cerebral perfusion pressure
	Asehnoune et al. 2017[54] Compared the mortality and outcomes in patients with TBI with ICH treated or not with continuous hyperosmolar therapy (CHT)	Multicenter prospective cohort study patients: 1086 systematic review (eight studies) patients: 1304 risk of survival at day 90, Glasgow Outcome Scale (GOS) at day 90 (GOS 1–3 vs. 4–5)	2a	Patients with ICH, the relative risk of survival at day 90 with CHT was 1.43, $P = 0.05$). The adjusted hazard ratio for survival was 1.74; $P < 0.001$). At day 90, favorable outcomes (Glasgow Outcome Scale 4–5): treated with CHT vs. not treated = 45.2% vs. 35.8% ($P = 0.06$). CHT is associated with a reduction of in-ICU mortality (intervention deaths = (23.6%) vs. control deaths = (31.2%); OR 1.42 $P = 0.03$, I2 = 15%). CHT for the treatment of post-traumatic ICH was associated with improved adjusted 90-day survival
Temperature control: four studies	*Lewis et al. 2020*[60] Effects of intention of reducing body temperature to 35–37.5°C in adults and children admitted to hospital after TBI	Cochrane Database of Systematic Reviews (one RCT) participants: 41. Death or dependency as measured by the Glasgow Outcome Score (GOS), further serious intracranial hemorrhage, extra cranial hemorrhage	1b	We could not be certain whether using paracetamol as a cooling therapy reduced or increased mortality (RR 2.86, 95% CI: 0.32–25.24; we found no studies that assessed physical interventions to reduce body temperature to 35–37.5 °C. We are uncertain of the effects of medicines and other physical cooling treatments to reduce body temperature to 35–37.5 °C, when given to people in-hospital after a traumatic head injury
	Chen et al. 2019[61] Evaluate the risks and benefits of therapeutic hypothermia management in patients with traumatic brain injury	Meta-analysis (23 trials) patients: 2796 6-month mortality, unfavorable functional outcome and pneumonia morbidity	1a	Show significantly more mortality in the therapeutic hypothermia group [risk ratio (RR) 1.26, 95% CI: 1.04–1.53, $P = 0.02$]. Lower mortality in the therapeutic hypothermia group occurred when therapeutic hypothermia was received within 24 h (RR 0.83, 95% CI: 0.71–0.96, = 0.01), The risk of unfavorable functional outcome following therapeutic hypothermia management appeared to be significantly reduced (RR 0.78, 95% CI: 0.67–0.91, $P = 0.001$). The meta-analysis suggested that there was a significant increase in the risk of pneumonia with therapeutic hypothermia management (RR 1.48, 95% CI:

Table 2

(*Continued*)

Topic and number of studies	Reference, study topic	Study design, *N*, and outcomes	Level of evidences	Results and conclusion
				1.11–1.97, $P = 0.007$). Therapeutic hypothermia did not reduce but might increase the mortality rate of patients with traumatic brain injury in some high-quality studies
	Clifton et al. 2010 Assess whether very early induction of hypothermia improves outcome in patients with severe brain injury	Randomized trial participant: 232 (intervention: 119 and control: 113) Glasgow outcome scale score at 6 months	1c	Outcome was poor (severe disability, vegetative state, or death) in 31 of 52 patients in the hypothermia group and 25 of 56 in the normothermia group (relative risk [RR] 1·08, 95% CI: 0·76–1·53; $P = 0·67$). Twelve patients in the hypothermia group died compared with eight in the normothermia group (RR 1·30, 95% CI: 0·58–2·52; $P = 0·52$. This trial did not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe traumatic brain injury
	Cooper et al. 2018[59] Effect of early sustained prophylactic hypothermia on neurologic outcomes in patients with severe TBI	Randomized clinical trial (POLAR-RCT Patients: 511 (intervention: 266 and control: 245). Favorable neurologic outcomes or independent living (Glasgow Outcome Scale–Extended score, 5–8 [scale range, 1–8]	1c	Favorable outcomes (Glasgow Outcome Scale–Extended score, 5–8) at 6 months occurred in 117 patients (48.8%) in the hypothermia group and 111 (49.1%) in the normothermia group (risk difference = 0.4% [95% CI: –9.4– 8.7%]; Relative risk with hypothermia RR = 0.99 [95% CI: 0.82–1.19]; $P = 0.94$). In the hypothermia and normothermia groups, the rates of pneumonia were 55.0 vs. 51.3%, respectively, and rates of increased intracranial bleeding were 18.1 vs. 15.4%, respectively. Among patients with severe traumatic brain injury, early prophylactic hypothermia compared with normothermia did not improve neurologic outcomes at 6 months
Steroids: one studies	*Prasad et al. 2021*[66] Steroids for delayed cerebral edema after traumatic brain injury	Retrospectively analyzed study patients: nine time to clinical deterioration after trauma (either a drop in GCS score or worsening of symptoms), dosage of steroids, duration of steroid treatment, time to clinical and radiological improvement, and Glasgow Outcome Scale score at discharge	3a	The mean interval to steroid administration after trauma = 7 days. The mean duration of steroid prescription = 6.3 days. The mean time to symptom resolution = 3.8 days. Steroids may be beneficial in at least in mild/ moderate head injuries. The timing of steroid usage and dose of steroids are important key aspects that might determine its efficacy in TBI
Barbiturate Coma: two studies	*Roberts et al.2012*[62] Comparison barbiturate vs. no barbiturate or pentobarbital vs. thiopental,	Cochrane Database of Systematic Reviews (seven trials) patients = 341 mortality, disability and raised ICP in people with acute traumatic brain injury	1c	Barbiturates versus no barbiturate, the pooled risk ratio (RR) of death = 1.09 Disability, measured using the Glasgow Outcome Scale the RR with barbiturates = 1.15. UncontrolledICP = (68% versus 83%). Death with pentobarbital versus thiopental = 1.78. Uncontrollable ICP with thiopental RR = 1.64. Barbiturate therapy in patients with acute severe head injury improves outcome, but results in a fall in blood pressure
	Pérez-Bárcena et al. 2008[63] Comparison pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury	Prospective, randomized, cohort study patients: 44 (22 in each group). Refractory ICH in patients with severe TBI, arterial hypotension	2a	Thiopental was more effective than pentobarbital in terms of controlling intracranial pressure (odds ratio = 5.1, $P = 0.027$). No significant differences between the two groups with respect to the incidence of arterial hypotension.

				Thiopental more effective than pentobarbital in controlling intracranial hypertension refractory to first-tier measures.
Decompressive cranioectomy: five studies	*Danfeng Zhang et al. 2017*[69] Prognostic value of decompressive craniectomy (DC) in patients with traumatic intracranial hypertension compared with medical therapies	Systematic review and meta-analysis (10 studies) Overall mortality, ICP reduction, length of hospitalization (LOH) and length of ICU stay (LO-ICU), complications	1b	Compared with medical therapies, DC could significantly reduce mortality rate [risk ratio (RR) = 0.59; $P < 0.001$), lower intracranial pressure (ICP) [mean difference (MD), − 2.12 mmHg; $P < 0.001$). Decrease the length of ICU stay (MD, − 4.63 days; $P < 0.001$). And hospital stay (MD, − 14.39 days; $P = 0.02$), but increase complications rate (RR, 1.94; $P < 0.001$). DC effectively lower ICP, reduce mortality rate but increase complications rate
	Sahuquillo et al. 2019[68] Decompressive craniectomy for the treatment of high intracranial pressure in closed traumatic brain injury	Cochrane Database of Systematic Reviews (three trials) participants: 590 mortality, neurological outcome at 6 or 12 months, significant reduction of ICP within 48 h, adverse events, including infections, complications	1a	Pooled results for risk of death at 6 months slightly reduced with DC RR = 0.66, ICP reduction, pooled results for DC was superior to standard care for reducing ICP within 48 h (MD − 4.66 mmHg), DC holds promise of reduced mortality, but the effects of long-term neurological outcome remain controversial
	Schur S et al. 2020[70] Compared small flaps and large flap effectiveness decompressive craniectomy refractory increased intracranial pressure	A retrospective study patients: 30 ICP control, neurologic outcome	2a	Postoperative ICP was significantly lower for the large craniectomy flap (13.3 mmHg; 99% (CI: 12.7–13.8) versus 16.9 mmHg; 99% (CI: 16.5–17.2), ($P = 0.01$), and this difference was maintained for 96 h postoperatively. Better ICP control was achieved with large decompressive craniectomy (ratio > 65%)
	Sedney et al. 2014[71] The effect of craniectomy size on mortality, outcome, and complications after decompressive craniectomy at a rural trauma center	Retrospective study patient: 20 Mortality, neurological outcome	2a	Significant relationship between increasing craniectomy size and decreased mortality, and decompressive craniectomy with an anteroposterior (AP) diameter of <10 cm was associated with 100% mortality ($P = 0.0323$), but that the size was not otherwise associated with improved outcome or increased complications
	Cornelius et al. 2018[28] Compared the decompressive craniectomy and medical care	Multicenter randomized trial Patents: 408 death, vegetative state, disability, good recovery	1c	Compared the decompressive craniectomy and medical care found that, death (26.9 versus 48.9%), vegetative state (8.5 versus 2.1%), disability (21.9 vs. 14.4%), and good recovery (4.0 Versus 6.9%), but had a higher rate of adverse events (16.3 vs. 9.2%, $P = 0.03$) respectively. Decompressive craniectomy lower mortality and higher rates of vegetative state, and lower severe disability than medical care

Corticosteroids

Brain edema is a common occurrence after TBI and is attributed to several inflammatory mediators, which play a significant role in the pathogenesis[64]. The vasogenic type is characterized by increased blood brain barrier permeability and extracellular water accumulation, while the cytotoxic edema is marked by intracellular water accumulation due to substrate and energy failure, leading to cell death. Anti-inflammatory agents and steroids hypothetically reduce cerebral edema and improve functional outcomes[65]. Retrospective analysis of studies has revealed that steroids may be beneficial in vasogenic brain edema, especially in mild/moderate head injuries. The efficacy of steroid usage in TBI is determined by the timing and dose of administration[66] (3a). The use of steroids for managing brain edema following TBI lacks conclusive evidence, but we suggest their use be considered in cases of delayed brain edema after TBI (level III).

Decompressive craniectomy (DC)

If standard medical interventions fail to control ICP, decompressive craniectomy (DC) may be considered. DC involves the surgical removal of a portion of the skull to alleviate pressure on the brain[35]. A multicenter randomized trial consisting of 408 patients with TBI and refractory elevated ICP (>25 mmHg) compared the effects of DC and medical care. Results showed that DC resulted in lower rates of death (26.9 vs. 48.9%), vegetative state (8.5 vs. 2.1%), and severe disability (21.9 vs. 14.4%), but higher rates of adverse events (16.3 vs. 9.2%). This study concluded that DC lowers mortality and increases the rate of vegetative state while reducing severe disability compared to medical care[67] (1c).

A Cochrane Database of Systematic Reviews of three trials involving 590 participants examined DC combined with standard care and found that the risk of death at 6 months was reduced with DC (RR = 0.66, 95% CI: 0.43–1.01) and unfavorable outcomes at six months (RR = 1.06, 95% CI: 0.69–1.63). The use of DC shows promise in reducing mortality rates, but the long-term effects on neurological outcomes remain controversial[68] (1b). A systematic review and meta-analysis of 10 studies compared DC with medical therapies and found that DC significantly reduced mortality rates (RR = 0.59 95% CI: 0.47–0.74), lowered ICP (mean difference (MD) = – 2.12 mmHg; 95% CI: – 2.81– – 1.43), and decreased the length of ICU stay (MD = – 4.63 days; 95% CI: – 6.62– – 2.65). However, this approach also increased complication rates (RR = 1.94; 95% CI: 1.31–2.87). The study concluded that while DC effectively lowers ICP and reduces mortality rates, it also increases complications rates[69] (1a).

A retrospective study involving 30 patients with TBI and refractory increased ICP compared small flap and large flap DC. Results demonstrated that postoperative ICP was significantly lower for those who underwent a large craniectomy flap (13.3 mmHg; (99% CI: 12.7–13.8) versus 16.9 mmHg; 99% CI: 16.5–17.2), and this difference was maintained for 96 h postoperatively. The study concluded that better ICP control was achieved with a large DC (ratio $>65\%$)[70] (2a). Another retrospective study involving 20 patients reported a significant relationship between increasing craniectomy size and decreased mortality. DC with an anteroposterior (AP) diameter of less than 10 cm was associated with 100% mortality, but size was not otherwise associated with improved outcomes or increased complications[71] (2a). Based on the available evidence, we recommend the use of large flap DC for severe ICP ($\geq$ 25 mmHg) refractory to conventional medical treatment, utilizing the most appropriate surgical techniques (level II A).

The examined reviews comprise top-quality randomized controlled trials with a considerable number of participants and meta-analyses, primarily disseminated in recent years. This aspect of the review showcases its strength. However, certain limitations such as the restricted publication year and language, present some constraints. Furthermore, the review only covers the management of TBI with ICP in the ICU, and the overall management remains unexplored.

Conclusion

Despite invasive ICP monitoring remains the cornerstone of IH treatment, physical examination findings [pupillary dilation, motor posturing (GCS motor score ≤ 3), and decreased level of consciousness (GCS ≤ 8)] and noninvasive ICP monitoring has correlation with increased ICP, and used as diagnosis and monitoring of increased ICP in low-resource settings. US assessment of ONSD is one of a simple noninvasive, high-reliable modality to detect raised ICP, monitoring, and helpful in the early initiation of treatment of elevated ICP in neuro-trauma patients at low-resources settings, but no agreed threshold exists, and the method's accuracy can be influenced by provider expertise.

TBI with increased ICP should be managed in an algorithmic fashion using a prophylactic measures maneuvers: maintain adequate sedation and analgesia, early seizure prophylaxis, maintain optimum angle of the HBE and early aggressive control of increased temperature are effective management to reduce increased ICP. Furthermore, acute intervention should be maintained by using of hyperosmolar therapy (mannitol or hypertonic saline), and temporary mild hyperventilation, but prolonged prophylactic hyperventilation during the first 24 h after injury should be avoided. Additionally, consider high-dose thiopental therapy and DC to control severs elevated ICP refractory to standard medical treatment to minimize secondary brain injury and improve neurological outcome (Fig. 2).

Ethical approval

This review has been exempted by the Institutional Review Board (IRB) of Dilla University College of Medicine and Health Science from requiring ethical approval.

Consent

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Author contribution

All authors have made substantial contributions to conception, and design, and participated in the critical review, and editing of the manuscript drafts for scientific quality and depth.

Conflicts of interests disclosure

Nothing to declare.

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