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REVIEW

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Beta-blockers in adults with acute traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Traumatic brain injury (TBI) remains a leading cause of death and disability worldwide. Beyond the primary insult, excessive sympathetic activation contributes to secondary brain injury and poor outcomes. Beta-blockers may attenuate this hyperadrenergic surge and provide neuroprotective benefits, but their efficacy in improving long-term functional recovery remains uncertain.

Methods We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating beta-blockers in adults with acute TBI. We searched MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov for RCTs comparing beta-blockers with placebo, usual care, or non-adrenergic comparators. Our primary outcome was long-term functional outcome, assessed with the Glasgow Outcome Scale (GOS) or its Extended version (GOS-E). Secondary outcomes included mortality, intensive care unit (ICU) and hospital length of stay, duration of mechanical ventilation, and adverse events.

Results Seven RCTs ($n=559$) met inclusion; six ($n=445$) contributed data to meta-analyses. Only two trials ($n=259$) reported functional outcomes. Beta-blockers did not significantly reduce the risk of unfavorable neurological outcome (RR 0.81; 95% CI 0.57–1.15; very low certainty). In contrast, beta-blocker therapy was associated with a reduction in mortality (RR 0.57; 95% CI 0.39–0.82; 6 trials, $n=440$; low certainty) and a shorter duration of mechanical ventilation (–1.58 days; 95% CI –2.91 to –0.26; 2 trials, $n=85$; low certainty). No effect was observed on ICU or hospital stay. Adverse event reporting was sparse, but no consistent safety concerns were identified.

Conclusions In adults with acute TBI, beta-blockers did not decrease unfavorable long-term neurological outcomes but were associated with lower mortality and shorter duration of mechanical ventilation. Given the small number of trials and very low certainty of evidence, definitive conclusions cannot be drawn, and routine use cannot be recommended. A large, well-designed RCT is needed to establish the efficacy and safety of beta-blockers in this population.

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Keywords Traumatic brain injury, Beta-blockers, Sympathetic hyperactivity, Meta-analysis, Randomized controlled trials, Glasgow Outcome Scale, Mortality, Mechanical ventilation

Introduction

Traumatic brain injury (TBI) is a major cause of mortality and long-term disability globally [1]. Beyond the initial insult, secondary brain injury plays a critical role in patients' outcomes. Despite advances in acute care, effective interventions to mitigate secondary damage remain limited. In moderate-to-severe TBI, excessive sympathetic activation represents a potential mechanism contributing to secondary brain injury [2]. This phenomenon appears to result from a disconnection syndrome, in which the loss of inhibitory control over excitatory autonomic centers leads to sympathetic overactivity [3]. Clinically, this excessive activation can manifest as episodes of tachycardia, arterial hypertension, tachypnea and hyperthermia, which are associated with unfavorable outcomes in acute brain injury [4, 5]. Prolonged hypersympathetic tone may also suppress the immune system [6] and is closely related to intracranial pressure [7].

The management of sympathetic hyperactivity has gained increasing attention in recent years, but considerable heterogeneity in current treatment protocols exists which reflect a lack of high-quality data to guide evidence informed decision-making [8, 9]. One potential strategy to reduce the frequency and severity of sympathetic hyperactivity are beta-blockers. By attenuating the adrenergic response and lowering the resting metabolic rate, beta-blockers may provide both neuroprotective and cardioprotective benefits, explaining their potential effects in patients with TBI [10, 11]. Lipophilic non-selective beta-blockers are theoretically more appealing due to their ability to cross the blood–brain barrier and exert central effects [12]. Their use has been associated with improved paroxysm control and decreased mortality compared to hydrophilic agents [13]. Despite these promising findings, there is insufficient evidence to recommend the routine use of beta-blockers in acute TBI. Recent systematic reviews primarily included observational studies and did not evaluate long-term functional outcomes as a primary outcome [14–16]. To clarify this setting, we conducted a systematic review and meta-analysis of randomized controlled trials to evaluate whether the use of beta-blockers improves long-term neurological outcomes in hospitalized adult patients with acute TBI.

Methods

Study design

Our study was conducted following the recommendations of the Cochrane Handbook for Systematic Reviews and Meta Analyses [17]. The protocol is registered in PROSPERO (CRD42024565361). We reported our findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) recommendations [18].

Eligibility criteria

We included randomized controlled trials comparing the effect of beta-blockers in patients with acute TBI to placebo, any control groups (without alpha- or beta-adrenergic action), or standard of care. Our study population included hospitalized adult patients (defined as individuals aged 18 years or older for at least 80% of participants) with acute TBI of any severity. To be eligible, trials must have evaluated the administration of beta-blockers initiated within two weeks post-TBI and assessed at least one of our outcomes of interest. All types and routes of administration were included. We applied no date or language restrictions.

Outcomes

Our primary outcome was long term neurological function assessed using the Glasgow Outcome Scale (GOS) or its extended version (GOS-E) [19, 20]. The GOS-E scale is an 8-point ordinal scale ranging from 1 (death) to 8 (upper good recovery) with intermediate levels including neurovegetative state, lower and upper severe disability, lower and upper moderate disability, and lower good recovery. We dichotomized the outcome into "unfavorable" (GOS 1–3; GOS-E 1–4) and "favorable" (GOS 4–5; GOS-E 5–8) neurological outcomes [21, 22]. Secondary outcomes included mortality, intensive care unit (ICU) and hospital length of stay, and duration of mechanical ventilation. Incidence of adverse events (bradycardia, hypotension, heart failure, bronchospasm, kidney injury) were also assessed.

Search strategy

We searched MEDLINE (Ovid), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and Clinical Trials.gov database

from their inception to June 27th, 2024. The search strategy was developed with an information specialist and validated according to the Peer Review of Electronic Search Strategies (PRESS) 2015 guidelines [23]. The search strategy is presented in Appendix 1.

Trial selection and data extraction

Two reviewers (NB, THT) independently screened titles, abstracts, and full publications for eligibility. Three reviewers (MB, NB, THT) extracted data, with disagreements resolved by another reviewer (AFT). Authors were contacted for missing information. Extracted trial characteristics included author, year, duration, country, sample size. Participant data included demographics, TBI severity, clinical data (e.g., admission GCS), type of injury, ICU and hospital length of stay, and adverse events. Intervention details included drug name, dosing, timing, comparator and duration. Outcome data (GOS/GOS-E, mortality, follow-up duration) and trial methodology were recorded. Data from diagrams or graphs were extracted using WebPlotDigitizer v4.1 [24].

Risk of bias assessment

Three reviewers (MB, NB, THT) independently assessed the risk of bias of the included trials using the Cochrane RoB 2 tool [25]. This tool consists of five domains representing potential sources of bias, which reviewers categorized as "high", "low" or "some concerns". For each trial, we assessed the overall risk of bias based on the worst category obtained across all domains. Another reviewer was consulted in case of disagreement (AFT).

Statistical analysis plan

For continuous data, we extracted means and standard deviations, while for dichotomous data, we recorded event counts and total participants per group. We converted medians and ranges to means and standard deviations using standardized equations [26]. We conducted our analyses using Review Manager, version 8.11.0 (RevMan web, The Cochrane Collaboration, Oxford, United Kingdom) with the Der Simonian & Laird random effects models and the inverse variance method. Pooled continuous data were expressed as mean differences (MD), and dichotomous data as risk ratios (RR) with 95% confidence intervals (CI). Heterogeneity was assessed with the I^2 statistic; we considered values > 50% as representing substantial [27]. We performed prespecified subgroup analyses to test the robustness of our findings and explore potential sources of heterogeneity, including the lipophilicity of beta-blockers (high vs moderate/low), TBI severity (GCS < 13 vs. ≤ 8 vs ≥ 9), risk of bias (low vs. high/some concerns), duration of intervention (≤ 48 h vs > 48 h), or cointervention vs no cointervention.

To assess whether the accumulated evidence was sufficient to support firm conclusions, we performed a trial sequential analysis (TSA) for the primary outcome using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) [28]. The required information size was determined based on the event rates, anticipated effect size, and heterogeneity observed in the meta-analysis. Cumulative Z-scores were calculated according to the O'Brien–Fleming alpha-spending function. All analyses were two-sided, with a 5% significance level and 80% statistical power.

Strength of evidence

We evaluated the strength of evidence for each outcome according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group statement [29]. The GRADE approach involved grading the quality of the evidence on a continuum from high, moderate, low, or very low for each outcome based on a structured approach. This grading was performed in duplicate independently by two reviewers (NB and THT).

Results

Literature research

Our initial search identified 3,567 citations, of which 477 were duplicates and removed prior to title and abstract screening. After excluding 3,090 records that did not meet the eligibility criteria and screening 35 full-text article, seven randomized controlled trials [30–36] ($n = 559$) were included. Of the seven randomized controlled trials included in the systematic review, data from six trials [31–36] ($n = 445$) could be pooled in the meta-analysis; quantitative data from one trial were not reported [30]. All trials except for one [31] were published in peer-reviewed journals. The characteristics of included trials are detailed in Table 1.

Characteristics of trials

All trials were single-center trials except one [30]. Three trials were conducted in Egypt [31, 35, 36], two in North America [33, 34], one in Europe [30] and one in Iran [32]. Patient follow-up varied across trials: Four trials [30, 34–36] assessed outcomes only during hospitalization, while others [31–33] included long-term follow-ups ranging from 6 to 12 months. The trials also differed in TBI severity: three [31, 33, 36] focused on severe TBI (GCS ≤ 8), two [32, 34] on moderate to severe TBI (GCS ≤ 12), one [35]on mild to moderate TBI (GCS > 10) and one [30] included all severities. Propranolol, a highly lipophilic beta-blocker, was evaluated in five trials [32–36], whereas metoprolol, a moderately lipophilic beta-blocker, was assessed in one trial [31], and atenolol in another [30].

Table 1 Characteristics of included trials

Study ID	Age. Mean (± SD)	TBI Severity	Intervention protocol	N Intervention	Control protocol	N Control	Co-intervention (associated with B-Blockers)	Surgical Management	Outcomes reported	Follow-up period
Cruickshank et al. 1987 [30]	35.8 (22.3)	All severities	Atenolol 10 mg IV q 6 h for 3 days followed by 100 mg PO × 4/days	56	Normal saline or placebo pills matching intervention	58	Normal saline/6 h IV for 7 days	Not reported	Mortality (narrative) Creatine Kinase-MB levels	In hospital Long term follow-up (1 year) not completed
Khaber et al. 2010 [31]	38.4 (12.2)	GCS 4–8	Metoprolol 25 mg q 6 h ad 100 mg/6 h for 24 h to target HR < 100	30	Placebo (not described)	30	None	Not reported	Mechanical ventilation duration ICU and Hospital lengths of stay In-hospital mortality GOS	1 month
Khalili et al. 2020 [32]	38 (18)	GCS ≤ 12	Propranolol 20 mg PO twice a day for 10 days	102	No placebo	120	None	- Craniotomy or decompressive craniectomy in 36.5% of patients - extracranial emergency surgeries excluded	In-hospital mortality ICU and Hospital lengths of stay GOS-E at discharge GOS-E at 6 months Adverse events	6 months
Mansour et al. 2023 [35]	43.6 (11.4)	GCS > 10	Propranolol 1 mg IV q 6 h for 48 h	20	Normal saline IV/6 h for 48 h	20	None	Mixed population including postoperative trauma patients; type and timing of surgery not reported	ICU and Hospital lengths of stay for patients staying ≤ 14 days Mortality	Duration of hospitalization
Megahed et al. 2017 [36]	31.1 (9.7)	GCS ≤ 8	Propranolol 40 mg twice a day PO for 7 days	25	No placebo	25	Clonidine 150mcg PO twice a day	Patients with craniotomy or craniectomy were excluded	Norepinephrine levels Coma-free days Ventilator-free days ICU length of stay In-hospital mortality Vital signs	Duration of hospitalization

Table 1 (continued)

Study ID	Age. Mean (± SD)	TBI Severity	Intervention protocol	N Intervention	Control protocol	N Control	Co-intervention (associated with B-Blockers)	Surgical Management	Outcomes reported	Follow-up period
Nordness et al. 2023 [33]	27.32 (11.5)	GCS < 8	Propranolol 1 mg IVq 6 h for 7 days	21	Normal saline IV/6 h for 7 days	26	Clonidine 0.1 mg PO for 7 days Matching placebo	Patients requiring craniotomy were excluded	Ventilator-free days Change in plasma and urine catecholamine Coma-free days ICU and Hospital lengths of stay In-hospital agitation In-hospital mortality Functional status at discharge GOS-E at 3 and 12 months Adverse events	12 months
Schroeppel et al. 2019 [34]	51.3 (20.1)	GCS ≤ 12	Propranolol 20 mg PO q 12 h and 200 mg PO/12 h to target HR between 60–100 for 14 days	13	No placebo	13	None	Surgical evacuation of hemorrhage in 44% of patients; craniectomy in 32% (most common procedure)	Urinary catecholamines Mortality ICU and Hospital lengths of stay Mechanical ventilation duration	Duration of hospitalization

ICU intensive care unit, *GOS-E* Glasgow outcome scale extended, *IV* intravenous, *PO* Per Os, *GCS* Glasgow Coma Scale

Four trials [31, 32, 34, 35] used the enteral route and two trials [33, 35] administered treatment intravenously and one intravenously followed by the enteral route [30]. Treatment durations ranged from 1 to 14 days, with each trial using a distinct duration. Additionally, two trials [33, 36] used clonidine as a co-intervention [33, 36]. In all trials, the treatment was initiated within 24 to 72 h after the injury. Details of beta-blocker interventions, including type, dose, route, timing of initiation and duration, are provided in Supplemental Table S1.

Risk of bias

The risk of bias assessment of trials is provided in Table 2. Most trials presented at least some concerns in one or more domains, primarily due to unclear randomization processes and potential deviations from the intended interventions [30–32, 35, 36]. Three studies [30, 32, 36] were judged to have a high overall risk of bias, mainly related to missing outcome data and measurement of the outcome. Two trials [33, 34] were considered at low risk of bias across all domains. Details on the risk of bias for secondary outcomes are provided in Supplemental Fig. S1, Fig. 1.

Primary outcome

Two RCTs [32, 33] ($n=259$) contributed to the primary outcome analysis. One was a single-center trial evaluating propranolol in combination with clonidine, was terminated early for futility, and assessed the GOS-E at three months [33]. The other trial evaluated the use of propranolol alone and assessed the GOS-E at six months [32]. Using random-effects models, an unfavorable neurological outcome occurred in 24.3% of patients (28/115) in the beta-blockers group compared to 33.3% (48/144) in the control group (RR, 0.81; 95% CI [0.57 to 1.15], $I^2=30\%$) (very low certainty) (Fig. 2, Table 3). No subgroups analyses could be performed due to the small number of trials. With an estimated relative risk reduction of 20% of unfavorable neurological outcome, the TSA showed that the required information size to draw definitive conclusions would be 1,355 patients, suggesting that the pooled analysis of available trials is likely prone to a type II error (Fig. S2).

Secondary outcomes

Mortality

Mortality data were available for six trials ($n=440$) [31–36]. The use of beta-blockers was associated with a decreased mortality (RR 0.57; 95% CI [0.39 to 0.82], $I^2=0\%$) (Fig. 3, Fig. S3) and results were consistent across all subgroups (Fig. S4). One trial [30] reported mortality only qualitatively, stating that "there was no significant drug effect on in-hospital mortality, which was directly related to the severity of the head injury". The evidence was graded as low due to indirectness and the risk of bias (Table 3).

Intensive care unit and hospital length of stay

There was no significant difference observed in lengths of stay between the beta-blocker and control groups. For ICU length of stay, the mean difference (MD) was 0.81 days longer in the beta-blocker group (95% CI

Table 2 Risk of bias for the main outcome reported by trials

Study ID	Experimental	Comparator	Outcome	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Cruickshank et al 1987[30]	Atenolol	Placebo	Mortality (narrative)	!	+	-	+	!	-
Khalili et al. 2020[32]	Propranolol	Standard of care	GOS-E	!	!	+	-	+	-
Khaber et al. 2020[31]	Metoprolol	Placebo	Mortality	!	!	+	+	+	!
Mansour et al. 2003[35]	Propranolol	Placebo	Mortality	+	+	+	+	!	!
Megahed et al. 2017[36]	Propranolol (+Clonidine)	Standard of care	Mortality	!	!	-	-	+	-
Nordness et al. 2023[33]	Propranolol (+Clonidine)	Placebo	GOS-E	+	+	+	+	+	+
Schroeppel et al. 2019[34]	Propranolol	Standard of care	Mortality	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

GOS-E Glasgow Outcome Scale-Extended

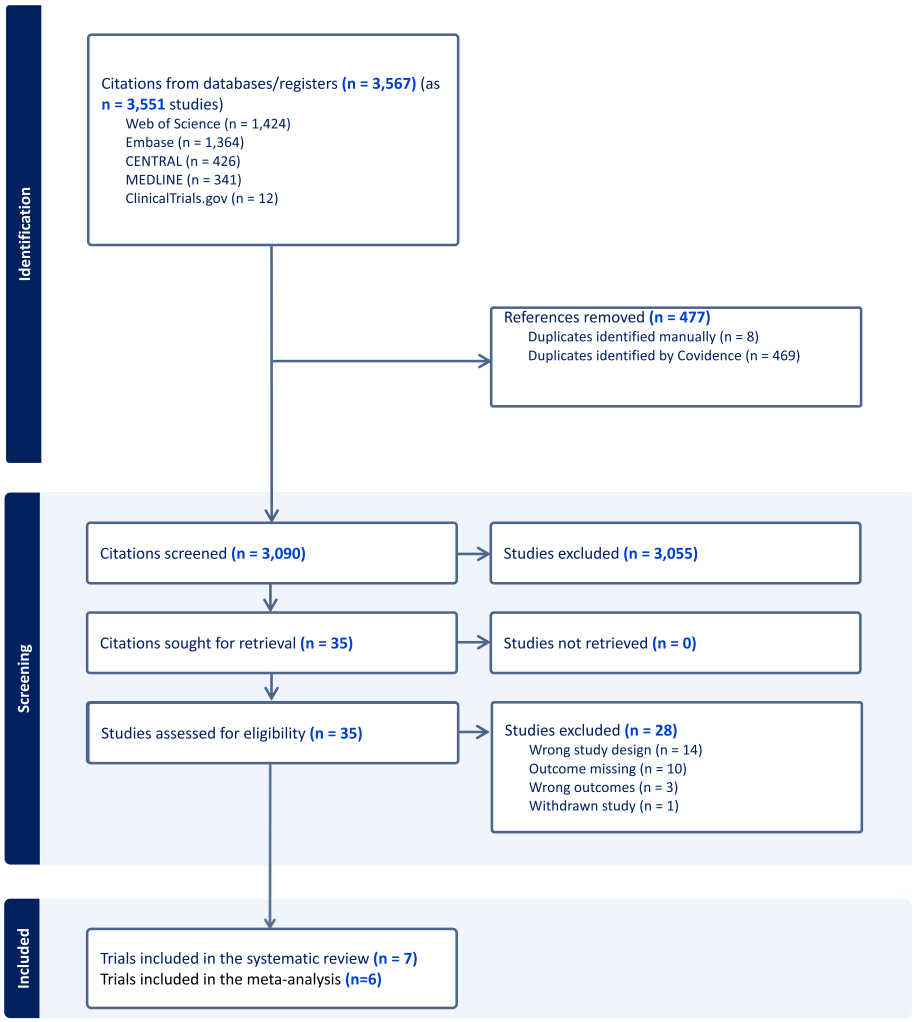

Fig. 1 Flowchart of included trials

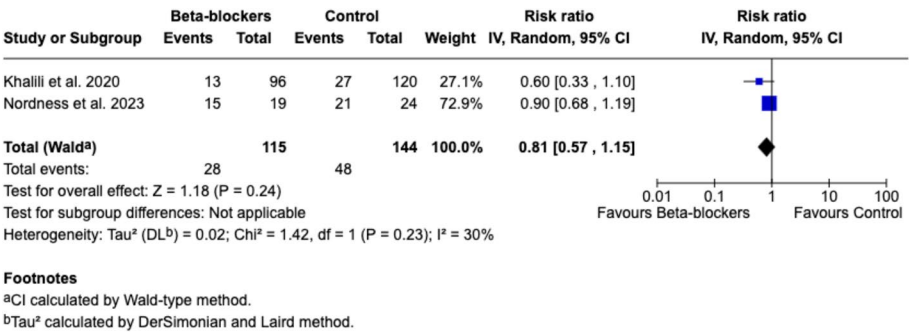

Fig. 2 Meta-analysis of unfavorable neurological outcome. *Legend:* Glasgow Outcome Scale–Extended (GOS-E) at 6 months for Khalili et al., and at 3 months for Nordness et al.

−1.74 to 3.35; five trials [30–33, 35] $n = 401$, $I^2 = 45\%$). For hospital length of stay, the MD was 1.4 days longer in the beta-blocker group (95% CI −5.98 to 8.74; four trials [31–34], $n = 351$, $I^2 = 48\%$) (Fig. 3, Figs. S5 and S6). The results were consistent across all subgroups (Figs. S7 and S8). The certainty of evidence was graded as low due to inconsistencies between trials and imprecision (Table 3).

Table 3 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Beta-blockers				
Unfavorable neurological outcome assessed with GOS-E	333 per 1000	**270 per 1000** (190 to 383)	**RR 0.81** (0.57 to 1.15)	259 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of beta-blockers on unfavorable neurological outcome
In-Hospital Mortality	270 per 1000	**154 per 1000** (105 to 222)	**RR 0.57** (0.39 to 0.82)	440 (6 RCTs)	⨁⨁◯◯ Low[b,d]	Beta-blockers may result in a reduction in mortality
ICU length of stay (days)	The mean ICU length of stay (All studies) was **12.5** days	MD **0.81 days higher** (1.74 lower to 3.35 higher)	-	401 (5 RCTs)	⨁⨁◯◯ Low[b,c]	
Hospital length of stay (days)	The mean hospital length of stay was **15.7** days	MD **1.4 days higher** (5.93 lower to 8.74 higher)	-	351 (4 RCTs)	⨁⨁◯◯ Low[b,c]	
Duration of mechanical ventilation (days)	The mean duration of mechanical ventilation was **8.1** days	MD **1.58 days lower** (2.91 lower to 0.26 lower)	-	85 (2 RCTs)	⨁◯◯◯ Very low[b,c,d]	Beta-blockers may reduce/have little to no effect on duration of mechanical ventilation, but the evidence is very uncertain

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI confidence interval, *MD* mean difference, *RR* risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

[a] The certainty of evidence was downgraded due to concerns regarding risk of bias. Specifically, approximately 50% of the included studies did not blind outcome assessors, which increases the risk of detection bias in the measurement of the primary outcome

[b] The certainty of evidence was downgraded due to indirectness. There was substantial variability in the timing of outcome assessment (GOS or GOS-E) and administration of betablockers across studies, which limits the comparability of the results and may affect their applicability to clinical decision-making

[c] The certainty of evidence was downgraded due to imprecision. The estimated effect was associated with a wide 95% confidence interval, indicating uncertainty about the magnitude and direction of the effect

[d] The certainty of evidence was downgraded due to risk of bias related to the randomization process. Several included trials had inadequate or unclear methods of random sequence generation and/or allocation concealment, raising concerns about selection bias

Duration of mechanical ventilation

The duration of mechanical ventilation was available from two trials [31, 34] ($n=85$). Beta-blockers were associated with a reduced duration of mechanical ventilation, with patients requiring ventilation for 1.58 days less than those in the control group (95% CI [−2.91 to −0.26], 2 trials, $n=85$, $I^2=0\%$) (Fig. 3, Fig. S9). We did not perform subgroup analyses due to the number of trials. The evidence was graded as low because of imprecision related to small sample sizes and a risk of bias in trial randomization (Table 3).

Adverse events

We predefined adverse events of interest as cardiovascular (bradycardia, hypotension, heart failure) bronchospasm, and acute kidney injury, based on the known safety profile of beta-blockers. Three trials reported adverse events [32–34]. One trial reported no cardiac complications or other serious adverse events [33] Another found no renal, cardiac, or hypotensive events attributed to the study drug [34]. One trial reported three cases of persistent bradycardia that led to discontinuation of the intervention [32]. These patients were enrolled in the study but discontinued beta-blocker therapy due to bradycardia. None of them experienced clinically significant complications, and all were reported to achieve a good functional recovery at discharge. No trial reported bronchospasm. Other trials did not report any adverse events.

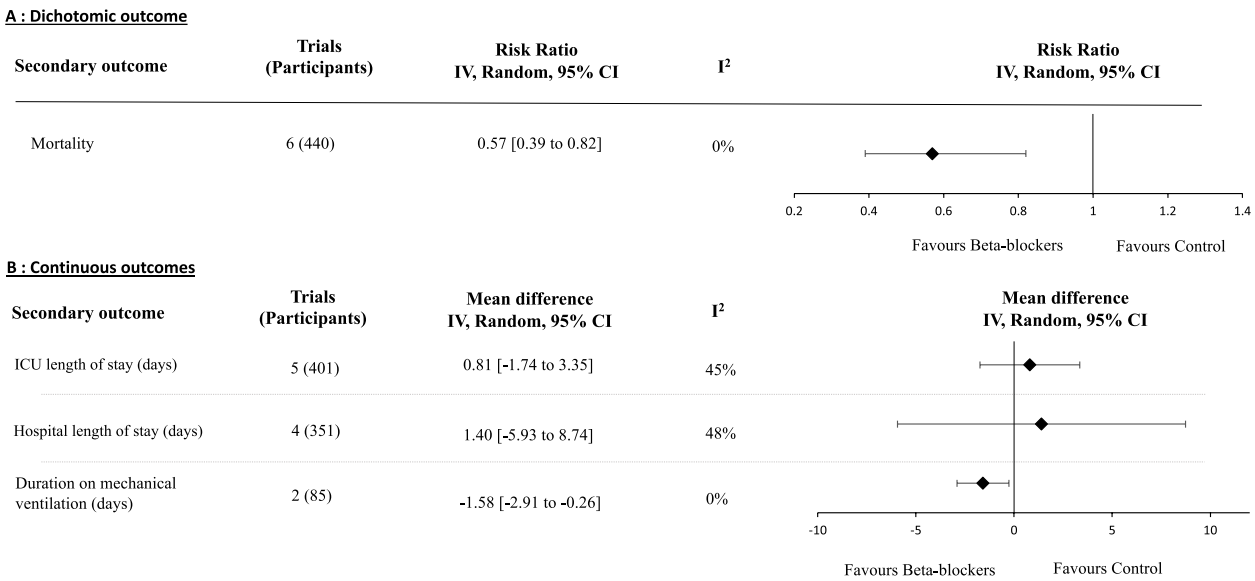

Fig. 3 Secondary outcomes. *Legend:* ICU = intensive care unit; IV = inverse variance

Discussion

In our systematic review and meta-analysis, we found no significant effect of beta-blockers on long-term neurological function. Nevertheless, beta-blockers were associated with a significant reduction in mortality and duration of mechanical ventilation. No difference was observed in ICU or hospital length of stay. The incidence of reported adverse events was low. The certainty of evidence was very low for neurologic functional outcomes and the duration of mechanical ventilation, and low for other outcomes. These findings highlight the absence of high-quality trials assessing the impact of beta-blocker therapy on long-term neurological outcomes following acute TBI.

Our findings differ from those of two recent systematic reviews and meta-analyses, suggesting that beta-blockers were associated with improved neurologic functional outcomes [15, 37]. A large propensity-matched cohort study also reported a significant association between beta-blockers and improved long-term functional outcomes in patients with severe TBI [38]. This discrepancy is likely multifactorial. First, prior reviews included observational studies, which are inherently subject to confounding, even when using propensity-score matching, which cannot fully account for unmeasured variables. Second, these reviews were conducted prior to the publication of a recent randomized controlled trial [33].

In our study, we observed a reduction in hospital mortality consistent with findings from previous reviews [14, 15, 37, 39]. This finding is also consistent with evidence from other acute neurological conditions, such as subarachnoid haemorrhage (SAH), where beta-blocker therapy has been associated with improved survival [40]. Nevertheless, the mechanisms underlying this potential mortality benefit remain unclear. In the context of TBI, a neuroprotective effect is often hypothesised, whereas in SAH, the benefit might be partly explained by the mitigation of cardiac complications frequently observed in this population. Similarly, in broader critically ill populations [41], and in patients with sepsis [42, 43] beta-blockers have also been associated with reduced mortality, although conflicting results have been reported, with some suggesting an increased risk of complications [44, 45]. These data collectively underscore the need for caution, as the effect may be context-dependent and mediated through distinct mechanisms, particularly in patients with TBI.

One of the main barriers of using beta-blockers in the acute phase TBI is safety concerns. The primary potential adverse effects include hypotension and bradycardia, with hypotension being particularly concerning due to its association with increased morbidity and mortality in TBI patients [46]. A prospective study reported that early administration of low-dose propranolol after TBI did not increase hypotensive events, although bradycardia was more frequent in the control group [47]. Among the randomized controlled trials included in our systematic review, only one reported discontinuation of beta-blocker therapy in three patients due to persistent bradycardia, without severe clinical consequences [32]. Furthermore, a recent systematic review and meta-analysis found no increased risk of cardiopulmonary adverse effects associated with the use of beta-blocker following TBI [15].

Our findings should be interpreted with caution given the incomplete and inconsistent reporting of clinically relevant safety outcomes across trials. Only a few trials systematically monitored adverse events. Although no major safety signals were identified, this lack of standardized and comprehensive safety reporting limits the ability to draw firm conclusions regarding the tolerability of beta-blockers after TBI. On the other hand, all trials in our review administered beta-blockers prophylactically, aiming to limit the early sympathetic surge following TBI. However, it remains unclear whether a prophylactic approach is optimal. A strategy focused on treating patients with clinical evidence of sympathetic hyperactivity might improve the risk–benefit balance and warrants further investigation. Similarly, although paroxysmal sympathetic hyperactivity has been proposed as one possible manifestation of sustained sympathetic overactivity following TBI [2, 48], none of the included trials were specifically designed to target it. Only one trial [33] prospectively collected Clinical Features Scale (CFS) scores [49], a component of the Paroxysmal Sympathetic Hyperactivity-Assessment Measure (PSH-AM) [49, 50]. Whether early beta-blocker therapy can reduce the risk or severity of paroxysmal sympathetic hyperactivity remains speculative and requires dedicated studies using standardized PSH definitions.

Our systematic review has several strengths. It provides the highest level of evidence available for evaluating the effects of beta-blockers in TBI. We developed a highly sensitive search strategy across multiple databases and trial registries to ensure the identification of all trials. Additionally, we strictly adhered to standardized methodological guidelines, ensuring a rigorous systematic review and meta-analysis. All clinically relevant and safety outcomes that could influence the clinical decision to use beta-blockers were carefully considered, providing a broad and nuanced perspective on their potential benefits and risks.

Our study also has limitations. First, despite the high global burden of TBI, with millions of cases annually, the total number of patients randomized in clinical trials evaluating beta-blockers after TBI remains extremely limited. Second, our meta-analysis of the primary outcome relied on data from only two small RCTs [32, 33], which limited statistical power. These trials also differed in design: one trial evaluated propranolol in combination with an α2-agonist [33], while the other assessed propranolol monotherapy [32], with functional outcomes measured at different follow-up time points. This methodological heterogeneity, combined with the limited sample size, resulted in a very low certainty of evidence and limits the robustness of our findings, underscoring the need for a large, well-designed randomized trial to properly address this question. Consistent with this, our TSA confirmed that the current cumulative evidence remains below the required information size to draw firm conclusions. Third, key questions remain regarding the optimal type, timing, dosage, administration route, and duration of beta-blocker therapy after TBI. The trials included in our review varied widely across these parameters, with some using lipophilic agents such as propranolol or metoprolol, others using hydrophilic agents such as atenolol, and with treatment durations ranging from a few days to two weeks. Such differences in design makes it difficult to determine whether the observed signals of benefit are drug-specific, dose-dependent, or related to treatment strategy (e.g., prophylactic versus targeted to sympathetic hyperactivity). Subgroup analyses can help assess whether these differences explain the direction of effect. However, we were unable to perform all planned subgroup analyses due to limited data availability, which prevented us from adequately exploring potential variations in treatment effect. According to the GRADE framework [29], these unexplained differences contribute to the indirectness of the evidence and were considered when downgrading the certainty of the evidence.

Conclusion

In patients with TBI, we found that the use of beta-blockers was not associated with a reduced risk of unfavorable long-term neurological outcome. It was however associated with a significant reduction in in-hospital mortality and duration of mechanical ventilation. The limited power of our study and the very low certainty of evidence prevent definitive conclusions and do not support the routine clinical use of beta-blockers to improve outcomes. A well-designed and adequately powered randomized controlled trial investigating the efficacy and safety of beta-blockers in this population is needed.

Abbreviations

CI	Confidence interval
CFS	Clinical Features Scale
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale–Extended
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
ICU	Intensive care unit
MD	Mean difference
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSH-AM	Paroxysmal Sympathetic Hyperactivity–Assessment Measure
RCT	Randomized controlled trial
RR	Risk ratio
SAH	Subarachnoid haemorrhage
TBI	Traumatic brain injury

Supplementary Information

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Supplementary Material 1. Search Strategies.

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Authors' contributions
Conceptualization: MB, NB, AFT Data curation: MB, NB, THT, SO Formal analysis: MB, NB, SO Investigation: MB, NB, THT, SO, AFT Methodology: MB, NB, AFT Project administration: AFT Software: MB, NB, SO Supervision: AFT Validation: MB, NB, THT, SO, OC, FL, RZ, MV, SE, BT, IB, MS, AFT Writing – original draft: MB, NB, AFT Writing – review & editing: MB, NB, THT, SO, OC, FL, RZ, MV, SE, BT, IB, MS, AFT All authors read and approved the final manuscript.

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Data availability
All data relevant to the study are included in this article or uploaded as supplementary information.

Declarations

Ethics approval and consent to participate
This meta-analysis involved secondary data from published studies, exempting it from Institutional Review Board approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Maas AIR, Menon DK, Manley GT et al (2022) Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol 21(11):1004–1060. https://doi.org/10.1016/S1474-4422(22)00309-X
2. Meyfroidt G, Baguley IJ, Menon DK (2017) Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet Neurol 16(9):721–729. https://doi.org/10.1016/S1474-4422(17)30259-4
3. Hinson HE, Puybasset L, Weiss N et al (2015) Neuroanatomical basis of paroxysmal sympathetic hyperactivity: a diffusion tensor imaging analysis. Brain Inj 29(4):455–461. https://doi.org/10.3109/02699052.2014.995229
4. Rizoli SB, Jaja BNR, Di Battista AP et al (2017) Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. Crit Care 21(1):37. https://doi.org/10.1186/s13054-017-1620-6
5. Bao L, Chen D, Ding L, Ling W, Xu F (2014) Fever burden is an independent predictor for prognosis of traumatic brain injury. PLoS ONE 9(3):e90956. https://doi.org/10.1371/journal.pone.0090956
6. Bouras M, Asehnoune K, Roquilly A (2022) Immune modulation after traumatic brain injury. Front Med 9:995044. https://doi.org/10.3389/fmed.2022.995044
7. Schmidt EA, Despas F, Pavy-Le Traon A et al (2018) Intracranial pressure is a determinant of sympathetic activity. Front Physiol 9:11. https://doi.org/10.3389/fphys.2018.00011
8. Ley EJ, Leonard SD, Barmparas G et al (2018) Beta blockers in critically ill patients with traumatic brain injury: results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. J Trauma Acute Care Surg 84(2):234–244. https://doi.org/10.1097/TA.0000000000001747
9. Tu JSY, Reeve J, Deane AM, Plummer MP (2021) Pharmacological management of paroxysmal sympathetic hyperactivity: a scoping review. J Neurotrauma 38(16):2221–2237. https://doi.org/10.1089/neu.2020.7597
10. Nguembu S, Meloni M, Endalle G et al (2021) Paroxysmal sympathetic hyperactivity in moderate-to-severe traumatic brain injury and the role of beta-blockers: a scoping review. Emerg Med Int 2021:5589239. https://doi.org/10.1155/2021/5589239
11. Edavettal M, Gross BW, Rittenhouse K et al (2016) An analysis of beta-blocker administration pre-and post-traumatic brain injury with subanalyses for head injury severity and myocardial injury. Am Surg 82(12):1203–1208
12. Cove-Smith JR, Kirk CA (1985) CNS-related side-effects with metoprolol and atenolol. Eur J Clin Pharmacol 28(S1):69–72. https://doi.org/10.1007/BF00543713
13. Schroeppel TJ, Sharpe JP, Magnotti LJ et al (2014) Traumatic brain injury and β-blockers: not all drugs are created equal. J Trauma Acute Care Surg 76(2):504–509. https://doi.org/10.1097/TA.0000000000000104
14. Chen Z, Tang L, Xu X, Wei X, Wen L, Xie Q (2017) Therapeutic effect of beta-blocker in patients with traumatic brain injury: a systematic review and meta-analysis. J Crit Care 41:240–246. https://doi.org/10.1016/j.jcrc.2017.05.035
15. Ding H, Liao L, Zheng X et al (2021) **B**-blockers for traumatic brain injury: a systematic review and meta-analysis. J Trauma Acute Care Surg 90(6):1077–1085. https://doi.org/10.1097/TA.0000000000003094
16. Zagales I, Selvakumar S, Ngatuvai M et al (2023) Beta-blocker therapy in patients with severe traumatic brain injury: a systematic review and meta-analysis. Am Surg 89(5):2020–2029. https://doi.org/10.1177/00031348221101583
17. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 1st ed. Wiley; 2019. https://doi.org/10.1002/9781119536604
18. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71. https://doi.org/10.1136/bmj.n71
19. Jennett B, Snoek J, Bond MR, Brooks N (1981) Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 44(4):285–293. https://doi.org/10.1136/jnnp.44.4.285
20. Jennett B (1975) Assessment of outcome after severe brain damage a practical scale. Lancet 305(7905):480–484. https://doi.org/10.1016/S0140-6736(75)92830-5
21. Cooper DJ, Rosenfeld JV, Murray L et al (2011) Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364(16):1493–1502. https://doi.org/10.1056/NEJMoa1102077
22. Cooper DJ, Nichol AD, Bailey M et al (2018) Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury: the POLAR randomized clinical trial. JAMA 320(21):2211. https://doi.org/10.1001/jama.2018.17075
23. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C (2016) PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 75:40–46. https://doi.org/10.1016/j.jclinepi.2016.01.021
24. Rohatgi A. WebPlotDigitizer. https://automeris.io/.

25. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Published online August 28, 2019:l4898. https://doi.org/10.1136/bmj.l4898
26. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5(1):13. https://doi.org/10.1186/1471-2288-5-13
27. Higgins JPT (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
28. Wetterslev J, Thorlund K, Brok J, Gluud C (2008) Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 61(1):64–75. https://doi.org/10.1016/j.jclinepi.2007.03.013
29. Guyatt G, Oxman AD, Akl EA et al (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64(4):383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026
30. Cruickshank JM, Neil-Dwyer G, Degaute JP et al (1987) Reduction of stress/catecholamine-induced cardiac necrosis by beta 1-selective blockade. Lancet Lond Engl 2(8559):585–589. https://doi.org/10.1016/s0140-6736(87)92984-9
31. Khaber H, Fayed A, Khattab A. A prospective randomized study comparing metoprolol to placebo in the management of severe traumatic brain injury. *40th Crit Care Congr Vol 38*. Published online December 1, 2010:U21.
32. Khalili H, Ahl R, Paydar S et al (2020) Beta-blocker therapy in severe traumatic brain injury: a prospective randomized controlled trial. World J Surg 44(6):1844–1853. https://doi.org/10.1007/s00268-020-05391-8
33. Nordness MF, Maiga AW, Wilson LD et al (2023) Effect of propranolol and clonidine after severe traumatic brain injury: a pilot randomized clinical trial. Crit Care 27(1):228. https://doi.org/10.1186/s13054-023-04479-6
34. Schroeppel TJ, Sharpe JP, Shahan CP et al (2019) Beta-adrenergic blockade for attenuation of catecholamine surge after traumatic brain injury: a randomized pilot trial. Trauma Surg Acute Care Open 4(1):e000307. https://doi.org/10.1136/tsaco-2019-000307
35. Mansour MS, Seidy NSE, Fathey YI (2023) Evaluation of beta-blocker effects on patients with traumatic brain injury: interventional double-blinded randomized controlled trial. Ain-Shams J Anesthesiol 15(1):65. https://doi.org/10.1186/s42077-023-00364-0
36. Mohamed Mostafa Megahed, Tamer Nabil Habib, Zeyad Moqbel, Riyad Abdullah Almogahed, Islam El Sayed Mohamed Ahmed. Role of Propranolol and Clonidine in Sympathetic Hyperactivity After Severe Traumatic Brain Injury. *Clin Neurol Neurosci*. 2017;1(4):96–103. https://doi.org/10.11648/j.cnn.20170104.14
37. Hart S, Lannon M, Chen A, Martyniuk A, Sharma S, Engels PT (2023) Beta blockers in traumatic brain injury: a systematic review and meta-analysis. Trauma Surg Acute Care Open 8(1):e001051. https://doi.org/10.1136/tsaco-2022-001051
38. Ahl R, Thelin EP, Sjölin G et al (2017) **B**-blocker after severe traumatic brain injury is associated with better long-term functional outcome: a matched case control study. Eur J Trauma Emerg Surg 43(6):783–789. https://doi.org/10.1007/s00068-017-0779-5
39. Alali AS, Mukherjee K, McCredie VA et al (2017) Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern Association for the Surgery of Trauma guideline. Ann Surg 266(6):952–961. https://doi.org/10.1097/SLA.0000000000002286
40. Ramesh AV, Banks CFK, Mounstephen PE, Crewdson K, Thomas M (2020) Beta-blockade in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurocrit Care 33(2):508–515. https://doi.org/10.1007/s12028-020-00915-5
41. Heliste M, Pettilä V, Berger D, Jakob SM, Wilkman E (2022) Beta-blocker treatment in the critically ill: a systematic review and meta-analysis. Ann Med 54(1):1994–2010. https://doi.org/10.1080/07853890.2022.2098376
42. Lee YR, Seth MS, Soney D, Dai H (2019) Benefits of beta-blockade in sepsis and septic shock: a systematic review. Clin Drug Investig 39(5):429–440. https://doi.org/10.1007/s40261-019-00762-z
43. Hasegawa D, Sato R, Prasitlumkum N et al (2021) Effect of ultrashort-acting β-blockers on mortality in patients with sepsis with persistent tachycardia despite initial resuscitation. Chest 159(6):2289–2300. https://doi.org/10.1016/j.chest.2021.01.009
44. Whitehouse T, Hossain A, Perkins GD et al (2023) Landiolol and organ failure in patients with septic shock: the STRESS-L randomized clinical trial. JAMA 330(17):1641. https://doi.org/10.1001/jama.2023.20134
45. Alexandru MG, Niewald P, Krüger S et al (2024) Mortality in septic patients treated with short-acting betablockers: a comprehensive meta-analysis of randomized controlled trials. Crit Care 28(1):392. https://doi.org/10.1186/s13054-024-05174-w
46. Lee JW, Wang W, Rezk A et al (2024) Hypotension and adverse outcomes in moderate to severe traumatic brain injury: a systematic review and meta-analysis. JAMA Netw Open 7(11):e2444465. https://doi.org/10.1001/jamanetworkopen.2024.44465
47. Murry JS, Hoang DM, Barmparas G et al (2016) Prospective evaluation of early propranolol after traumatic brain injury. J Surg Res 200(1):221–226. https://doi.org/10.1016/j.jss.2015.06.045
48. Xu SY, Zhang Q, Li CX (2024) Paroxysmal sympathetic hyperactivity after acquired brain injury: an integrative review of diagnostic and management challenges. Neurol Ther 13(1):11–20. https://doi.org/10.1007/s40120-023-00561-x
49. Baguley IJ, Perkes IE, Fernandez-Ortega JF et al (2014) Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma 31(17):1515–1520. https://doi.org/10.1089/neu.2013.3301
50. Samuel S, Lee M, Brown RJ, Choi HA, Baguley IJ (2018) Incidence of paroxysmal sympathetic hyperactivity following traumatic brain injury using assessment tools. Brain Inj 32(9):1115–1121. https://doi.org/10.1080/02699052.2018.1482002

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