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Beta blockers in traumatic brain injury: a systematic review and meta-analysis

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ABSTRACT

Background Traumatic brain injury (TBI) is a major cause of death and disability worldwide. Beta blockers have shown promise in improving mortality and functional outcomes after TBI. The aim of this article is to synthesize the available clinical data on the use of beta blockers in acute TBI.

Methods A systematic search was conducted through MEDLINE, Embase, and Cochrane Central Register of Controlled Trials for studies including one or more outcomes of interest associated with use of beta blockers in TBI. Independent reviewers evaluated the quality of the studies and extracted data on all patients receiving beta blockers during their hospital stay compared with placebo or non-intervention. Pooled estimates, CIs, and risk ratios (RRs) or ORs were calculated for all outcomes.

Results 13 244 patients from 17 studies were eligible for analysis. Pooled analysis demonstrated a significant mortality benefit of overall use of beta blocker (RR 0.8, 95% CI 0.68 to 0.94, I^2=75%). Subgroup analysis of patients with no preinjury use of beta blocker compared with patients on preinjury beta blockers showed no mortality difference (RR 0.99, 95% CI 0.7 to 1.39, I^2=84%). There was no difference in rate of good functional outcome at hospital discharge (OR 0.94, 95% CI 0.56 to 1.58, I^2=65%); however, there was a functional benefit at longer-term follow-up (OR 1.75, 95% CI 1.09 to 2.8, I^2=0%). Cardiopulmonary and infectious complications were more likely in patients who received beta blockers (RR 1.94, 95% CI 1.69 to 2.24, I^2=0%; RR 2.36, 95% CI 1.42 to 3.91, I^2=88%). Overall quality of the evidence was very low.

Conclusions Use of beta blockers is associated with decreased mortality at acute care discharge as well as improved functional outcome at long-term follow-up. Lack of high-quality evidence limits definitive recommendations for use of beta blockers in TBI; therefore, high-quality randomized trials are needed to further elucidate the utility of beta blockers in TBI.

PROSPERO registration number CRD42021279700.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Traumatic brain injury (TBI) is a major cause of death and disability worldwide. Beta blockers have shown promise in improving mortality and functional outcomes after TBI.

WHAT THIS STUDY ADDS

⇒ The current study is a systematic review and meta-analysis that shows that beta blockers are associated with improved mortality and long-term functional outcome in TBI. Use of beta blockers may also be associated with cardiopulmonary and infectious complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study determines that the current evidence for beta blocker use in TBI is overall of low quality, and further research is required to elucidate these findings. However, beta blockers have potential to be integrated into the clinical management of TBI in the future if high quality studies determine they are effective for reducing secondary injury.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability worldwide, with nearly one-half of all trauma-related deaths involving head injuries.[1] Head injuries are associated with significant morbidity, long-term disability, and economic burden.[2] The major focus of TBI management is on limiting secondary injury, which is the expansion of the injured territory by physiological responses. After primary injury, there is a disruption in cerebral blood flow leading to anoxia and edema, subsequent neuronal cell death, further deterioration, and eventual neurodegeneration.[3] Secondary injury can develop for the days and weeks after the initial insult and is a major contributor to subsequent brain damage and overall outcome. Unfortunately, few strategies exist to mitigate this process. No therapeutic intervention has been approved to prevent progression of secondary neural injury, leaving a great need for optimization of treatment options to improve outcomes in patients with TBI.

Catecholamines are an integral part of the neuroendocrine-immune inflammatory network and are markers of TBI functional outcome and mortality.[4] The catecholamine surge is a well-documented process after TBI where the circulating levels of these neurotransmitters increase in correlation with the severity of the injury.[4 5] This can persist for more than 10 days,[6] leading to inflammation and apoptosis of neural cells, thus contributing to secondary injury.[7]

Although the exact mechanism is not yet known, beta blockers have shown promise in improving patient outcomes after TBI.[8–16] The hypothesized mechanism is related to the catecholamine surge, such that beta blockade may reduce the actions of catecholamines after TBI and therefore reduce or slow the progression of secondary injury. In humans, a recent meta-analysis summarizing the

available clinical data established lower mortality with beta blockade and conditionally recommends the use of in-hospital beta blockers after TBI in adult patients, with an emphasis on holding beta blockers to avoid bradycardia and hypotension.[16] Propranolol, in particular, has shown a lower mortality rate even when compared with other beta blockers.[17] However, the objective of trauma care is not limited to survival and acute management, but rather includes functional recovery and reintegration into work and community settings. Although a reduction in mortality rate may be beneficial on its own, there exists the possibility that improved patient survival comes at the cost of increased incidence of severe debilitation. Although the use of beta blockers in patients with TBI has been investigated for years, there is a lack of consensus on the effect of beta blockers on functional outcome. Although there are recent meta-analyses on this subject, there is a need for more rigorous analysis and quality assessment of available evidence.

The aim of this systematic review and meta-analysis is to synthesize the available clinical data to better understand the role of beta blockers in TBI. Namely, we aim to update the consensus on mortality benefit and summarize the documented effect on functional outcome. As there has been some evidence of a mortality benefit of propranolol. Specifically, we will complete subset analyses for propranolol compared with other beta blockers. Finally, we will analyze outcomes for patients who were on beta blockers prior to their injury compared with those that were initiated in the hospital.

METHODS

This systematic review was registered with the International Prospective Register of Systematic Reviews (ID: CRD42021279700).

Search strategy

Systematic searches covering the period from database inception through February 22, 2022, were conducted in MEDLINE (Ovid platform), Embase (Ovid platform), and Cochrane Central Register of Controlled trials (CENTRAL). Keywords and Medical Subject Headings terms related to TBI and adrenergic beta antagonists were used. Full search strategy for the Ovid platform and CENTRAL may be found in online supplemental appendix A. Studies were not restricted by language or full text.

Study selection

All screening was completed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement was followed at all review stages.[18] All citations obtained from the search strategies were imported into Covidence. After removal of duplicates by the Covidence software, two reviewers (SH and AC) independently evaluated the systematically searched titles and abstracts using a standardized, pilot-tested form. Screened studies were then subjected to full-text review for eligibility. Discrepancies regarding study inclusion or exclusion were reviewed and resolved through discussion or, if needed, a third reviewer (ML) was consulted.

We included articles that compared the use of any beta-adrenergic receptor blockers with placebo or non-intervention in patients with TBI. Included studies focused on adult patients (aged 18 years and older) that reported our primary outcomes (mortality and functional outcome). Randomized or non-randomized control trials, prospective, and retrospective study designs were included. Exclusion criteria included exclusively pediatric populations, case reports, review articles, animal studies, and any article that did not report our primary outcomes. Studies that combined beta-adrenergic receptor blockers with other medications (eg, clonidine) were excluded. There were no restrictions on the type or dose of beta blocker used, the timing of beta-blocker initiation, or severity of TBI. Intensive care unit admission was not required.

Data abstraction

Two reviewers (SH and AC) independently conducted data abstraction onto a data collection manual designed a priori. Abstracted data included study characteristics, patient demographics, type and dose of beta blocker administered, functional outcome, mortality, number of patients requiring surgical intervention, Glasgow Coma Scale at presentation, number of patients with blunt versus penetrating injury, and cardiopulmonary and infectious complications.

Data analysis

All statistical analyses and meta-analyses were performed using DataParty (DataParty, Hamilton, Canada). The statistical significance was set a priori at a p value of <0.05. A pairwise meta-analysis was performed using an inverse variance random effects model for all meta-analyzed outcomes. Weights were calculated using the Mantel-Haenzel method. Pooled effect estimates were obtained by calculating the mean difference in outcomes for continuous variables and risk ratios (RRs) for dichotomous variables with their respective 95% CIs to confirm the effect size estimation. Assessment of heterogeneity was completed using the inconsistency (I^2 statistic). An I^2 greater than 50% was considered to represent considerable heterogeneity.

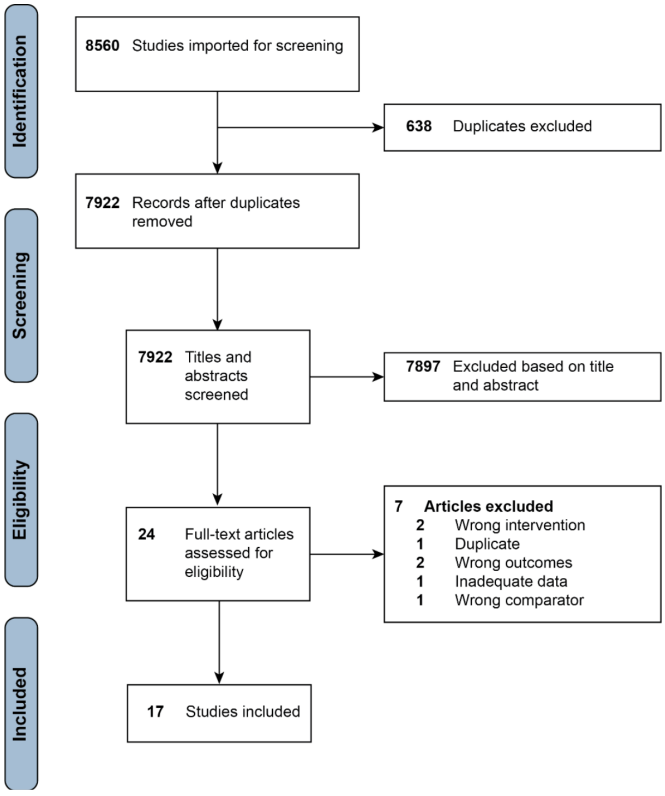

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram detailing search results.

Table 1 Characteristics of included studies

Author, year	Study type	Intervention arm	n (%)	Age (years)*	Male, N (%)	Penetrating injury, n (%)	Neurosurgical intervention, n (%)
Ahl *et al*, 2017[22]	Retrospective	BB+	76 (50)	57.2±14	57 (75.0)	0	ICP monitoring 49 (64.5) Operation 46 (60.5)
		BB−	76 (50)	57.9±15.8	60 (78.9)	0	ICP monitoring 48 (63.2) Operation 37 (48.7)
Asmar *et al*, 2021[23]	Retrospective	BB+	772 (50)	64.2±15.3	437 (56.6)	137 (18.8)	EVD 69 (9.0) Craniotomy/craniectomy 84 (10.8)
		BB−	772 (50)	62.6±15.4	431 (55.8)	144 (19.6)	EVD 67 (8.7) Craniotomy/craniectomy 86 (11.1)
Bukur *et al*, 2012[14]	Retrospective	BB+	866 (35.4)	43±22	684 (79.0)	0	Craniotomy/craniectomy 130 (15.0)
		BB−	1580 (64.6)	39±21	1201 (76.0)	0	Craniotomy/craniectomy 63 (4.0)
Cotton *et al*, 2007[8]	Retrospective	BB+	174 (41.4)	50.5 (28–70)	105 (60.3)	6 (3.4)	–
		BB−	246 (58.6)	30.5 (21–47)	162 (65.8)	11 (4.5)	–
Edavettal *et al*, 2016[24]	Retrospective	BB+	56 (33.3)	–	–	–	–
		BB−	112 (66.7)	–	–	–	–
Inaba *et al*, 2008[11]	Retrospective	BB+	203 (17.6)	50.1±21.1	158 (78)	0	Craniectomy 47 (23)
		BB−	953 (82.4)	38.1±20.4	705 (74)	0	Craniectomy 35 (4)
Jang *et al*, 2018[25]	Retrospective	BB+	18 (19)	–	–	–	–
		BB−	77 (81)	–	–	–	–
Khalili *et al*, 2020[26]	Randomized control trial	BB+	99	37±17	86 (86.9)	0	Craniotomy/craniectomy 30 (30.3)
		BB−	120	39±20	103 (85.8)	0	Craniotomy/craniectomy 50 (41.7)
Ko *et al*, 2016[27]	Prospective	BB+	109	49.6±20.8	77 (70.6)	–	Craniotomy/craniectomy 12 (11.0)
		BB−	331	60.4±23.1	216 (65.3)	–	Craniotomy/craniectomy 51 (15.4)
Ley *et al*, 2018[17]	Prospective	BB+	1120 (49.7)	57±22	784 (0.7)	0	EVD 134 (12) Craniotomy/craniectomy 257 (23)
		BB−	1132 (50.3)	49±21	770 (0.68)	0	EVD 79 (7) Craniotomy/craniectomy 148 (13)
Mohseni *et al*, 2015[15]	Retrospective	BB+	287 (32.8)	62±16	210 (0.73)	–	Craniotomy/craniectomy 32 (0.11)
		BB−	587 (67.2)	49±21	429 (0.73)	–	Craniotomy/craniectomy 141 (0.24)
Riordan *et al*, 2007[9]	Retrospective	BB+	138 (30.9)	35.8 (23.6–49.7)	113 (81.9)	–	–
		BB−	308 (69.1)	28.7 (20.6–41.0)	232 (75.3)	–	–
Salim *et al*, 2008[10]	Retrospective	BB+	91 (21.7)	53.9±21.6	70 (76.9)	0	–
		BB−	329 (78.3)	41.1±20.3	243 (73.9)	0	–
Schroeppel *et al*, 2010[12]	Retrospective	BB+	506 (19.5)	51±20	–	0	–
		BB−	2095 (80.5)	38±17	–	0	–
Schroeppel *et al*, 2014[28]	Retrospective	BB+	427 (24.3)	49±20	333 (0.78)	–	–
		BB−	1328 (75.7)	40±18	983 (0.74)	–	–
Schroeppel *et al*, 2019[29]	Randomized control trial	BB+	13 (52.0)	49.7±19.0	9 (69.2)	2 (0.15)	–
		BB−	12 (48.0)	53.0±21.9	7 (58.3)	1 (0.08)	–
Zangbar *et al*, 2016[30]	Retrospective	BB+	178 (50.0)	57.6±19.9	130 (73)	0	Craniotomy/craniectomy 32 (18)
		BB−	130 (50.0)	59.7±20.9	125 (70)	0	Craniectomy/craniotomy 23 (13)

*Mean±SD or median (IQR).
BB, beta blocker; EVD, external ventricular drain; ICP, intracranial pressure.

Assessing methodological quality

Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[19] by two independent reviewers (SH and AC). Evidence was ranked as being of very low quality, low quality, moderate quality, and high quality, based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk of bias was assessed using ROBINS-I tool for observational studies and the RoB-2 tool for randomized controlled trials (RCTs).[20 21] Disagreement was resolved by consensus with a third arbitrator (ML) available for any necessary cases.

RESULTS

Study characteristics

From 7922 relevant citations, 17 studies met the inclusion criteria (2 prospective, 2 RCTs, and 13 retrospective).[8–12 14 15 17 22–30] A PRISMA flow diagram of the study selection is illustrated in figure 1. A total of 13 244 patients were included in this review. From the 17 studies, 4533 received beta blockers and 8711 did not receive beta blockers. Detailed study characteristics of included studies are reported in table 1. Average age was 51.1±8.1 for those receiving beta blockers and 45.7±11.0 for those who did not. Penetrating injuries were reported in 12 studies, with a total of 301 subjects suffering from penetrating injury (145 beta blockers and 156 controls). Neurosurgical intervention occurred in 947 patients in the beta-blocker group (18%) and 873 controls (11%), including external ventricular drain or intracranial pressure monitor insertion, craniotomy, or craniectomy. The majority of studies (11 of 17) broadly included all patients who received at least one dose of any beta blocker while in the hospital. Only three studies included information on specific dosing.[23 27 29]

Mortality and functional outcome

Results of the meta-analyses for outcomes of interest are displayed in figures 2–4. All included studies reported mortality

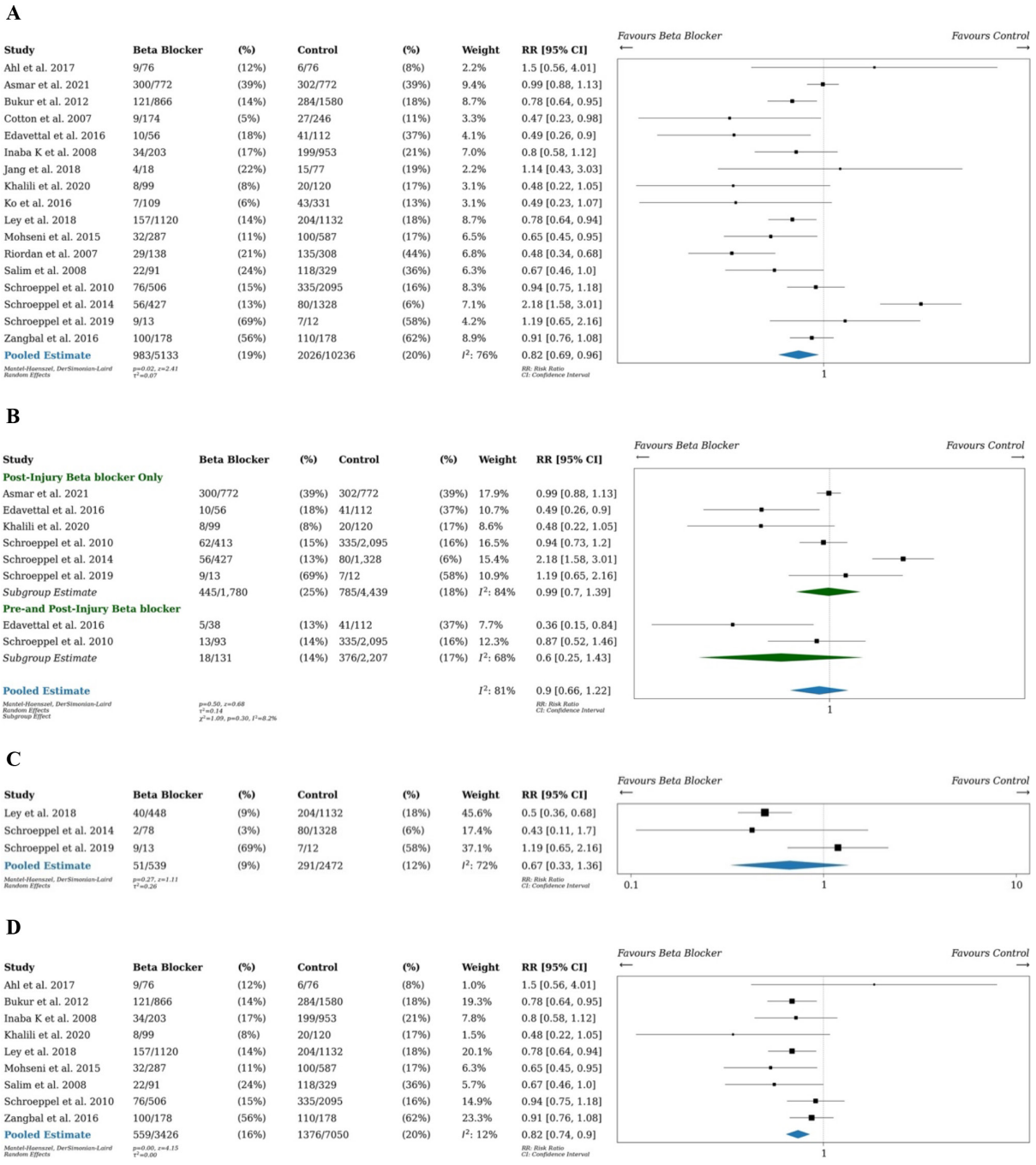

Figure 2 Results of meta-analyses comparing mortality with use of beta blockers to placebo or non-intervention. Outcomes evaluated are (A) overall pooled in-hospital mortality; (B) In hospital mortality, subgroup analysis for patients maintained on home beta blocker prior to TBI and those who were started on beta blocker post injury only; (C) in-hospital mortality for use of propranolol only; and (D) in-hospital mortality for blunt injury only. RR, risk ratio; TBI, traumatic brain injury.

(figure 2). Pooled analysis of the 15 cohort studies and 2 RCTs revealed a significant difference between patients receiving beta blockers and those who did not, with decreased in-hospital mortality for the beta blocker group (RR 0.8, 95% CI 0.68 to 0.94, I^2=75%). Most studies (13 of 17) included all patients who had received beta blockers during their hospital stay in their analysis, regardless of whether participants had been prescribed these prior to their injury or not. A select few studies (6 of 17) included data on patients who were prescribed beta blockers for the first time after their injury, excluding those maintained on home beta blocker prior to the injury. Unlike the pooled data, this subgroup analysis did not show a significant mortality benefit for those starting beta blockers post injury (RR 0.99, 95% CI 0.7 to 1.39, I^2=84%). Only two studies included specific data for patients who were on preinjury beta blocker and continued post injury, which also did not exhibit a mortality benefit (RR 0.6, 95% CI 0.25 to 1.43, I^2=68%). Three studies[28 29 31] included data for propranolol only, which did not show a significant mortality benefit over control (RR 0.67, 95% CI 0.33 to 1.36, I^2=72%). Although some studies did include patients with penetrating injury, mortality data specifically for this cohort were not reported. As penetrating injuries are fundamentally different

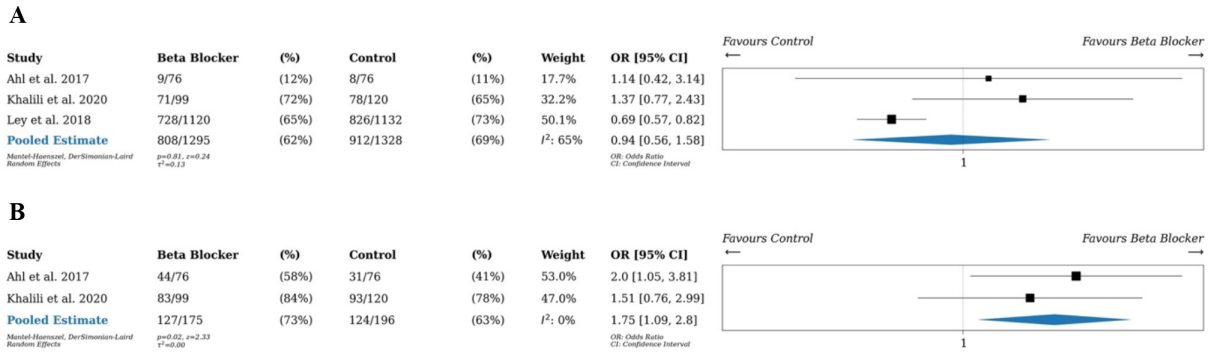

Figure 3 Results of meta-analyses comparing functional outcome with use of beta blockers to placebo or non-intervention. (A) Good functional outcome at acute care discharge. (B) Good functional outcome at long-term (≥6 month) follow-up.

from blunt injuries, subset analysis was undertaken for studies that specified blunt injury only. Beta blockers inferred a mortality benefit over the control in this group (RR 0.82, 95% CI 0.74 to 0.9, I^2=12%).

Three studies reported on functional outcome, all of which used the Glasgow Outcome Score-Extended (GOS-E) (figure 3). All three studies measured GOS-E at time of acute care discharge, one study reported GOS-E at 6 months post-injury, and another reported GOS-E at 12 months post-injury. Reported data for all studies was number of subjects above a certain GOS-E score predetermined by the authors to represent a good functional outcome. There was no significant difference in rates of good functional outcome at the time of hospital discharge between groups (OR 0.94, 95% CI 0.56 to 1.58, I^2=65%); however, those who received beta blockers were more likely to have good functional outcome at long term (≥6 month) follow-up (OR 1.75, 95% CI 1.09 to 2.8, I^2=0%). All of these studies were on blunt injury only. Only one study included functional outcome for propranolol only; therefore, analysis was not completed for this subgroup. In this study, propranolol did not show any difference in the rate of good functional outcome compared with other beta blockers (OR 1.29, 95% CI 0.86 to 1.95, p=0.21).

Complications

Complications were not commonly reported among studies. Cardiopulmonary complications were reported in three studies and included respiratory failure, life-threatening tachyarrhythmias, bradycardia, acute myocardial infarction, cardiogenic shock, cardiac arrest, or requirement of vasopressors. Use of beta blocker was associated with an increased rate of these complications (RR 1.94, 95% CI 1.69 to 2.24, I^2=0%). Only two studies reported infectious complications, which showed overall increased infectious complications with beta blocker use (RR 2.36, 95% CI 1.42 to 3.91, I^2=88%) (figure 4).

Quality assessment

For RCTs, the risk of bias was serious for one study and low for the other (figure 5). Risk of bias was serious for all observational studies, mainly due to the inherently non-blinded nature of the studies (figure 6). The overall quality of the included studies was very low according to the GRADE approach (figure 7).

DISCUSSION

This systematic review and meta-analysis analyzed current available evidence for the utility of beta blockers in TBI to reduce mortality and improve functional outcome. Our meta-analyses showed that patients who received beta blockers during their hospital admission exhibited lower mortality rates and better functional outcome, though at the cost of an increased risk of cardiopulmonary and infectious complications. Nevertheless, our study demonstrates the need for a larger scale, RCT to further clarify the benefit and safety of in-hospital initiation of beta blockers in TBI.

The proposed explanation for the benefit of beta blockers in TBI is based on the assumed reduction in secondary injury by limiting the catecholamine surge. The catecholamine surge is well documented to occur up to 10 days after the injury and increases cerebral edema, hypoxia, and neural apoptosis. Preventing the resultant secondary injury leads to decreased mortality and improved functional outcome, which are the main goals of TBI management. Propranolol administration in rodent TBI models increases cerebral perfusion, decreases hypoxia, and improves cerebral glucose metabolism in a dose-dependent

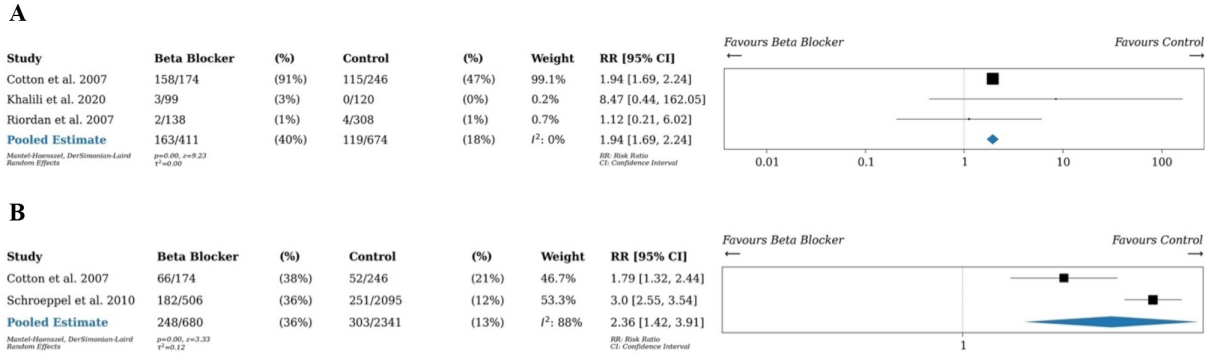

Figure 4 Results of meta-analyses comparing complications with use of beta blockers to placebo or non-intervention. Outcomes evaluated are (A) cardiopulmonary complications and (B) infectious complications. RR, risk ratio.

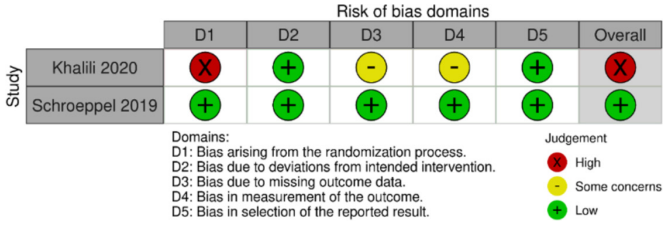

Figure 5 Cochrane Risk of Bias Tool for Randomized Controlled Trials V.2.0 per individual study.

manner.[31 32] Additionally, knockout mice lacking beta-adrenergic receptors demonstrate less motor deficiency after head trauma.[31 32] Although not officially included in the Brain Trauma Foundation guidelines, and despite the lack of high-quality data, several societies conditionally recommend beta blocker use in patients with severe TBI with no existing contra-indications, provided that beta-blocker-related complications (eg, hypotension or bradycardia) do not occur.[16 33] According to our summation of the current human data, use of beta blocker in hospitals is associated with decreased all-cause in-hospital mortality in patients with TBI. This was a pooled analysis of anyone who received a beta blocker at all during their hospital stay. However, when we separated the available data for patients who had started a beta blocker for the first time post injury and those who had been maintained on a beta blocker before their injury, the mortality benefit was no longer seen in either group. Although it is an interesting question whether the total length of beta-blocker therapy has an impact on mortality and what effect preinjury beta blocker has on outcomes, our findings do not suggest any definitive conclusion regarding this. It is possible that the proposed blunting of the catecholamine surge occurs more effectively with longer-term beta-blocker therapy prior to the injury and that acute initiation has less of an impact. However, our data presented here are not without significant bias. Relative to the total amount of patients in the overall analysis, very few data points were available for the subgroups. Few studies included analysis specifically on beta blockers initiated post injury. Instead, the majority of studies broadly included any and all patients who received one or more doses of beta blocker at any point during their admission, which leads to considerable variability and limits what effect we can reasonably attribute to the beta blockers themselves, no matter when they were started. Additionally, all of the studies in this subgroup analysis had a high risk of bias and were overall low quality as per the GRADE assessment.

Although most studies give prominence to mortality outcomes, it is certainly not the only focus in the management and rehabilitation after TBI. Despite the primary clinical goal in TBI management being full recovery and return to baseline level of function, there is limited evidence available for the effect of beta blockers on this. In fact, only three studies were identified in our review that included functional outcome in their analysis. Pooled analysis was undertaken for functional outcome at hospital discharge and at long-term follow-up despite the small number of studies, and though there was no difference in outcomes at

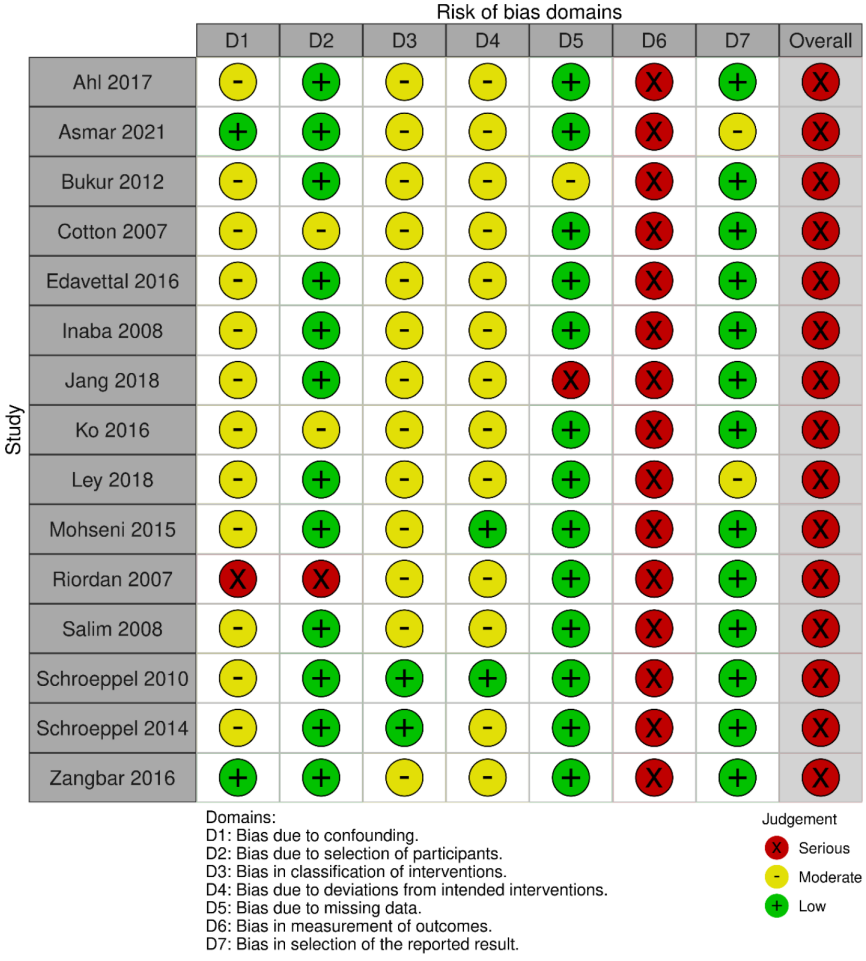

Figure 6 Risk of Bias in Non-randomized Studies of Intervention assessment tool results per individual observational study.

Summary of findings:

Beta blockers compared to placebo for Traumatic Brain Injury

Patient or population: Traumatic Brain Injury
Setting: Inpatient
Intervention: Beta blockers
Comparison: Placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Beta blockers				
Mortality	198 per 1,000	**168 per 1,000** (158 to 180)	**RR 0.85** (0.80 to 0.91)	15369 (17I studies)	⊕◯◯◯ Very low[a,b,c]	Substantial heterogeneity
Good Functional Outcome	687 per 1,000	**673 per 1,000** (551 to 776)	**OR 0.94** (0.56 to 1.58)	2623 (3 studies)	⊕◯◯◯ Very low[a,c,d]	Outcome largely dominated by a singular observational study with a large cohort
Cardiopulmonary complications	177 per 1,000	**344 per 1,000** (298 to 397)	**RR 1.95** (1.69 to 2.25)	1085 (3 studies)	⊕⊕◯◯ Low[a,c]	
Infectious complications	129 per 1,000	**340 per 1,000** (295 to 393)	**RR 2.63** (2.28 to 3.04)	3021 (2 studies)	⊕⊕◯◯ Low[a,e]	Substantial heterogeneity

***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; **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. Serious risk of bias for all observational studies as per the ROBINS-I tool.
b. Substantial heterogeneity within results; I^2=77%, P<0.001
c. Many studies exhibited wide confidence intervals
d. Substantial heterogeneity within studies; I^2=0.61%, P<0.001
e. Substantial heterogeneity within studies; I^2=88%, P<0.001

Figure 7 GRADE summary of findings. GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

acute care discharge, pooled long-term follow-up showed a functional benefit of using beta blockers. Functional recovery is often slow after brain injury; therefore, GOS-E as measured at discharge from acute care may not be the most appropriate time to compare this outcome. Longer-term measurements at 6 or 12 months are likely more realistic to true functional outcome. However, there are several issues to be addressed with these results. First, each study had a different definition of the GOS-E score, which showed a 'good' functional outcome. Each reported the number of patients above this predetermined level and not average scores for each group. The measurements ranged from including any patient with a score above 3, to those only including a score above or equal to 5. A score of 3 or 4 still signifies a severe upper or lower limb deficit and dependency on others for major daily tasks of living. This is vast difference from a score of 5, which is only a moderate disability. This inconsistency in measurements limits practical conclusions that can be made from our analysis, as these represent vast discrepancies in true function. In addition, the data on long-term follow-up is based on two smaller studies,[22 26] each of which had a different time point for follow-up. Six months compared with 12 months is relatively significant in the rehabilitation from a brain injury; therefore, this inconsistency lends to the uncertainty of these results. This lack of consistent and comprehensive data regarding functional outcome outlines the need for rigorous controlled trials addressing this gap in the literature.

Cardiac, respiratory, and infectious complications are common after TBI, and in many cases are directly related to the catecholamine surge and resultant autonomic imbalances.[8] The use of beta blockers in hyperadrenergic states has previously been shown to be beneficial in decreasing adverse cardiopulmonary and infectious events.[34–36] Contrary to this evidence, the use of beta blockers was associated with higher risk of these complications in our analyses. For pooled cardiopulmonary complications, two studies showed no difference between groups in the rates of these complications; however, they only measured bradycardia and cardiac uncoupling, respectively.[9 26] The third study included had much more thorough criteria for assessing cardiopulmonary complications and was weighed heavily in our analysis.[8] However, many of their complications were diagnosed prior to beta-blocker initiation; the beta-blocker group had a higher burden of chest injury, and a broad definition of respiratory failure was used. Despite these confounding factors, it is still essential to avoid bradycardia and hypotension after initiation of beta blockers in TBI. For infectious complications, the same study that diagnosed many cardiac complications prior to beta-blocker initiation also stated that many infections were diagnosed prior to beta-blocker initiation. There are growing data emerging regarding the use of beta blockers in sepsis, which, to date, suggests that use of beta blockers is associated with not only a decrease in mortality but also improved management of cardiorespiratory abnormalities.[37–39] In our case, only two observational studies included data on infectious outcomes with use of beta blockers in TBI and brought with them substantial bias. Thus, this finding may not be a true phenomenon and requires further investigation.

Our study resembles a recent meta-analysis completed in 2020,[40] with some key differences. We obtained similar results for the analysis of in-hospital mortality, functional outcome, and cardiopulmonary complications. In addition to updating this literature review, we built on these findings by including subgroup analyses for patients who had not been on beta blockers prior to the injury, for propranolol use specifically, for blunt injury only, and for infectious complications. Finally, our study used the more rigorous GRADE approach to systematically assess the quality of the evidence, developing a more comprehensive understanding of the quality of the available evidence and thus the reliability of recommendations based on this.

Limitations

Limitations of this study are largely due to the number of available studies on this topic, as well as the quality of the literature. Limited number of studies were available for high-yield analysis of functional outcome, further complicated by the variability in reporting of good functional outcome. Studies were predominantly retrospective cohort analyses, limiting our ability to make definitive conclusions due to inherent lack of prospective data collection and blinding. Observational studies are by definition low quality, and in our case, this was further lowered by the serious risk of bias, inconsistency, an imprecision of the included studies. There were only two RCTs available, of which neither were blinded and both had small sample sizes, and therefore were weighted very low in our analysis. Additionally, most studies did not include subset analyses for suspected confounding factors such as premorbid patient conditions, time of beta-blocker initiation within hospital, beta-blocker therapy prior to their injury, or the need for surgical intervention. A small proportion of studies did identify an inherent difference between patients who received beta blockers compared with those who did not. For example, patients receiving beta blockers tended to be older and have more severe injuries.[11 17 28] However, subgroup outcomes stratified by these confounders were not provided to allow for an adjusted analysis in our case; therefore, our analysis is based on unadjusted mortality. Some studies did not assess isolated TBI but rather included all multisystem trauma patients. Although beta blockers could be beneficial for all general trauma patients, this is a significant confounder when trying to assess the effect on TBI alone. For example, Khalili *et al*[26] did not find a benefit of beta blockers in all multisystem trauma patients, but their subgroup analysis did reveal a survival benefit of propranolol in patients with isolated severe TBI. Few studies included specific information about the dosing, time of initiation, duration, and type of beta blocker used. For those that did, there was substantial variability between studies in all of these factors. For example, some studies included patients in their beta-blocker cohort who received only one dose of beta blocker during their entire hospital stay, and timing of initiation varied from 24 hours post injury to up to 30 days after admission. Overall, there was wide variability in the methods of patient selection and beta-blocker administration, resulting in significant heterogeneity between studies. Additionally, although we attempt here to consider complications and assess long-term outcomes between groups, this is challenging to accomplish. If beta blockers do in fact decrease mortality, then patients who survive most likely will require a longer hospital stay and thus are at increased risk of inherent complications of hospital admission. Therefore, the benefit of beta blockers may lead to additional complications due to patients surviving who would have otherwise died.

CONCLUSION

This systematic review and meta-analysis reviewed the effect of use of beta blockers in patients with TBI on mortality and functional outcome. Our findings suggest that the use of beta blockers is associated with an overall decrease in in-hospital mortality and higher rate of good functional outcome at discharge from acute care. However, lack of available high-quality studies limits definitive conclusions and recommendations for use of beta blockers in TBI. Further RCTs are needed to analyze mortality as well as both short-term and long-term functional outcomes with use of beta blockers.

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REFERENCES

1 *Neurological disorders: public health challenges*. World Health Organization, 2006.
2 Fu TS, Jing R, McFaull SR, Cusimano MD. Health & economic burden of traumatic brain injury in the emergency department. *Can J Neurol Sci* 2016;43:238–47.
3 Shetty T, Raince A, Manning E, Tsiouris AJ. Imaging in chronic traumatic encephalopathy and traumatic brain injury. *Sports Health* 2016;8:26–36.
4 Rizoli SB, Jaja BNR, Di Battista AP, Rhind SG, Neto AC, da Costa L, Inaba K, da Luz LT, Nascimento B, Perez A, *et al*. Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. *Crit Care* 2017;21:37.
5 Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. *Ann Neurol* 1987;21:438–43.
6 Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag B, Friberg P. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. *Stroke* 2000;31:901–6.
7 Lozano D, Gonzales-Portillo GS, Acosta S, de la Pena I, Tajiri N, Kaneko Y, Borlongan CV. Neuroinflammatory responses to traumatic brain injury: etiology, clinical consequences, and therapeutic opportunities. *Neuropsychiatr Dis Treat* 2015;11:97–106.
8 Cotton BA, Snodgrass KB, Fleming SB, Carpenter RO, Kemp CD, Arbogast PG, Morris JA. Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. *J Trauma* 2007;62:26–33.
9 Riordan WP, Cotton BA, Norris PR, Waitman LR, Jenkins JM, Morris JA. Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. *J Trauma* 2007;63:503–10.
10 Salim A, Hadjizacharia P, Brown C, Inaba K, Teixeira PGR, Chan L, Rhee P, Demetriades D. Significance of troponin elevation after severe traumatic brain injury. *J Trauma* 2008;64:46–52.

11 Inaba K, Teixeira PGR, David J-S, Chan LS, Salim A, Brown C, Browder T, Beale E, Rhee P, Demetriades D. Beta-blockers in isolated blunt head injury. *J Am Coll Surg* 2008;206:432–8.
12 Schroeppel TJ, Fischer PE, Zarzaur BL, Magnotti LJ, Clement LP, Fabian TC, Croce MA. Beta-adrenergic blockade and traumatic brain injury: protective? *J Trauma* 2010;69:776–82.
13 Heffernan DS, Inaba K, Arbabi S, Cotton BA. Sympathetic hyperactivity after traumatic brain injury and the role of beta-blocker therapy. *J Trauma* 2010;69:1602–9.
14 Bukur M, Mohseni S, Ley E, Salim A, Margulies D, Talving P, Demetriades D, Inaba K. Efficacy of beta-blockade after isolated blunt head injury: does race matter? *J Trauma Acute Care Surg* 2012;72:1013–8.
15 Mohseni S, Talving P, Thelin EP, Wallin G, Ljungqvist O, Riddez L. The effect of β-blockade on survival after isolated severe traumatic brain injury. *World J Surg* 2015;39:2076–83.
16 Alali AS, Mukherjee K, McCredie VA, *et al*. Beta-blockers and traumatic brain injury: a systematic review and meta-analysis. *Ann Surg* 2017;266:952–61.
17 Ley EJ, Leonard SD, Barmparas G, Dhillon NK, Inaba K, Salim A, O'Bosky KR, Tatum D, Azmi H, Ball CG, *et al*. 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* 2018;84:234–44.
18 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med* 2009;6:e1000097.
19 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
20 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
21 Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
22 Ahl R, Thelin EP, Sjölin G, Bellander B-M, Riddez L, Talving P, Mohseni S. **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* 2017;43:783–9.
23 Asmar S, Bible L, Chehab M, Tang A, Khurrum M, Castanon L, Ditillo M, Douglas M, Joseph B. Traumatic brain injury induced temperature dysregulation: what is the role of β blockers? *J Trauma Acute Care Surg* 2021;90:177–84.
24 Edavettal M, Gross BW, Rittenhouse K, Alzate J, Rogers A, Estrella L, Miller JA, Rogers FB. An analysis of beta-blocker administration pre-and post-traumatic brain injury with subanalyses for head injury severity and myocardial injury. *Am Surg* 2016;82:1203–8.
25 Jang H, Bushell T, Mukherjee K, Luo-Owen X. 1568: the effect of early beta-blockers on ICU mortality in patients with traumatic brain injury (TBI). *Crit Care Med* 2018;46:768.
26 Khalili H, Ahl R, Paydar S, Sjolin G, Cao Y, Abdolrahimzadeh Fard H, Niakan A, Hanna K, Joseph B, Mohseni S. Beta-blocker therapy in severe traumatic brain injury: a prospective randomized controlled trial. *World J Surg* 2020;44:1844–53.
27 Ko A, Harada MY, Barmparas G, Thomsen GM, Alban RF, Bloom MB, Chung R, Melo N, Margulies DR, Ley EJ. Early propranolol after traumatic brain injury is associated with lower mortality. *J Trauma Acute Care Surg* 2016;80:637–42.
28 Schroeppel TJ, Sharpe JP, Magnotti LJ, Weinberg JA, Clement LP, Croce MA, Fabian TC. Traumatic brain injury and β-blockers: not all drugs are created equal. *J Trauma Acute Care Surg* 2014;76:504–9;
29 Schroeppel TJ, Sharpe JP, Shahan CP, Clement LP, Magnotti LJ, Lee M, Muhlbauer M, Weinberg JA, Tolley EA, Croce MA, *et al*. Beta-Adrenergic blockade for attenuation of catecholamine surge after traumatic brain injury: a randomized pilot trial. *Trauma Surg Acute Care Open* 2019;4:e000307.
30 Zangbar B, Khalil M, Rhee P, Joseph B, Kulvatunyou N, Tang A, Friese RS, O'Keeffe T. Metoprolol improves survival in severe traumatic brain injury independent of heart rate control. *J Surg Res* 2016;200:586–92.
31 Ley EJ, Clond MA, Bukur M, Park R, Chervonski M, Dagliyan G, Margulies DR, Lyden PD, Conti PS, Salim A. **B**-Adrenergic receptor inhibition affects cerebral glucose metabolism, motor performance, and inflammatory response after traumatic brain injury. *J Trauma Acute Care Surg* 2012;73:33–40.
32 Han R-Q, Ouyang Y-B, Xu L, Agrawal R, Patterson AJ, Giffard RG. Postischemic brain injury is attenuated in mice lacking the beta2-adrenergic receptor. *Anesth Analg* 2009;108:280–7.
33 Koskinen L-O, Olivecrona M, Grände PO. Severe traumatic brain injury management and clinical outcome using the Lund concept. *Neuroscience* 2014;283:245–55.
34 Walter P, Neil-Dwyer G, Cruickshank JM. Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage. *Br Med J (Clin Res Ed)* 1982;284:1661–4.
35 Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B, O'Gorman P. Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage. *Br Med J* 1978;2:990–2.
36 Deng J, Muthu K, Gamelli R, Shankar R, Jones SB. Adrenergic modulation of splenic macrophage cytokine release in polymicrobial sepsis. *Am J Physiol Cell Physiol* 2004;287:C730–6.
37 Gadallah RR, Aboseif EMK, Ibrahim DA, Zaki HV, Abdelmaksoud MNM. Evaluation of the safety and efficacy of beta blockers in septic patients: a randomized control trial. *Ain-Shams J Anesthesiol* 2020;12.
38 Chacko CJ, Gopal S. Systematic review of use of β-blockers in sepsis. *J Anaesthesiol Clin Pharmacol* 2015;31:460–5.
39 Lescroart M, Pequignot B, Kimmoun A, Klein T, Levy B. Beta-blockers in septic shock: what is new? *J Intensive Med* 2022;2:150–5.
40 Ding H, Liao L, Zheng X, Wang Q, Liu Z, Xu G, Li X, Liu L. **B**-blockers for traumatic brain injury: a systematic review and meta-analysis. *J Trauma Acute Care Surg* 2021;90:1077–85.