Beta Blockers for Acute Traumatic Brain Injury: A Systematic Review and Meta-analysis

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Abstract

Background Traumatic brain injury (TBI) is associated with a systemic hyperadrenergic state. Through activation of beta adrenoreceptors, catecholamines may induce hypermetabolism and increase both cardiac and cerebral oxygen demands. We conducted a systematic review to appraise the available evidence examining the safety and efficacy of beta blockers in patients with acute TBI.
Methods We systematically searched CENTRAL, MED-LINE, EMBASE and the reference lists of relevant articles from database inception until March 19, 2013. The outcomes assessed were in-hospital mortality, functional outcome and quality of life. Common adverse effects of beta blockers were examined including clinically significant hypotension, bradycardia, bronchospasm and congestive heart failure. Data on study outcomes and quality were abstracted in duplicate. The results were summarized descriptively and quantitatively.
Results One randomized controlled trial was found with a high risk of bias. Eight retrospective cohort studies were found with a moderate risk of bias; however, only four of these studies were identified as unique after excluding overlapping cases. The cohort studies reported mortality outcomes; however, none of these included studies assessed functional outcomes or quality of life. Meta-analysis on the cohort studies ($n = 4{,}782$ patients) demonstrated that exposure to beta blockers after TBI was associated with a reduction in the adjusted odds of in-hospital mortality by 65 % (pooled adjusted odds ratio 0.35; 95 % CI 0.27–0.45).
Conclusions The current body of evidence is suggestive of a benefit of beta blockers following TBI. However, methodologically sound randomized controlled trials are indicated to confirm the efficacy of beta blockers in patients with TBI.

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Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide. It is a major health and socioeconomic problem that results in an estimated 1.5 million injuries, more than 50,000 deaths, and the loss of over US $60 billion per year in the USA alone [1–4].

Because the primary injury cannot be reversed, the mainstay of TBI management to improve neurological outcome is the prevention of secondary injury. Currently, there is no targeted pharmacological treatment that effectively limits the progression of secondary injury and thereby improves the outcome [5]. However, extensive research focusing on the mechanisms of secondary insult following TBI has recently highlighted numerous potential targets for intervention.

TBI has been shown to be associated with a systemic hyperadrenergic state [6]. Through activation of beta adrenoreceptors, catecholamines may induce hypermetabolism and increase both cardiac and cerebral oxygen demands [6–8]. There are animal data that suggest potential neuroprotective effects of beta blockers by improving surrogate immunohistochemical markers of cerebral perfusion and decreasing cerebral oxygen demand, as observed with positron emission tomography [9–11]. In addition, beta blockers have been associated with beneficial cardioprotective and metabolic effects and improved outcomes in burn patients who have a similar hyperadrenergic state [12, 13]. A component of the Lund protocol to manage TBI that has been popular in Sweden is the use of the beta blocker metoprolol, in addition to other agents including an alpha-2 agonist and an angiotensin II inhibitor [14, 15]. These treatments are thought to decrease the intracapillary hydrostatic pressure and subsequently decrease the vasogenic edema that often complicates TBI. This protocol was derived from experimental animal studies and the physiological principles of cerebral autoregulation [14, 16].

Beta blockers have shown promising results in animal studies, case series and historical control studies in addition to multiple recent cohort studies [17, 18]. Therefore, a review of high-quality clinical studies examining the efficacy and safety of beta blockers after TBI is needed. The objectives of this review were as follows: (1) to determine the efficacy of beta blockers in reducing the mortality of hospitalized TBI patients; (2) to determine the efficacy of beta blockers in improving the functional outcomes and the quality of life of TBI patients; and (3) to determine the safety profile of beta blockers in the acute TBI population.

Methods

Types of Studies

We recognize that randomized controlled trials (RCTs) specifically designed to compare beta blockers against placebo in patients with TBI may not exist because beta blockers are medications that are used primarily for cardiovascular indications. Regardless, such trials were sought out so that they may be included in this review. Because of the high likelihood of a lack of RCTs, we also included quasi-randomized and non-randomized controlled trials, as well as cohort studies (prospective and retrospective) comparing TBI patients who received beta blockers after injury to those who did not. Other non-randomized study designs were excluded. Among the included studies, RCTs and observational studies were analyzed separately, as a direct comparison between the estimates of observational studies and RCTs can be misleading.

Types of Participants

We included studies that incorporated adult patients hospitalized with acute TBI.

Types of Interventions

All types, doses and routes of administration of beta blockers were included, provided they were given during the acute hospital stay and continued for any duration of time. The comparison group may have received either placebo or no treatment.

Types of Outcome Measures

The primary outcome of this review was in-hospital mortality. The secondary outcomes considered were as follows: (1) functional outcome at the latest time measured, as assessed using scales such as the Glasgow Outcome Score (GOS) scale, Extended Glasgow Outcome Score (GOSE) scale, Functional Independence Measure (FIM), or Disability Rating Scale (DRS); (2) quality of life at the latest time measured, as measured using standardized scales; (3) the safety of beta blockers use after TBI as assessed by the rate of common adverse effects of beta blockers such as clinically significant hypotension (i.e., systolic blood pressure <90 mm Hg, which requires fluid resuscitation, discontinuation of the study drug, an inotropic agent), clinically significant bradycardia (i.e., bradycardia requiring a temporary pacemaker, a sympathomimetic agent, atropine or discontinuation of the study drug), bronchospasm (i.e., bronchospasm requiring discontinuation of the

beta blocker or use of a bronchodilator) and congestive heart failure.

Search Methods for Identification of Studies

We searched MEDLINE (from 1950 to March 19, 2013), EMBASE (from 1980 to March 19, 2013) and Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2013). The search was not restricted by date, language or publication status. The search strategy was based on the MEDLINE search strategy and was modified as necessary for the other databases (Supplementary Appendix). In addition, we searched the reference lists of relevant articles and the following registers to identify ongoing trials:

- Clinical Trials (http://www.clinicaltrials.gov);
- Current Controlled Trials (http://www.controlled-trials.com/mrct).

Data Collection and Analysis

Two of the review authors (AA and VM) independently examined all of the abstracts of the studies identified by our search and determined the eligibility of each study. Any disagreements were resolved by consensus. We scanned the titles and abstracts of every record retrieved to determine which of the studies should be assessed further. If it was clear from the title and abstract that the article was irrelevant, the article was rejected. The full texts of the remaining articles were then retrieved. The reference lists of the retrieved articles were also searched for additional citations.

Data abstraction forms were created and used to collect the relevant data from the included studies (Supplementary Appendix). Two of the review authors (AA and VM) independently extracted data on patients, methods, interventions (or exposures in the cohort studies), outcomes and results.

Two of the review authors (AA and VM) independently assessed the risk of bias for each included study. Any disagreement was resolved through discussion and consensus. Each included study was classified as a RCT or a cohort study, and the risk of bias was assessed differently for each type of study. For RCTs, we used the Cochrane Collaboration's tool for assessing risk of bias [5] according to the following domains: sequence generation, allocation concealment, blinding of outcomes, incomplete outcome data, selective outcome reporting and baseline imbalances. For the cohort studies, selection of the exposed and non-exposed cohorts, the comparability of the cohorts, the assessment of the outcomes and the adequacy of follow-up were addressed. The Newcastle–Ottawa Scale (NOS) was used for assessing the risk of bias in the cohort studies (Supplementary Appendix) [20]. The scale was modified to include a number of TBI prognostic variables [age,

pupillary reactivity and Glasgow Coma Scale (GCS) Score] under the comparability category and therefore allowed the reviewers to optimize the applicability of the scale to the TBI cohort studies. Our selection for these prognostic variables was based on the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) core prognostic model [21]. When considering comparability in the NOS, we assessed whether these important variables were adjusted for in the analysis. One to three points were awarded if age, the GCS motor score and/or the pupillary reaction were adjusted for by the study.

We calculated the odds ratio (OR) to measure the treatment effect for the dichotomous outcomes with corresponding 95 % confidence intervals (CI). Pooling of overall estimates of effect was performed using generic inverse variance weighting methods. Using these methods, each study estimate of the relative treatment is given a weight that is equal to the inverse of the variance of the effect estimate (i.e., one divided by the standard error squared). Clinical heterogeneity across the studies was assessed by examining the details of the subjects, the baseline data, and the interventions and the outcomes to determine whether the studies were sufficiently similar. Statistical heterogeneity was determined using the I^2 statistic and the chi-square test. There were too few studies to use a funnel plot to assess for reporting bias.

We used the Review Manager 5.1 software (RevMan 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to carry out a quantitative analysis. We performed a meta-analysis using a fixed-effect model because there was no evidence of significant clinical or statistical heterogeneity between the studies.

Results

Description of Studies

A total of 5,298 potentially relevant citations were screened for retrieval. 363 duplicates were excluded. A total of 4,911 were excluded after scanning the titles and/or abstracts because they did not meet our inclusion criteria (Fig. 1). A total of 24 citations were retrieved for detailed evaluation of the full text articles. Fifteen of those citations were excluded because they were case series, historical control studies or the measured outcomes were different than our set criteria for primary or secondary outcomes (further details are in the Supplementary Appendix).

After applying our selection criteria, we identified one RCT (by Cruickshank et al.) and eight retrospective cohort studies (Fig. 1) [22–30]. The cohort studies by Salim et al. [23], Inaba et al. [25], Hadjizacharia et al. [26] and Bukur et al. [29] appear to originate from the same cohort and

were conducted mostly by the same group of investigators. The Salim et al. study sample appears to be a subgroup of the Inaba et al. but with a different analysis plan and objectives [23, 25]. The main objective of the Salim et al. cohort study was to investigate the relationship between troponin elevation and the outcome of severe TBI [23]. Similarly, the Hadjizachria et al. and the Bukur et al. cohorts appear to overlap with the Inaba et al. cohort. The primary objective of the Hadjizachria et al. study was to determine the association between atrial arrhythmias and the outcomes of trauma patients, while the Bukur et al. study evaluated the association between beta blockers and the outcomes of TBI across different racial groups [26, 29]. Therefore, we included only the Inaba et al. study and excluded the Salim et al., Hajizacharia et al. and Bukur et al. studies, because the Inaba et al. cohort was more representative of the general TBI population and the primary objective of the Inaba et al. study addressed the same question as our review. A similar overlapping case was found between the Cotton et al. and the Riordan et al. cohorts [24, 28]. We elected to include the Cotton et al. study and exclude the Riordan et al. study because the primary focus of the Riordan et al. study was to examine the relationship between beta blocker exposure and the outcome of a subgroup of TBI population who had early cardiac uncoupling [24]. Cotton et al. on the other hand included a sample that was more representative of the general TBI population [28]. Hence, the eight cohort studies that we reviewed constituted four unique cohorts.

Two ongoing trials were also identified. Ley et al. (ClinicalTrials.gov, NCT01202110) are conducting a phase II, dose escalation, single-center study on the effects of early propranolol on heart rate, blood pressure and cerebral

Fig. 1 Flowchart of study selection process

perfusion pressure in subjects with moderate to severe TBI. Patel et al. (ClinicalTrials.gov, NCT01322048) are recruiting patients with acute severe TBI for a pilot RCT comparing propranolol and clonidine treatments versus a placebo. The primary outcome for this trial is ventilator-free days.

Included Studies

Descriptive statistics were extracted from the RCT by Cruickshank et al. and each of the eight cohort studies (Tables 1 and 2, a more detailed description is provided in the Supplementary Appendix). However, only data from the four unique cohort studies were used for the meta-analysis (Fig. 2).

The Cruickshank et al. study was a double-blinded placebo-controlled trial, published in 1987, that examined the safety and impact of atenolol on cardiac morbidity of patients with acute TBI [27]. This trial included patients aged 11–70 years old, with a primary diagnosis of acute TBI, and were admitted to the intensive care or neurosurgical unit of one of the four study centers in three European countries [27]. The study drug was initiated immediately after hemodynamic stabilization (mean time was 20.2 h following injury) [27].

The cohort studies included only hospitalized adult patients with TBI as defined by the head Abbreviated Injury Scale (AIS) score or by using the International Statistical Classification of Diseases, Ninth Revision (ICD-9CM) code for blunt TBI [22–26, 28–30]. The exposures in the included studies were defined as any beta blocker agent, regardless of dose or route of administration; however, all beta blockers were initiated during the acute hospital stay following TBI and continued for a variable length of time. The four unique cohort studies included a total of 4,782 patients. All of the cohort studies were conducted in the USA and were published between 2007 and 2012. None of the included studies declared sponsorship [22–30].

Risk of Bias in the Included Studies

The RCT by Cruickshank et al. had a high risk of bias because of a small sample size ($n = 114$), an unclear randomization and allocation concealment method, and incomplete outcome data (Table 3).

The risk of bias assessment of the included cohort studies was carried out using a modified NOS (Supplementary Appendix). Each one of the four unique cohort studies (Arbabi et al., Cotton et al., Inaba et al. and Schroeppel et al.) had a moderate risk of bias and reached 6–7 out of 9 points (Table 4).
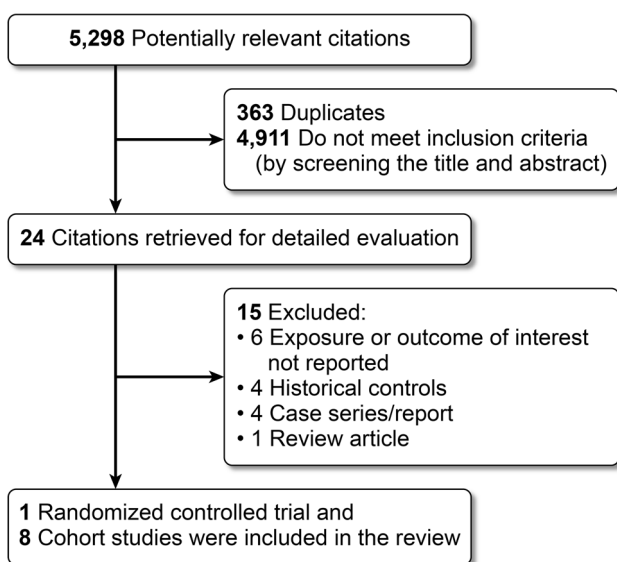
Table 1 Summary of results from randomized controlled trials

Study	N	Intervention	Outcome measure	Result	p value	Overall quality assessment
Cruickshank et al. [27]	114 (intervention: 56, control: 58)	After initial stabilization: atenolol 10 mg IV every 6 h for 3 days then 100 mg PO OD for 4 days versus matching placebo	Cardiac morbidity defined as: CK-MB level, noradrenaline level, arrhythmia, ST/T wave changes. Secondary outcomes include: hypotension bronchospasm and heart failure	Lower risk of high CK-MB (i.e., >3 % of total CK) level (2/27 vs. 9/30); similar noradrenaline levels; lower risk of supraventricular tachycardia (6/46 vs. 28/49); lower risk of ST/T wave changes (15 vs. 26). No significant difference in other outcomes: hypotension (5/56 vs. 2/58), bradycardia (6/56 vs. 6/58) heart failure (0/56 vs. 0/58), and bronchospasm (1/56 vs. 0/58)	<0.05 for CK-MB, <0.0001 for supraventricular tachycardia, <0.05 for ST/T wave changes, 0.27 for hypotension, 0.95 for bradycardia, 1.0 for heart failure, 0.49 for bronchospasm	Poor

IV: intravenous; PO: oral; OD: once a day; CK-MB: MB isoform of creatine kinase enzyme

Outcome Assessment

In-hospital mortality was assessed by all cohort studies but not by the RCT [22, 25, 28, 30]. None of the included studies examined functional outcome or quality of life measures.

The findings of the cohort studies are summarized in Table 2. All of the cohort studies demonstrated that beta blocker exposure after TBI was associated with older age, higher comorbidity burden and more severe injuries. The investigators of these studies attempted to adjust for potential confounding variables (Table 2). In adjusted analyses, all of the four unique cohort studies showed that beta blocker exposure following TBI was associated with reduced in-hospital mortality [22, 25, 28, 30].

Meta-analysis of the four unique cohort studies (Fig. 2) showed that exposure to beta blockers after TBI was associated with a reduction in the adjusted odds of in-hospital mortality by 65 % (pooled OR 0.35; 95 % CI 0.27–0.45; $p < 0.00001$, $I^2 = 0$ %).

Salim et al. suggested that beta blocker therapy was associated with a larger survival advantage among the subgroup of patients with isolated blunt TBI who had elevated troponin levels at some point during the first 48 h of their hospital stay [23]. None of the included cohort studies adequately described the different subgroups of TBI (mild, moderate and severe) to allow for a subgroup analysis of the relationship between beta blocker therapy and hospital mortality of the different TBI severity subgroups.

The only study that assessed for potential adverse events associated with beta blocker therapy in TBI population was the RCT by Cruickshank et al. (Table 1) [27]. Compared to the placebo group, there was a lower proportion of patients with abnormally high CK-MB level (2/27 vs. 9/30, respectively, $p = 0.05$) and a lower incidence of supraventricular tachycardia in the atenolol group (6/46 vs. 28/49, $p < 0.0001$). In addition, there was no significant difference between both groups in terms of the incidence of the other outcomes including hypotension, bradycardia, congestive heart failure and bronchospasm (Table 1) [27].

Discussion

Our review summarizes the mounting clinical evidence suggesting the safety and benefit of beta blocker therapy in patients with acute TBI. This meta-analysis suggests that beta blocker administration following acute TBI was associated with lower in-hospital mortality. There are no data regarding impact on functional outcomes or quality of

Table 2 Summary of results from cohort studies

Study	N	Intervention	Outcome measure	Result[a]	p value	Comments	Modified Newcastle–Ottawa Scale score
Arbabi et al. [30]	605 (exposure = 94, control = 511)	Any beta blocker given for >24 h during hospital stay	In-hospital mortality	Lower adjusted odds of mortality (OR 0.2)[b]	<0.0001	Adjusted for age, ISS, total GCS, head AIS, systolic blood pressure	7/9
Bukur et al. [29]	2,446 (exposure = 886, control = 1,580)	Any beta blocker exposure during ICU stay	In-hospital mortality	Lower adjusted odds of mortality (120 vs. 297 deaths, OR 0.63)	0.001	Adjusted for age, total GCS (≤8), ISS, head AIS (>3), hypotension, subarachnoid hemorrhage, basal skull fracture	7/9
Cotton et al. 2007 [28]	420 (exposure = 173, control = 247)	Metoprolol, propranolol, labetalol, esmolol, atenolol or sotalol given for ≥48 h during hospital stay for ≥2 consecutive days	In-hospital mortality	Lower adjusted odds of mortality (9 vs. 27 deaths, OR 0.29)	<0.0001	Adjusted for age, race, gender, mechanism of injury, ISS, Revised Trauma Score (RTS), calculated probability of survival using the Trauma-Related Injury Severity Score (TRISS) methodology.	6/9
Hadjizacharia et al. [26]	695 (exposure = 320, control = 375)	Any beta blocker exposure during ICU stay	In-hospital mortality	Lower odds of mortality (20 vs. 81 deaths, OR 0.30)	Not reported	Not clear if adjusted analysis was done	5/9
Inaba et al. [25]	1,156 (exposure = 203, control = 953)	Any beta blocker exposure during ICU stay	In-hospital mortality	Lower adjusted odds of mortality (34 vs. 199 deaths, OR 0.54)	0.01	Adjusted for age, total GCS (≤8), ISS, head AIS (>3), hypotension, subarachnoid hemorrhage, basal skull fracture	7/9
Riordan et al. [24]	446 (exposure = 138, control = 308)	Esmolol, propranolol, labetalol, metoprolol, atenolol or carvedilol regardless of dose, duration or route of administration	In-hospital mortality	Lower odds of mortality (29 vs. 135 deaths, OR 0.83)	Reported as non-significant	Adjusted for age, ISS and length of stay using propensity score methods	5/9
Salim et al. [23]	420 (exposure = 91, control = 329)	Any beta blocker exposure during hospital stay	In-hospital mortality	Lower odds of mortality (22 vs. 118 deaths, OR 0.59), even lower odds in subgroup of patients with elevated troponin during admission (OR 0.38)	0.09 (0.03)	Adjusted for age, total GCS (≤8), ISS, head AIS (>3), days ventilated, ventilated, peak troponin, admission troponin, subarachnoid hemorrhage, basal skull fracture	6/9

Table 2 continued

Study	N	Intervention	Outcome measure	Result[a]	p value	Comments	Modified Newcastle–Ottawa Scale score
Schroeppel et al. [22]	2,601 (exposure = 506, control = 2095)	Atenolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, propranolol or sotalol. Exposure was defined by receiving >one dose of a beta blocker during hospital stay	In-hospital mortality	Lower odds of mortality (76 vs. 335 deaths, OR 0.35)	<0.0001	Adjusted for age, total GCS, ISS, blood transfusion	7/9

[a] The effect estimate (i.e., odds ratio) compares the exposure group (beta blockers) to the control group (reference)

[b] Number of events (i.e., deaths) was not reported for traumatic brain injury subgroup in this study

OR odds ratio, *GCS* Glasgow Coma Scale, *ISS* injury severity score, *AIS* Abbreviated Injury Score, *ICU* intensive care unit
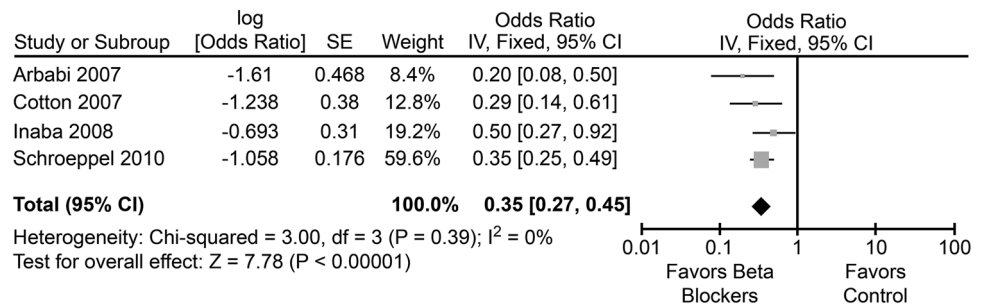
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life measures. Safety data from one study revealed no increase in adverse events in beta blockers group.

Beta blocker therapy in acute TBI is appealing, as an increasing body of physiological literature supports the hypothesis that beta blockers might be beneficial following TBI [7–10, 31–35]. Among the proposed mechanisms of benefit is the reduction in cerebral metabolic rate and oxygen demands as protective mechanism for the acutely injured and highly vulnerable parts of the brain [9, 10]. Systemically, beta blockers might also protect other end organs that are prone to damage by the TBI-induced catecholamine surge [31, 33, 36, 37]. In addition, a group from Lund, Sweden, has long advocated for the use of a management protocol for severe TBI based on the physiological principles of cerebral autoregulation, which includes the administration of the beta blocker metoprolol, to decrease the intracapillary hydrostatic pressure and thereby limit the formation of brain edema. [14]. However, our review indicates the lack of evidence from prospective studies to support this management protocol, although multiple case series and historical control studies have suggested a significant reduction in TBI mortality after the introduction of this protocol [15, 16, 38, 39]. The use of a historical control group fails to account for multiple important confounders including the change in the quality of general care of the critically ill patients over the last few decades. Thus, the Lund protocol, although promising, has not gained wide acceptance, and it needs to be evaluated by well-designed prospective studies.

In this systematic review, we used a very sensitive search strategy to identify all relevant observational studies and controlled trials without any restriction by date, language or publication status. In addition, two reviewers independently applied the inclusion criteria and assessed the risk of bias of the included studies using well-structured and validated tools.

The evidence supporting the use of beta blockers in TBI is certainly limited by the lack of well-designed controlled trials that address critically important outcomes in TBI population (e.g., mortality, functional and quality of life outcomes), and the fact that most relevant studies were retrospective in nature. The limitations of retrospective cohort studies in this area include the possibility of a survivor-treatment bias. Patients in the beta blockers group may have simply lived long enough to receive beta blockers, whereas those in the comparison group may have died prior to having the opportunity to receive beta blockers. Some of the included studies tried to address this bias. Cotton et al. attempted to address this bias by excluding patients with a length of stay <4 days, which implies the exclusion of early deaths [28]. The survival advantage of beta blockers, after excluding these early deaths, remains statistically significant [28]. Schroeppel

Fig. 2 Forest plot of comparison: beta blocker exposure after acute traumatic brain injury versus no exposure; outcome: in-hospital mortality

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Odds Ratio IV, Fixed, 95% CI
Arbabi 2007	-1.61	0.468	8.4%	0.20 [0.08, 0.50]	
Cotton 2007	-1.238	0.38	12.8%	0.29 [0.14, 0.61]	
Inaba 2008	-0.693	0.31	19.2%	0.50 [0.27, 0.92]	
Schroeppel 2010	-1.058	0.176	59.6%	0.35 [0.25, 0.49]	
Total (95% CI)			**100.0%**	**0.35 [0.27, 0.45]**	

Heterogeneity: Chi-squared = 3.00, df = 3 (P = 0.39); I^2 = 0%
Test for overall effect: Z = 7.78 (P < 0.00001)

0.01　0.1　1　10　100
Favors Beta Blockers　　Favors Control

Table 3 Risk of bias assessment for randomized controlled trials (based on Cochrane Collaboration's tool of assessing risk of bias [19]

Study	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Baseline imbalance
Cruickshank et al. [27]	Unclear risk	Unclear risk	Low risk	High risk (CK-MB) was measured in only 60 patients, noradrenaline was measured in only 69 patients, daily ECG was obtained in 104 patients, continuous blood pressure monitoring was available in 3 out of 4 study centers, 3 patients had incomplete outcome data because they were discharged from ICU to floor)	Low risk	High risk (more patients with severe traumatic brain injury in the intervention group than in the control group; 14 vs. 6, respectively)

ICU intensive care unit, ECG electrocardiogram

Table 4 Risk of bias assessment for cohort studies (based on modified Newcastle–Ottawa Scale)

Study	Selection	Comparability	Outcome	Total score
Arbabi et al. [30]	***	**	**	7/9
Bukur et al. [29]	***	**	**	7/9
Cotton et al. [28]	***	*	**	6/9
Hadjizacharia et al. [26]	***	–	**	5/9
Inaba et al. [25]	***	**	**	7/9
Riordan et al. [24]	**	*	**	5/9
Salim et al. [23]	**	**	**	6/9
Schroeppel et al. [22]	***	**	**	7/9

et al. showed that the survival advantage was smaller, but still significant, after excluding deaths within the first 24 h and non-significant after excluding deaths within 48 h post-injury [22]. Although the results from Cotton et al. study and the sensitivity analyses of Schreoppel et al. study appear reassuring, the optimal way to address the survivor-treatment bias will be to conduct a RCT. The included studies are also limited by the inclusion of multiple beta blocking agents with variable affinity to different types of beta receptors, the different dosing regimens, and the variable timing and duration of beta blocker administration. Nevertheless, the relative homogeneity, consistency and

magnitude of the survival advantage shown in the meta-analysis, among the older, more severely injured and chronically ill patients who received beta blockers, provide an argument for designing RCTs in the future to address this important research question.

Issues that should be addressed by RCTs in the future include the safety of beta blockers in the acute TBI population, the optimal beta blocker agent and dosing regimen for this indication, the impact of beta blockers use on the long-term functional and quality of life outcomes of TBI patients, and whether beta blockers are more beneficial in specific subgroups of TBI patients.

Conclusions

The current body of evidence is suggestive of a benefit of beta blocker therapy in patients hospitalized with acute TBI. Prior to making any practice recommendations, well-designed randomized controlled trials are needed to better evaluate the safety and impact of this promising intervention on long-term mortality, functional outcome and quality of life of patients following TBI.

Conflict of interest No competing financial interests exist.

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