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Beta-Blockers and Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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Abstract

OBJECTIVE—To determine if beta-(β)-blockers improve outcomes after acute traumatic brain injury (TBI).

BACKGROUND—There have been no new inpatient pharmacologic therapies to improve TBI outcomes in a half-century. Treatment of TBI patients with β-blockers offers a potentially beneficial approach.

METHODS—Using MEDLINE, EMBASE, and CENTRAL databases, eligible articles for our systematic review and meta-analysis (PROSPERO CRD42016048547) included adult (age≥16 years) blunt trauma patients admitted with TBI. The exposure of interest was β-blocker administration initiated during the hospitalization. Outcomes were mortality, functional measures, quality of life, cardiopulmonary morbidity (e.g. hypotension, bradycardia, bronchospasm, and/or congestive heart failure). Data were analyzed using a random-effects model, and represented by pooled odds ratio (OR) with 95% confidence intervals (CI) and statistical heterogeneity (I^2).

RESULTS—Data were extracted from 9 included studies encompassing 2005 unique TBI patients with β-blocker treatment and 6240 unique controls. Exposure to β-blockers after TBI was associated with a reduction of in-hospital mortality (pooled OR 0.39, 95%CI: 0.27–0.56; I^2=65%, p<0.00001). None of the included studies examined functional outcome or quality of life measures, and cardiopulmonary adverse events were rarely reported. No clear evidence of reporting bias was identified.

CONCLUSIONS—In adults with acute TBI, observational studies reveal a significant mortality advantage with β-blockers; however, quality of evidence is very low. We conditionally recommend the use of in-hospital β-blockers. However, we recommend further high-quality trials to answer

questions about the mechanisms of action, effectiveness on subgroups, dose-response, length of therapy, functional outcome, and quality of life after β-blocker use for TBI.

INTRODUCTION

Traumatic brain injury (TBI) is a public health problem with profound consequences (1). Acute TBI is associated with a hyperadrenergic state that, in the context of a disrupted blood brain barrier, leads to high local norepinephrine levels and increased cerebral metabolic rate (CMR) for both oxygen and glucose. The increased CMR in the injured brain, with defective autoregulation, can exacerbate the pre-existing ischemia and metabolic crisis following TBI (2). This hyperadrenergic state may contribute to increased mortality after TBI (3) and, conversely, patients with low levels of adrenergic stress as evidenced by a normal heart rate may have reduced mortality after TBI (4).

Treatment with beta-adrenergic receptor antagonists offers a potentially beneficial approach to blunting this cascade of sympathetic activation after TBI (3,5). However, β-blockers are negative inotropes and can induce bradycardia. Either adverse effect can lead to hypotension, which is associated with poor outcomes in the TBI population (6–8). β-blockers have been evaluated mostly in retrospective cohort studies and a meta-analysis of the literature through mid-2013 demonstrated a potential mortality benefit with exposure to β-blockers (9). However, additional studies have been published since then and an updated systematic review is required to summarize the current evidence and offer guidance to clinicians. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (10–12), we performed a systematic review, meta-analysis, and guideline that could aid decision-making for in-hospital β-blockers after traumatic brain injury.

METHODS

Objective

Our PICO (Population, Intervention, Comparator, and Outcomes) question was structured as follows:

Population:In adults with acute TBI,

Intervention: in-hospital β-blockers should be used

Comparator: in-hospital β-blockers should not be used

Outcome: To improve mortality, functional outcomes, quality of life outcomes, without worsening cardiopulmonary morbidity (e.g. hypotension, bradycardia, bronchospasm, and/or congestive heart failure).

Study Eligibility

Our protocol was registered with the PROSPERO international prospective register of systematic reviews (Registration Number: CRD42016048547). This study is transparently built upon a previously published systematic review, using similar methods and eligibility

criteria(9). We searched for randomized controlled trials (RCTs), quasi-randomized and non-randomized controlled trials, and cohort studies (prospective and retrospective) comparing TBI patients who received in-hospital β-blockers after injury to those who did not. We excluded case reports, letters to the editor, articles in the lay press, abstracts, and review articles. RCTs and observational studies were analyzed separately, as a direct comparison between the estimates of observational studies and RCTs could be misleading.

Population

We included studies that involved adult patients aged ≥ 16 years with acute TBI of any severity requiring hospital admission.

Interventions and Comparators

All forms of in-hospital β-blockers were included, provided they were given during the hospital stay and continued for any duration of time. The comparison group could have received either placebo or no treatment. We included any dose of beta-blockers and planned sensitivity analyses if different dose and regimens were utilized.

Outcome measures

Per GRADE methodology, outcomes were chosen by the team and rated in importance from 1 to 9, with scores of 7–9 representing critical outcomes. The critical outcomes were in-hospital mortality, functional recovery, and quality of life with scores of 9, 8, and 7 respectively. The important (i.e., secondary) outcomes all related to cardiopulmonary morbidity. We broadly accepted functional outcome, as assessed using the Glasgow Outcome Score (GOS) scale, Extended Glasgow Outcome Score (GOSE) scale, Functional Independence Measure (FIM), or Disability Rating Scale (DRS). Similarly, we allowed quality of life metrics that used any standardized scale. Our secondary outcomes consisted of common cardiopulmonary adverse effects of β-blockers, such as cardiac biomarker elevation, arrhythmia, clinically significant hypotension (i.e., systolic blood pressure < 90 mm Hg, which required fluid resuscitation, discontinuation of the study drug, and/or an inotropic agent), clinically significant bradycardia (i.e., bradycardia requiring a temporary pacemaker, a sympathomimetic agent, atropine, or discontinuation of the study drug), bronchospasm, and/or congestive heart failure.

Information Sources

Similar to the original systematic review and meta-analysis on this topic, we searched MEDLINE (from January 1, 1950), EMBASE (from January 1, 1980), and Cochrane Central Register of Controlled Trials (CENTRAL, all years). The search was not restricted by date, language or publication status. The search was last updated on May 9, 2016. The search strategy was based on the MEDLINE search strategy (Supplementary Material, **Table: Search Strategy**), and was modified as necessary for the other databases. In addition, we searched the reference lists of relevant articles.

Data collection and analysis

Two authors 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 and including a third author. 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 manuscripts of the remaining articles were then retrieved.

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

Risk of Bias Assessment

Two authors independently assessed the risk of bias for each included study. Any disagreement was resolved through discussion and consensus. Each included study was classified as an 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 of assessing risk of bias according to the following domains: sequence generation, allocation concealment, blinding of outcomes, incomplete outcome data, selective outcome reporting, and baseline imbalances (13). For cohort studies, selection of the exposed and unexposed cohorts, the comparability of the cohorts, the assessment of the outcomes, and the adequacy of follow-up were addressed using the Newcastle-Ottawa Scale (NOS, Supplementary Material, Figure 1) (14). The scale was modified to include important 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 (15). When considering comparability in the modified NOS, we assessed whether these important variables were adjusted for in a multivariate analysis (e.g., age, GCS score, pupillary reaction).

Quantitative Assessment

We calculated the odds ratio (OR) to measure the treatment effect for the dichotomous outcomes with corresponding 95% confidence intervals (CI). The generic inverse variance method was used when the included study reported only the odds ratio (OR) and its standard error. 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. We used a funnel plot to assess for reporting bias (Supplementary Material, Figure 2).

We used the Review Manager software (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to conduct a quantitative analysis. We performed a meta-analysis using a random-effect model because there was a suggestion statistical heterogeneity between the studies, although there was no evidence of clinical heterogeneity.

RESULTS

Qualitative Synthesis, Excluded Studies

A total of 8,004 potentially relevant citations were screened for retrieval. 499 duplicates were excluded. 7,459 were excluded after scanning the titles and/or abstracts because they did not meet our inclusion criteria (Figure 1). A total of 46 citations were retrieved for detailed evaluation of the full text articles. We excluded 32 of those citations. Ten studies were excluded as the key exposure or outcome was not reported (16–25). Three were excluded due to the study population (26–28). Five were excluded due to the use of historical controls.(29–33) Four were excluded as they were case series or case reports (34–37). Seven were excluded as they were review articles (2,38–43). Three were excluded as they were studies in animals (44–46). These exclusions left a total of 14 manuscripts, including 1 randomized controlled clinical trial (47) and 13 cohort studies (48–60). This represents 5 new cohorts since our original systematic review.

In this section, we describe the overlapping non-unique cohorts that we excluded from the meta-analysis. There were four overlapping non-unique cohorts derived from the same cohort and were conducted mostly by the same group of investigators (50,57–59). One study cohort (57) was a subgroup of a larger cohort (50) but with a different analysis plan and objectives, specifically to investigate the relationship between troponin elevation and the outcome of severe TBI. Two other cohorts, designed to study the association between atrial arrhythmias and trauma patient outcomes (58) and to evaluate the association between β-blockers and TBI outcomes across different racial groups (59) were both subsets of the same larger cohort (50) study. Therefore, we included only the larger cohort (50) which was more representative of the general TBI population and the primary objective addressed the same question as our review. A similar overlapping example was found between a cohort study including a sample that was more representative of the general TBI population (49) and a cohort designed to examine the relationship between the β-blockers exposure and the outcome of a subgroup of the TBI population who had early cardiac uncoupling (60). Hence, we meta-analyzed 9 unique cohorts (i.e., quantitative synthesis) among the 13 studies identified by qualitative synthesis (Figure 1).

Qualitative Synthesis, Included studies

Descriptive statistics were extracted from the RCT by Cruickshank *et al.*(47) and each of the 13 cohort studies (Tables 1A and 1B). Again, only data from the 9 unique cohort studies were used for the meta-analysis (Figure 2).

The Cruickshank *et al.* (47) 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(47). This trial included patients with ages of 11–70 years old with acute TBI, admitted to the intensive care or neurosurgical unit of one of four study centers in three European countries. The study drug was initiated immediately after hemodynamic stabilization (mean time was 20.2 hours following injury) (47).

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 (48–50,54,57–60). The exposures in the included studies were defined as any β-blockers agent, regardless of dose, route of administration, or pre-hospital exposure. All β-blockers were initiated during the acute in-hospital stay following TBI and continued for a variable length of time. The 9 unique cohort studies included a total of 8,245 patients. All of the cohort studies were conducted in the United States except one (Mohseni *et al.* (52) was conducted in Sweden). The studies were published between 2007 and 2016.

The RCT by Cruickshank *et al.* had a high risk of bias because of unclear randomization and allocation concealment method, and incomplete outcome data (Table 2). The risk of bias assessment of the included cohort studies was carried out using a modified NOS. Each one of the 9 cohort studies had a moderate risk of bias and reached scores of 5–7 out of 9 points (Table 3).

Outcome assessment, Critical Outcomes

Hospital mortality was assessed by all cohort studies but not by the RCT (48–50,54). None of the included studies examined functional outcome or quality of life measures. The findings of the cohort studies are summarized in Table 1B. Of the 9 cohort studies, 8 demonstrated that β-blockers exposure after TBI was associated with older age, higher comorbidity burden and more severe injuries. The investigators of 8 of the 9 cohort studies attempted to adjust for potential confounding variables (Table 1B). Seven of the 8 cohort studies that adjusted for potential confounders showed that β-blockers exposure following TBI was associated with statistically significant lower in-hospital mortality. In a subgroup analysis of the Schroeppel *et al.* (54) study, propranolol use was associated with lower mortality while use of other β-blockers did not show a significant association with mortality. The other study that showed no difference in mortality did not present an adjusted analysis. In general, propranolol was the most frequently studied, although there are also a limited number of studies employing metoprolol or labetalol.

Outcome assessment, Important Outcomes

Two studies assessed for potential cardiopulmonary adverse events associated with β-blockers therapy in TBI patients (47, 53). Compared to the placebo group in the RCT by Cruickshank *et al.* (47), the atenolol group had a lower proportion of patients with abnormally high CK-MB cardiac biomarker level (2/27 vs. 9/30, $p=0.05$) and a lower incidence of supraventricular tachycardia (6/46 vs. 28/49, $p<0.0001$). 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 1A). In the Murry *et al.* (53) cohort, there was no significant difference in the rate of hypotensive events but more bradycardia episodes (defined as heart rate < 60 beats/min) were recorded in the control group relative to the patients who received propranolol. It was not reported whether these bradycardia events were clinically significant and symptomatic (i.e. events requiring a temporary pacemaker, a sympathomimetic agent, atropine, or discontinuation of the propranolol).

Quantitative assessment (Meta-analysis)

Meta-analysis of the cohort studies (Figure 2) showed that exposure to β-blockers after TBI was associated with a significant reduction in the adjusted odds of in-hospital mortality (9 studies, 8,245 patients, pooled OR 0.39, 95% CI: 0.27–0.56; I^2=65%, p<0.00001). None of the included cohort studies adequately described the different severity subgroups of TBI to allow for a subgroup analysis of the relationship between β-blockers therapy and hospital mortality of the different TBI subgroups. No clear evidence of reporting (i.e., publication) bias was noted from the funnel plot (Supplementary Material, Figure 2).

Grading the Evidence

In reference to our critical outcome, hospital mortality, the study designs were observational and retrospective. The risk of bias is serious with flawed measurements of exposure (i.e., no study reported dose or timing) and confounders (i.e. no study reported pre-injury exposure, daily ICU covariates). Furthermore, there is a potential publication bias as the included RCT states: “total deaths and in-hospital deaths will be fully reported elsewhere”, but this critical outcome is not found elsewhere in the literature despite lack of measurable publication bias by funnel plot. Inconsistency is very serious due to wide and unassessed baseline risk factors such as pre-injury cardiopulmonary comorbidities and pre-injury β-blocker use. There is substantial heterogeneity (I^2 = 65%) indicating serious statistical inconsistency. Indirectness is very serious due to differences in population (e.g. TBI severity, polytrauma severity, cardiovascular risk factors, age), differences across intervention (e.g., type dose, length, target of β-blocker), and differences across comparator (i.e., reasons for control or non-exposure). Imprecision is also very seriously compromised with inability of the pooled sample to achieve optimal information size. For example, to witness the raw unadjusted mortality effect (16.9% with β-blocker, versus 17.7% with control), using a Type I error of 5%, power of 80%, over 35,000 *subjects per arm* would be required to enroll in a clinical trial. So, the quality rating for the in-hospital mortality outcome is very low. But, we see a strong association of β-blocker use with our critical outcome of in-hospital mortality (i.e., 61% lower odds of mortality or 2.6 lower odds of mortality), thus upgrading its quality from very low to low. Despite this quality upgrade, the overall quality of evidence across all outcomes ultimately remains very low due to the total lack of evidence for our critical outcomes of functional outcome and quality of life. Our hierarchy of outcomes and summary of findings are detailed in Table 4.

Recommendation

In adults with acute TBI with no contraindications for β-blockers, we conditionally recommend the use of in-hospital β-blockers (Figure 3) provided that hypotension (defined as systolic blood pressure<90mmHg) and symptomatic bradycardia (defined as heart rate<50 with symptoms) are avoided. The evidence is limited about whether these thresholds are too restrictive or irrelevant, but it would be cavalier to employ permissive hypotensive strategies in the face of known TBI outside of clinical trials (6,15). The majority of cohort studies included patients with Head AIS of 4–5. Therefore, we limit our recommendation to patients with severe TBI who are admitted to ICU where monitoring for and prevention of adverse cardiovascular events is feasible. Although this recommendation

is based on a synthesis of very low-quality studies, most of these studies demonstrate a consistent effect and do not report significant cardiopulmonary harm from administration of β-blockers. However, we cannot provide a recommendation on when to initiate β-blockers, which β-blockers to use, or how to titrate β-blockers to a specific heart rate, blood pressure, and/or length of time.

DISCUSSION

This multispecialty-authored systematic review, meta-analysis, and guideline identified that quality of evidence is very low for in-hospital β-blockers to reduce mortality after TBI, and supports a weak recommendation for the use of in-hospital β-blockers after acute TBI in adults. Despite the paucity of randomized studies, this systematic review and meta-analysis of the observational data suggests that β-blockers reduce mortality after TBI with no major adverse effects. There are no data on the impact of β-blockers use on functional outcome or quality of life measures in TBI patients (61).

Although the results of this meta-analysis (Figure 2) appear to be quite compelling, with an odds ratio for in-hospital mortality of 0.39 [95%CI 0.27–0.56], one must be careful due to the likelihood of selection bias in most of the included studies due to the lack of randomization. We draw the parallel of this evolving story to the practice-changing Corticosteroid Randomization After Significant Head injury (CRASH) trial published in the Lancet (62), which debunked the decades old practice of corticosteroid treatment after TBI. The pre-trial foundational meta-analysis (63) suggested corticosteroid should be moved forward into the large-scale RCT phase, however it could have been heavily influenced by one study (64,65). As we now know, the CRASH trial found corticosteroids increased mortality, as opposed to the prior notion of survival benefit. Therefore, we can only offer a conditional (i.e., weak) recommendation in favor of in-hospital β-blocker use after TBI. This recommendation is conditional on the avoidance of symptomatic bradycardia and hypotension, which may be associated with poor outcome following TBI (6,15). Furthermore, we limit our recommendation to patients with severe TBI who are admitted to ICU where monitoring for adverse cardiovascular events is feasible.

It is evident that mortality is not a perfect endpoint for patients with TBI, who might survive only to be inflicted with life-long functional impairment of a vegetative or severely disabled state (e.g., RESCUE-ICP (66) and DECRA (67) RCTs). Unfortunately, the value to society and to individuals for small changes in functional status is not well-defined, thus limiting the interpretation of the extended Glasgow Outcome Scale (GOS-E) often used in TBI RCTs (68–71). “The 100 percent failure rate for TBI clinical trials strongly suggests that” future TBI RCTs should use A) “quantitative outcome measures”, B) "require more optimization of dose", and C) “adopt adaptive designs” (72).

A number of ongoing studies will likely provide more insight on the mechanism of action, safety, and efficacy of these agents in the TBI population (Decreasing Adrenergic or Sympathetic Hyperactivity after severe traumatic brain injury using propranolol and clonidine (73), NCT01322048 and NCT02957331 (accessible at https://clinicaltrials.gov), and the AAST multi-center prospective, observational study on immune dysfunction in

subjects who present with TBI and receive β-blockers (accessible at http://www.aast.org)). All the studies to date only report the dichotomous use (i.e., yes/no) of β-blockers. There are no real-world data on standardized β-blocker dose-equivalents, or time-varying adjustment accounting for daily confounders of complex ICU care. Although propranolol is a cheap, centrally acting agent with intravenous and oral formulations, perhaps making it easier to initially study, consideration should also be given to determine the comparative effectiveness of other mixed-receptor agents (e.g., labetalol) or rapidly metabolized intravenous agents (e.g., esmolol). We do not know if the survival benefit observed in our analysis may be related to the degree of heart rate control (56) and whether competing pressor use influenced outcomes, as studied in septic ICU populations without TBI (74). Given that the only reported effect is on mortality, future studies should focus on patients with a significant risk of death. These patients could include those requiring ICU care, moderate or higher TBI, specific pathoanatomic classes of intracranial hemorrhage, and/or a combination of prognostic covariates for mortality. These additional studies should help answer questions about β-blocker mechanism of action, while adjusting for covariates (e.g. brain injury severity, polytrauma, associated co-morbidities, daily ICU events) to reveal effects on long-term patient-centered outcomes on cognition, neurologic function, and quality of life. Given the complexity of TBI management as well as subtle possible differences in clinical signs and symptoms, imaging, and genetic variances in the population, a large federally supported trauma consortium should provide the funding and research infrastructure necessary to advance the field in this regard (75).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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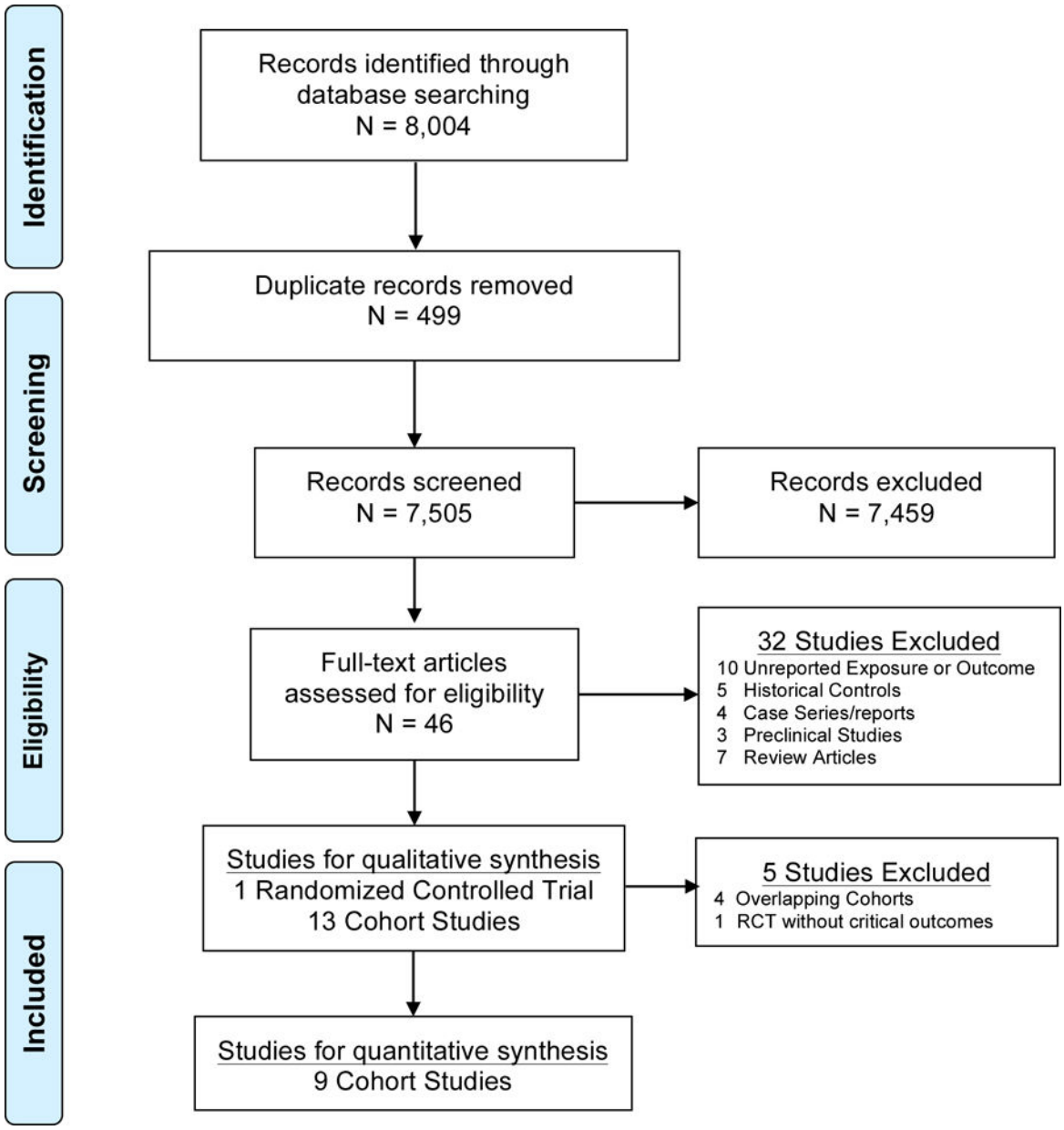

Figure 1.
PRISMA flow diagram for systematic review phases of Beta-Blockers after traumatic brain injury

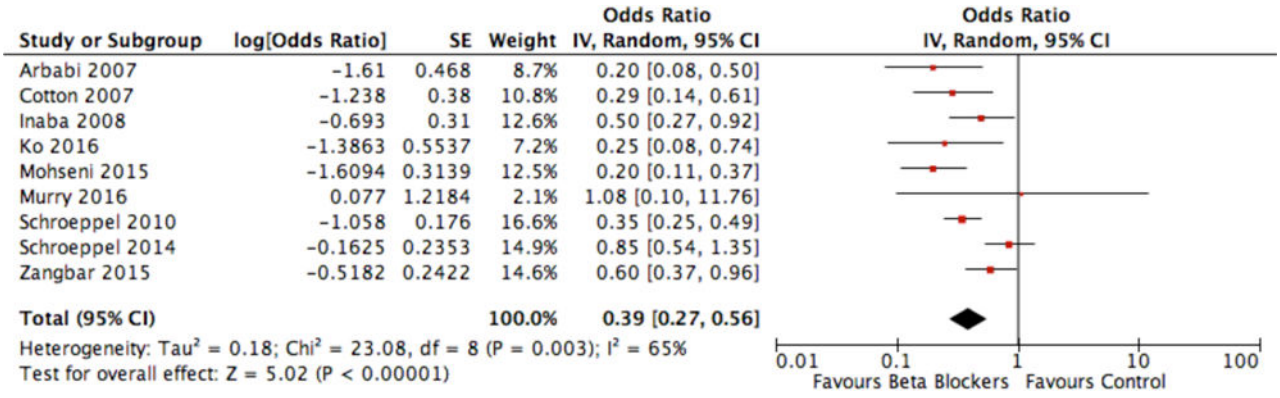

Figure 2.

Forest plot of Beta-blocker exposure after acute traumatic brain injury versus no exposure with in-hospital mortality outcome

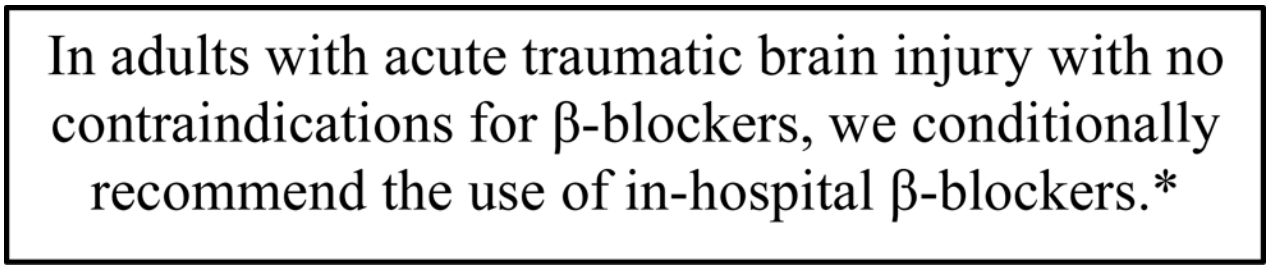

Figure 3.
Practice management guideline for Beta-Blockers after traumatic brain injury
*Provided that common ICU complications of hypotension (i.e., usually defined as systolic blood pressure<90mmHg) and symptomatic bradycardia (is, usually defined as heart rate<50 with symptoms) are avoided

Table 1A

Detailed Results from Randomized Controlled Trials of Beta-Blockers after TBI

Author Year (Reference)	N	Intervention	Outcome Measure	Result	P value	Overall Quality Assessment
Cruickshank 1987 (47)	114 (intervention=56, control= 58)	After initial stabilization: Atenolol 10 mg IV every 6 hours for 3 days then 100 mg PO OD for 4 days Vs. 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 (6/56 vs. 28/58); lower risk of ST/T wave changes (15/56 vs. 26/58), 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

Table 1B

Detailed Results from Cohort Studies of Beta-Blockers after TBI

Author Year (Reference)	N	Intervention	Outcome Measure	Result¶	P value	Comments
Arbabi 2007 (48)	605 (exposure=94, control=511)	Any β-blockers given for >24 Hours during hospital stay	In-hospital Mortality	Lower adjusted odds of mortality (9 vs. 27 deaths, OR 0.2)*	<0.0001	Adjusted for age, ISS, total GCS, Head AIS, SBP
Cotton 2007 (49)	420 (exposure=173, control=247)	Metoprolol, propranolol, labetalol, esmolol, atenolol or sotalol given for >48 Hours 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.
Inaba 2008 (50)	1,156 (exposure=203, control=953)	Any β-blockers 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, ISS, Head AIS, hypotension, subarachnoid hemorrhage, basal skull fracture
Ko 2016 (51)	440 (exposure=109, control=331)	Propranolol at 1-mg intravenous every 6 h starting within 12 hours of admission for a minimum of 48 hours.	In-hospital mortality	Lower adjusted odds of mortality (7 vs. 43, OR 0.25)	0.012	Adjusted for age, total GCS, ISS, SBP, type of intracranial injury and neurosurgical intervention
Mohseni 2015 (52)	874 (exposure=287, control=587)	Any β-blockers exposure during hospital stay	In-hospital mortality	Lower adjusted odds of mortality (30 vs. 102 deaths, OR 0.20)	0.001	Adjusted for age, total GCS, ISS, Head AIS, neurosurgical intervention and type of intracranial injury
Murry 2016 (53)	38 (exposure=28, control=10)	Propranolol at 1 -mg intravenous every 6 h starting within 12 hours of admission for a minimum of 48 hours.	Primary outcomes: hypotension & bradycardia. Secondary outcomes: In-hospital mortality	No difference in hypotension but more bradycardic episodes in the control group. Similar odds of mortality (3 vs. 1 deaths, OR1.08)	0.60 for hypotension, 0.05 for bradycardia	No adjusted analysis was done
Schroeppel 2010 (54)	2,601 (exposure=506, control=2095)	Atenolol, carvedilol, esmolol, labetolol, metoprolol, nadolol, propranolol or sotalol. Exposure was defined by receiving > one dose of a P- blockers during hospital stay	In-hospital mortality	Lower adjusted odds of mortality (76 vs. 335 deaths, OR 0.35)	<0.0001	Adjusted for age, total GCS, ISS, blood transfusion

Author Year (Reference)	N	Intervention	Outcome Measure	Result[¶]	P value	Comments
Schroeppel 2014 (55)	1,755 (exposure=427, control=1,328)	Atenolol, carvedilol, esmolol, labetolol, metoprolol, nadolol, propranolol or sotalol. Exposure was defined by receiving > one dose of a P- blockers during hospital stay	In-hospital mortality	Similar adjusted odds of mortality (56 vs. 80 deaths, OR 0.85 95% CI: 0.54–1.35). Lower odds in subgroup of patients who received propranolol (OR 0.2, 95% CI: 0.04–0.92)	Not reported	Adjusted for age, total GCS, Head AIS, admission SBP, blood transfusion
Zangbar 2015 (56)	356 (exposure=178, control=178)	Metoprolol. Exposure was defined as receiving at least one dose during hospital stay.	In-hospital mortality	Lower adjusted odds of mortality (100 vs. 110 deaths, OR 0.79)	0.04	Using propensity score matching, patients were matched controlling for age, gender, race, admission vital signs, total GCS, ISS, average heart rate monitored during ICU admission, and standard deviation of heart rate during the ICU admission
Salim 2008 (57)	*420 (exposure=91, control=329)*	*Any fi-blockers exposure during hospital stay*	*In-hospital mortality*	*Lower adjusted 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, ISS, Head AIS, days ventilated, ventilated, peak troponin, admission troponin, subarachnoid hemorrhage, basal skull fracture*
Hadjizacharia 2011 (58)	*695 (exposure=320, control=375)*	*Any fi-blockers 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*
Bukur 2012 (59)	*2,446 (exposure=886, control=1,580)*	*Any fi-blockers 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, ISS, Head AIS, hypotension, subarachnoid hemorrhage, basal skull fracture*
Riordan 2007 (60)	*446 (exposure=138, control=308)*	*Esmolol, propranolol, labetalol, metoprolol, atenolol or carvedilol regardless of dose, duration or route of administration*	*In-hospital mortality*	*Lower adjusted odds of mortality (29* vs. *135 deaths, OR 0.83)*	*Non-significant*	*Adjusted for age, ISS and length of stay using propensity score methods*

[¶]The effect estimate (i.e. odds ratio) compares the exposure group (β-blockers) to the control group (reference).

[*]Number of events (i.e. deaths) was derived from population rates but not directly reported for traumatic brain injury subgroup in this study.

OR: odds ratio; GCS: Glasgow Coma Scale; ISS: Injury Severity Score; AIS: Abbreviated Injury Score; OR: odds ratio; ICU: intensive care unit; CI: confidence interval; SBP: systolic blood pressure

Italics of lower 4 rows of cohorts represent overlapping cohorts from higher rows of original cohorts

Table 2

Risk of Bias Assessment for a Randomized Controlled Trial (based on Cochrane Collaboration's tool of assessing risk of bias[19]) of Beta-Blockers after TBI

Study, Year	Random Sequence Generation	Allocation concealment	Blinding of Outcome Assessment	Incomplete Outcome data	Selective Reporting	Baseline Imbalance
Cruickshank 1987 (47)	**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 3

Risk of Bias Assessment for Cohort Studies (based on modified Newcastle-Ottawa scale) of Beta-Blockers after TBI

Study	Selection	Comparability	Outcome	Total Score
Arbabi *et al.*, 2007(48)	***	**	**	7/9
Cotton *et al.*, 2007(49)	***	*	**	6/9
Inaba *et al.*, 2008(50)	***	**	**	7/9
Ko *et al.* 2016(51)	***	**	**	7/9
Mohseni *et al.* 2015(52)	***	**	**	7/9
Murry *et al.* 2016(53)	***	–	**	5/9
Schroeppel *et al.*, 2010(54)	***	**	**	7/9
Schroeppel *et al.*, 2014(55)	***	**	**	7/9
Zangbar *et al.* 2015(56)	***	**	**	7/9
Salim *et al.*, 2008(57)	**	**	**	6/9
Hadjizacharia *et al.*, 2011(58)	***	–	**	5/9
Bukur *et al.*, 2012(59)	***	**	**	7/9
Riordan *et al.*, 2007(60)	**	*	**	5/9

Lower Total Score means Higher Risk of Bias.

Table 4

Summary of Findings for Beta-Blockers after TBI

QUALITY ASSESSMENT							SUMMARY OF FINDINGS			
Participants (Studies)	**Study Design**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Quality of Evidence**	**Study Event Rates (%)**		**Relative Effect**	**Anticipated Absolute Effects**
							With β-Blocker after TBI	**No β-Blocker after TBI**		**Risk Difference using β-Blocker after TBI**
CRITICAL OUTCOME: In-hospital Mortality										
8,245 (9 studies)	Cohorts	Very Serious[1]	Very Serious[2]	Very Serious[3]	Serious[4]	++, low[5]	338/2005 (16.9%)[6]	1103/6240 (17.7%)[6]	0.39 (0.27 to 0.56)	99 fewer per 1000 (from 69 to 122 fewer)
CRITICAL OUTCOME: Function										
0 (0 studies)	N/A	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	+, very low	N/A	N/A	N/A	N/A
CRITICAL OUTCOME: Quality of Life										
0 (0 studies)	N/A	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	+, very low	N/A	N/A	N/A	N/A
IMPORTANT OUTCOME: Cardiac Morbidity by Biomarker/Arrhythmia										
114 (1 study)	Randomized Clinical Trial	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	Unable to Assess[7]	+, very low	2/27 (CK-MB) 6/46 (SVT)	9/30(CK-MB) 28/49 (SVT)	N/A	N/A
IMPORTANT OUTCOME: Hypotension										
152 (2 studies)[8]	Randomized Clinical Trial	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	+, very low	5/56[8]	2/58[8]	N/A	N/A
IMPORTANT OUTCOME: Bradycardia										
152 (2 studies)[8]	Randomized Clinical Trial	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	+, very low	6/56[8]	6/56[8]	N/A	N/A
IMPORTANT OUTCOME: Congestive Heart Failure										
114 (1 study)	Randomized Clinical Trial	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	+, very low	0/56	0/58	N/A	N/A
IMPORTANT OUTCOME: Bronchospasm										
114 (1 study)	Randomized Clinical Trial	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	Unable to Assess[3]	+, very low	1/56	0/58	N/A	N/A

[1] Inconsistency is very serious due to wide and unassessed baseline risk factors such as pre-injury cardiopulmonary comorbidities and pre-injury β-blocker use; substantial heterogeneity (I2 = 65%) indicating serious statistical inconsistency

[2] Indirectness is very serious due to differences in population (e.g. TBI severity, non-TBI severity, age), differences across intervention (e.g., type dose, length, target of β-blocker), and differences across comparator (i.e., reasons for control or non-exposure)

[3] Imprecision is also very seriously compromised with inability of the pooled sample to achieve optimal information size, as using a Type I error of 5%, power of 80%, over 35,000 subjects per arm would be required to enroll in a clinical trial

[4] Known publication bias, as reviewed not but included RCT for this outcome states, "in-hospital deaths will be fully reported elsewhere", but this critical outcome is not found elsewhere in the literature, despite being unable to quantify publication bias by funnel plot

[5] Upgraded quality of evidence from very low to low quality given the consistent large magnitude of effect, 61% lower odds of mortality or 2.6 lower odds of mortality)

[6] Number of deaths were derived from population rates but not directly reported for 1 of the pooled cohort studies

[7] No published studies or No studies available for comparison

[8] We only report the Randomized Clinical Trial; the other study is a prospective cohort that reports group statistical characteristics but not patient level data for these outcomes