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A Systematic Review and Meta-Analysis on Effect of Beta-Blockers in Severe Traumatic Brain Injury

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ABSTRACT

Objectives: Systematically review the medical literature for the impact of beta-blockers on mortality and functional capacity in patients who suffered severe traumatic brain injury.
Data Sources: The search included MEDLINE, EMBASE, and Ovid Evidence-Based Medicine, clinical trial registries, and bibliographies.
Study Selection: All articles that reported outcome in TBI patients treated with beta-blockers.
Data Extraction: Publication year, number of patients, outcome and follow-up. We performed a meta-analysis for each variable for which there were sufficient data to estimate mean differences.
Data Synthesis: 12 studies were included, which involved retrospectively and prospectively collected data on 14,057 patients. The treatment with beta-blockers was associated with a reduction in mortality in patients who were treated with beta-blockers compared to the control group (OR 0.40, 95% CI 0.30–0.54p = <0.00001), with acceptable heterogeneity between studies (I2 = 65% p = 0.00008). Beta-blocker therapy decreases the risk of negative neurological and functional outcomes (OR 0.59, 95% CI 0.38–0.92 p = <0.00001), a very high statistical heterogeneity between the included studies (I2 = 80% p = 0.00004), being able to influence the results. An increase in favorable neurological and functional outcomes is shown (OR 1.19, 95% CI 1.07–1.31 p = 0.001) with acceptable heterogeneity (I2 = 52% p = 0.08)
Conclusions: The beta-blockers therapy is associated with significantly improves outcome in patients with TBI. Treatment with beta-blockers in patients with TBI is a promising frontier in neurotrauma.

Abbreviations:CI: confidence interval; BB: Beta-Blockers; OR = odds ratio; TBI: Traumatic Brain Injury SD: Standard deviation; SNS: Sympathetic nervous system

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Beta-(β)-blockers improve outcomes after acute traumatic brain injury (TBI)

Introduction

Traumatic Brain Injury (TBI) is a cause of morbidity and mortality in people of all ages worldwide. There have been an estimated 73 cases per 100,000 people each year, with 90% of deaths occurring in low- and middle-income countries [1]. After the primary injury, various pathophysiological mechanisms are activated, including the release of significant amounts of catecholamines [2]. Empirical evidence has supported the implementation of beta-blockers in TBI. The production of catecholamines activates apoptotic and inflammatory mechanisms are deleterious for brain tissue [3]. Some studies have shown that plasma catecholamine levels are related to the outcome in TBI [4–6]. From this point of view, treatment with drugs that exert sympathetic cascade blockade can decrease the physiological effects of the hyperadrenergic state. Drugs belonging to the family of beta-blockers have shown in some studies effects of improving the outcome in patients with TBI[6].

The rationale for using is that physiological and pharmacological evidence suggests a favorable effect of intervention with beta-blockers in patients with TBI. The use of beta-blockers drugs has been widely used in cardiology for the treatment of cardiac pathologies. They have also been useful in managing migraine and essential tremor with proven effectiveness. The purpose of this study is to investigate the effect on outcome and functional capacity in patients with TBI who have received beta-blockers treatment in different cohorts published in the literature.

Methods

Literature search

We used the search strategies recommended for the preferred reporting items for systematic reviews and

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meta-analyses (PRISMA) reporting guidelines and the meta-analysis of observational studies in epidemiology (MOOSE) reporting guidelines. Titles, abstracts, key words, and free text were searched using combinations of the following key words : ('Traumatic brain injury' OR 'Brain trauma' OR 'craniocerebral trauma' [all fields]) AND ('Beta-adrenergic antagonist' OR 'Beta blockers' OR 'Propranolol' OR 'Metoprolol') AND ('observational studies' OR 'clinical study') AND 'Humans' NOT 'Animals' NOT 'preclinical studies'. We searched PubMed, MEDLINE (Ovid), EMBASE, and Scopus from database inception to June 2020 for RCT, not RCT, prospective and retrospective cohort studies that reported data on the use of beta-blockers for management of TBI. We added studies from the reference list of included studies and other relevant data in addition to potentially eligible studies.

Inclusion and exclusion criteria

This analysis included: The studies to be included are screened separately using the following inclusion criteria: 1. Patients with TBI 2. RCT, non-RCT, prospective and retrospective cohort studies describing various risk factors 3. Patients of any age. Exclusion criteria: 1. Studies with poly trauma 2. Studies that include penetrating trauma, firearm projectile trauma, blast wave trauma 3. Animal studies, in vitro, simulations in virtual reality or by computer.

Data collection process

Two review authors (L.R.M.S. and W.F.P.) independently extracted data from the included studies using a piloted data extracted form, resolving any discrepancies through discussion. We retrieved any articles identified as potentially relevant by at least 1 review author. Two review authors (L.R.M.S. and W.F.P.) independently screened full-text articles, with discrepancies resolved through discussion. The references of relevant studies were cross-checked for additional studies not identified by the electronic search.

Data extraction

The following data is extracted: 1) study characteristics; 2) patient characteristics (number of patients, demographics, and clinical characteristics); 3) eligibility, based on the abovementioned study selection criteria; 4) mortality and morbidity; 5) adverse technical events; 6) We also categorized adverse procedural events as follows: symptomatic ischemic events, hemorrhagic events, and symptoms derived from mass effect. The doubts were clarified by consensus.

Quality assessment and statistical analysis

Statistical analysis was performed through the Odds ratio with Generic inverse variance methodology for studies only report OR. Studies that do not report risk

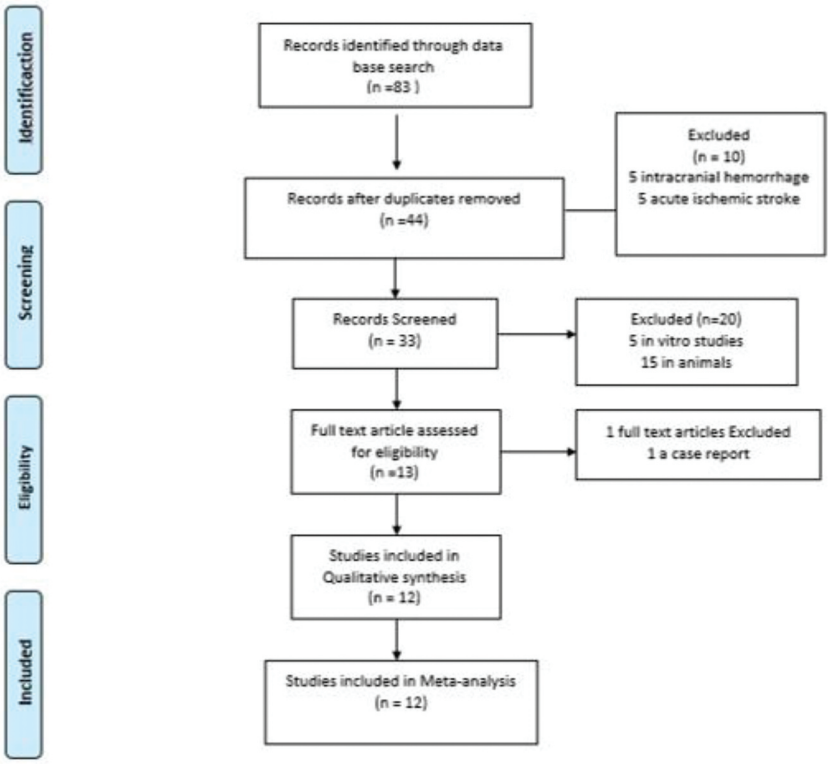

Figure 1.

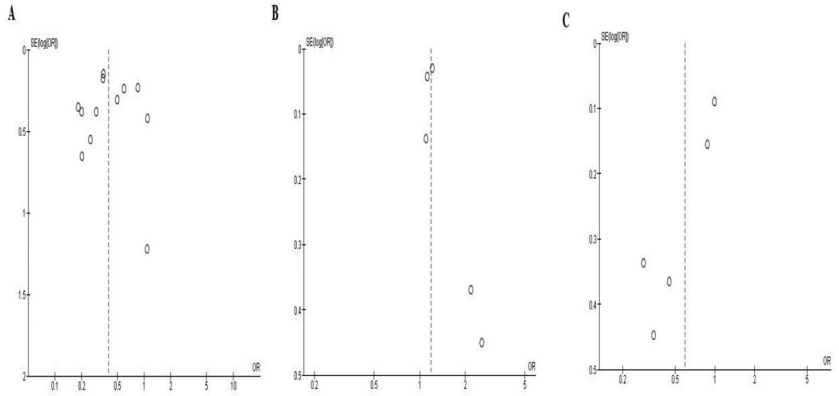

Figure 2. Funnel plot that assesses the presence of risk of publication bias is the outcomes (a). mortality (b). Good outcome (c). Poor Outcome.

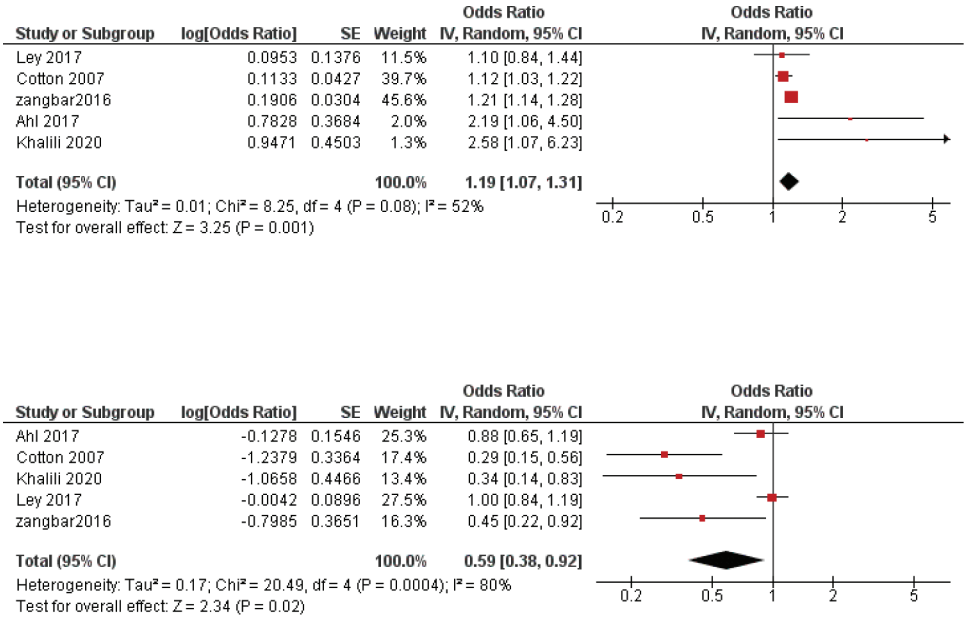

Figure 3. Forest plot of the reported outcomes.

measures will be calculated with a Fixed effect analysis model calculated using RevMan 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). We analyzed the Odds ratio (OR) of each of the predictive factors using the generic method of the inverse of the variance to combine these data, some studies did not explicitly report them, which we calculated using the OR calculator of Review manager. Heterogeneity was assessed by calculating Chi-square (I^2), with a high heterogeneity of the studies included in the analysis being above 60%. The modified Newcastle–Ottawa scale (NOS)2[6] was used for assessing the quality and risk of bias of the included studies. One reviewer (WF) assessed the risk of bias of each study using this scale and high, moderate and low risk of bias were defined as NOS<4, between 4 and 6, and >6, respectively, as in the original NOS. The risk of publication bias was further assessed using and comparing the Egger's test. A P-value of less than 0.1 for Egger's test was considered statistically significant.

Results

Study selection

After conducting the systematic search of the information following our strategy, 83 bibliographic citations were identified, 44 were considered potentially eligible based on the title or abstract, or both, and the full texts After a review of the full text, 13 studies were considered eligible, 1 was ruled out because it did not meet the inclusion criteria and did not answer the research question and 12 met the inclusion criteria for the review (Figure 1) [7–15].

Study characteristics

From the studies included, 7 were retrospective cohort observational studies [9,10,13–17] and 5 Prospective [7,8,11,12,18]. Summary of characteristics of included studies is summarized in Table 1.

Table 1. Summary of studies included in the meta-analysis.

Study	Type	Patients	Outcomes	Length following	GRADE Quality
Ahl [14]	Retrospective cohort study	N = 152 Beta-blockers N = 76 Control = 76 Glasgow Come Scale 8 (±3)	In-hospital mortality 12-month Mortality Glasgow outcome scale (GOS) Length stay in NICU	12 Months	⊕ ⊕ ⊕OMODERATE
Arbabi [16]	Retrospective cohort study	N = 4117 Beta-blockers N = 303 Control = 3814 Head AIS 3 (±2.3)	Mean length of hospital stay (days) Mortality	In Hospital	⊕OOOVERY LOW
Cotton [18]	Prospective cohort study	N = 414 Beta-blockers N = 174 Control = 240	Mean length of hospital stay (days) Mortality Mean Length of ICU Functional discharge*	In Hospital	⊕ ⊕ ⊕OMODERATE
Inaba [17]	Retrospective cohort study	N = 1156 Beta-blockers N = 203 Control = 953 Glasgow Come Scale 8 (±3)	Mean length of hospital stay (days) Mortality Mean Length of ICU	In Hospital	⊕ ⊕OOLOW
Kahlili [12]	Prospective Randomized clinical trial	N = 154 Beta-blockers N = 68 Control = 86 Head AIS C 4	Mortality Length of stay ICU ICU LOS days, mean [SD] Craniectomy/craniotomy GOSE	6 months	⊕ ⊕ ⊕ ⊕HIGH
Ko [7]	Prospective cohort study	N = 440 Beta-blockers N = 109 Control = 331 Glasgow Come Scale 8 (±3)	Mortality Length of stay ICU ICU LOS days, mean [SD]	In Hospital	⊕ ⊕OOLOW
Ley [11]	Prospective cohort study	N = 2252 Beta-blockers N = 1120 Control = 1132 Glasgow Come Scale 9 (±3)	Mortality Glasgow Outcome Scale	In Hospital	⊕ ⊕ ⊕OMODERATE
Mohseni [13]	Retrospective cohort study	N = 622 Beta-blockers N = 159 Control = 463	Mortality Length of stay ICU ICU LOS days, mean [SD]	In Hospital	⊕ ⊕ ⊕OMODERATE
Murry [8]	Prospective cohort study	N = 38 Beta-blockers N = 28 Control = 10	Mortality Length of stay ICU ICU LOS days, mean [SD]	In Hospital	⊕ ⊕ ⊕OMODERATE
Schroeppel [9]	Retrospective cohort study	N = 2601 Beta-blockers N = 506 Control = 2095 AIS 3.88 (±0.92)	Mortality Length of stay ICU Transfusion	24 to 48 hours	⊕ ⊕OOLOW
Schroeppel [10]	Retrospective cohort study	N = 1755 Beta-blockers N = 427 Control = 2095 AIS 4.4 (±0.91)	Mortality Length of stay ICU	In Hospital	⊕ ⊕OOLOW
Zangbar [15]	Retrospective cohort study	N = 356 Beta-blockers N = 178 Control = 178	Mortality Length of stay ICU ICU LOS days, mean [SD] Functional prognosis *	In Hospital	⊕ ⊕OOLOW

*Was need contact to corresponding author for this date. No reported in published version, in their protocol is available

Risk of bias

The risk of bias assessment was performed using the ROBINS-I tool, which evaluates the following 7 domains: D1: Bias due to confounding; D2: Bias in selection of participants; D3: Bias in classification of interventions; D4: Bias due to deviations from intended intervention; D5: Bias due to missing data; D6: Bias in measurement of outcomes; D7: Bias in selection of the reported results, based on the presence or absence of some characteristic in 'Low Risk', 'moderate risk', 'serious Risk', 'critical Risk' and 'no information'. The quality of the evidence was used on the GRADE scale. (Figure 2).

Systematic review

The cohort study by Ahl et al. [14] report in a prospective series of 362 patients treated with TBI that exposure to β-blockers was associated with improve functional outcome. In this study, 21% of patients received β-blockers upon admission. It also highlights that the poor long-term functional outcome was higher in the untreated group. Arbabi et al. [16],

showed in a retrospective study in a cohort of burns victims recruited between 1996 and 2001, who received treatment with beta-blockers during their hospitalization presented decrease in fatal outcome compared to the control group. Cottom et al. [18], showed using a retrospective series of patients obtained from the Trauma Registry of the American College of Surgeons database recruited between 2004 and 2005 show a reduction in mortality in patient users of beta-blockers. It is noteworthy in this study that patients benefited from the effect of beta-blockers even though the user group of blockers were older, with more severe injuries and lower predicted survival. Inaba et al., demonstrated in patients recruited from a surgical ICU database requiring intensive management from 1998 to 2005 that use of beta-blockade in patients with TBI was associated with improved survival. In a randomized trial, Khalil et al. show that propranolol treatment is associated with decreased mortality and improves the term functional outcome. Ko et al., show that treatment with early treatment with propranolol is associated with lower mortality. Ley et al. [11], in a multicenter study performed in US and Canada with 2,252 recruited from 2015 to 2017 show that beta-blocker treatment in patient suffering TBI is observed an effect on improving survival. Mohseni et al. [13], using data from an urban academic trauma center from 2007 to 2011, establish that patient with preinjury β-blockade treatment have a better survival regarding isolated TBI. Murry et al. [8], found that intravenous propranolol treatment after TBI is associated with decreased ICU and hospital length of stay. Schroeppel et al. [9] show that beta-blocker treatment in patients with TBI is an economic strategy to reduce mortality using data from trauma registry from 2003 to 2007. Schroeppel et al. [10] analyzing a series of 1,755 patients admitted to a trauma center for 48 months with TBI shows that propanolol is useful for limiting secondary injury as well as reducing mortality. Zangbar et al. [15], reported that using metoprolol in a cohort of patients is possible improved survival in TBI patients and independent of heart rate.

Meta-analysis

After performing the search following the previously described strategy, 88 citations were found, 44 after eliminating duplicates of these, 10 were discarded (5 to be evaluated in intracranial hemorrhage and 5 to be evaluated in ischemic stroke), 33 studies were screened and 20 were eliminated as studies, preclinical (in vitro 5 and 15 experimental animals), 13 were considered potentially eligible on the basis of title or abstract, or both, and full texts were obtained. After reading and analyzing the full texts, 1 was discarded as a case report, 12 were included in the meta-analysis (see Figure 1 and Table 1).

Risk of bias was assessed following the established in the ROBINS-I Tool. A risk was found in the global assessment of bias of moderate and low bias in 80% of the included studies, the Arbabi et al. and Ko et al. studies presented a high risk of bias, as no significant bias was assessed in the D2 and D1 domains on the evaluated scale, most had a moderate risk of bias, which is expected for observational studies. Twelve studies were chosen for the final analysis, involving 13,517 patients. A total of 3351 was administered and 10,166 only standard trauma care protocol was applied without administration of beta-blockers. A reduction in mortality was evident in patients who were treated with beta-blockers compared to the control group (OR 0.40, 95% CI 0.30–0.54p = <0.00001), with acceptable heterogeneity between studies. (I2 = 65% p = 0.00008). Beta-blocker therapy decreases the risk of negative neurological and functional outcomes (OR 0.59, 95% CI 0.38–0.92 p = <0.00001), a very high statistical heterogeneity between the included studies (I2 = 80% p = 0.00004), being able to influence the results. An increase in favorable neurological and functional outcomes is shown (OR 1.19, 95% CI 1.07–1.31 p = 0.001) with acceptable heterogeneity (I2 = 52% p = 0.08). (Figure 3).

Discussion

In this paper, we report a meta-analysis about beta-blockers used in patients with TBI. Despite the heterogeneity of the results evaluated in this study, the included and published data demonstrate that beta-blocker treatment is associated with outcome increased. The main merit of our study is that we include all the clinical experiences published to date. This systematic review is the most comprehensive that evaluates the role of beta-blockers in the treatment of TBI. Beta-blockers are widely used drugs in medicine. Its mechanism of action is antagonizing beta-adrenergic receptors that modulates multiple physiological functions. Beta-adrenergic receptors are a type of family of receptors coupled to abundant G proteins in multiple tissues. Possible pathophysiological effects of the action of beta-blockers is focused on reducing the risk of injury associated with the stimulation of catecholaminergic receptors, as well as reducing tissue oxygen demand and modifying brain metabolism.

The development of a hyperadrenergic state is a phenomenon frequently found in patients with TBI [19]. Clinically and physiologically, the elevation of blood levels of catecholamines and the action on adrenergic receivers leads to: Tachycardia, hypertension, tachypnea, and agitation. The elevation of catecholamines is associated with a hypermetabolic state that is associated with a worse prognosis[20].

Modulation of the adrenergic system by antagonism of beta adrenergic receptors would potentially block

activation of the sympathetic nervous system after primary injury[21]. In a meta-analysis by Alali et al., they conclude that the use of beta-blocking drugs in TBI is conditionally recommended in the acute phase[22].

Establishing which beta-blocker drug is best is another question to define in future studies, propranolol and metoprolol are the most widely used in the series. It is also unknown how the protective effect occurs considering the central and peripheral actions of beta-blockers. We have no reason to choose the pharmacological dose, dose, and timing, but doses of 1 mg every 6 hours administered in the first 6 hours of the attending phase seem a reasonable strategy that needs to be established.

This review was designed to be comprehensive with a robust search strategy; however, it is possible that not all studies were identified. Our results demonstrated a significant increase in survival of patients with TBI that receive beta-blocker treatment. Further evidence is required to increase confidence in the effects of pharmacological intervention and detect subcategory of patients that could be benefited from the treatment.

The benefits of our study are 3-fold. First, we conducted a thorough literature review, to establish the real effect of beta-blocker treatment on TBI patients. Second, we establish how treatment with beta-blockers decreases the negative neurological result and increases survival, thus confirming previously published data. Third, our data invite future research to establish in robust multicenter studies the role of beta-blockers for their incorporation into the routine practice of managing patients with TBI.

Limitations

Our study has several limitations. Studies included in this analysis were retrospective. All articles included in this review are peer-reviewed. There is a possibility of publication bias. The inclusion of only articles in English could affect the generalization of our findings. Like any other study of a meta-analytical nature that uses pooled data without access to original patient data, it falls into another of our limitations. Publication bias was assessed by assessing funnel plot symmetry, asymmetry is evident in most of the risk factors analyzed, which could be interpreted as the presence of publication bias, however, it should be taken into account that built with few studies (5), according to the Cochrane manual for systematic reviews This indicates that the assessment of this bias is less than 10 included studies, decreases the statistical power and confidence of the analysis, besides in many included studies show a range of broad confidence, which indicates a possible heterogeneity of the intra-study population.

Conclusion

Our results highlight some results regarding the beta-blockers use: (1). The use of beta-blockers is associated with a decrease in negative outcome. (2). It favors a good neurological outcome. There is a need for further, larger prospective studies to determine the impact of beta-blockers treatment in TBI. Furthermore, to know how such information could be used in specific patients populations.

Disclosure statement

The authors report no conflict of interest concerning the materials or methods used in this study or findings specific.

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Author Contributions

Conception and design: WF, SAS, EFLT. Acquisition of data: WF, SAS, EFLT. Analysis and interpretation of data: WF, LRMS, EFLT Drafting the article: WF, LRMS, TJ Critically revising the article: WF, LRMS, EFLT Reviewed submitted version of manuscript: WF, LRMS. Approved the final version of the manuscript on behalf of all authors: WF LRMS, TJ, EFLT, SAS Statistical analysis: LRMS. Administrative/technical/material support: WF, TJ, LRMS. Study supervision: WF, LRMS, TJ, EFLT, SAS

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