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Metoprolol improves survival in severe traumatic brain injury independent of heart rate control

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ABSTRACT

Background: Multiple prior studies have suggested an association between survival and beta-blocker administration in patients with severe traumatic brain injury (TBI). However, it is unknown whether this benefit of beta-blockers is dependent on heart rate control. The aim of this study was to assess whether rate control affects survival in patients receiving metoprolol with severe TBI. Our hypothesis was that improved survival from beta-blockade would be associated with a reduction in heart rate.

Methods: We performed a 7-y retrospective analysis of all blunt TBI patients at a level-1 trauma center. Patients aged >16 y with head abbreviated injury scale 4 or 5, admitted to the intensive care unit (ICU) from the operating room or emergency room (ER), were included. Patients were stratified into two groups: metoprolol and no beta-blockers. Using propensity score matching, we matched the patients in two groups in a 1:1 ratio controlling for age, gender, race, admission vital signs, Glasgow coma scale, injury severity score, mean heart rate monitored during ICU admission, and standard deviation of heart rate during the ICU admission. Our primary outcome measure was mortality.

Results: A total of 914 patients met our inclusion criteria, of whom 189 received beta-blockers. A propensity-matched cohort of 356 patients (178: metoprolol and 178: no beta-blockers) was created. Patients receiving metoprolol had higher survival than those patients who did not receive beta-blockers (78% *versus* 68%; $P = 0.04$); however, there was no difference in the mean heart rate (89.9 ± 13.9 *versus* 89.9 ± 15; $P = 0.99$). Nor was there a difference in the mean of standard deviation of the heart rates (14.7 ± 6.3 *versus* 14.4 ± 6.5; $P = 0.65$) between the two groups. In Kaplan–Meier survival analysis, patients who received metoprolol had a survival advantage ($P = 0.011$) compared with patients who did not receive any beta-blockers.

Conclusions: Our study shows an association with improved survival in patients with severe TBI receiving metoprolol, and this effect appears to be independent of any reduction in heart rate. We suggest that beta-blockers should be administered to all severe TBI patients irregardless of any perceived beta-blockade effect on heart rate.

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in trauma patients causing approximately 52,000 deaths per year [1,2]. Although most morbidity and mortality are related to the primary injury, at this time, there are very few evidence-based therapeutic options available to affect outcomes in these patients [3]. Those who survive the initial injuries may benefit from limiting the secondary injury caused by hypotension, hypoxia, and severe hypertension [4].

Secondary TBI can be associated with a systematic hyperadrenergic state increasing both cardiac and cerebral oxygen demand [5–8]. Severe TBI patients usually present with tachycardia, hypertension, and agitated state especially during the transitional phase from a low Glasgow coma score (GCS) to a higher GCS level. This arousal phase has been correlated with increase in catecholamine levels [6–8]. Animal studies have confirmed the potential neuroprotective effect of beta-blockers in modulating the catecholamine levels, in addition to increasing the cerebral perfusion as well as cardioprotective and metabolic effects of these medications [9–12]. Also, in clinical studies, multiple reports have suggested an association between survival and beta-blocker administration in patients with severe TBI [13–16]. However, this survival benefit has not been inspected independently from the cardioprotective effect of beta-blocker induced through heart rate control.

Metoprolol as a lipophilic β1-receptor antagonist can cross the blood–brain barrier and is the most commonly used beta-blocker in the trauma patients admitted to intensive care unit (ICU) [17]. We sought out to assess the survival benefit of metoprolol independent from its cardioprotective effect. The aim of this study was to compare the survival in patients receiving metoprolol with the patients who did not receive any beta-blockers in a matched cohort of severe TBI patients. Our hypothesis was that improved survival from beta-blockade would be associated with a reduction in mean heart rate.

2. Methods

2.1. Study settings and patients

After obtaining approval from the Institutional Review Board at the University of Arizona, College of Medicine, we performed a 7-y (2007–2013) retrospective analysis of all blunt severe TBI patients at a level-1 trauma center. Patients aged >16 y with head abbreviated injury scale (AIS) of 4 or 5 who were admitted to the ICU from the operating room or emergency department (ED) were included. We excluded the patients with a head AIS score of 6, patients with other body parts AIS >3, and patients who died in the ED or within the first 24 h of admission. For the matching, we also excluded patients who received beta-blockers other than metoprolol. We used head AIS as an indicator of severity of head injury as ED admission GCS may be misleading as it may not reflect the overall severity of injury and can be affected by drugs, both legal and illegal. Also, the GCS can be lower or higher during the admission for the patient with similar severity of injuries. Head AIS and injury severity score (ISS), however, are calculated based on findings during the admission and discharge.

2.2. Data points and definitions

Patients' medical records were reviewed, and the following data points were abstracted: patient demographics (age and gender), mechanism of injury, vitals on presentation (systolic blood pressure, heart rate, and temperature), GCS score, hospital and ICU length of days, and inhospital mortality. The ISS, AIS, intubation status in ED, neurosurgical intervention details, revised trauma score, and trauma injury severity score (TRISS) were obtained from the trauma registry. We also obtained patients' 24-h monitored heart rates during their ICU stay from vital signs recorded in our ICU's electronic medical record. The average heart rate and standard deviation was calculated for each patient during their ICU stay.

We cross matched our registry data with the pharmacy database to identify those patients who had received at least one dose of a beta-blocker during their hospital stay. The data we extracted from the pharmacy database included the exact type of beta-blocker, number of doses, and the total cumulative dose administered during their hospital stay. All data were then subsequently combined, matched by unique visit numbers.

We defined a neurosurgical intervention as either craniotomy or craniectomy.

2.3. Data presentation and statistical analysis

2.3.1. Propensity score matching

Propensity matching is an analog to the process of randomization of a clinical trial that is commonly used in observational studies. The propensity score denotes the conditional probability of an individual to receive a certain treatment. A propensity score is generated for each patient based on all the confounding factors using a logistic regression model. We used logistic regression estimation algorithm and nearest neighbor matching algorithm without replacement.

Patients were stratified into two groups: metoprolol and no beta-blockers (NBB). Using propensity score matching, we matched the patients in two groups in a 1:1 ratio controlling for age, gender, race, admission vital signs, GCS, ISS, average heart rate monitored during ICU admission, and standard deviation of heart rate during the ICU admission. To assure appropriate balance between the two groups, we computed absolute standardized differences for the continuous and binary variables.

AIS and ISSs are predictor of mortality in trauma patients; we also included GCS as a covariate in propensity score matching. Studies have shown that addition of GCS to AIS increases the value of both in predicting the outcomes in isolated TBI.

2.3.2. Survival analysis

We performed a Kaplan–Meier survival analysis of the matched cohort to estimate the survival curve. We used Breslow (generalized Wilcoxon) test, Tarone–Ware test, and paired log-rank (Mantel–Cox) test to confirm the difference in

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