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Prospective evaluation of early propranolol after traumatic brain injury

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ABSTRACT

Background: Although beta-adrenergic receptor blockade may improve outcomes after traumatic brain injury (TBI), its early use is not routine. We hypothesize that judicious early low-dose propranolol after TBI (EPAT) will improve outcomes without altering bradycardia or hypotensive events.

Methods: We conducted a prospective, observational study on all patients who presented with moderate-to-severe TBI from March 2010–August 2013. Ten initial patients did not receive propranolol (control). Subsequent patients received propranolol at 1-mg intravenous every 6 h starting within 12 h of intensive care unit (ICU) admission (EPAT) for a minimum of 48 h. Heart rate and blood pressure were recorded hourly for the first 72 h. Bradycardia and hypotensive events, mortality, and length of stay (LOS) were compared between cohorts to determine significant differences.

Results: Thirty-eight patients were enrolled; 10 control and 28 EPAT. The two cohorts were similar when compared by gender, emergency department (ED) systolic blood pressure, ED heart rate, and mortality. ED Glasgow coma scale was lower (4.2 *versus* 10.7, $P < 0.01$) and injury severity score higher in control. EPAT patients received a mean of 10 ± 14 doses of propranolol. Hypotensive events were similar between cohorts, whereas bradycardia events were higher in control (5.8 *versus* 1.6, $P = 0.05$). ICU LOS (15.4 *versus* 30.4 d, $P = 0.02$) and hospital LOS (10 *versus* 19.1 d, $P = 0.05$) were lower in EPAT. Mortality rates were similar between groups (10% *versus* 10.7%, $P = 0.9$). The administration of propranolol led to no recorded complications.

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Conclusions: Although bradycardia and hypotensive events occur early after TBI, low-dose intravenous propranolol does not increase their number or severity. Early use of propranolol after TBI appears to be safe and may be associated with decreased ICU and hospital LOS.

1. Background

Traumatic brain injury (TBI) is a leading cause of death among trauma patients accounting for one-third of all trauma mortalities [1]. For those patients that survive the initial trauma, there remains a large injury burden [2] and treatment goals are aimed at reducing secondary injury [3]. Maintaining adequate brain perfusion, limiting cerebral edema, and optimizing oxygen delivery are part of established treatment protocols [2]. Numerous therapeutics have been evaluated as potential treatment for TBI with very limited success [4–6] and there is no medication that alters survival [7]. Complex neurohormonal cascades including substantial catecholamine secretion after TBI contribute to secondary injury in patients who are otherwise optimized [8,9] and recently it has been proposed that blunting this response will lead to better outcomes [10–14].

Murine models demonstrate that catecholamine blockade with the use of early beta-adrenergic receptor inhibition increases cerebral perfusion, decreases cerebral hypoxia and edema, and improves neurologic recovery [15–20]. Several large retrospective reviews of patients who received beta blockers in the peri-TBI period report improved outcomes [10–13,21–23]. However, the routine use of beta blockers has not been incorporated into the early management of TBI patients as there are concerns that episodes of hypotension or bradycardia may increase secondary brain injury. In choosing which beta blocker to provide at admission after TBI, propranolol may be the optimal choice as it penetrates the blood–brain barrier because of its lipophilic properties [21], increases cerebral oxygen delivery [15], and is provided early for burn patients to reduce catabolism and oxygen consumption [24]. Given the potential for propranolol to reduce secondary injury after TBI, there may be an enhanced benefit to initiating therapy early during the hospital course.

To date, no prospective studies have focused on the early use of any beta blocker after TBI. We hypothesize that administration of early low-dose propranolol after TBI (EPAT) will improve outcomes without increasing bradycardia and hypotensive events.

2. Methods

A prospective, observational study on the early use of propranolol was conducted in the surgical intensive care unit (ICU) at our level I trauma center. All patients who required ICU admission immediately after TBI from May 2010–August 2013 were screened for moderate-to-severe TBI. Inclusion criteria included computed tomography evidence of TBI and ICU admission. Exclusion criteria included patients with head abbreviated injury score (AIS) = 6 or <3 and nonsurvivable injuries. Patients were excluded at admission for nonsurvivable injuries by the rounding trauma attending. Head AIS was determined after discharge or death.

An initial 10 patients were managed with standard-of-care treatment that could include beta blockers, although early propranolol was not provided (control). Additional patients received propranolol at 1-mg intravenous (IV) every 6 h starting within 12 h of admission (EPAT) for a minimum of 48 h. Initiation and cessation of propranolol were at the discretion of the rounding attending and the therapeutic could be continued until discharge or transfer if symptoms of sympathetic storming were present. Patients who did not receive propranolol within 12 h of admission were excluded from the EPAT cohort. Heart rate (HR) and systolic blood pressure (SBP) were continuously monitored in all patients who received propranolol. Propranolol was held for HR <70 bpm, SBP <100 mm Hg, patient deterioration, or physician preference. Bradycardia and hypotensive events were recorded hourly for the first 72 h after surgical ICU admission. This prospective study was conducted after an initial trial (ClinicalTrials.gov NCT01202110) demonstrated no difference in bradycardia or hypotensive events related to the early use of propranolol in the first 20 patients enrolled.

Patient demographics were compared including age, sex, mechanism of injury, injury severity score, head AIS, emergency department (ED) SBP, ED Glasgow coma scale (GCS), beta-blocker use, TBI type, interventions required for intracranial pressure (ICP) monitoring, complications such as acute respiratory distress syndrome or pneumonia, length of stay (LOS), and mortality. Primary study end points were bradycardia events (HR <60 bpm) or hypotension events (SBP <90 mm Hg) during the first 72 h. Secondary end points included mortality, ICU LOS, and hospital LOS. Data were analyzed to determine if EPAT compared with control altered the primary or secondary outcome. Descriptive statistics were summarized using raw percentages, means, and standard deviations. The Pearson χ^2 test and Fisher exact test were used to compare differences in proportions for categorical variables. Numerical variables were summarized by means and with P value of ≤ 0.05 considered significant. This study was approved by the Institutional Review Board of Cedars-Sinai Medical Center.

3. Results

Over the 40-mo period, 695 patients were admitted to the ICU with computed tomography evidence of TBI and a discharge head AIS ≥ 3. The initial 10 patients who received standard-of-care therapy (control) were enrolled between May 2010–March 2011 (Figure). Subsequently, 28 patients met EPAT criteria from April 2011–August 2013 and were enrolled