Beta blockers in critically ill patients with traumatic brain injury: Results from a multicenter, prospective, observational American Association for the Surgery of Trauma study

Eric J. Ley, MD, Samuel D. Leonard, Galinos Barmparas, MD, Navpreet K. Dhillon, MD, Kenji Inaba, MD, Ali Salim, MD, Karen R. O'Bosky, MD, Danielle Tatum, PhD, Hooman Azmi, MD, Chad G. Ball, MD, MSc, Paul T. Engels, MD, Julie A. Dunn, MD, Matthew M. Carrick, MD, Jonathan P. Meizoso, MD, MSPH, Sarah Lombardo, MD, MSc, Bryan A. Cotton, MD, MPH, Thomas J. Schroeppel, MD, Sandro Rizoli, MD, PhD,

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BACKGROUND: Beta blockers, a class of medications that inhibit endogenous catecholamines interaction with beta adrenergic receptors, are often administered to patients hospitalized after traumatic brain injury (TBI). We tested the hypothesis that beta blocker use after TBI is associated with lower mortality, and secondarily compared propranolol to other beta blockers.

METHODS: The American Association for the Surgery of Trauma Clinical Trial Group conducted a multi-institutional, prospective, observational trial in which adult TBI patients who required intensive care unit admission were compared based on beta blocker administration.

RESULTS: From January 2015 to January 2017, 2,252 patients were analyzed from 15 trauma centers in the United States and Canada with 49.7% receiving beta blockers. Most patients (56.3%) received the first beta blocker dose by hospital day 1. Those patients who received beta blockers were older (56.7 years vs. 48.6 years, $p < 0.001$) and had higher head Abbreviated Injury Scale scores (3.6 vs. 3.4, $p < 0.001$). Similarities were noted when comparing sex, admission hypotension, mean Injury Severity Score, and mean Glasgow Coma Scale. Unadjusted mortality was lower for patients receiving beta blockers (13.8% vs. 17.7%, $p = 0.013$). Multivariable regression determined that beta blockers were associated with lower mortality (adjusted odds ratio, 0.35; $p < 0.001$), and propranolol was superior to other beta blockers (adjusted odds ratio, 0.51, $p = 0.010$). A Cox-regression model using a time-dependent variable demonstrated a survival benefit for patients receiving beta blockers (adjusted hazard ratio, 0.42, $p < 0.001$) and propranolol was superior to other beta blockers (adjusted hazard ratio, 0.50, $p = 0.003$).

CONCLUSION: Administration of beta blockers after TBI was associated with improved survival, before and after adjusting for the more severe injuries observed in the treatment cohort. This study provides a robust evaluation of the effects of beta blockers on TBI outcomes that supports the initiation of a multi-institutional randomized control trial. (*J Trauma Acute Care Surg.* 2018;84: 234–244. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

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KEY WORDS: Beta blockade; beta blockers; catecholamines; propranolol; traumatic brain injury.

Traumatic brain injury (TBI) affects over 1.7 million Americans annually causing up to 30% of all injury-related deaths, as well as significant morbidity, long-term disability, and economic burden.[1] Guidelines for the management of TBI emphasize preventing secondary injury largely by averting hypotension and hypoxia.[2] Therapeutics, such as prehospital hypertonic saline[3] and early administration of progesterone,[4] failed to improve outcomes while cooling patients[5] or administering corticosteroids[6] led to higher mortality. Currently, there is no treatment to prevent the progression of secondary injury that occurs after the initial traumatic event.

The brain response to trauma has been well characterized; it includes blood flow disruption, anoxia, and edema, followed by neuronal cell death, further deterioration, and eventual neurodegeneration in a large percentage of TBI patients.[7] Catecholamine levels surge immediately after TBI to levels reflecting the severity of the injury,[8,9] causing inflammation and apoptosis in brain tissues[10] and are markers of functional outcome and mortality.[9] The surge can persist for up to 10 days.[11] The class of medications that inhibit catecholamine interaction with beta adrenergic receptors, called beta blockers, is often administered to patients hospitalized with TBI. Several retrospective studies of moderate-to-severe TBI have found that beta blockers dosed after hospital admission reduce mortality[12–17] with propranolol performing better than other beta blockers.[18] In addition, propensity matching,[19] routine early administration of propranolol,[20] and a recent meta-analysis[21] all demonstrated lower mortality when beta blockers were provided after TBI. Despite these optimistic findings, beta blocker dosing is not routine in the setting of TBI.

Given the evidence that demonstrates favorable outcomes related to beta blocker use after TBI, the premise of this trial was that the catecholamine surge plays a role in post-TBI deterioration and proactively providing beta blockers may reduce

From the Cedars-Sinai Medical Center, Department of Surgery, Division of Trauma and Critical Care (E.J.L., G.B., N.K.D., T.L.), Los Angeles, California; University of Texas at Houston, Department of Surgery, Division of Acute Care Surgery (S.D.L., B.A.C.), Houston, Texas; Los Angeles County and USC Medical Center, Department of Surgery, Division of Trauma and Critical Care (K.I., L.A.d.L.), Los Angeles, California; Brigham and Women's Hospital, Department of Surgery, Division of Trauma, Burns, and Surgical Critical Care (A.S., L.A.B.), Boston, Massachusetts; Loma Linda University and Medical Center, Department of Surgery, Division of Acute Care Surgery (K.R.O., D.S.J.C.), Loma Linda, California; Our Lady of the Lake Regional Medical Center, Trauma Specialist Program (D.T., T.J.), Baton Rouge, Louisiana; Hackensack University Medical Center, Department of Neurosurgery (H.A., S.K.), Hackensack, New Jersey; University of Calgary, Foothills Medical Centre, Department of Surgery (C.G.B., J.X.), Calgary, Alberta; McMaster University/Hamilton General Hospital, Department of Surgery (P.T.E., A.C.), Hamilton, Ontario, Canada; Medical Center of the Rockies, Department of Trauma and Acute Care Surgery (J.A.D., L.W.), Loveland, Colorado; Medical City Plano, Trauma Services Department (M.M.C., G.M.), Plano, Texas; Ryder Trauma Center, DeWitt Daughtry Family Department of Surgery (J.P.M., K.R.), University of Miami/Jackson Memorial Medical Center, Miami, Florida; Division of General Surgery, University of Utah (S.L., R.N.), Salt Lake City, Utah; Memorial Hospital, Department of Surgery (T.J.S., S.G.), Colorado Springs, Colorado; and St. Michael's Hospital, Department of Trauma and Acute Care Surgery (S.R., J.R.-N.), Toronto, ON, Canada.

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Address for reprints: Eric J. Ley, MD, Cedars-Sinai Medical Center Department of Surgery 8700 Beverly Blvd, Suite 8215NT Los Angeles, CA 90048; email: Eric.Ley@cshs.org.

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secondary injury and prevent or slow the progression of brain injury and related mortality. We tested the hypothesis that beta blocker use after brain trauma is associated with lower mortality and secondarily compared propranolol with other beta blockers.

METHODS

This was a multi-institutional, prospective, observational trial, approved and conducted through the American Association for the Surgery of Trauma Multi-Institutional Trials (AAST-MIT) committee. All adult trauma patients with a TBI requiring intensive care unit (ICU) admission from January 1, 2015, to January 31, 2017, at 15 trauma centers in the United States and Canada were screened for eligibility for enrollment. Inclusion criteria included 18 years or older, blunt traumatic injury, a computed tomography (CT) of the brain demonstrating an acute TBI, and ICU admission at presentation. If transferred from an outside hospital, the injury must have occurred within 12 hours before arrival. Those patients who expired in the emergency department (ED) or whose data required additional privacy access authorization were excluded. Data for patients who met inclusion criteria from each participating center were collected prospectively and entered into the AAST-MIT online data entry tool (see Supplementary Document, http://links.lww.com/TA/B52). These data included age, gender, mechanism of injury, admission Glasgow Coma Scale (GCS) score, admission systolic blood pressure (SBP), and initial CT head findings, including contusion, subdural hematoma (SDH), subarachnoid hemorrhage (SAH), epidural hematoma (EDH), intraparenchymal hemorrhage (IPH), herniation, diffuse axonal injury (DAI), or other findings of acute injury. Previously prescribed medications were recorded and these included beta blockers and all anticoagulants (warfarin, low molecular weight heparin, antiplatelet agents including acetylsalicylic acid and/or clopidogrel, and novel anticoagulants including apixaban, dabigatran and rivaroxaban). All procedures throughout the hospital stay were also collected, including endotracheal intubation in the ED, laparotomy, thoracotomy/sternotomy, and placement of a bolt and/or external ventricular drain (EVD) for intracranial pressure monitoring. Injury scores including head Abbreviated Injury Scale (AIS) score and Injury Severity Score (ISS) were extracted from the trauma registry after patient discharge. Mortality and the Glasgow Outcome Scale (GOS) score (one for death, two for a persistent vegetative state, three for severe disability, four for moderate disability, and five for a good recovery) were also collected upon discharge.

The use of beta blockers was at the discretion of the attending physicians. Indication for their use was tracked and included prophylaxis against sympathetic hyperactivity, treatment of hypertension, treatment of tachycardia, treatment of arrhythmias, and/or resumption of a home medication. Justification for withholding beta blockers was also recorded and included physician preference, hemodynamic instability, congestive heart failure (CHF), and/or chronic obstructive pulmonary disease. All types of beta blockers administered were recorded (see Supplementary Document, http://links.lww.com/TA/B52). For the most commonly used beta blocker (atenolol, esmolol, propranolol, metoprolol, and labetalol) the administration time, route, and dose were also recorded.

Duration of the study was predetermined to continue until an adequate sample size was included. Sample size calculation was based on an overall mortality of 10% for a similar group of TBI patients who survived until ICU admission.[20] Assuming an alternative mortality rate of 8% with the use of beta blockers, a sample size of 2,165 would achieve 90% power to detect a difference of 0.02 using a two-sided binomial test.

Statistical Analysis

Patients receiving any beta blocker during their admission (beta blocker group) were compared with those who did not (no beta blocker group). Patients who received their first dose of beta blocker more than 30 days after their admission were included in the no beta blocker group. Descriptive statistics were reported as raw percentages or means ± SD and medians. A Student's t test or Mann-Whitney U test was used when appropriate to compare means for parametric or nonparametric data, respectively. A χ^2 test or Fisher's exact test was performed for comparison of categorical variables. A p value less than 0.05 was considered statistically significant. In a subgroup analysis, patients receiving propranolol were compared with all other patients who received any other beta blocker. The primary outcome was 30-day mortality. Secondary outcomes included GOS (4 to 5 compared with 1 to 3) and hospital length of stay (days). To account for confounding factors, variables that were clinically and statistically significantly different between the two groups were included in a multivariate logistic regression model and adjusted odds ratio (AOR) and 95% confidence intervals (CI) were calculated.

Given the variability in the timing from admission to beta-blocker administration, a Kaplan-Meier curve was performed and a Cox-regression model with a time-dependent variable adjusting for statistically significant differences between the two groups was conducted to calculate the adjusted hazard ratio (AHR) and 95% CI. For this calculation, patients with unknown timing of beta blocker administration and patients who received beta blockers other than the most commonly used ones (atenolol, esmolol, propranolol, metoprolol, and labetalol) were excluded. The variables adjusted for in these regressions are reported under the relevant tables. All statistical analyses were performed using the IBM SPSS Statistics package, version 24.

The study was developed by the four study principal investigators (Ley, Inaba, Salim, and Rizoli) in consultation with the AAST-MIT Advisory Committee. The authors vouch for the accuracy and completeness of the data and analyses. Data were gathered by investigators with institutional review board approval obtained through each site as well as an additional approval for multi-institutional data collection by the Cedars-Sinai Medical Center Institutional Review Board. As this was an observational trial that did not alter the care for patients, written consent was waived.

RESULTS

Over the 25-month study period, 2,337 patients with a blunt TBI were admitted to the ICU at one of the 15 enrolling sites and had data finalized through the AAST-MIT online data entry tool. After excluding 85 patients due to incomplete

TABLE 1. Comparison of Patients Who Received Beta Blocker and Those Who Did Not

	Total (n = 2,252)	BB (n = 1,120)	No BB (n = 1,132)	*p*
Age: mean ± SD [median], y	53 ± 22 [53]	57 ± 22 [59]	49 ± 21 [47]	<0.01
Age > 65 y	32%	39%	25%	<0.01
Male	69%	70%	68%	0.29
Mechanism of injury				
MVC	23%	21%	24%	<0.01
MCC	6%	6%	6%	
Fall	39%	43%	35%	
AvP	12%	12%	12%	
Bicycle crash	2%	2%	3%	
Found down	7%	8%	6%	
Other	11%	8%	14%	
Any anticoagulant	18%	24%	13%	<0.01
Coumadin/Lovenox	4%	5%	2%	<0.01
NOAC	2%	2%	1%	0.02
Antiplatelet(s)	14%	18%	10%	<0.01
Prehospital BB	9%	17%	1%	<0.01
Intubated in field	18%	18%	19%	0.79
Intubated in ED	27%	30%	24%	<0.01
SBP: mean ± SD [median], mm Hg	137 ± 30 [134]	140 ± 31 [139]	134 ± 29 [131]	<0.01
SBP < 90 mm Hg	4%	5%	4%	0.33
GCS score mean ± SD [median]	10 ± 5 [13]	10 ± 5 [12]	11 ± 5 [13]	0.06
GCS score = 3	22%	21%	22%	0.86
GCS score ≤ 8	38%	40%	36%	0.09
GCS score = 15	31%	28%	35%	<0.01
ISS mean ± SD [median]	21 ± 11 [18]	21 ± 11 [20]	21 ± 11 [17]	0.11
ISS < 16	31%	29%	34%	<0.01
ISS 16–25	37%	38%	37%	
ISS > 25	31%	34%	29%	
AIS head mean ± SD [median]	4 ± 1 [3.0]	4 ± 1 [4]	3 ± 1 [3]	<0.01
< 3	16%	13%	18%	<0.01
3	36%	34%	37%	
4	28%	31%	25%	
5	21%	22%	20%	
6	0%	0%	0%	
Type of injury on initial CT				
Contusion	31%	31%	31%	0.81
EDH	9%	8%	11%	<0.01
SDH	59%	62%	56%	<0.01
SAH	63%	62%	65%	0.25
IPH	21%	25%	16%	<0.01
Herniation	8%	7%	9%	0.06
DAI	3%	3%	3%	0.36
Other	13%	13%	14%	0.53
Laparotomy	4%	4%	3%	0.34
Thoracotomy/sternotomy	2%	2%	1%	0.59
Craniotomy	9%	12%	5%	<0.01
Craniectomy	10%	11%	8%	<0.01
EVD	9%	12%	7%	<0.01
Bolt	10%	14%	6%	<0.01
Comorbid conditions				
DM	15%	19%	11%	<0.01
Cirrhosis	2%	2%	2%	0.72
HIV	1%	1%	1%	0.26
Organ transplantation	0%	0%	0%	0.29
Rheumatoid arthritis	0%	1%	0%	0.55
History of splenectomy	0%	0%	0%	0.62
Other immunosuppressive disorder	2%	2%	1%	0.16
Admitted to:				
Surgical ICU	47%	52%	42%	<0.01
Neuro-ICU	48%	43%	53%	
Medical ICU	5%	5%	5%	
Trauma center ACS Level I	81%	81%	81%	0.97

p values were extracted from χ^2 or Fisher's exact test for categorical variables and from *t* test or Mann-Whitney test for continuous variables.

MVC, motor vehicle collision; MCC, motorcycle collision; AvP, auto versus pedestrian; NOAC, novel anticoagulants (Eliquis/Pradaxa/Xarelto); DM, diabetes mellitus; HIV, human immunodeficiency virus; ACS, American College of Surgeons.

imaging results, 2,252 patients were considered for the analysis (see Supplementary Figure 1, http://links.lww.com/TA/B53). The mean ± SD number of recruited subjects per center was 150 ± 144 (median, 99; interquartile range, 58–174), while the percent recruitment per center was 6.7% ± 6.4% (median, 4.4%; interquartile range, 2.6–7.7%). The proportion of patients receiving beta blockers at each participating trauma

TABLE 2. Patterns of Beta Blocker Use

Indication for BB use (n = 1,120)	
Prophylaxis against sympathetic hyperactivity	27%
Treatment of hypertension	64%
Treatment of tachycardia	15%
Treatment of arrhythmias	4%
Resumption of a home medication	13%
BB used (n = 1,120)	
Propranolol PO	27%
Propranolol IV	13%
Metoprolol PO	29%
Metoprolol IV	20%
Labetalol PO	8%
Labetalol IV	46%
Atenolol PO	4%
Atenolol IV	0%
Esmolol IV	7%
Other	5%
BB use duration:* mean ± SD [median], d	10 ± 11 [6]
No. different BB used* mean ± SD [median]	2 ± 1 [1]

*Excluding patients receiving BB other than metoprolol, labetalol, propranolol, atenolol and esmolol and patients with unknown start and/or end day of administration (n = 68).

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

TABLE 3. Comparison of Unadjusted and Adjusted Outcomes Between Patients Who Received Beta Blocker and Those Who Did Not

	Total (n = 2,252)	BB (n = 1,120)	No BB (n = 1,132)	*p*	Adjusted* OR (95% CI)	Adjusted* *p*
Mortality	16%	14%	18%	0.01	0.35 (0.26–0.47)	<0.01
GOS 4 to 5**	69%	65%	73%	<0.01	1.10 (0.84–1.43)	0.48
				p	Adjusted* mean difference (95% CI)	Adjusted* *p*
Hospital stay: mean ± SD [median], d	12 ± 36 [7]	21 ± 25 [19]	10 ± 37 [6]	<0.01	8.00 (4.82–11.15)	<0.01

*Logistic regression adjusting for age (y), mechanism of injury, any anticoagulant before admission, BB before admission, intubation in ED, GCS, ISS, AIS head, SDH on initial CT, IPH on initial CT, EDH on initial CT, EVD, Bolt., Craniotomy, Craniectomy, DM, ICU type.

**Compared with GOS of 1 to 3. Overall, 180 subjects (8.0%) had an unknown GOS at discharge.

center was 49.7% ± 14.9% (median, 48.9%; interquartile range, 38.3–57.6%).

Patients who received beta blockers (n = 1120, 49.7%) were significantly older, more likely to be on anticoagulants or preinjury beta blockers, and admitted more frequently after a fall compared with those who did not. Beta blocker patients were more often intubated in the ED and were more likely to have a higher head AIS. There were no differences noted with regards to gender, admission hypotension (SBP < 90 mm Hg), and intubation in the field (Table 1). Although there was no difference in the total mean GCS and ISS between the two cohorts, beta-blockers patients were significantly less likely to have a GCS of 15 and more likely to have an ISS greater than 25.

Patterns of injury on the initial CT varied with a higher rate of SDH and IPH and a lower incidence of EDH in the beta-blocker cohort (Table 1). Craniotomy, craniectomy, EVD, and bolt placement were also more likely in the beta blocker cohort, while no difference in the rate of laparotomy or thoracotomy/sternotomy were observed. When comparing comorbidities, diabetic patients were more likely to have received beta blockers. Beta blockers were also more likely to be administered to patients admitted to surgical ICUs while neuro-ICUs were less likely to provide beta blockers. Admission to an ACS Level I trauma center did not alter the rate of beta blocker administration.

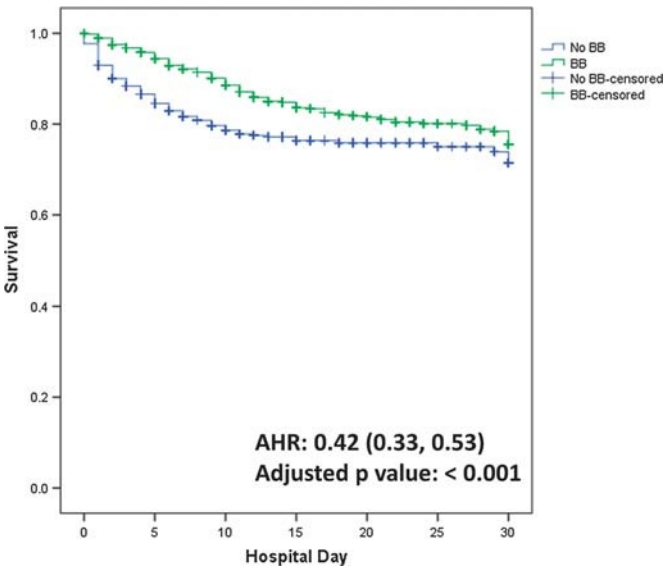

Figure 1. Kaplan-Meier survival curve based on whether a BB was administered or not. BB, beta blocker.

The most common type of beta blocker and administration route used was labetalol IV, followed by metoprolol PO, propranolol PO, metoprolol IV, and propranolol IV (Table 2). Beta blockers were used for 9.5 ± 11.4 days, and there was a mean of 1.6 ± 0.8 types of beta blockers administered per patient.

Overall 30-day mortality was 15.8% with a significantly lower mortality observed in patients who received beta blockers (13.8% vs. 17.7%, $p = 0.013$). After adjusting for age, mechanism of injury, any anticoagulant before admission, beta blockers before admission, intubation in ED, GCS, ISS, AIS head, SDH on initial CT, IPH on initial CT, EDH on initial CT, EVD, bolt, craniotomy, craniectomy, diabetes, and ICU type, the use of beta blockers was associated with a lower adjusted mortality (AOR, 0.35; 95% CI, 0.26, 0.47; adjusted $p < 0.001$) (Table 3). Despite the non–beta blocker patients having a more favorable neurologic score (GOS score of 4 or 5) at hospital discharge, this difference was not significant after adjusting for the same confounding variables. The overall hospital stay was 11.7 ± 35.8 days and was significantly higher in the beta-blockers group. After adjusting for all confounding factors mentioned above, the beta blocker group continued to have a significantly longer hospital stay (Table 3).

Among patients who received beta blockers, 31.6% were dosed on hospital day 0 and 24.7% on hospital day 1 with a total of 82.7% receiving beta blockers by hospital day 5 (see Supplementary Figure 2, http://links.lww.com/TA/B54). To account for survival bias and for the effect of timing of beta blocker administration on 30-day mortality, a Kaplan-Meier curve was used to depict the difference in this outcome between the two cohorts (Fig. 1). A Cox-regression model using a time-dependent variable and adjusting for age, mechanism of injury, any anticoagulant before admission, beta blockers before admission, intubation in ED, GCS, ISS, AIS head, SDH on initial CT, IPH on initial CT, EDH on initial CT, EVD, bolt, craniotomy, craniectomy, diabetes, and ICU type demonstrated a statistically significant survival benefit for patients receiving beta blockers (AHR, 0.42; 95% CI, 0.33–0.53; adjusted p value < 0.001). Excluded from this regression were patients with unknown discharge date (n = 5) and patients who received beta blockers other than atenolol, esmolol, propranolol, metoprolol, and labetalol (n = 63) as timing of administration of these beta blockers was not recorded.

In a subgroup analysis comparing patients receiving propranolol (n = 354) with those receiving any other beta blocker (n = 766), those receiving propranolol were younger, more likely to be male, and more likely to be victims of a motor vehicle collision (see Supplementary Table 1, http://links.lww.com/TA/B55).

TABLE 4. Comparison of Unadjusted and Adjusted Outcomes Between Patients Who Received Propranolol Versus Other Beta Blockers

	Total (n = 1,120)	Propranolol (n = 354)	Other BB (n = 766)	*p*	Adjusted* OR (95% CI)	Adjusted* *p*
Mortality	14%	9%	16%	<0.01	0.51 (0.31–0.85)	0.01
GOS 4 to 5**	65%	64%	66%	0.55	1.29 (0.86–1.95)	0.21
				p	Adjusted* mean difference (95% CI)	Adjusted* *p*
Hospital stay: mean ± SD [median], d	16 ± 19 [11]	21 ± 25 [19]	13 ± 14 [9]	<0.01	3.87 (1.30–6.44)	<0.01

*Logistic regression adjusting for age (y), mechanism of injury, any anticoagulant before admission, BB before admission, intubation in field, intubation in ED, GCS, ISS, SAH on initial CT, SDH on initial CT, EDH on initial CT, DAI on initial CT, contusion on initial CT, bolt., laparotomy, craniectomy, DM, HIV, ICU type.
**Compared with GOS of 1 to 3. Overall, 180 (8.0%) subjects had an unknown GOS at discharge.

They were also more likely to be admitted hypotensive and require intubation both in the field and in the ED, corresponding to their lower total GCS and higher ISS and head AIS. In addition, in propranolol patients, findings on the initial CT head were more likely to demonstrate contusions, EDH, SAH, and DAI and less likely to demonstrate SDH. Although there was no difference in the need for thoracotomy/sternotomy and craniectomy, propranolol patients required more often a laparotomy, a craniectomy, and placement of a bolt. Lastly, propranolol patients were more likely to be admitted to a surgical ICU and to a Level I trauma center (see Supplementary Table 1, http://links.lww.com/TA/B55).

Mortality at 30 days was significantly lower in the propranolol cohort (9.3% vs. 15.9%, $p = 0.003$). In a multivariate logistic regression model adjusting for age, mechanism of injury, any anticoagulant before admission, beta blockers before admission, intubation in field, intubation in ED, GCS, ISS, SAH on initial CT, SDH on initial CT, EDH on initial CT, DAI on initial CT, contusion on initial CT, bolt, laparotomy, craniectomy, diabetes, HIV and ICU type, propranolol patients had significantly lower adjusted odds for death (AOR, 0.51; 95% CI, 0.31–0.85; adjusted p value = 0.010) (Table 4). There was no difference in neurologic outcomes based on the GOS score between the two cohorts. However, propranolol patients were more likely to require a longer period of hospitalization (Table 4).

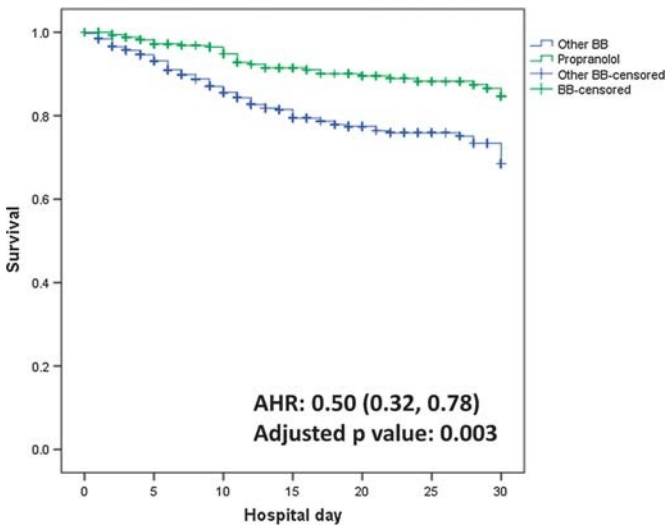

Figure 2. Kaplan-Meier survival curve based on whether propranolol or another BB was administered.

A Kaplan-Meier curve demonstrated the survival advantage of patients receiving propranolol compared with other beta blockers (Fig. 2) and a Cox regression model with a time-dependent variable adjusting for all the above-mentioned variables showed a significantly lower risk for mortality for patients receiving propranolol (AHR, 0.50; 95% CI, 0.32–0.78; adjusted p value = 0.003).

DISCUSSION

Traumatic brain injury is a leading cause of mortality and morbidity after trauma and limited options for medical treatment contribute to significant deterioration after the initial brain injury.[22] Given that several small, single-site trials demonstrate favorable outcomes related to beta blocker use, we conducted a multi-institutional, prospective, observational trial to validate these findings in a larger, more representative cohort of trauma patients and to avoid the inherent limitations of the smaller studies. Using data from 15 institutions in the United States and Canada, we established that patients who received beta blockers after TBI had a lower unadjusted and adjusted mortality rate, and this survival benefit persisted even after accounting for potential survival bias and the timing of initiation of beta blocker use. Additional logistic regression models indicated that discharge neurologic scores were similar regardless of beta blocker use and length of stay among patients who received these drugs was longer. In addition, propranolol was associated with a lower mortality when compared with all other beta blockers. This study is the first multi-institutional trial to demonstrate a mortality benefit related to beta blocker use.

The exact mechanism for how beta blockers are protective is yet to be established.[23] Catecholamines are ligands to adrenergic receptors which are a class of G protein-coupled receptors. Significant and longstanding research has been conducted on this class of receptors which led to the 1988 Nobel Prize in Medicine to James W. Black in part for introducing the first effective beta blocker, propranolol,[24] and the 2012 Nobel Prize in Chemistry to Brian Kobilika and Robert Lefkowitz for the characterization of the structure and function of beta-adrenergic receptors and how they are regulated.[25,26] Propranolol, a nonspecific β-adrenergic receptor antagonist that crosses the blood-brain barrier, has been shown to block the beta adrenergic signaling, relieve oxidative and inflammatory stress, increase vasodilation, and attenuate heart remodeling.[27]

Importantly, overexpression of the pathways of catecholamine breakdown or uptake in vitro is neuroprotective while models that are deficient in these pathways are neurotoxic.[28,29]

Propranolol administration in rodent TBI models increases cerebral perfusion, decreases hypoxia, and improves cerebral glucose metabolism in a dose-dependent manner.[30,31] Mice genetically engineered to lack beta adrenergic receptors demonstrate less motor deficiency after head trauma.[27,32,33] In lung contusion and laparotomy models systemic and central immune dysfunction was reduced with beta adrenergic receptor inhibition.[34–36] Propranolol is protective against the detrimental effects of trauma on gut permeability, villous, and lung injury.[37] In shock and other injury models, bone marrow dysfunction was limited with beta adrenergic receptor inhibition.[38,39]

The clinical evidence to support beta blocker use after TBI was noted in retrospective reviews that observed lower mortality when TBI patients received beta blockers.[12–17] Propranolol demonstrated superiority when compared to other beta blockers.[18] Single-institution propensity-matched case controls also noted lower mortality.[19] In observational studies, early routine administration of low dose propranolol was found to be safe and improved outcomes after severe TBI[18,20,40] and severe general trauma.[41,42] One randomized controlled study, demonstrated improved cardiac enzymes, supraventricular tachycardia, and T-wave change with atenolol[43] after TBI while another noted reduced mortality in those patients with nontraumatic SAH who were treated with early propranolol and phentolamine.[44] Preinjury beta blockade also improved survival, suggesting a role for prophylactic beta blockade.[45] A meta-analysis that summarized the available data established lower mortality with beta blockade and conditionally recommend the use of in-hospital beta blockers after TBI in adult patients with an emphasis on holding beta blockers to avoid bradycardia and hypotension.[21]

To better understand how beta blockers might impact other patient populations, additional exclusions were made to the beta blocker cohort, and the data were reanalyzed. Overall, 6.1% of the entire cohort died within 48 hours from admission. When these early deaths were excluded beta blockers remained associated with lower mortality (AHR, 0.57; adjusted $p < 0.001$). If the beta blocker cohort was narrowed to exclude those patients who received beta blockers after hospital day 5, the associated survival benefit related to beta blocker use remained (AHR, 0.50, adjusted $p < 0.001$). Among the beta-blocker cohort, those patients who were on beta blockers before admission did not have a survival benefit compared to those who were not (AOR, 1.25, adjusted $p = 0.47$). When the data set was analyzed for isolated TBI (head AIS ≥ 3 with all other AIS = 0), beta blockers were associated with lower mortality (AHR, 0.46, adjusted $p = 0.028$). To better understand how increasing severity of TBI-altered survival, subgroup analyses was performed on the 798 patients with head AIS score of 3, 622 patients with AIS score of 4, and 458 patients with AIS score of 5. In each instance, the beta blocker cohort was associated with lower mortality (head AIS score, 3; AHR, 0.39; adjusted $p = 0.008$; head AIS score, 4; AHR, 0.35; adjusted $p < 0.001$; head AIS score, 5; AHR, 0.31; adjusted $p < 0.001$). Beta blocker use was associated with a longer length of stay. If a mortality was assigned the maximum possible hospital stay (30 days), the unadjusted and adjusted LOS were still greater in the beta blocker cohort. Early mortalities may have reduced the mean hospital length of stay in the no-beta blocker cohort. Although the regression model indicated no difference in functional outcome at discharge when comparing cohorts, the unadjusted data determined that those patients who received beta blockers had a lower functional outcome at discharge due to an increase in the rate of GOS of 2 (3.8% vs. 1.2%, $p < 0.001$) and GOS of 3 (15.4% vs. 6.1%, $p < 0.001$).

This study and the related conclusions have several limitations. Although the Cox regression model with a time-dependent variable accounted for the timing of administration of the beta blocker and mortality, propensity matching may have provided alternative conclusions and will be the focus of future work. The management of TBI was not uniform among the study sites and as such the timing and type of beta blockers received by patients varied. The optimal type and dose required has yet to be delineated. There were differences in the baseline characteristics of the cohorts, such as age and GCS score, but these were accounted for with multivariate regression. Selection bias may have been a factor in the patients who did not receive beta blockers, and there may have been an additional element of survival bias, as those who died early may not have had the opportunity to receive beta blockers. Conversely, those who received a beta blocker may have survived because of its administration. Additional operative interventions, especially orthopedic operations, may contribute to the catecholamine state, increasing the apparent benefit noted related to beta-blocker use. As the data collection only tracked laparotomy and sternotomy/thoracotomy, the conclusion that beta blocker use is assoicated with lower mortality is limited due the lack of data on other interventions. Although 41.4% were declared brain dead, the exact cause of death and whether it was associated with head trauma was unknown for the deceased patients.

Whether beta blockers that primarily target the beta 1 adrenergic receptor are beneficial after TBI requires further research. A preliminary analysis of the data indicates that beta 1 blockers were associated with reduced mortality although less so than the nonselective beta 1/2 blockers. Given that the primary reason for beta blocker use was for hypertension treatment rather than a primary therapy for TBI, the true benefit related to beta blocker use is unknown and can only be determined with a randomized controlled trial. Of note, those who received beta blockers may have also received vitamin C which may be a confounding factor, as this agent can blunt the oxidative stress produced by catecholamine metabolites.[46] We were able to assess only the outcomes restricted to the hospital stay and did not evaluate long-term functional outcomes. Many of our limitations could be addressed with a randomized control trial.

The results of this study support the recent EAST guidelines on beta blocker administration after TBI although the ideal target heart rate is unknown.[21] After initial positive findings that supported dosing of beta blockers after noncardiac surgery, their use was tempered by the POISE trial when negative outcomes were observed.[47] Of importance, the POISE trial continued to administer beta blockers until the heart rate was consistently below 45 bpm. Because bradycardic and hypotensive events are associated with increased mortality after TBI,[48] avoiding these events should be mandatory in these patients through strict conservative hold parameters. The optimal heart rate after TBI is unknown although retrospective analysis indicates that 70s to 80s might be ideal,[49] alternatively, the potential benefit observed with beta blockade may be independent of heart rate.[50]

In conclusion, in this large, multi-institutional, prospective, observational trial, administration of beta blockers after TBI was associated with improved survival, before and after adjusting for the more severe injuries observed in the treatment cohort. This study provides a robust evaluation of the effects of beta blockers on TBI outcomes that supports the initiation of a multi-institutional randomized control trial.

AUTHORSHIP

E.J.L., K.I., A.S., and S.R. participated in the study conception and design. E.J.L., S.D.L., G.B., N.K.D., K.I., A.S., K.R.O., D.T., H.A., C.G.B., P.T.E., J.A.D., M.M.C., J.P.M., S.L., B.A.C., T.J.S., S.R. participated in the acquisition of data. E.J.L., G.B., N.K.D., K.I., A.S., S.R. participated in the analysis and interpretation of data. E.J.L., G.B., N.K.D., K.I., A.S., S.R. participated in the literature review. E.J.L., S.D.L., G.B., N.K.D., K.I., A.S., K.R.O., D.T., H.A., C.G.B., P.T.E., J.A.D., M.M.C, J.P.M., S.L., B.A.C., T.J.S., S.R. participated in the drafting of the article E.J.L., G.B., N.K.D., K.I., A.S., S.R. participated in the critical revision.

DISCLOSURE

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DISCUSSION

Dr. Saman Arbabi (Seattle, Washington): President Coimbra, Dr. Spain, members and guests. I want to thank AAST for the opportunity to discuss this important paper and congratulations to Dr. Ley for a very well-presented paper.

Beta blockers decrease oxygen consumption by the brain and heart. And they may improve immune response, nutritional status, and hematopoiesis in the critically-ill.

Initial single center studies demonstrating potential benefits of beta blockers in patients with blunt injury were presented by us and others during the 2006 AAST annual meeting. Further studies demonstrated that the groups that benefited the most were in patients with traumatic brain injury.

The current study is a well-done multi-center prospective cohort study of blunt trauma patients with traumatic brain injury, comparing patients that received beta blockers post-injury versus a group that did not.

The use of AAST institutional trial is outstanding. The goals of the study are clearly stated. The methods are well-described. The data is presented in a logical manner. And the discussion is outstanding.

I have five comments and questions.

Number 1. The authors excluded all deaths in the ER. Should the authors have excluded all patients that died in the first 48 hours after injury?

The patients that died in the first 48 hours may present a group that were not stable or did not have time to receive beta blockers. This may have created a significant bias in their analysis.

Number 2. While the statistical analysis is well-done and appropriate, a better test may have been propensity score adjustment where the data is analyzed by propensity to receive beta blockers.

Number 3. Could the analysis of hospital length-of-stay have been affected by the observed improved mortality in the beta blocker cohort? The improved mortality is presumably in patients with worse status that would require longer hospital stay, which may have otherwise died in the non-beta blocker group. Therefore, some statisticians assigned a randomly high length-of-stay for mortality instead of just adjusting for length-of-stay in survivals.

Number 4. Was there any difference in outcomes among the beta blocker cohort patients who were on beta blockers pre-injury?

Number 5. While hypertension is deleterious in long-term outcomes, in part due to higher rates of cardiac dysfunction and stroke, is it possible that it is protective during acute trauma? The patients with high blood pressure may have better blood flow after an acute TBI.

Ultimately, without a randomized prospective study this possibility cannot be excluded since in all studies done hypertension is the main reason for beta blocker use.

Again, congratulations for a great study and I hope we can move on to randomized clinical trial. Thank you.

Dr. Marc A. deMoya (Milwaukee, Wisconsin): Great study, great presentation, Dr. Ley. We did a study a couple of years ago in our group that looked at the presenting emergency department blood pressures in TBI patients and their survival.

And we found, actually, a bimodal distribution of death where patients who had low blood pressures were more likely to die; but, also, interestingly, those patients that had blood pressures greater than 155 also had a higher mortality.

So my question is related to that subgroup of patients that present in a hypertensive state who have TBI. Using that subgroup you might be able to narrow down the group of patients that benefit the most from beta blockade?

Dr. Paula Ferrada (Richmond, Virginia): Congratulations on an excellent trial. My question has to do with the clinical applicability.

Severe traumatic brain injury can be associated with decreased cardiac contractility. We resuscitate all our patients using

transthoracic echo in our intensive care unit, and this allows us to physically see this decreased cardiac function. Beta blockers can decrease contractility further.

How did you monitor those patients while doing your trial in order to make sure that decreasing contractility further did not affect their perfusion? From previous trials, we know that decreased contractility in traumatic brain injury patients, translates into mortality.

Dr. David H. Livingston (Newark, New Jersey): Eric, great presentation, great paper, just two quick questions.

One, while there were no difference in thoracotomy and laparotomy patients but the overall numbers are really low so I am not that surprised. What I think drives a lot a lot of the hypercatecholanemia in a lot of our patients is the multiple fractures and need for multiple sequential operations. We often don't let these patients go to the OR early unless the fracture is really an emergency so a lot of the fracture work gets done days and days later. Do you have any data on fractures, fracture fixation in the various groups because I think that may drive it?

The second question is while beta blockers were better than nothing, and propranolol was better than other beta blockers, I didn't see any comparison of the beta blocker group minus the propranolol compared to nothing.

In other words, if you really think it's the propranolol, that important comparison seems to be missing.

Dr. David Harrington (Providence, Rhode Island): This is a tag-team of common therapy. I would suggest that this is an incidental observational trial of whether they got beta blockade or not and that's really not going to help anyone, really.

What's going to help you is if you do what was described in burn literature by very judiciously and carefully reducing basal heartrate by 20 percent.

So I would assume that anyone that used an old drug like propranolol is probably using it based on Herdon's studies and Herndon's observations so I bet the real intervention here was only propranolol.

If you have the heart rates on these patients or do you have the heart rates on the patients to show that people that got propranolol actually had a reduction in heart rate consistently?

Dr. Demetrios Demetriades (Los Angeles, California): Eric, nice large, practical study. I have the same concerns as Samir: The use of beta blockers was at physician discretion. Patients who are critically injured and have non-survivable injuries, I'm sure that they did not receive beta blockers. Why don't you exclude all those deaths in the first two or three days? Thank you.

Dr. Thomas J. Schroeppel (Colorado Springs, Colorado): Eric, excellent study. Thoughts on functional outcomes at data points further along than just discharge. Are we perhaps allowing these patients to survive to not have a functional outcome down the road? Comments. Thanks.

Dr. Eric J. Ley (Los Angeles, California): Dr. Arbabi, thank you for your insights and I appreciate all of your questions. I will do my best to answer these questions in the time allotted.

There were questions by Dr. Arbabi and DeMayo about targeting patients with hypertension. We also published a study that observed bimodal mortality with low and high blood pressure in TBI patients. And so with this study in mind we performed an analysis on patients who received beta blockers and presented with a known history of hypertension to determine if there was an additional effect, and noted that there was no significant difference in mortality. Those TBI patients who present with elevated admission blood pressure might a have greater benefit with beta blockers, although what the ideal blood pressure is and who benefits the most from beta blockers are unknown at this time.

Dr. Demetriades and Dr. Arbabi asked why we did not exclude patients who died during the first 48 hours after admission. So I will first say that we used a Cox Regression Model with time dependence that accounted for the timing of beta blocker administration and the timing of mortality. So exclusion of early or late mortality should not alter the mortality benefit observed with beta blockers in a multivariate regression model. When we redid the regression model and excluded mortality that occurred during the first 48 hours after admission, the adjusted hazard ratio was still significant with an AOR of 0.57 for those patients who received beta blockers. A similar protective effect was observed when we excluded mortality up to 72 hours and also when we excluded patients who received beta blockers after hospital day seven. And Dr. Livingston, although propranolol had the lowest mortality among beta blockers, when we excluded propranolol, the remaining beta blockers were still associated with lower mortality.

Dr. Ferrada commented about the effect of TBI on heart contractility which may lead to a reduced ejection fraction requiring pressors. In my opinion, this scenario is one that supports the early use of beta blockers, possibly in the ED, as they have been shown to be cardioprotective after TBI. In one of the few randomized controlled, double-blinded, trials on this subject, Cruickshank in a 1987 manuscript, noted TBI patients had elevated norepinephrine levels, but those patients who received beta blockers had lower levels of CKMB, SVT events, ST/T wave changes, and on autopsy lower rates of cardiac necrosis. So I agree that TBI can lead to a reduction in cardiac contractility, but I also believe that this complication can be prevented with early beta blockers. A retrospective study by Drs. Salim and Demetriades also supports my conclusion, TBI patients with elevated troponins who received beta blockers had a lower mortality.

Dr. Schroeppel, you questioned the long-term outcome in those patients who received beta blockers. We observed an increase in survivors with beta blocker use. We therefore would expect a range in functional outcomes among these survivors. Dr. Mohseni noted with propensity matching that long term functional outcome was improved with beta blockers after TBI and so I would expect the same.

Dr. Harrington questioned, should we target a heart rate with beta blockers or not? Drs. Mohr and Livingston in their study chose to provider higher doses of propranolol with increasing heart rate; we did not. Either treatment could work, I would argue that you would want to target norepinephrine level instead of heart rate as the elevated heart rate could be due to under resuscitation. And as Dr. Livingston noted, with increased injury severity we would expected higher levels of norepinephrine suggesting that polytrauma patients might have more benefit with beta blocker use than isolated TBI. Whatever method is chosen to dose propranolol, it's most important to avoid

bradycardia and hypotensive events as these will be associated with worse outcomes, as observed in the POISE trial.

As Dr. Arbabi questioned, why was there an elevated length of stay in those patients who received beta blockers? I think we're seeing survivors with beta blocker use and these patients were very sick and required an extended stay. I will reanalyze the data as suggested and set a maximum stay of 30 days but I suspect that the answer will require a randomized controlled trial.

Dr. Arbabi asked why we did not choose propensity matching for this analysis. As it was a prospective study, during the study design myself and the other PIs chose to analyze all patients who met inclusion criteria. We can reanalyze the data with propensity matching and will try to publish the results.

I thank you for your time and look forward to continuing this work.