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Authors

Kelly-Hedrick, Margot
Liu, Sunny
Temkin, Nancy
et al.

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Association of Early Beta-Blocker Exposure and Functional Outcomes in Critically Ill Patients With Moderate to Severe Traumatic Brain Injury: A Transforming Clinical Research and Knowledge in Traumatic Brain Injury Study

Margot Kelly-Hedrick, MBE[1,2]
Sunny Yang Liu, BA[1,2]
Nancy Temkin, PhD[3,4]
Jason Barber, MS[4]
Jordan Komisarow, MD[5]
Geoffrey Manley, MD, PhD[6]
Tetsu Ohnuma, MD, MPH, PhD[1,7]
Katharine Colton, MD[8]
Miriam M. Treggiari, MD, MPH, PhD[1,6,9]
Eric E. Monson, PhD[10]
Monica S. Vavilala, MD[11]
Ramesh Grandhi, MD, MS[12]
Daniel T. Laskowitz, MD, MHS[5,7,8]
Joseph P. Mathew, MD, MHS, MBA[7]
Adrian Hernandez, MD, MHS[13]
Michael L. James, MD[1,7,8]
Karthik Raghunathan, MD, MPH[1,7,9]
Ben Goldstein, PhD[14]
Amy J. Markowitz, JD[6]
Vijay Krishnamoorthy, MD, MPH, PhD[1,7,9]
the Transforming Clinical Research and Knowledge in Traumatic Brain Injury Investigators

OBJECTIVES: We aimed to 1) describe patterns of beta-blocker utilization among critically ill patients following moderate–severe traumatic brain injury (TBI) and 2) examine the association of early beta-blocker exposure with functional and clinical outcomes following injury.

DESIGN: Retrospective cohort study.

SETTING: ICUs at 18 level I, U.S. trauma centers in the Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) study.

PATIENTS: Greater than or equal to 17 years enrolled in the TRACK-TBI study with moderate–severe TBI (Glasgow Coma Scale of <13) were admitted to the ICU after a blunt TBI.

INTERVENTIONS: None.

MEASUREMENTS: Primary exposure was a beta blocker during the first 7 days in the ICU, with a primary outcome of 6-month Glasgow Outcome Scale-Extended (GOSE). Secondary outcomes included: length of hospital stay, in-hospital mortality, 6-month and 12-month mortality, 12-month GOSE score, and 6-month and 12-month measures of disability, well-being, quality of life, and life satisfaction.

MAIN RESULTS: Of the 450 eligible participants, 57 (13%) received early beta blockers (BB^+ group). The BB^+ group was on average older, more likely to be on a preinjury beta blocker, and more likely to have a history of hypertension. In the BB^+ group, 34 participants (60%) received metoprolol only, 19 participants (33%) received propranolol only, 3 participants (5%) received both, and 1 participant (2%) received atenolol only. In multivariable regression, there was no difference in the odds of a higher GOSE score at 6 months between the BB^+ group and BB^- group (odds ratio = 0.86; 95% CI, 0.48–1.53). There was no association between BB exposure and secondary outcomes.

CONCLUSIONS: About one-sixth of subjects in our study received early beta blockers, and within this group, dose, and timing of beta-blocker administration varied substantially. No significant differences in GOSE score at 6 months were demonstrated, although our ability to draw conclusions is limited by overall low total doses administered compared with prior studies.

KEY WORDS: beta blocker; cardioselective; disability; functional; traumatic brain injury

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality in the United States and internationally, and considerable heterogeneity in both patient pathology and management has hampered the

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KEY POINTS

Question: How are beta blockers used among critically ill patients following moderate–severe traumatic brain injury (TBI) and is early beta-blocker exposure associated with functional and clinical outcomes?

Findings: This retrospective cohort study examining 450 participants from the Transforming Clinical Research and Knowledge in TBI study found that 13% received early beta blockers (although timing, dose, and type varied), and early exposure was not associated with clinical and functional outcomes during hospitalization or at 6-month or 12-month postinjury.

Meaning: No significant differences in Glasgow Outcome Scale-Extended score at 6 months were demonstrated, although our ability to draw conclusions is limited by overall low total doses administered compared with prior studies, as well as substantial variation in timing, dose, and type of beta blocker.

development of high-quality evidence to guide therapy (1). Acute management of moderate–severe TBI is primarily supportive and aimed at preventing further damage after the primary brain injury—termed secondary injury—such as hypoxia and ischemia, which results in further disability (2, 3).

Cerebral pressure autoregulation allows the brain to maintain relatively constant blood flow over a range of blood pressures, allowing the brain to protect itself from both hyperemia and ischemia during normal or pathologic swings in systemic blood pressure. This autoregulation has been shown to be commonly dysfunctional after secondary brain injury following TBI (4, 5). This effect can be compounded by the profound hemodynamic lability and catecholamine surge seen in many patients after moderate–severe TBI, contributing to the cascade of metabolic insults that comprise secondary injury after TBI (6).

There has been increasing interest in blunting this sympathetic overdrive early in a patient's clinical course when the brain is felt to be most vulnerable to transient changes in cerebral blood flow (6). Multiple studies have investigated the use of medications that block catecholamine stimulation at beta-adrenergic receptors (i.e., beta-blockers) during the acute treatment of TBI. These studies—including three randomized controlled trials (RCTs)—have shown promising early results that beta-blocker exposure is associated with improved outcomes, and specifically a reduction in-hospital mortality (7–10). This promising evidence has led to a conditional recommendation for in-hospital beta-blocker use after acute TBI from the East Association for the Surgery of Trauma in 2017 (9). Despite this growing interest and current trials underway, multiple questions remain about the utilization of beta blockers in critically ill patients with TBI, including granular details of timing, dose, type, and frequency of use in the ICU. There is very limited data to date examining long-term functional outcomes following in-hospital beta-blocker exposure (6, 11).

To address these gaps, the present study aimed to 1) describe patterns of beta-blocker utilization in the first 7 days following moderate–severe TBI in the Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) cohort and 2) examine the association of early beta-blocker exposure (within the first 7 d of ICU admission) with long-term clinical and functional outcomes following injury. We hypothesized that significant variation would exist in early utilization of beta blockers, as well as observing a favorable association of beta blockers with clinical outcomes.

METHODS

Study Design and Database

This study is a retrospective cohort study using data from the TRACK-TBI study, a prospective study of patients presenting to one of 18 participating level I trauma centers following a blunt TBI (12). The study includes detailed clinical data from hospitalization (e.g., neurologic status, time-stamped medications, labs), patient demographics and characteristics (e.g., age, comorbidities) as well as clinical and functional outcomes for the year following injury (12–14). Date and time-stamped medication data were collected by trained research staff. Data for this study were collected from March 2014 to June 2018. The TRACK-TBI protocol which includes the study sample and variables collected has been described in detail elsewhere (12). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of

1975. The study was approved by the institutional review board at Duke University (Pro00100061, February 8, 2022, TIBY [MI Following TBI]).

Study Population

For our first research objective (to describe beta-blocker utilization patterns following injury), we examined critically ill patients with moderate–severe TBI. Our inclusion criteria included: patients greater than or equal to 17 years, admitted to the ICU, and Glasgow Coma Scale (GCS) of less than 13 after resuscitation in the emergency department (15). Patients who were not directly admitted to the ICU were excluded (i.e., deteriorated during hospitalization, necessitating ICU admission following hospitalization on the wards), as were those who did not have known timing of ICU admission, as this limited our ability to draw conclusions about timing of beta-blocker administration following injury.

For our second research objective (to examine the association of beta-blocker exposure on outcomes), we further restricted the study sample to only include those alive at the end of 7 days, to ensure that the entire cohort had the opportunity for beta-blocker exposure during the first 7 days of hospitalization. In an exploratory subgroup analysis, beta-blockers were further classified into cardioselective and noncardioselective, and patients who received them were compared. In this exploratory analysis, patients exposed to both cardioselective and noncardioselective beta blockers were excluded to avoid overlap in groups.

Exposure and Outcomes

For the first research objective, the outcome was defined as any beta-blocker exposure during the first 7 days in the ICU. Beta-blockers included cardioselective (acebutolol, atenolol, bisoprolol, metoprolol, nebivolol) and noncardioselective (nadolol, propranolol). For the second research objective, early beta-blocker (within the first 7 d of ICU stay) receipt was the exposure, and the primary outcome was Glasgow Outcome Scale-Extended (GOSE) at 6-month follow-up. Secondary outcomes included: length of hospital stay, in-hospital mortality, 6-month and 12-month mortality, 12-month GOSE score, and 6-month and 12-month multidimensional measures of disability, well-being, quality of life, and life satisfaction. These measures included:

Glasgow Outcome Scale-Extended (GOSE). The GOSE is an eight-point scale developed for TBI populations that grades recovery function, from dead (1) to upper good recovery, which indicates no problems (8), with varying levels of disability in between (16). We report the GOSE as both an ordinal score and a dichotomized variable where 1–4 is unfavorable and 5–8 is favorable.

Expanded Disability Rating Scale Postacute Interview (E-DRS-PI). The Expanded Disability Rating Scale Postacute Interview (E-DRS-PI) is an algorithmized score of the degree of disability based on a structured interview of the subject or their caregiver. A higher score indicates a higher degree of disability (17).

Short-Form Health Survey 12 (SF-12). The Short-Form Health Survey 12 (SF-12) is a widely used, 12-item measure of health and well-being. Scores are reported as physical health and mental health score, both ranging from 0 to 100, with a higher score indicating better-perceived health (18).

Quality of Life After Brain Injury-Overall Scale (QOLIBRI-OS). The six-item Quality of Life After Brain Injury-Overall Scale (QOLIBRI-OS) measures health-related quality of life (HRQoL) by asking about life satisfaction in the domains of physical health, cognition, function, emotion, personal, social, and the future. Scores are transformed to range from 0 (worst) to 100 (best possible HRQoL) (19).

Satisfaction With Life Scale (SWLS). The Satisfaction With Life Scale (SWLS) assesses life satisfaction through five items, which sum to a total score of 35 with higher scores indicating higher life satisfaction (20).

Statistical Analysis

Descriptive statistics were calculated for the overall sample, and for exposed versus nonexposed with regard to demographics, clinical characteristics, and injury-related information. Differences between the two cohorts were assessed for statistical significance using Mann-Whitney tests for continuous variables and Fisher exact tests for categorical variables. Descriptive statistics were used to look at medication types, timing, and doses. All IV doses were converted to oral dosing. To examine the association between beta blockers and outcomes, multivariable logistic and linear regression models (adjusted for preinjury

beta-blocker utilization, age, and history of hypertension as potential confounding effects given baseline differences) were used for categorical and continuous outcomes, respectively. A multivariable Cox proportional hazard model was used for the length of hospital stay to account for censoring due to in-hospital mortality. The same methodology was used for the exploratory subgroup analysis of cardioselective beta blockers versus nonselective beta blockers, adjusting instead for age and mannitol/saline administration in the emergency department as potential confounders. Deaths were excluded from analyses of DRS, QoLIBRI, SF-12, and SWLS. A two-sided significance threshold of *p* value of less than 0.05 was used for all analyses, and there were no adjustments for multiple comparisons. All analyses were performed using SPSS, version 26 (Armonk, NY) and SAS, version 9.4 (Cary, NC).

RESULTS

Demographic and Clinical Characteristics of Cohort

The demographic and characteristics of the sample are presented in **Table 1**. The total sample was on average 40 years old (SD = 17 yr) and 22% female; 16% had a history of hypertension, and 76% had a GCS less than 8 on presentation. Of the 450 eligible participants, 57 (13%) received beta blockers during the 7-day period in the ICU. The beta-blocker group was on average older (M = 47 yr, SD = 17 vs M = 39 yr, SD = 27 in no beta-blocker group, $p = 0.001$), more likely to be on a preinjury beta-blocker ($n = 9/57$, 16% vs $n = 11/393$, 3% in no beta-blocker group, $p < 0.001$), and were more likely to have a history of hypertension ($n = 18/57$, 32% vs $n = 48/393$, 12% in no beta-blocker group, $p < 0.001$), but had no significant difference in injury cause, GCS scores, injury severity score, or blood pressure measurements on presentation. Of the 450 participants, 354 (79%) and 332 (74%) had 6-month and 12-month outcomes, respectively.

Beta-Blocker Utilization During First 7 Days of Hospitalization

Of the 57 patients who received beta blockers during the first 7 days of their ICU stay, 34 (60%) received metoprolol only, 19 (33%) received propranolol only, 3 (5%) received both, and 1 (2%) received atenolol only. For patients who received metoprolol, the median total dose (converted to per os [PO] equivalent) was 25 mg with a median number of doses of 2 doses. For patients who received propranolol, the median total dose (converted to PO equivalent) was 30 mg with a median number of doses of 1.5 doses. Almost 40% of the sample ($n = 22/57$, 38%) received only one dose of a beta blocker (**Fig. 1**).

Association of Early Beta-Blocker Exposure With Clinical and Functional Outcomes

Nearly 80% of patients had 6-month data (overall sample $n = 354/450$, 79%; BB^- $n = 307/393$, 78%; BB^+ $n = 47/57$, 82%). For our primary outcome, the BB^+ group did not have increased odds of a higher GOSE score at 6 months compared with the BB^- group (OR = 0.86; 95% CI, 0.48–1.53) (**Fig. 2**). Three-quarters of the baseline patients had 12-month data (overall sample $n = 332/450$, 74%; BB^- $n = 286/393$, 73%; BB^+ $n = 46/57$, 81%). There was no significant difference in secondary outcomes of length of hospital stay, in-hospital mortality, 6-month and 12-month mortality, 12-month GOSE score, and 6-month and 12-month multidimensional measures of disability, well-being, quality of life, and life satisfaction (**Table 2**, **Figs. 2–4**).

Beta-Blocker Type and Clinical/Functional Outcomes

In an exploratory subgroup analysis, we examined outcomes for those who received only a cardio nonselective beta blocker (i.e., propranolol) versus only a cardioselective beta blocker (i.e., metoprolol or atenolol). Those who received cardioselective beta blockers were significantly older (M = 51 yr, SD = 17) compared with those who received a noncardioselective beta blocker (M = 39, SD = 14, $p = 0.022$) and were less likely to receive mannitol in the emergency department ($n = 4/29$, 14%) compared with the noncardioselective group ($n = 8/17$, 47%, $p = 0.019$) (**Supplemental Table 1**, http://links.lww.com/CCX/B230).

Overall, the two groups did not differ significantly in functional outcomes (**Supplemental Table 2**, http://links.lww.com/CCX/B230). At 12 months, the cardioselective beta-blockers group had higher odds of a higher GOSE score than the noncardioselective beta blocker (OR = 2.81; 95% CI, 0.77–10.2). At 12 months, the cardioselective beta-blockers group had a higher

TABLE 1.
Clinical and Demographic Characteristics of Those Who Received Beta Blockers and Those Who did not

Variables	Overall, *n* (%)	No Beta Blockers, *n* (%)	Beta Blockers During First 7 d, *n* (%)	*p*
Subjects	450	393 (87%)	57 (13%)	
Preinjury beta blockers				
No	430 (96%)	382 (97%)	48 (84%)	< 0.001
Yes	20 (4%)	11 (3%)	9 (16%)	
Age				
Mean (SD)	40.3 (17.2)	39.3 (17.0)	47.2 (17.0)	0.001
Sex				
Male	352 (78%)	312 (79%)	40 (70%)	0.12
Female	98 (22%)	81 (21%)	17 (30%)	
Race				
White	349 (80%)	301 (79%)	48 (84%)	0.66
Black	60 (14%)	53 (14%)	7 (12%)	
Other	29 (7%)	27 (7%)	2 (4%)	
Hispanic				
No	345 (79%)	300 (79%)	45 (82%)	0.72
Yes	91 (21%)	81 (21%)	10 (18%)	
Education years				
Mean (SD)	12.7 (2.6)	12.7 (2.7)	12.3 (2.2)	0.13
Less than high school	83 (21%)	69 (20%)	14 (27%)	
High school only	162 (42%)	137 (41%)	25 (48%)	
Some college	76 (19%)	71 (21%)	5 (10%)	
4-yr degree	52 (13%)	46 (14%)	6 (12%)	
Postgraduate	17 (4%)	15 (4%)	2 (4%)	
Injury cause				
MVC occupant	118 (26%)	107 (27%)	11 (19%)	0.63
Motorcycle crash	65 (14%)	58 (15%)	7 (12%)	
MVC (cyclist or pedestrian)	64 (14%)	55 (14%)	9 (16%)	
Fall	109 (24%)	91 (23%)	18 (32%)	
Assault	33 (7%)	30 (8%)	3 (5%)	
Other/unknown	61 (14%)	52 (13%)	9 (16%)	
Injury cause (multiple possible)				
Acceleration/deceleration	203 (45%)	178 (45%)	25 (44%)	0.89
Blow to head	112 (25%)	97 (25%)	15 (26%)	0.87
Head against object	299 (67%)	260 (66%)	39 (68%)	0.88
Crush	10 (2%)	10 (3%)	0 (0%)	0.62
Blast	0 (0%)	–	–	–
Ground level fall	71 (16%)	61 (16%)	10 (18%)	0.70
Fall from height	117 (26%)	102 (26%)	15 (26%)	1

(*Continued*)

TABLE 1. (*Continued*)

Clinical and Demographic Characteristics of Those Who Received Beta Blockers and Those Who did not

Variables	Overall, *n* (%)	No Beta Blockers, *n* (%)	Beta Blockers During First 7 d, *n* (%)	*p*
Gunshot	1 (0%)	1 (0.2%)	0 (0%)	1
Fragment	0 (0%)	–	–	–
Other	26 (6%)	24 (6%)	2 (4%)	0.56
Glasgow Coma Scale emergency department arrival				
Mean (SD)	5.8 (3.1)	5.8 (3.1)	5.1 (2.7)	0.10
Severe (3–8)	342 (76%)	294 (75%)	48 (84%)	0.14
Moderate (9–12)	108 (24%)	99 (25%)	9 (16%)	
Injury Severity Score non-head/neck				
Mean (SD)	7.5 (8.8)	7.6 (8.9)	7.1 (8.1)	0.70
Abbreviated Injury Scale head/neck				
Mean (SD)	3.8 (1.3)	3.8 (1.3)	3.7 (1.4)	0.62
Emergency department systolic blood pressure				
Mean (SD)	141 (31)	140 (31)	145 (33)	0.29
Emergency department mean arterial pressure				
Mean (SD)	106 (24)	105 (24)	110 (26)	0.20
Emergency department blood transfusion				
No	367 (83%)	319 (82%)	48 (84%)	0.85
Yes	76 (17%)	68 (18%)	8 (16%)	
Initial CT				
Negative	34 (8%)	33 (9%)	1 (2%)	0.10
Positive	386 (92%)	334 (91%)	52 (98%)	
Rotterdam Score				
Mean (SD)	3.4 (1.3)	3.3 (1.2)	3.7 (1.5)	0.15
History of hypertension				
No	352 (84%)	317 (87%)	35 (66%)	< 0.001
Yes	66 (16%)	48 (13%)	18 (34%)	
History of transient ischemic attacks				
No	417 (100%)	364 (100%)	53 (100%)	–
Yes	0 (0%)	–	–	
Emergency department mannitol/hypersaline				
No	349 (78%)	308 (78%)	41 (72%)	0.31
Yes	101 (22%)	85 (22%)	16 (28%)	
Placement of intracranial pressure monitor (emergency department or first 24 hr)				
No	213 (47%)	191 (49%)	22 (39%)	0.20
Yes	237 (53%)	202 (51%)	35 (61%)	

MVC = motor vehicle collision.

Statistical significance by Mann-Whitney or Fisher exact tests. Significance is unweighted. Missing values not reported or included in percentages so totals may not equal 450.

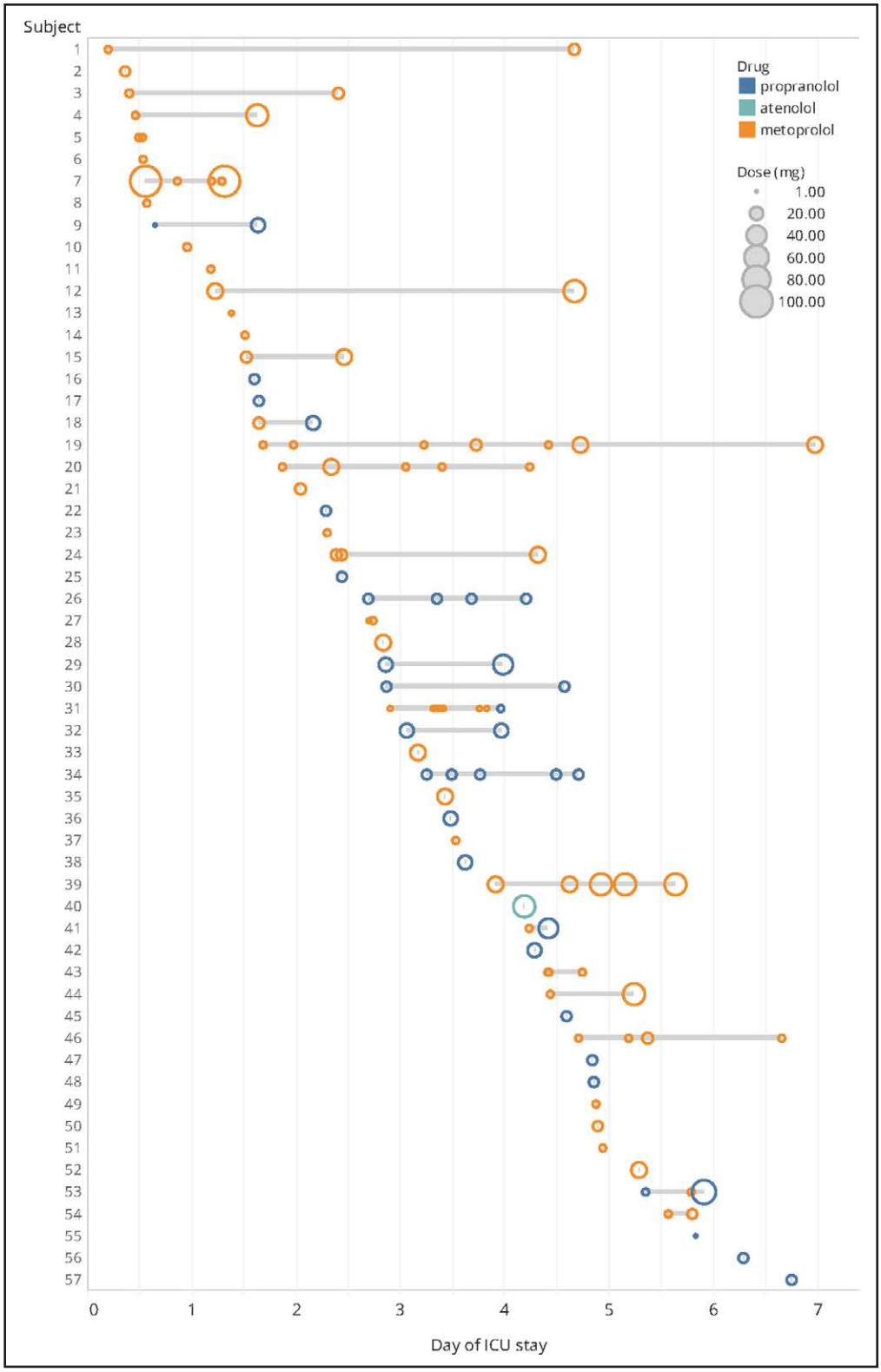

Figure 1. Beta-blocker drug, dose, and timing over the first 7 days of ICU stay for those who received at least one dose of a beta blocker ($n = 57$). Each *dot* represents a single dose of a beta blocker, with the color representing drug type and size proportional to dose. Subject numbers are arbitrary. For subjects who received multiple doses, trajectories are connected by *lines*.

mean disability score on the DRS-PI (M = 5.6, SD = 5.5) than the noncardioselective beta blocker (M = 1.4, SD = 1.5, B = –3.51, p = 0.028), indicating greater disability.

DISCUSSION

In this retrospective cohort study using the TRACK-TBI database, we found about one-sixth of subjects with moderate–severe TBI received beta blockers, and within this group, nearly half received a single dose, and a third received propranolol. We observed no significant differences in GOSE score at 6 months (primary outcome) or any secondary outcomes, but the substantial variation in beta-blocker dose and timing limit our ability to draw conclusions about the relationship between beta blockers and functional outcomes. Generally, those who received a cardioselective beta blocker did not differ in functional outcomes from those who received a noncardioselective beta blocker, but this subgroup analysis had a limited sample size.

Past observational studies have often considered beta-blocker exposure as a dichotomous variable (exposed vs unexposed) and have not reported on the details of the timing, frequency, dose, and type of beta blockers. Our study

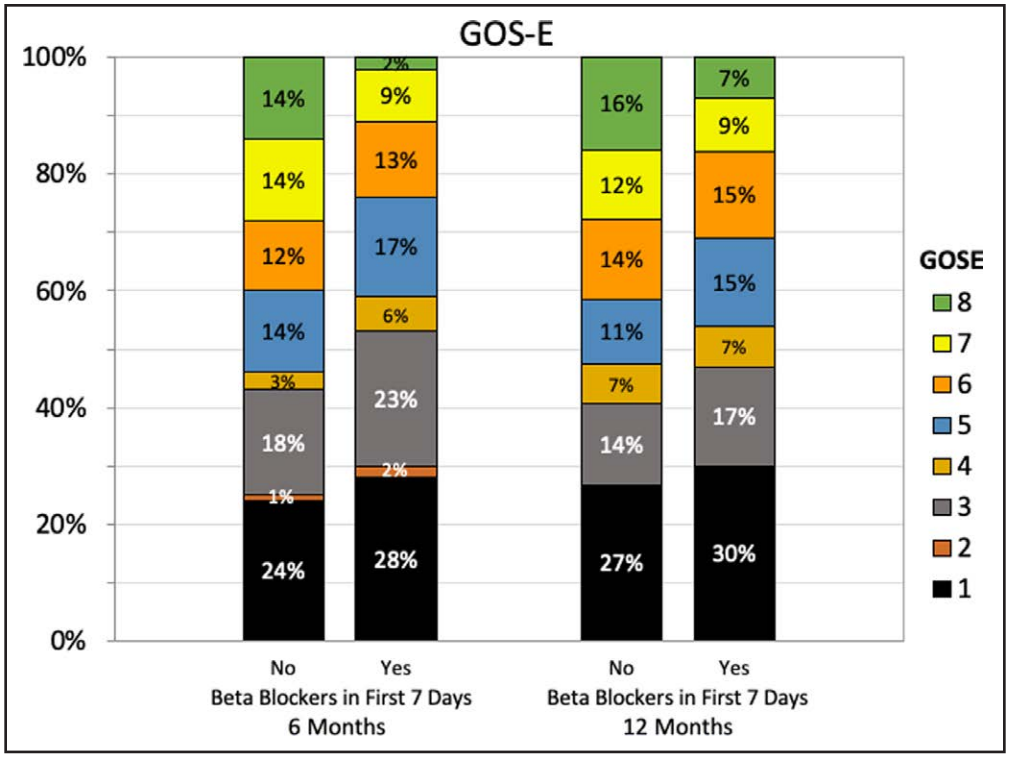

Figure 2. Glasgow Outcome Scale-Extended (GOSE) scores at 6 and 12 mo for those who received beta blockers in the first 7 d and those who did not.

finds that there is considerable variation among the minority of patients in the TRACK-TBI study who received beta blockers in the acute ICU period following TBI; patients received their first dose throughout the course of the 7 days, which limits comparisons with past studies (including RCTs) which often look at administering beta blockers within the first 48 hours following injury. Furthermore, many patients in our cohort received a much lower total dose of beta-blocker than subjects in past RCTs—with nearly 40% of our sample only receiving one dose, with a median dose of 25-30 mg, whereas the largest RCT involved 20 mg of propranolol every 12 hours for up to 10 days or discharge (6). This speaks to the challenge of drawing definitive conclusions from observational data when such wide variations in practice exist.

Three past studies have reported functional outcomes (specifically GOS or GOSE scores) of early beta-blocker exposure following TBI, with varied results (6, 11, 21). Our study adds multidimensional functional outcomes not previously reported—measures of disability, well-being, quality of life, and life satisfaction, which were not significantly associated with beta-blocker exposure. Unlike prior studies, we did not see a mortality benefit during hospitalization or at follow-up with beta-blocker exposure. In past studies, exposure to beta blockers during hospitalization had been associated with lower in-hospital mortality compared with unexposed patients in both cohort studies and three small RCTs (7–10). This discrepancy compared with our results raises the question of whether many patients in our study reached a sufficient level of exposure dose to see an impact on outcomes.

Several mechanisms for how beta blockers may provide a benefit have been proposed—yet, these remain largely speculative and mostly explored in experimental animal models. Autoregulation dysfunction following TBI can lead to the cerebral perfusion pressure becoming directly related to the systolic blood pressure (SBP), underscoring the importance of tight SBP control in the acute setting, which could be managed in part by beta blockers (4, 5, 22, 23). Beta blockers may also modulate the post-TBI catecholamine surge which can also contribute to secondary cerebral injury through worsening cerebral hypertension and edema (24). It is also possible that lipid-soluble beta blockers could cross the blood-brain barrier and exert their effects directly on cerebral tissue and vasculature, preventing ischemia by decreasing vasoconstriction, though this mechanism is largely theoretical (24, 25). Finally, beta blockers' cardioprotective effects may be a driving benefit, by reducing the risk of subsequent myocardial infarction by decreasing stroke volume, heart rate, blood pressure, and myocardial oxygen demand (24, 26).

Beta-blocker use following TBI has been supported by the Lund concept guidelines, a set of clinical guidelines developed at Sweden's University of Lund (27). The Lund guidelines are based primarily on the theoretical reasoning about intracranial pressure control

TABLE 2.
Clinical and Functional Outcomes for Those Who Received Beta Blockers During the First 7 Days of ICU Stay Versus Those Who Did Not

		Beta Blockers During First 7 d			
	Total ($n = 450$)	No ($n = 393$)	Yes ($n = 57$)	Effect Size[a]	p[b]
Primary outcome					
6 mo Glasgow Outcome Scale-Extended					
Unfavorable, *n* (%)	166 (48%)	138 (46%)	28 (60%)	OR = 0.87 (0.43, 1.76)	0.70
Favorable, *n* (%)	180 (52%)	161 (54%)	19 (40%)		
Total score, mean (SD)	4.3 (2.5)	4.4 (2.5)	3.7 (2.1)	OR = 0.86 (0.48, 1.53)	0.60
1	86 (25%)	73 (24%)	13 (28%)		
2	3 (1%)	2 (1%)	1 (2%)		
3	66 (19%)	55 (18%)	11 (23%)		
4	11 (3%)	8 (3%)	3 (6%)		
5	50 (14%)	42 (14%)	8 (17%)		
6	42 (12%)	36 (12%)	6 (13%)		
7	45 (13%)	41 (14%)	4 (9%)		
8	43 (12%)	42 (14%)	1 (2%)		
Secondary outcomes					
Discharged alive					
No	72 (16%)	63 (16%)	9 (16%)	OR = 1.66 (0.70, 3.96)	0.25
Yes	374 (84%)	326 (84%)	48 (84%)		
Length of hospital stay					
Mean (SE)	29.4 (6.1)	30.3 (7.0)	24.2 (2.2)	HR = 0.83 (0.60, 1.15)	0.26
Survival					
6 mo, cumulative rate	79.70%	80.60%	74.50%	HR = 0.74 (0.40, 1.37)	0.34
12 mo, cumulative rate	78.40%	79.10%	74.50%	HR = 0.71 (0.39, 1.31)	0.28
Disability					
6 mo E-DRS-PI, mean (SD)	4.0 (5.4)	4.0 (5.5)	4.6 (5.4)	B = 0.15 (−1.98, 2.29)	0.89
12 mo E-DRS-PI, mean (SD)	3.4 (4.8)	3.4 (5.0)	3.1 (4.0)	B = −0.74 (−2.50, 1.01)	0.41
Well-being					
6 mo SF-12					
Mental, mean (SD)	49.2 (10.4)	49.5 (10.2)	46.8 (12.3)	B = −3.23 (−8.20, 1.73)	0.20
Physical, mean (SD)	45.2 (10.8)	45.4 (11.1)	43.6 (8.3)	B = 3.05 (−1.79, 7.89)	0.22
12 mo SF-12					
Mental, mean (SD)	49.1 (10.0)	49.4 (10.2)	46.9 (8.9)	B = −1.36 (−5.76, 3.04)	0.54
Physical, mean (SD)	46.6 (10.2)	46.5 (10.4)	47.3 (9.5)	B = 5.59 (1.41, 9.77)	0.001
Health-related quality of life					
6 mo QoLIBRI, mean (SD)	63.1 (24.4)	64.0 (24.5)	56.0 (22.6)	B = −4.55 (−16.1, 7.0)	0.44
12 mo QoLIBRI, mean (SD)	63.9 (24.8)	64.6 (24.9)	59.0 (23.9)	B = 2.01 (−8.9, 13.0)	0.72

(*Continued*)

TABLE 2. (*Continued*)

Clinical and Functional Outcomes for Those Who Received Beta Blockers During the First 7 Days of ICU Stay Versus Those Who Did Not

		Beta Blockers During First 7 d			
	Total ($n = 450$)	No ($n = 393$)	Yes ($n = 57$)	Effect Size[a]	p[b]
Satisfaction with life					
6 mo SWLS, mean (SD)	22.5 (8.0)	22.6 (8.2)	21.9 (6.0)	B = −1.22 (−5.16, 2.72)	0.54
12 mo SWLS, mean (SD)	23.0 (8.0)	23.1 (8.3)	22.2 (6.4)	B = 0.23 (−3.24, 3.69)	0.90
12 mo Glasgow Outcome Scale-Extended					
Unfavorable, *n* (%)	158 (48%)	133 (48%)	25 (54%)	OR = 1.10 (0.54, 2.22)	0.80
Favorable, *n* (%)	168 (52%)	147 (53%)	21 (46%)		0.80
Total score, mean (SD)	4.3 (2.6)	4.4 (2.6)	3.9 (2.4)	OR = 0.99 (0.55, 1.77)	0.97
1	90 (28%)	76 (27%)	14 (30%)		0.97
2	0 (0%)	0 (0%)	0 (0%)		
3	46 (14%)	38 (14%)	8 (17%)		
4	22 (7%)	19 (7%)	3 (7%)		
5	39 (12%)	32 (11%)	7 (15%)		
6	45 (14%)	38 (14%)	7 (15%)		
7	37 (11%)	33 (12%)	4 (9%)		
8	47 (14%)	44 (16%)	3 (7%)		

E-DRS-PI = Expanded Disability Rating Scale Postacute Interview, HR = hazard ratio, OR = odds ratio, QoLIBRI = Quality of Life After Brain Injury-Overall Scale, SF-12 = Short-Form Health Survey 12, SWLS = Satisfaction With Life Scale.

[a]Beta blockers $(BB)^-$ group was the reference group; OR and HR > 1 and B > 0 indicate a higher outcome value for BB^+ group

[b]Statistical significance by linear/logistic/ordinal/Cox regression. Deaths are excluded from the analysis of DRS-PI, QoLIBRI, SF-12, and SWLS. significance weighted for beta blockers, age, and history of hypertension. Deaths are treated as censored observations. Discharge = risk of discharge. Missing values are not reported or included in percentages so totals may not equal 450.

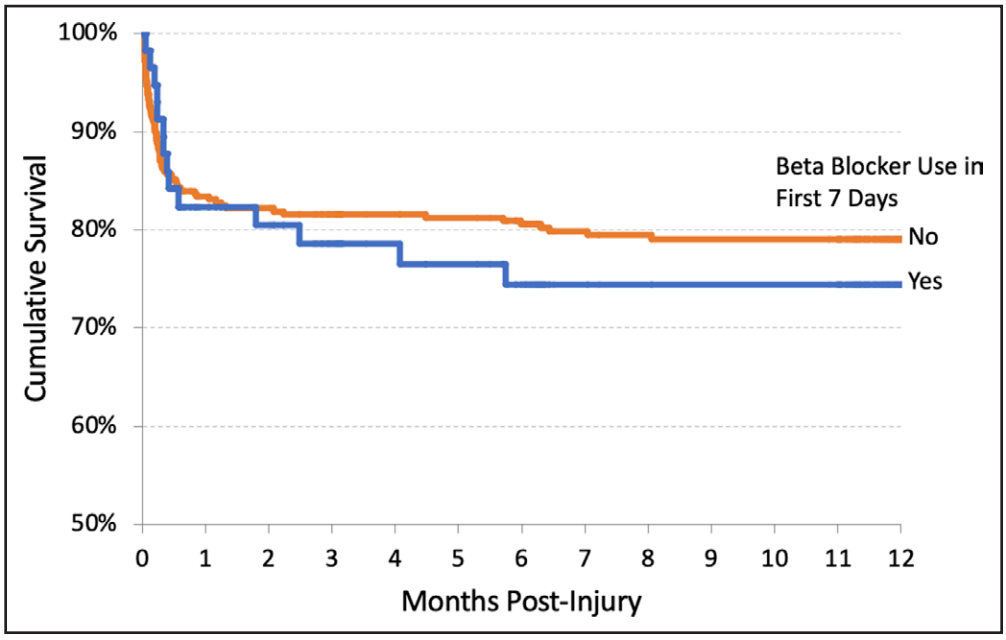

Figure 3. Cumulative survival in the 12 months following moderate–severe traumatic brain injury for those who received beta blockers in the first 7 d of ICU stay and those who did not.

(ICP) following blood-brain barrier disruption, and the recommendation for beta-blocker used to manage ICP in a "volume-targeted" strategy that is based on osmotic and hydrostatic pressures (27, 28). In contrast, the Brain Trauma Foundation guidelines for TBI care—widely followed in the United States—do not mention beta blockers as a therapy in acute treatment (2). The Eastern Association for the Surgery of Trauma (EAST) conditionally recommends beta-blocker use in

patients hospitalized for severe TBI provided they do not have contraindications, based on their conducted systematic review and meta-analysis (9). EAST classifies the level of evidence for this recommendation as low, although the largest RCT was published in 2020 after their 2017 recommendations (9). These more recent changes may impact the uptake of beta-blocker use for data collected after 2020. Still, data from our study suggests use remains low within the TRACK-TBI centers, which includes data up until 2018. Recent meta-analyses have not found an increased risk of adverse cardiopulmonary events, suggesting that while the level of evidence for benefit may be weak, there is no evidence of harm (7, 8). Our study begins to address functional outcomes beyond just GOSE and while little benefit was demonstrated, beta-blocker use was not associated with worse outcomes (7, 9).

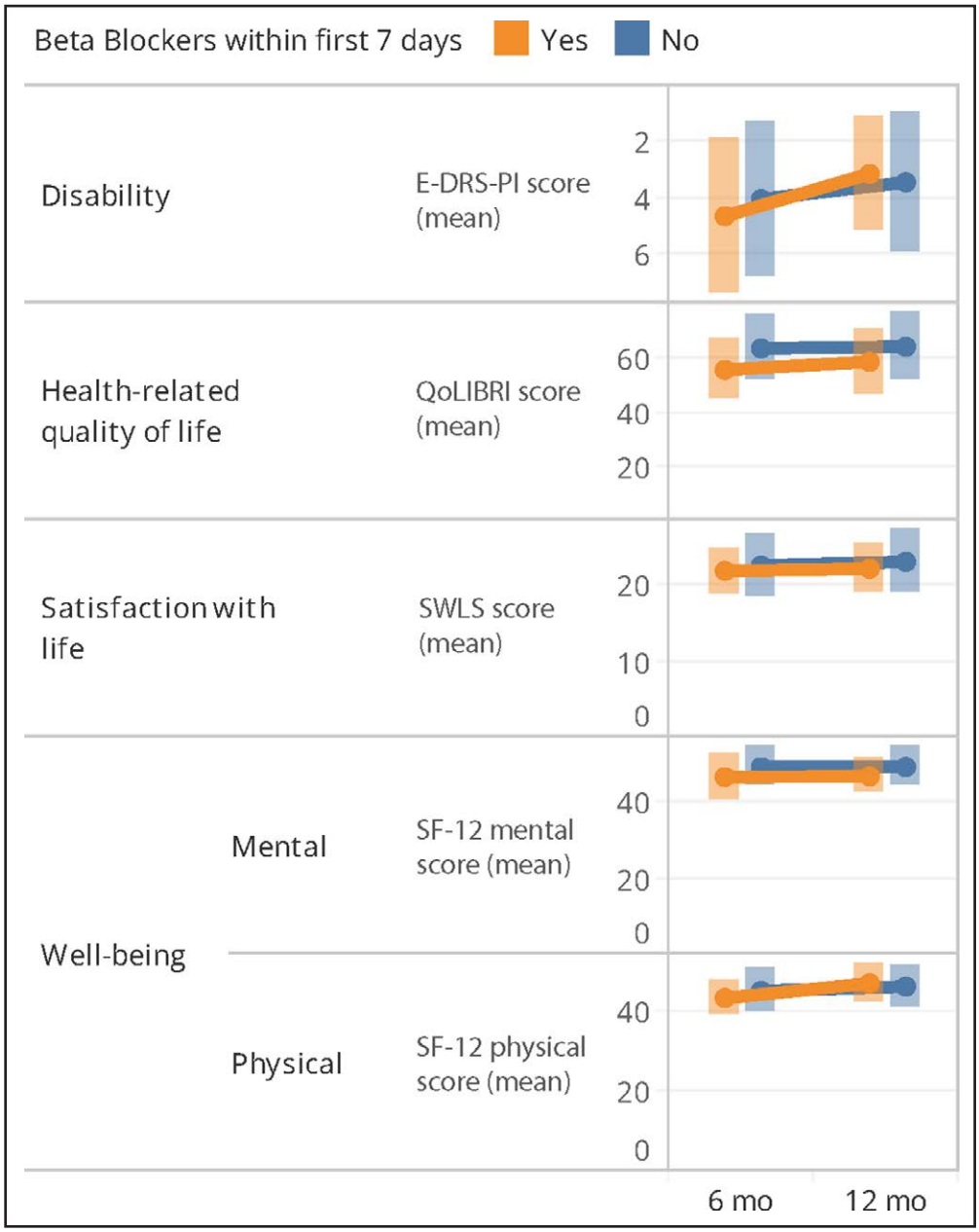

Figure 4. Functional outcomes at 6 and 12 mo post-traumatic brain injury for those who received beta blockers in the ICU and those who did not. Length of error *bars* represents 1 SD from the mean. The disability outcome (Expanded Disability Rating Scale Postacute Interview [E-DRS-PI]) is scored such that a higher score represents a higher disability; this outcome is presented with a flipped *y*-axis to be in line with other outcomes where a higher score indicates a more favorable outcome. QoLIBRI = Quality of Life After Brain Injury-Overall Scale, SF-12 = Short-Form Health Survey 12, SWLS = Satisfaction With Life Scale.

Our study has several limitations. TRACK-TBI is a rich dataset with granular details about the timing and dose of medications, which allows an increased understanding of how beta blockers are administered in the ICU but results in a wide variation of dose of exposure in subjects. Similarly, the timing of exposure was spread across the first week in the ICU; while the ideal timing of exposure is not established, past RCTs have started exposure within 48 hours of injury (6, 29). This variability with a relatively small number of patients who received beta blockers may limit our ability to detect differences between groups, particularly the subgroup analysis of beta-blocker type; this also constrains generalizability of the study. Further, the age difference between groups—though adjusted for in analyses—may indicate unmeasured confounders. The size of the sample also limited our ability to control for many sociodemographic and clinical characteristics,

increasing the chance of residual confounding. We were not able to ascertain the indications for beta-blocker administration, and while we reported history of hypertension and preinjury beta-blocker use, some comorbidities helping to explain use—like atrial fibrillation—were not collected. The small sample size also limited our ability to explore whether a dose-response relationship exists. At the follow-up periods at 6 and 12 months, 20-25% of subjects were lost to follow-up, who may be potentially different from those who remained in the study.

About one-sixth of the subjects in our study received beta blockers, and within this group, dose, and timing of beta-blocker administration varied. No significant differences in GOSE score at 6 months were observed. This suggests that the low doses and short courses of beta blockers (as was used in this cohort) appear to be safe in this patient population. Our ability to draw conclusions about benefits is in part limited by overall low total doses compared with past randomized trials and further studies are needed to determine what dose threshold may bring benefit to patients following TBI, and how this may impact functional outcomes.

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1 *Critical Care and Perioperative Population Health Research (CAPER) Unit, Department of Anesthesiology, Duke University, Durham, NC.*

2 *Duke University School of Medicine, Duke University, Durham, NC.*

3 *Departments of Biostatistics, University of Washington, Seattle, WA.*

4 *Departments of Neurosurgery, University of Washington, Seattle, WA.*

5 *Departments of Neurosurgery, Duke University, Durham, NC.*

6 *Departments of Brain and Spinal Injury Center, University of California, San Francisco, San Francisco, CA.*

7 *Departments of Anesthesiology, Duke University, Durham, NC.*

8 *Departments of Neurology, Duke University, Durham, NC.*

9 *Departments of Population Health Sciences, Duke University, Durham, NC.*

10 *Libraries Center for Data and Visualization Sciences, Duke University, Durham, NC.*

11 *Departments of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA.*

12 *Department of Neurosurgery, University of Utah, Salt Lake City, UT.*

13 *Departments of Medicine, Duke University, Durham, NC.*

14 *Departments of Biostatistics and Bioinformatics, Duke University, Durham, NC.*

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For information regarding this article, E-mail: vijay.krishnamoorthy@duke.edu

REFERENCES

1. Taylor CA, Bell JM, Breiding MJ, et al: Traumatic brain injury-related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. *Morb Mortal Wkly Rep* 2017; 66:1–16
2. Carney N, Totten AM, O'Reilly C, et al: Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; 80:6–15
3. Pearn ML, Niesman IR, Egawa J, et al: Pathophysiology associated with traumatic brain injury: Current treatments and potential novel therapeutics. *Cell Mol Neurobiol* 2017; 37:571–585
4. McGinn MJ, Povlishock JT: Pathophysiology of traumatic brain injury. *Neurosurg Clin N Am* 2016; 27:397–407
5. Bouma GJ, Muizelaar JP: Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. *J Neurotrauma* 1992; 9:S333–S348
6. Khalili H, Ahl R, Paydar S, et al: Beta-blocker therapy in severe traumatic brain injury: A prospective randomized controlled trial. *World J Surg* 2020; 44:1844–1853

7. Ding H, Liao L, Zheng X, et al: β-Blockers for traumatic brain injury: A systematic review and meta-analysis. *J Trauma Acute Care Surg* 2021; 90:1077–1085
8. Alali AS, McCredie VA, Golan E, et al: Beta blockers for acute traumatic brain injury: A systematic review and meta-analysis. *Neurocrit Care* 2014; 20:514–523
9. Alali AS, Mukherjee K, McCredie VA, et al: Beta-blockers and traumatic brain injury: A systematic review, meta-analysis, and eastern association for the surgery of trauma guideline. *Ann Surg* 2017; 266:952–961
10. Ko A, Harada MY, Barmparas G, et al: Early propranolol after traumatic brain injury is associated with lower mortality. *J Trauma Acute Care Surg* 2016; 80:637–642
11. Ahl R, Thelin EP, Sjölin G, et al: β-Blocker after severe traumatic brain injury is associated with better long-term functional outcome: A matched case control study. *Eur J Trauma Emerg Surg* 2017; 43:783–789
12. Yue JK, Vassar MJ, Lingsma HF, et al; TRACK-TBI Investigators: Transforming research and clinical knowledge in traumatic brain injury pilot: Multicenter implementation of the common data elements for traumatic brain injury. *J Neurotrauma* 2013; 30:1831–1844
13. Bodien YG, McCrea M, Dikmen S, et al; TRACK-TBI Investigators: Optimizing outcome assessment in multicenter TBI trials: perspectives from TRACK-TBI and the TBI endpoints development initiative. *J Head Trauma Rehabil* 2018; 33:147–157
14. Nelson LD, Temkin NR, Dikmen S, et al; and the TRACK-TBI Investigators: Recovery after mild traumatic brain injury in patients presenting to us level I trauma centers: A transforming research and clinical knowledge in traumatic brain injury (TRACK TBI) study. *JAMA Neurol* 2019; 76:1049–1059
15. Jain S, Iverson LM: Glasgow Coma Scale. In: *StatPearls*. Treasure Island, StatPearls Publishing, 2022.
16. Wilson L, Boase K, Nelson LD, et al: A manual for the Glasgow Outcome Scale-Extended interview. *J Neurotrauma* 2021; 38:2435–2446
17. International Traumatic Brain Injury Research Initiative: Standard operating procedures for outcome assessment version 10, 2018. Available at: https://tracktbi.ucsf.edu/sites/tracktbi.ucsf.edu/files/Outcome%20Assessment%20SOP_04-12-18_V10_clean.pdf. Accessed February 16, 2023
18. Ware J, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34:220–233
19. von Steinbuechel N, Wilson L, Gibbons H, et al: QOLIBRI overall scale: A brief index of health-related quality of life after traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2012; 83:1041–1047
20. Diener E, Emmons RA, Larsen RJ, et al: The Satisfaction with Life Scale. *J Pers Assess* 1985; 49:71–75
21. Ley EJ, Leonard SD, Barmparas G, et al; Beta Blockers TBI Study Group Collaborators: Beta blockers in critically ill patients with traumatic brain injury: Results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. *J Trauma Acute Care Surg* 2018; 84:234–244
22. Overgaard J, Tweed WA: Cerebral circulation after head injury. 1. Cerebral blood flow and its regulation after closed head injury with emphasis on clinical correlations. *J Neurosurg* 1974; 41:531–541
23. Schmalbruch IK, Linde R, Paulson OB, et al: Activation-induced resetting of cerebral metabolism and flow is abolished by β-adrenergic blockade with propranolol. *Stroke* 2002; 33:251–255
24. Tran TY, Dunne IE, German JW: Beta blockers exposure and traumatic brain injury: A literature review. *Neurosurg Focus* 2008; 25:E8
25. Lopez AJ, ElSaadani M, Jacovides CL, et al: Betablockade in TBI: Dose dependent reductions in BBB leukocyte mobilization and permeability in vivo. *J Trauma Acute Care Surg* 2022; 92:781–791
26. Riordan WP, Cotton BA, Norris PR, et al: Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. *J Trauma* 2007; 63:503–10; discussion 510
27. Koskinen LOD, Olivecrona M, Grände PO: Severe traumatic brain injury management and clinical outcome using the Lund concept. *Neuroscience* 2014; 283:245–255
28. Sharma D, Vavilala MS: Lund concept for the management of traumatic brain injury: A physiological principle awaiting stronger evidence. *J Neurosurg Anesthesiol* 2011; 23:363–367
29. Schroeppel TJ, Sharpe JP, Shahan CP, et al: Beta-adrenergic blockade for attenuation of catecholamine surge after traumatic brain injury: A randomized pilot trial. *Trauma Surg Acute Care Open* 2019; 4:e000307