An Analysis of Beta-Blocker Administration Pre-and Post-Traumatic Brain Injury with Subanalyses for Head Injury Severity and Myocardial Injury

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A growing body of literature indicates that beta-blocker administration after traumatic brain injury (TBI) is cerebroprotective, limiting secondary injury; however, the effects of preinjury beta blocker status remain poorly understood. We sought to characterize the effects of pre- and post-injury beta-blocker administration on mortality with subanalyses accounting for head injury severity and myocardial injury. In a Level II trauma center, all admissions of patients ≥18 years with a head Abbreviated Injury Scale Score ≥2, Glasgow Coma Scale ≤13 from May 2011 to May 2013 were queried. Demographic, injury-specific, and outcome variables were analyzed using univariate analyses. Subsequent multivariate analyses were conducted to determine adjusted odds of mortality for beta-blocker usage controlling for age, Injury Severity Score, head Abbreviated Injury Scale, arrival Glasgow Coma Scale, ventilator use, and intensive care unit stay. A total of 214 trauma admissions met inclusion criteria: 112 patients had neither pre- nor postinjury beta-blocker usage, 46 patients had preinjury beta-blocker usage, and 94 patients had postinjury beta-blocker usage. Both unadjusted and adjusted odds ratios of preinjury beta-blocker were insignificant with respect to mortality. However, postinjury in-hospital administration of beta blockers was found to significantly in the decrease of mortality in both univariate ($P = 0.002$) and multivariate analyses ($P = 0.001$). Our data indicate that beta-blocker administration post-TBI in hospital reduces odds of mortality; however, preinjury beta-blocker usage does not. Additionally, myocardial injury is a useful indicator for beta-blocker administration post-TBI. Further research into which beta blockers confer the best benefits as well as the optimal period of beta-blocker administration post-TBI is recommended.

Introduction

TRAUMATIC BRAIN INJURY (TBI) results in significant mortality and morbidity, affecting more than two million people in the United States each year. These injuries are responsible for over 50,000 deaths and 80,000 long-term disabilities annually, costing the health-care industry approximately $56 billion.[1, 2] Despite numerous randomized controlled trials and retrospective studies contributing to novel treatments, TBI prognosis remains poor.[3] Consequently, identifying therapies to improve TBI outcome continues to be an area in need of significant research.

One area of research presently receiving attention is the use of beta blockers to prevent secondary injury and improve outcome after TBI.[4–8] A significant catecholamine surge has been associated with TBI,[9–14] resulting in a hyperadrenergic state. Although previous research has characterized the effects of the catecholamine surge on cardiac, endocrine, immune, and pulmonary systems,[4, 15–21] the impact of the catecholamine surge and hyperadrenergic state on the brain remains poorly understood. In the past few decades, research has correlated reduced morbidity and mortality with drugs blocking catecholamine stimulation

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of beta-adrenergic receptors, most notably in burn and subarachnoid hemorrhage patients.[4, 22] Although a recent study challenged the protective effects of beta blockers during the perioperative period,[23] there is sustained interest in improved TBI outcome with beta-blocker administration. This is due, in part, to the paucity of therapeutic TBI interventions presently available. Prevention of secondary brain injury is the primary goal of neurointensive care, and after numerous randomized clinical trials, there remains no level 1 evidence to support a particular therapeutic maneuver.[4]

This study sought to provide a comprehensive view of the effects of beta-blocker administration both pre- and postinjury in a moderate-to-severe head injured trauma population with subanalyses accounting for patients presenting with evidence of myocardial injury. As the sympathetic nervous system is crucial to the maintenance of physiological parameters in the immediate period after traumatic injury, it was hypothesized that patients on beta-blockers preinjury would be at a survival disadvantage, and would thus show increased mortality. Conversely, in the post-TBI period, beta-blocker administration was hypothesized to confer improved odds of survival by limiting long-term activation of the hyperadrenergic state. Additionally, it was hypothesized that beta-blocker administration post-TBI would have similar survival effects for moderate and severe head injury populations when analyzed separately rather than in composite. Finally, it was hypothesized that beta-blocker administration would have a greater survival benefit for patients presenting with myocardial injury compared with patients with no myocardial injury.

Methods

In a study reviewed and approved by the Institutional Review Board of Lancaster General Health, a list of adult trauma admissions for patients of age 18 years and older with an arrival head Abbreviated Injury Scale (AIS) score ≥ 2 and arrival Glasgow Coma Scale (GCS) score ≤ 13 from May 2011 to May 2013 was obtained from the trauma registry (Digital Innovations, Forest Hill, MD) of a Level II trauma center accredited by the Pennsylvania State Trauma Foundation. Patients presenting dead on arrival to the emergency department were excluded from analysis. Information on age, gender, arrival GCS, head AIS, Injury Severity Score (ISS), intensive care unit (ICU) stay, ventilator days, mechanism of injury (MOI), total pre-existing conditions (PECs), complications, and mortality were collected. Additionally, first cardiac troponin I level, beta blocker use preadmission, and beta-blocker administration in hospital were queried from the Epic electronic patient record system (EpicSystems Corporation, Verona, WI). Beta blockers were broken down into two classes: selective and nonselective. Drugs targeting mostly beta-1 adrenoreceptors were classified as selective; drugs targeting multiple adrenoreceptors were classified as nonselective. We defined moderate TBI as head AIS 2 to 3, GCS ≤ 13, and severe TBI as head AIS ≥ 4, GCS ≤ 13. Additionally, myocardial injury was identified by an elevated initial cardiac troponin I level ≥ 0.01 μg/L.

Univariate binary logistic regression models were used to calculate unadjusted odds ratios of mortality for gender (male), age, total PECs, MOI fall, ISS, head AIS, arrival GCS, ICU stay, ventilator use, total complications, elevated troponin, beta blocker use preinjury, and beta blocker use postinjury in hospital. A multivariable binary logistic regression model of mortality was subsequently used to calculate an adjusted odds ratio of beta blocker use preinjury as well as beta-blocker administration postinjury in hospital. A subsequent multivariable binary logistic regression model of mortality was used to calculate adjusted odds ratios of selective and nonselective beta blockers preinjury and postinjury in hospital. A P value < 0.05 was considered significant.

Furthermore, two subanalyses were conducted to determine if TBI severity or myocardial injury affected the impact of beta blockers on outcome. Multivariable binary logistic regression models of moderate TBI (head AIS = 2–3, GCS ≤ 13) and severe TBI (head AIS≥ 4, GCS≤ 13) populations were conducted separately to determine if the effect of beta blockers differed between the two populations. Additionally, multivariable binary logistic regression models of the population of patients with elevated cardiac troponin I levels and patients without elevated cardiac troponin I levels were conducted separately to determine whether treating TBI patients who also had evidence of myocardial injury with beta blockers would decrease mortality.

Results

There were a total of 4,463 trauma admissions for patients of age 18 years and older between May 2011 and May 2013. Of these admissions, 224 were associated with patients with a head AIS ≥ 2, GCS ≤ 13. Ten patients were pronounced dead on arrival to the emergency department and were subsequently excluded from analysis, producing a final study population of 214. Patients in the study population ranged in age from 18 to 99 years, with a median age of 54 years. There were a total of 141 (66%) males and 73 (34%) females in this population. The most common mechanism of injury was fall (49%), followed by

motor vehicle collision (23%). ISS ranged from 4 to 75, with a median score of 25. Arrival GCS ranged from 3 to 13, with a median score of 10. A majority of patients had at least one PEC (73%) and had elevated cardiac troponin I levels on admission (69%). Additionally, 173 (81%) patients were admitted to the ICU, 115 (54%) patients were put on a ventilator during their hospitalization, and 58 (27%) patients had complications. Sixty-two (29%) patients died in hospital (all-cause mortality).

Within the study population, 112 (52%) patients were not on pre- or postinjury beta blockers. Of the remaining 102 patients on beta blockers, 46 (45%) patients were on beta blockers preinjury (selective = 33 patients; nonselective = 13 patients), 38 of which were on beta blockers preinjury and received beta blockers in hospital, and 8 of which were on beta blockers preinjury but did not receive beta blockers in hospital. The remaining 56 (55%) patients were not on beta blockers preinjury but did receive beta blockers in hospital. A total of 94 patients were administered beta blockers in hospital (selective = 69 patients; nonselective = 25 patients) (Fig. 1). Postinjury beta-blocker administration was at the discretion of the attending trauma surgeon for patients believed to be experiencing a heightened hyperadrenergic state. Analysis of variance revealed no statistically significant differences between the groups under investigation in terms of gender ($P = 0.499$), ISS ($P = 0.421$), head AIS ($P = 0.475$), or arrival GCS ($P = 0.312$). Significant differences in terms of age, however, were found between groups ($P = 0.001$), with patients presenting with preinjury beta blockers and not receiving beta blockers in hospital demonstrating the highest mean age (73.5), whereas patients only receiving postinjury beta blockers showing the lowest mean age (45.7). Of the beta-blocker populations and one control population, patients on beta blockers preinjury who also received beta blockers in hospital demonstrated the lowest unadjusted mortality, and patients on beta blockers preinjury who did not receive beta blockers in hospital demonstrated the highest mortality (Table 1; $P = 0.001$).

Univariate analysis found age, ISS, AIS, and ventilator use to be significantly correlated with increased odds of mortality. Arrival GCS, ICU stay, and beta-blocker administration in hospital (selective and nonselective) were significantly correlated with decreased odds of mortality (Table 2). In a multivariable binary logistic regression model of mortality controlling for age, ISS, head AIS, and arrival GCS, beta-blocker administration postinjury was associated with an 83 per cent reduction in mortality (adjusted odds ratio [AOR] = 0.17; 95% confidence interval [CI] = 0.06–0.48; $P = 0.001$). Beta blocker use preinjury was found insignificant (AOR = 1.13; 95% CI = 0.34–3.73; $P = 0.842$). This model has excellent discrimination with an area under the receiver operating characteristic (AUROC) value of 0.88 (Table 3). In a subsequent multivariable logistic regression model adjusting for both pre- and postinjury selective and nonselective beta blocker use, both nonselective (AOR = 0.05; 95% CI = 0.01–0.34; $P = 0.002$) and selective (AOR = 0.27; 95% CI = 0.09–0.81; $P = 0.020$) beta-blocker administration in hospital were significant predictors of decreased odds of mortality. Both nonselective and selective beta blocker use preinjury remained insignificant (Table 4).

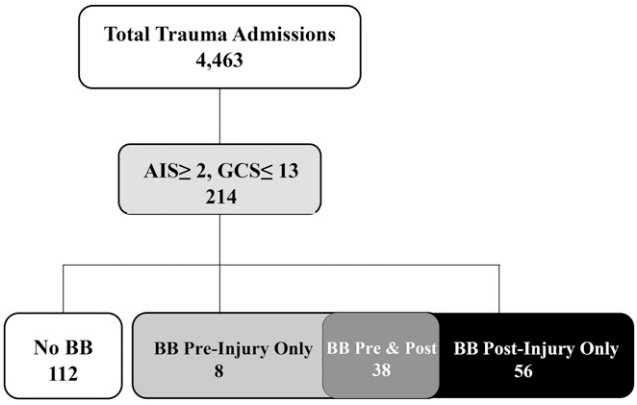

FIG. 1. Study population (AIS ≥2, GCS ≤13): Beta blocker (BB) *versus* no BB.

TABLE 1. *Mortality of BB Groups*

Group	Number	Mortality, % (N)
No BB	112	36.6 (41)
BB preinjury only	8	75.0 (6)
BB preinjury and in hospital	38	13.16 (5)
BB in hospital only	56	17.9 (10)

BB, beta blockers.

TABLE 2. *Unadjusted Odds of Mortality*

	Unadjusted Odds Ratio (95% CI)	*P* Value
Male	0.83 (0.45–1.54)	0.557
Age	1.02 (1.00–1.03)	0.002
Total PECs	1.10 (0.96–1.25)	0.186
MOI fall	0.79 (0.52–1.04)	0.347
ISS	1.08 (1.05–1.11)	<0.001
Head AIS	4.13 (2.62–6.49)	<0.001
Arrival GCS	0.70 (0.63–0.77)	<0.001
ICU stay	0.93 (0.87–0.99)	0.034
Ventilator use	3.87 (1.99–7.51)	<0.001
Total complications	0.84 (0.63–1.13)	0.246
Elevated troponin	1.31 (0.63–2.72)	0.474
BB preinjury	0.72 (0.34–1.53)	0.395
Selective BB	0.53 (0.21–1.36)	0.185
Nonselective BB	1.58 (0.50–5.03)	0.440
BB in hospital	0.30 (0.15–0.57)	0.002
Selective BB	0.47 (0.22–0.98)	0.043
Nonselective BB	0.28 (0.09–0.83)	0.021

BB, beta blockers.

TABLE 3. *Multivariable Logistic Regression Model for Mortality*

	AOR (95% CI)	*P* Value
Age	1.04 (1.02–1.07)	0.001
ISS	1.03 (0.98–1.09)	0.212
Head AIS	2.69 (1.32–5.48)	0.006
Arrival GCS	0.64 (0.55–0.75)	<0.001
BB preinjury	1.13 (0.34–3.73)	0.842
BB in hospital	0.17 (0.06–0.48)	0.001
AUROC: 0.88		

BB, beta blockers.

TABLE 4. *Multivariable Logistic Regression for Mortality: Selective vs Nonselective BB*

	AOR (95% CI)	*P* Value
Age	1.04 (1.02–1.07)	0.001
ISS	1.05 (0.99–1.11)	0.119
Head AIS	2.19 (1.06–4.56)	0.035
Arrival GCS	0.62 (0.52–0.74)	<0.001
Selective BB preinjury	0.64 (0.15–2.84)	0.560
Nonselective BB preinjury	5.06 (0.56–45.5)	0.148
Selective BB in hospital	0.27 (0.09–0.81)	0.020
Nonselective BB in hospital	0.05 (0.01–0.34)	0.002
AUROC: 0.87		

BB, beta blockers.

To determine if beta blocker usage affected the moderate and severe TBI populations differently, subanalyses of these two groups were conducted. There were a total of 90 (42%) patients with moderate TBI and 124 (58%) patients with severe TBI. Multivariable binary logistic regression models adjusting for age, ISS, head AIS, and arrival GCS of these two populations revealed that beta-blocker administration in hospital had similar AOR of mortality for both moderate TBI (AOR = 0.19; 95% CI = 0.04–0.82; $P = 0.002$) and severe TBI (AOR = 0.18; 95% CI = 0.05–0.55; $P = 0.003$) patients. Beta blocker use preinjury remained insignificant for both populations.

Furthermore, to determine if beta-blocker administration affected patients with evidence of myocardial injury and patients without evidence of myocardial injury differently, subanalyses of the two populations were conducted. There were a total of 125 (69%) patients with evidence of myocardial injury, defined as an initial cardiac troponin I level ≥0.01 μg/L, and 55 (31%) patients without evidence of myocardial injury. Multivariable binary logistic regression models adjusting for age, ISS, head AIS, and arrival GCS found beta-blocker administration to have a protective effect by decreasing mortality in the myocardial injury population (AOR = 0.13; 95% CI = 0.06–0.61; $P = 0.017$), but not the nonmyocardial injury population (AOR = 0.38; 95% CI = 0.12–1.52; $P = 0.279$). Moreover, beta blocker use preinjury remained insignificant in both the myocardial injury (AOR = 2.37; 95% CI = 0.44–12.9; $P = 0.433$) and the nonmyocardial injury (AOR = 0.29; 95% CI = 0.07–3.54; $P = 0.294$) groups.

Discussion

We were able to demonstrate a significant decreased odds of mortality with beta-blocker administration in hospital for patients presenting with moderate and severe TBI, defined by head AIS ≥2, GCS ≤13 (AOR = 0.17; 95% CI = 0.06–0.48; $P = 0.001$); however, preinjury beta blocker use was not found to confer any survival benefits to this patient population. This study supports a growing body of literature detailing the protective benefits of beta blockers administered post-TBI.[4–8] As TBI prognosis remains poor,[3] the potential of beta-blocker administration postinjury to improve outcome is exciting. However, little research has been generated identifying specific indications for beta-blockers post-TBI.

Salim et al.[8] began to address this issue by evaluating the effect of beta blockers on TBI patients with and without myocardial injury, who are identified by elevated cardiac troponin I levels at hospital admission or during hospitalization. Beta blockers were found to reduce mortality in patients with elevated cardiac troponin I levels, but not in patients without elevated cardiac troponin I levels. In our study, we conducted subgroup analyses of patients with and without elevated cardiac troponin levels at hospital admission and found similar results. Beta blockers administered in hospital were found to have a protective effect on patients with elevated cardiac troponin I levels, but not on patients without elevated cardiac troponin I levels. Consequently, myocardial injury, determined by elevated troponin I levels, is a promising indicator for beta-blocker administration post-TBI.

Additionally, to date, no research has identified the safest and most effective beta blocker for TBI patients. The Lund group recommends the use of metoprolol, a selective beta-1 receptor blocker.[24] However, a 1982 prospective randomized trial found propranolol, a nonselective beta blocker, to improve mortality in an aneurismal subarachnoid hemorrhage population.[20] In this study, we found both nonselective (AOR = 0.05; 95% CI = 0.01–0.34; $P = 0.002$) and selective (AOR = 0.27; 95% CI = 0.09–0.81; $P = 0.020$) beta blockers to decrease odds of mortality postinjury for TBI patients. However, nonselective beta blockers were found to confer a greater reduction in odds of mortality. This may be due to the fact that nonselective beta blockers target all three types of beta-adrenergic receptors found in the brain, whereas selective beta blockers target only the beta-1 receptor. As the

population analyzed in this study was small, a larger study comparing the impact of nonselective *versus* selective beta blockers on TBI outcome is recommended. Moreover, this study did not analyze the specific impact of beta blockers, such as propranolol, which pass through the blood-brain barrier, on TBI outcome. The clinical significance of this property on TBI outcome remains to be answered.

Furthermore, the question of how long after head injury beta blockers should be administered is unknown. Findings by Neideen et al.[25] indicate that preinjury beta blocker use does not confer survival benefits to TBI patients. Our study supported these findings with an insignificant adjusted odds ratio for mortality (AOR = 1.13; 95% CI = 0.34–3.73; P = 0.842). These results indicate that the protective benefits of beta blockers are insignificant at the time of TBI. We hypothesize the reason for this finding is that in the acute phase of TBI, the full employment of the beta-adrenergic receptor system is beneficial to the patient. However, in the chronic phase of TBI, beta-blocker administration promotes survivability by alleviating the hyperadrenergic state. The only research we found addressing the timing of beta-blocker administration post-TBI was conducted by Schmitz et al.[26] This study found beta-blocker administration to be effective in increasing blood flow when administered in two periods post-TBI (15 and 60 min) in a murine model. However, no studies have addressed the optimal timing of beta-blocker administration post-TBI in humans. Consequently, in addition to identifying specific indications for beta-blocker administration and determining which beta blocker confers the greatest benefit, identifying the optimal period for beta-blocker administration post-TBI is an area in need of future research.

Although this study supports a growing body of literature providing evidence of survival advantage provided by beta-blocker administration post-TBI, this research has the inherent limitations of all retrospective studies, including patient selection bias and misreported variables. Additionally, as the population of this 2-year, single-institution study was limited, Type II errors are a concern. To best evaluate the impact of beta blockers on TBI outcome, a prospective, double-blind, multicenter randomized trial is needed. However, additional research addressing the indications and optimal administration of beta blockers post-TBI is necessary before the conduction of such a study.

Conclusion

This study found that beta blocker, both selective and nonselective, administration in hospital decrease odds of mortality for patients with moderate and severe TBI. As improved TBI survivability with beta-blocker administration in hospital was found only in patients with myocardial injury, elevated cardiac troponin I levels may be a useful indication for beta-blocker administration post-TBI. Additionally, as preinjury beta blocker use was not found to improve survival to TBI patients, beta blockers likely do not confer their protective benefits at the time of TBI.

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