Beta-Blocker Exposure is Associated With Improved Survival After Severe Traumatic Brain Injury

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Background: **Beta-blocker use in elective noncardiac surgery has been associated with a reduction in mortality and cardiovascular complications. Traumatic brain injury (TBI) is often associated with a hyperadrenergic state. We hypothesized that adrenergic blockade would confer improved survival among TBI patients.**

Methods: **Retrospective review of the Trauma Registry of the American College of Surgeons database at a Level I trauma center was conducted. All trauma patients admitted from January 2004 to March 2005 with head Abbreviated Injury Scale score of 3 or greater were evaluated. Patients with length of stay <4 or >30 days were excluded. Beta-blocker exposure was defined as receiving beta-blockers for 2 or more consecutive days.**

Results: **In all, 420 patients met inclusion criteria: 174 patients exposed to beta-blockers [BB(+)] and 246 not exposed [BB(−)]. Mean age in BB(+) group was 50 years and 36 years in BB(−) group ($p < 0.001$). Mean Injury Severity Score was 33.6 for BB(+) group and 30.8 for BB(−) group ($p = 0.01$). Predicted survival (by Trauma and Injury Severity Score) for BB(+) group was 59.1% compared with 70.3% for BB(−) group ($p < 0.001$). Observed mortality for BB(+) group was 5.1%, 10.8% for BB(−) group ($p = 0.036$). Adjusted incidence rate ratio of mortality among those exposed to beta-blockers compared with those not exposed was 0.29 (95% confidence interval).**

Conclusions: **Beta-blocker exposure was associated with a significant reduction in mortality in patients with severe TBI. This reduction in mortality is even more impressive, considering that the BB(+) group was older, more severely injured, and had lower predicted survival.**

Key Words: **Beta-blocker, Trauma, Brain injury.**

J Trauma. 2007;62:26–35.

Numerous studies have documented the beneficial effects of perioperative beta blockade in patients undergoing noncardiac surgery. In addition to a significant reduction in perioperative cardiac mortality, decreases in long-term overall mortality, long-term cardiac mortality, postoperative myocardial infarction, and postoperative myocardial ischemia have been demonstrated in patients receiving beta-blockade in the perioperative period.[1–6] The current American College of Cardiology/American Heart Association guidelines recommend perioperative beta blockade as a Class I recommendation for patients who required use of beta blockers in the recent past for control of angina, arrhythmia, or hypertension, and high-risk patients with findings of ischemia on preoperative testing undergoing vascular surgery.[7]

Intracranial hemorrhage, both traumatic and nontraumatic, is frequently associated with a hyperadrenergic state.[8–12] Among patients with severe traumatic brain injury (TBI), this is most commonly observed during the initial transition from a lower-level Glasgow Coma Scale (GCS), comatose phase, to higher GCS levels, the regeneration-arousal phase. These patients present with varying degrees of tachycardia, tachypnea, hypertension, and a generalized agitated state. Although often dismissed as an exaggerated but benign form of the systemic inflammatory response state (SIRS), this phase has been correlated with significant increases (threefold or greater) in plasma catecholamine levels.[9–11] Some of the more severe injuries (especially those involving the hypothalamus and periventricular areas) demonstrate a biochemistry and presentation similar to that of malignant hyperthermia, thyroid storms, and pheochromocytoma.[11,12]

Several authors have examined the potential benefits, if any, of adrenergic blockade in the acutely injured patient. In burn patients (who frequently exhibit a hypermetabolic, tachycardic state), adrenergic blockade has proven not only to be a safe and inexpensive intervention, but also to decrease mortality, shorten healing time, and reduce length of stay.[13,14] Morel and colleagues evaluated the effect of labetalol on the early SIRS presentation in severely injured patients.[15] The authors demonstrated that the sympathetically mediated hyperdynamic state after severe injury could be successfully reduced through the utilization of adrenergic blockade.[15] Additionally, a blinded, randomized trial has previously demonstrated that early adrenergic blockade confers improved survival and overall outcomes in patients with subarachnoid hemorrhage (SAH) from nontraumatic causes.[16] In light of the hyperadrenergic state that has been described after severe head injury, we hypothesized that ad-

Submitted for publication September 30, 2006.

Accepted for publication October 9, 2006.

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Presented at the 65th Annual Meeting of the American Association for the Surgery of Trauma, September 28–30, 2006, New Orleans, Louisiana.

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DOI: 10.1097/TA.0b013e31802d02d0

renergic blockade would confer improved survival among TBI patients.

MATERIALS AND METHODS

Study Design and Setting

This study was approved by the Vanderbilt University Institutional Review Board. We conducted a retrospective review of the trauma registry and trauma patient care cost center at Vanderbilt University Medical Center (VUMC). VUMC is an academic Level I trauma center that provides trauma care for approximately 65,000 square miles of the southeastern United States. The trauma center admits approximately 3,000 acutely injured patients annually with over 900 being admitted to the trauma intensive care unit (ICU). Approximately 750 of these patients require mechanical ventilation for greater than 24 hours. The 14-bed trauma ICU is located within a 31-bed trauma unit. The non-ICU beds include a 7-bed acute admission area and a 10-bed subacute care unit.

Selection of Participants

We queried the institution's Trauma Registry of the American College of Surgeons for all trauma patients admitted from January 2004 to March 2005 with head Abbreviated Injury Scale (AIS) of 3 or greater (n = 1,233; Fig. 1). As "head" AIS includes injuries to the head, neck, and cervical spine, we reviewed the computerized patient chart and excluded those patients whose head AIS of 3 or greater was *not* attributable to traumatic brain injury (n = 189). We excluded those patients whose length of stay (LOS) was less than 4 days (n = 551) to eliminate those patients who died (n = 178) or were discharged (n = 373) in the first 3 days of their hospitalization. These patients were unlikely to have had an opportunity to be exposed to beta-blockers during this time frame and, therefore, the impact of beta-blockers on mortality would be difficult to evaluate. Given the interest in evaluating the impact of beta-blockers on mortality in the "acute" setting, we excluded those patients with a LOS >30 days (n = 33). By doing so, we hoped to eliminate (as much as possible) the effect of prolonged LOS on the development of complications, including iatrogenic issues and late nosocomial infections. We also excluded those patients, regardless of age, who were not managed by the adult trauma service but rather by the pediatric trauma team (n = 40). The remaining 420 patients were then cross referenced with pharmacy cost-center database for all trauma patients who received beta-blockers during this same time frame.

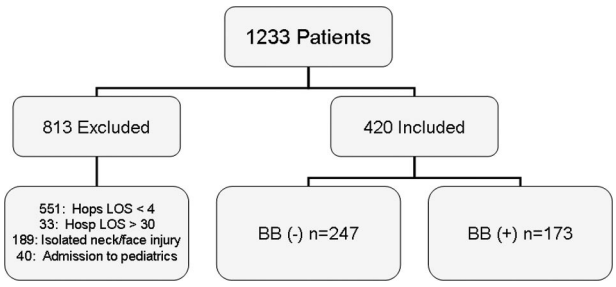

Fig. 1. *Selection of participants.*

Definitions

Beta-blocker exposure was defined as receiving beta-blockers for 2 or more consecutive days. Beta-blocker exposure was determined by charges in the pharmacy database and included metoprolol, propranolol, labetalol, atenolol, esmolol, and sotalol. Infectious complications were defined as clinical or culture positive diagnosis of ventilator-associated pneumonia, bacteremia, surgical site infection, intra-abdominal infection, or sepsis/septic shock. Sepsis and septic shock were defined in accordance with the guidelines of the American College of Chest Physicians and the Society of Critical Care Medicine.[17] Respiratory failure was defined as the presence of PaO_2/FiO_2 (P/F) ratio <300 while receiving mechanical ventilation. Cardiac complications included life-threatening tachyarrhythmias, acute myocardial infarction (AMI), cardiogenic shock, or cardiac arrest. Life-threatening tachyarrhythmias were defined as ventricular tachycardia or fibrillation, atrial fibrillation or flutter, or hemodynamically unstable supraventricular tachycardia. Acute myocardial infarction was defined by attending clinical documentation with confirmatory troponin elevation. Cardiogenic shock was defined as a sustained cardiac index less than 2.0 L/min/m^2 or requirement of dobutamine or milrinone infusion for greater than 24 hours. Cardiac arrest was defined as the documentation of a cardiac arrest event, performance of cardiopulmonary resuscitation, or implantation of Advanced Cardiac Life Support protocol in the patient's chart. The need for vasopressors (vasopressor dependence) was defined as the requirement of vasopressor agents for 24 hours or more to sustain mean arterial pressure greater than 60 mm Hg.

Demographic and Outcome Data

We evaluated trauma registry data including age, gender, race, and mechanism of injury. Injury scores, including initial Glasgow Coma Scale (GCS) score, weighted Revised Trauma Score (RTS), and Injury Severity Scale (ISS) score were evaluated as well. The weighted RTS incorporates the initial GCS, systolic blood pressure, and respiratory rate, using coded and weighted values which range from 4 (normal) to 0 (poor) for each of the physiologic variables (yielding a high of 7.841 and a low of 0). AIS is an anatomic injury scoring system that quantifies injuries in various body regions from a score of 1 (minor injury) to 6 (nonsurvivable). ISS is calculated by summing the squares of the three highest AIS scores in three different body regions (values range from 1–75).

The incidence of mortality, as well as cardiac, pulmonary, and infectious complications, were recorded and evaluated. Secondary outcomes included hospital days, intensive care unit days, ventilator days, and ventilator-free days (days alive and off the ventilator). Predicted survival based on

Table 1 Demographic Data by Beta-Blocker Exposure Status

	Beta-Blocker Negative (n = 246)	Beta-Blocker Positive (n = 174)	*p* Value
Sex			0.259
Male	162 (65.8%)	105 (60.3%)	
Female	84 (34.2%)	69 (39.7%)	
Race			0.621
White	209 (85.0%)	150 (86.2%)	
Black	20 (8.1%)	16 (9.2%)	
Hispanic	15 (6.1%)	6 (3.4%)	
Asian	1 (0.4%)	1 (0.6%)	
Mechanism			0.802
Penetrating	11 (4.5%)	6 (3.4%)	
Blunt	235 (95.5%)	168 (96.6%)	
Age	30.5 (21, 47)	50.5 (28, 70)	<0.001
Injury severity scale score	29 (22, 38)	34 (26, 42)	0.0129
Weighted revised trauma score	6.68 (4.09, 7.84)	5.74 (3.87, 7.84)	0.2699
Probability of survival	0.848 (0.458, 0.9548)	0.649 (0.304, 0.886)	<0.001
Motor glasgow coma scale score	5 (3, 6)	5 (2, 6)	0.3679

Data are n (%) or median (25th, 75th percentile).

previously described Trauma Related Injury Severity Score (TRISS) methodology was calculated and evaluated. TRISS is calculated and weighted for the patient's ISS score, RTS, age, and mechanism of injury. More important than its use in evaluating the individual patient, TRISS is an objective evaluation for comparing a trauma center's outcome results against the expected survival.

Statistical Analysis

Univariate analyses comparing categorical risk factors by beta-blocker use were conducted using χ^2 and Fisher's exact test. Univariate analyses comparing continuous risk factors by beta-blocker use were conducted using either a two-sample *t* test or the Wilcoxon rank-sum test. Unadjusted relative risks of mortality were calculated for beta-blocker exposure. Poisson regression was used to estimate the association between beta-blocker use and mortality while adjusting for age, sex, race, and mechanism of injury, ISS score, RTS and calculated probability of survival using the robust standard error adjustment.

Because the multiple Poisson regression model included seven covariates and our sample had 36 events, the number of events per variable was small. As it has been demonstrated that in these settings the measures of association may be biased and the confidence intervals incorrect, propensity score analyses were also conducted.[18–20] The propensity score is the estimated probability of being exposed to beta-blockers (after adjusting for potential confounders) and is derived from logistic regression models. Our propensity score model was adjusted for age, sex, race, mechanism of injury, ISS score, RTS, and calculated probability of survival. The adequacy of the propensity scores in adjusting for the effect of potential confounders was assessed by graphically comparing its distribution between patients exposed to beta-blockers and those not exposed and by testing for differences in individual covariates between the beta-blocker positive [BB(+)] group and the beta-blocker negative [BB(−)] group after stratifying by quintiles of propensity score. The propensity score was then categorized into quintiles and included in the Poisson regression models, replacing the risk factors included in the previously described multiple Poisson regression model. Statistical analysis was performed using the STATA 8.2 (College Station, TX).

RESULTS

Table 1 contains patient demographic information by beta-blocker exposure. Patients in the BB(+) group were older, had higher ISS, and had lower calculated probability of survival. There were no significant differences in sex, race, mechanism of injury, weighted RTS, and initial motor GCS score between beta-blocker groups. AIS score by body region (head, chest, and abdomen) demonstrated no difference between those exposed to beta-blockers and those not exposed.

Table 2 provides information regarding categorical and continuous outcomes. BB(+) patients had significantly

Table 2 Outcomes by Beta-Blocker Exposure Status

	Beta-Blocker Negative (n = 246)	Beta-Blocker Positive (n = 174)	*p* Value
Mortality	27 (10.8%)	9 (5.1%)	0.03
Infectious complication	52 (21%)	66 (38%)	<0.001
Respiratory failure	115 (47%)	121 (70%)	<0.001
Cardiac complication	25 (10%)	27 (16%)	0.132
Need for vasopressors	15 (6%)	11 (6%)	1.000
Hospital days	7 (5, 11)	11 (7, 20)	<0.001
ICU days	2 (0, 5)	5 (2, 9)	<0.001
Ventilator days	1 (0, 4)	4 (1, 8)	<0.001
Ventilator-free days	5 (4, 8)	7 (4, 13)	<0.001

Data are n (%) or median (25th, 75th percentile).

higher rates of infectious and pulmonary complications. BB(+) group also required a longer period of ventilator support and intensive care management, and had an overall longer hospital length of stay. Arrhythmias were documented in seven (3%) patients in the BB(−) group and nine (5%) patients in the BB(+) group ($p = 0.301$). Cardiac arrest occurred in eight (3%) BB(−) patients and in seven (4%) BB(+) patients ($p = 0.791$). AMI was documented in only one (0.4%) patient in the BB(−) group, but in four (2.3%) of the BB(+) patients ($p = 0.165$). However, although these patients were included in the BB(+) group, none of these four patients received any BB medications until *after* the cardiac complication (AMI) had already been diagnosed. Despite these findings, the BB(+) patients had a statistically lower mortality rate compared with the younger, less injured BB(−) group. The overall mortality for the 174 patients exposed to beta-blockers was 5.1% (9) compared with 10.8% (27) among the 246 patients who were not exposed to beta-blockers ($p = 0.03$). Of the deaths attributed to a single cause, 60% of patients died from non-survivable TBI, while 40% died as a result of a nonneurologic cause. Overall, nonsurvivable TBI and brain death were noted as contributing to death in 52.6% and 28.1% of patients, respectively. Cardiovascular and respiratory dysfunction (excluding pneumonia) contributed to mortality in 51.1% and 34.1% of patients, respectively.

Table 3 and Figures 2 to 5 provide unadjusted and adjusted relative risks for mortality. The unadjusted relative risk indicates that patients receiving beta-blockers for at least 2 days during their hospitalization have less than half the risk

Table 3 Relative Risk of Mortality Given Beta-Blocker Exposure

Model	Relative Risk	95% Confidence Interval	*p* Value
Unadjusted	0.47	NA	NA
Adjusted	0.29	0.15–0.61	0.001
Propensity score adjusted	0.29	0.14–0.60	0.001

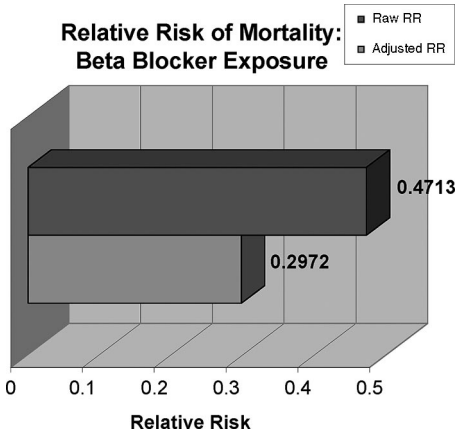

Fig. 2. *Base-adjusted relative risk.*

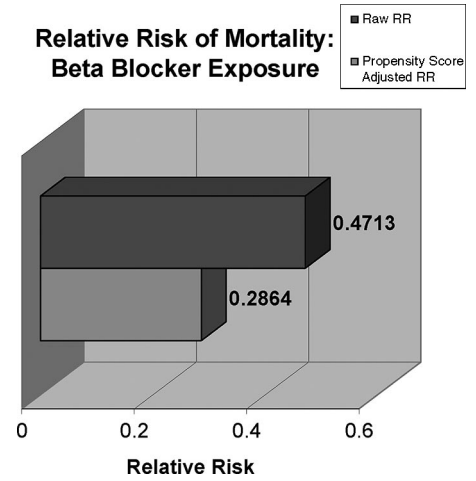

Fig. 3. *Propensity score–adjusted relative risk after BB exposure.*

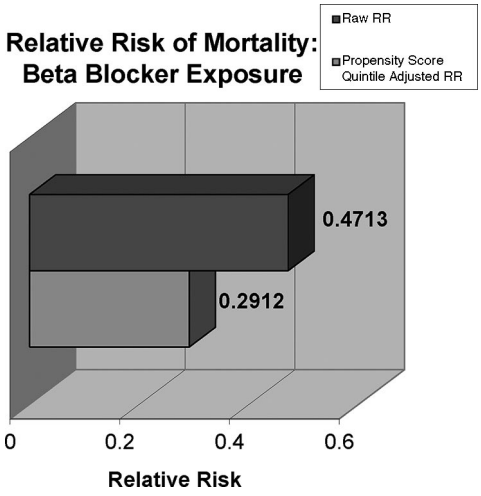

Fig. 4. *Quintiled propensity score–adjusted relative risk after BB exposure.*

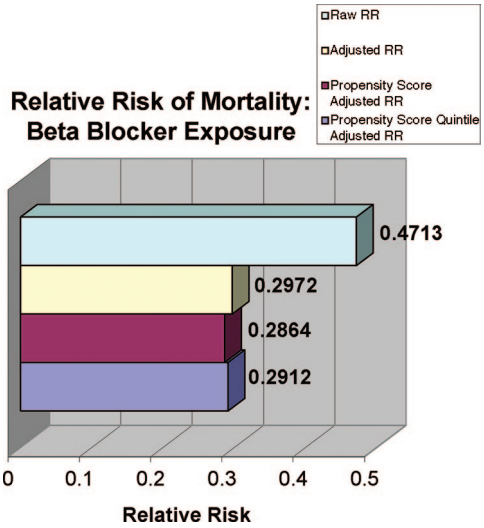

Fig. 5. *Summary of relative risk after exposure to beta-blockers.*

of dying during their hospitalization. After adjusting for potential confounders, beta-blocker exposure was associated with an even stronger protective effect. In the propensity score analysis, there was sufficient overlap in the distributions of propensity scores between beta-blocker exposure and nonexposure. There were no significant differences in covariates between those exposed to beta-blockers and those who were not exposed after stratifying by propensity score quintiles. The rate ratios and confidence intervals for beta-blocker exposure from the propensity-score adjusted regression model were similar to the adjusted Poisson regression.

We calculated the likelihood (relative risk) of dying among TBI study patients who were and were not exposed to beta-blockers. The unadjusted in-hospital mortality reduction was even more pronounced after application of Poisson regression to adjust for the seven covariates of direct interest. We took the conservative step of performing propensity score analysis given the relatively high number of covariates considered relative to events (deaths) observed within this study. The findings of this additional analysis were consistent. Figures 2 through 5 provide graphical representation to facilitate comparison between these forms of analysis. Figure 2 demonstrates the results of univariate and Poisson regression analysis. However, as significant differences in covariate distribution may exist between exposed groups, multivariate regression models may not adequately balance the groups. As such, the propensity score method was chosen for further analysis. The propensity score serves as a condition of probability (between 0 and 1) that a subject will be exposed based on the groups covariates. Confounding variables are collapsed into one score to bring the groups (exposed and nonexposed) into a "quasi-randomized" state (Fig. 3). Stratifying the sample further into "quintiles" based on propensity score ranges has been suggested as an even more effective and rigorous method of providing an unbiased estimate of the true exposure effect (Fig. 4). Figure 5 summarizes the results of the various methods of analysis.

DISCUSSION

Head injury is the leading cause of death among trauma patients who arrive alive to a trauma center.[21–23] TBI accounts for almost one-third of all trauma mortalities, resulting in over 50,000 deaths per year. Of these, almost 75% will die within the first 3 days after injury.[21,24] Among those patients with longer survival time but fatal outcomes, these individuals are usually younger, have isolated TBI, and undergo craniotomy. The underlying causes of death in the majority of this subpopulation of patients are a result of the primary head injury, but the "immediate" cause of death is usually attributed to respiratory failure or cardiovascular dysfunction.[25] This is consistent with recent literature, which demonstrated a strong association between neurologic trauma and the development of nonneurologic organ dysfunction, which appears to be a result of sympathetic hyperactivity.[26,27]

A hyperadrenergic state has long been demonstrated in those patients with severe TBI, as well as nontraumatic subarachnoid hemorrhage.[8,10–12,28,29] This sympathetic hyperactivity may present anywhere along the continuum; from a mild and apparently benign SIRS state to the disruptive and difficult to control paroxysmal sympathetic storms (PSS). The most severe form of the hyperadrenergic states, PSS, presents with paroxysmal sympathetic system activation and adrenal release of catecholamines. These PSS events, with their associated tachycardia, hypertension, tachypnea, mydriasis, and diaphoresis, often resemble those of pheochromocytoma and hyperthyroid storms (earning them the nickname "brain storms"). Several investigators have evaluated the post-TBI state (with regards to the plasma and urinary correlates of a hyperadrenergic phenomenon) and noted a greater than sevenfold increase in norepinephrine, epinephrine, and their urine-excreted metabolites. Elevations appear to correlate with significant increases in sympathetic hyperactivity and are most pronounced during the first week after injury.[10,11]

Beginning in the late 1970s and continuing throughout the 1980s, Neil-Dwyer and colleagues published several studies on the hyperadrenergic state after intracranial hemorrhage.[8,12,16,30–34] Although the majority of these related to patients with nontraumatic SAH, the group later published findings regarding the TBI population as well. The authors noted that in both groups, patients with a clinically and/or biochemically significant hyperadrenergic state appeared to have an increased morbidity and mortality. Mechanisms involved included a severe hypermetabolic state, myocardial ischemia/infarction, and pulmonary dysfunction. In addition, the authors noted (as did Woolf and colleagues almost a decade later) that other severely injured patients *without* TBI lacked the catecholamine surge and were noted to have better survival rates.[35] More importantly, this group of investigators demonstrated that administration of beta-blockers in patients with severe TBI could attenuate the hyperadrenergic response, thereby decreasing cardiac complications and improving neurologic recovery.[30,32,34] The present study did not focus on the neurologic outcomes or recovery, but did attempt to investigate the incidence of cardiac outcomes and, more importantly, the impact of beta-blocker exposure on mortality in a larger population of patients.

After isolated TBI, cardiac dysfunction as a result of autonomic imbalance will be observed in 20% or more of the patients.[26,35–44] Several authors have described the development of ST-T wave changes, as well as fatal ventricular arrhythmias in these patients.[26,36] In fact, 5% or more of patients with intracranial hemorrhage will suffer fatal arrhythmias.[37–39] TBI-associated hyperadrenergic states have also been demonstrated to cause ventricular wall motion abnormalities (such as hypokinesis) in over 50% of patients.[39–41] TBI patients with electrocardiographic distur-

bances and elevated cardiac enzymes have been noted to suffer myocardial ischemia and infarction. These findings have been confirmed by autopsy and resemble those of patients who have died from pheochromocytoma and cocaine overdose.[31,42–44] The use of beta-blockers has been shown to decrease the incidence, and impact, of adverse cardiac events in patients with hyperadrenergic states after both SAH and TBI.[16,31,34] In the present study, we noted that approximately 12% of patients suffered cardiac complications. Although there was no difference in complications between those exposed to beta-blockers (16%) and those without exposure (10%), many of those counted in the BB(+) group did not actually receive beta-blockade until after their cardiac complications had already occurred. In fact, all 4 of the patients in the BB(+) group who sustained AMI did not receive beta-blockade until after the event was diagnosed.

Hyperadrenergic states after intracranial hemorrhage have been associated with significant disturbances of pulmonary function via several mechanisms. The pulmonary circulation is often acutely and severely overloaded after a catecholamine surge. Severe pulmonary edema likely results from a disruption of the capillary endothelium and basement membrane. Pulmonary vasoconstriction and increased pulmonary capillary pressures produce pulmonary vascular endothelial and alveolar injury, resulting in acute lung injury and or neurogenic pulmonary edema.[45–47] In fact, autopsy studies have identified neurogenic pulmonary edema in over 70% of patients with fatal intracranial hemorrhage.[48] Recently, Zygun and colleagues noted that respiratory failure was the most common nonneurologic organ system failure in patients with severe TBI.[26] The authors noted that almost 25% of the patients developed respiratory failure and, as with cardiac dysfunction, this was independently associated with a worse outcome. We noted a much higher incidence of respiratory failure (58%, overall). This is likely because of the definition of respiratory failure in our study (P/F ratio <300) compared with that of the Zygun study (P/F ratio <150). Although the incidence of respiratory failure was significantly higher in the BB(+) group, this group had a higher chest AIS score (2.22 versus 2.02) and these adverse events did not translate into higher mortality rates. This may reflect attenuated responses to the catecholamine-mediated acute lung injury.

Epinephrine and norepinephrine have been shown to alter the cellular immune response at multiple levels. Patients who sustain severe TBI may demonstrate higher incidences of infections because of catecholamine-mediated release of interleukin-10 (a potent immunosuppressant) from monocytes.[49] In the severely injured patient, elevated catecholamines appear to inhibit normal macrophage cytokine responses. However, these effects appear to be reversed with beta-2 adrenergic receptor antagonists.[50] Our study actually noted a higher incidence of infectious complications in those exposed to beta-blockers (38%) compared with those not exposed (21%). Similar to those of respiratory complications, the higher incidences of infectious complications in the BB(+) group are not surprising in this older, more severely injured group, with significantly longer lengths of stay. However, as with cardiac complications, many of the patients placed into the BB(+) group did not actually receive these medications until after infectious complications were diagnosed. More importantly, the higher rate of infections did not translate into higher mortality rates in those exposed to beta-blockers.

Nonneurologic organ dysfunction after TBI may also manifest in the form of hematological disturbances and protein-calorie malnutrition as a result of the hyperadrenergic response. Although mediated by a hyperadrenergic state, the marked increase in energy expenditure and protein catabolism may often rival that of the burn patient.[51–53] This period of markedly increased catecholamines can produce a resistance to nutritional support attempts, thereby inducing weight loss and worsening outcomes. Although norepinephrine and epinephrine have a stimulatory effect on bone marrow progenitor cells, the sustained and markedly elevated catecholamine response seen in this patient population results in a considerable dysfunction and attenuation of the erythropoietic process.[54] Although the nutritional and hematological impact of the post-TBI hyperadrenergic response is significant, these outcome measurements were not obtained in this initial study. Ongoing data collection is focusing on several other secondary outcome measurements, including both nutrition and anemia.

Several small studies have attempted to evaluate the impact of beta-blockade on outcomes in patients with SAH, as well as TBI. In those with severe TBI, two randomized, controlled trials have noted a decrease in intensity and duration of the hyperadrenergic state in those patients treated with propranolol.[55,56] Unfortunately, these studies were small and the authors did not evaluate mortality as a primary outcome. Neil-Dwyer and colleagues evaluated the impact of propranolol administration on patients with SAH and noted improved neurologic recovery and less cardiac and respiratory complications.[32] Although not significant (and not powered for such), there was a trend toward improved survival in those treated with beta-blockers ($p = 0.09$). Other authors have demonstrated a reduction (through double-blinded, random controlled trials) in the incidence of myocardial infarction when this population is treated with beta-blockade.[30,57] Our result demonstrated a significant reduction (70%) in mortality in patients exposed to beta-blockers. This is even more impressive when considering the BB(+) group was older, more severely injured, and had higher respiratory and infectious complications. In addition, the BB(+) group had a predicted mortality of 35% with an observed mortality of only 5%. Although the observed mortality was significantly less, the predicted mortality among those patients exposed to beta-blockers was 20% higher than that of the nonexposed group of patients ($p < 0.001$). Unlike the BB(+) group, the actual mortality in the BB(−) group was similar to that predicted by TRISS (11% versus 15%).

The relative risk (0.47) indicates that patients receiving beta-blockers for at least 2 days during their hospitalization have less than half the risk of dying during their hospitalization. After adjusting for numerous confounding variables, the relative risk of mortality in patients exposed to beta-blockers was further reduced to 0.29.

Limitations to this study include the relatively small sample size for each cohort and the retrospective design using data collected via a trauma registry database. In addition, a notable limitation is the fact that the indication for beta-blocker administration was quite varied and in some circumstances difficult to determine from a retrospective review of the computerized patient chart. Some of these patients were likely receiving beta-blockers in the prehospital setting, but many who were exposed to beta-blockers were quite young (almost one-third were less than 30 years of age) and unlikely to be taking this class of medications as outpatients. Many appeared to have received beta-blockade based on the individual clinical judgment of the attending trauma surgeon assigned to the service at that time. This was generally based on the recognition of a hyper-adrenergic state after severe TBI, but this application was not part of a defined protocol, nor was this indication utilized by all faculty members. As we eliminated those with a hospital LOS greater than 30 days, we cannot speak as to the impact of BB exposure on extended mortality among this cohort of TBI patients.

CONCLUSIONS

Despite extensive research and advances in the critical care arena, mortality after severe TBI has remained unacceptably high. Poor outcomes are generally attributed to the severity of the primary brain injury and little (if any) real progress has been made on improving survival. In 1998, however, Eker and colleagues proposed that poor outcomes from severe TBI were not a consequence of the primary insult that that could not be prevented, but rather a failure to utilize less "traditional" therapeutic approaches.[58] By treating intracranial hypertension with a multidrug regimen, including scheduled intravenous metoprolol and clonidine, the authors noted a reduction in arterial inflow pressure. Through the use of this protocol, the Lund group demonstrated a significant reduction in mortality and improvement in Glasgow Outcome Scale score at 6 months ($p < 0.001$).

By investigating and treating the extracranial manifestations (or nonneurologic organ dysfunction) of severe TBI, these previously overlooked and harmful secondary insults become potential avenues for improving survival in this population. In the current study, exposure to beta-blockers in patients with severe TBI was associated with a significant reduction in mortality (adjusted RR 0.29). This reduction in mortality is even more impressive when considering that the BB(+) group was older, more severely injured, had higher respiratory and infectious complications, and had a lower predicted survival. However, as the study is retrospective and our population relatively small, these findings warrant a prospective, randomized trial to demonstrate the impact of beta-blockers on mortality after TBI. Future studies should answer the following: (1) are the results of the current retrospective study valid, (2) what population(s) benefit from this intervention, (3) what population(s), if any, are harmed from this intervention, and (4) is there a physiologic "titration" point for beta-blockers similar to that for preventing cardiac complications in elective surgery?

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DISCUSSION

Dr. Blaine L. Enderson (Knoxville, Tennessee): Traumatic brain injury is the most common cause of death in injured patients. There are also limited therapeutic options to improve outcome once the injury has occurred. Rapid recognition of and surgical intervention for lesions amenable to surgery plus control of intracranial pressure and maintenance of cerebral perfusion pressure to prevent secondary insult to the injured brain have been the hallmarks of therapy.

The relationship between brain injury and altered cardiovascular function has been known for many years. Harvey Cushing described his response in 1902, consisting of increased intracranial pressure, hypertension, and bradycardia. Many of the brain-injured patients who survive the initial swelling of the brain from injury develop a pattern of hyper-

tension, tachycardia, and increased temperature and metabolic rate, which has often been termed "storming." This is clearly associated with increased catecholamine production from the sympathetic nervous system and can be blocked by beta adrenergic blocking agents. These agents have not become standard therapy, however, because of concern that they are blocking physiologic responses that are necessary for survival.

Beta blockers have become more important clinically, since their development, because of their benefit in various cardiovascular-disease states. It is well accepted that they reduce mortality in high-risk patients when used perioperatively. Limited work in the 1980s hinted at improved survival when used in patients with non-traumatic subarachnoid hemorrhage. A paper presented by the Michigan group at this meeting in 2003 demonstrated improved outcome in patients with burn injury who were given beta blockers.

The paper prior to this one demonstrated improved outcome with beta-blocker use in trauma patients. Now Dr. Cotton and his colleagues from Vanderbilt have told us that beta-blocker exposure in patients with severe traumatic brain injury improved survival, as well. Despite obvious limitations, not the least of which is their retrospective nature, I believe that these are some of the most exciting potential papers of this meeting, because of the future avenues of research that they present and because of the potential for therapeutic benefit that they offer.

I have several questions for Dr. Cotton. First, beta-blocker exposure was determined by charges in your pharmacy database for any of six beta blockers. Do you have any information on which were used most commonly? And do you think this matters, because many of the beta blockers have different effects, as we heard earlier? Several of the studies that you cited used specific beta blockers such as labetalol for their specific effects.

Secondly, you mention that some of your patients may have been taking beta blockers prior to admission, but many were young and most likely received beta blockers in response to problems during the hospitalization. In the burn paper that Michigan presented in 2003, differences were noted between the groups that came in using beta blockers and those that received them during the hospitalization and after the burn insult. What role do you think that timing of beta-blocker administration will play? When should they be given: on admission, after resuscitation, or at the beginning of the secondary hyperdynamic phase? Should we treat all patients or only the so-called "high-risk" patients, as some studies have done?

Thirdly, what were the causes of death in your patients? You discuss several mechanisms through which beta blockers may work, including reduction of cardiac dysfunction, reduction of pulmonary dysfunction, changes in immune response and changes in metabolism. Do you think these problems cause death primarily or contribute to further injury to the brain? Are the beta blockers preventing delayed progression of injury to the brain due to hypermetabolism or decreased oxygen delivery and consumption, as we heard earlier?

Fourth, what protocol are you using now in the management of these patients? Are you giving beta blockers to all your severely head-injured patients or have you put in a research protocol to study this? And if so, when and for how long?

Many of my questions will be difficult to answer based on the way this study was done, but I think they demonstrate how much work remains to be done in this area. Data from a number of traumatic disease states now indicate the potential benefit of the use of beta blockers despite the fears of potential negative side effects. It is time to investigate this topic in a prospective, randomized, multi-center fashion to better understand when and how to use them.

Dr. Bryan A. Cotton (Nashville, Tennessee): As to the questions regarding which beta blockers were used most commonly within our study group, propanolol was the most commonly utilized, followed by metoprolol. There was only a handful of people that received atenolol, almost all of which we identified as outpatient usage. As to the least used, it was actually sotalol, which I think we had one or two patients. Esmolol was only used in a few patients, all with blunt aortic injury. As to which one we preferred to use and where to go, non-selective beta blockers such as labetalol and propanolol are the most widely studied with regards to intracranial hemorrhage, whether it be traumatic or nontraumatic. These appear to penetrate the brain barrier as opposed to the other options, and that is why they were specifically chosen in previous studies by Criuckshank and colleagues and Neil-Dwyer and colleagues from England back in the late '70s, early '80s.

As to the timing, it appeared that with the exception of esmolol or the patients that were coming in on beta blocker from home, the lag time was approximately 48 to 72 hours. This timing is just happenstance or luck that a disruption of the blood-brain barrier and detrimental effects that have been described in small studies with beta blockers occur within that first 48 hours. After 48 hours the blood-brain barrier integrity appears to be restored, and the detrimental effects of beta blockers have not been demonstrated, except when evaluating patients at the rehabilitation level.

Who gets these? They are primarily based on physician acumen and a majority of these are guided on a persistent SIRS state where we've ruled out an infectious cause and ruled out other sources, including obtaining thyroid-function studies, etc., to evaluate a potential missed diagnosis. Once this is done, an aggressive pursuit, usually with propanolol, is initiated on a Q8 basis.

Causes of death we did not interrogate closely for this study; however, in a study to be discussed and presented at the American College of Surgeons in a few weeks, we demonstrated cardiac complications contributed to the deaths of 35% of patients with TBI. Thirty percent had respiratory complications contribute to their mortality. The remaining

experienced coagulopathy and the other causes were insignificant; however, there were approximately one-third on top of that that sustained non-survivable traumatic brain injury. We are currently preparing a study protocol to evaluate this in a prospective fashion and have also looked at more severe TBI patients and stratified by AIS and found similar findings.

Dr. Eric Streib (Indianapolis, Indiana): The widespread use of beta blocker prior to the trauma of elective surgery is based on the observed decrease in cardiac events during the postoperative period, and the most benefit is shown in the patient with known cardiac-risk factors. In fact, there is even some data that would suggest that in patients without risk factors there is some harm to perioperative beta-blocker use. So I think addressing the question of what are these patients dying from is very important. Are they dying from cardiac disease or not? And if not, what is the mechanism that beta blockade is helping?

Dr. Bryan A. Cotton: Just to address one of those, we only had nine deaths in the beta-blocker group. Five of those nine were from acute MIs with subsequent death within a 48-hour to 72-hour period. Four out of five of those patients never received beta blockers until after their MI. So, many of the complications were actually occurring before they were actually even exposed to beta blocker. So had we controlled for that, or had we gone through a time series and evaluated whether the complication occurred while on a beta blocker, I think we would actually find even more impressive results and less cardiac complications.

Dr. Slate Wilson (Portland, Oregon): I'm wondering, particularly in the older people—you know, guys my age—if I fall off my bike and hurt my brain, I think the evidence in these last two papers has really demonstrated the efficacy of beta blockers in brain injury. In older people, are we really justified in doing a prospective study, or is there enough evidence of this efficacy to give it on an empiric basis? I mean we like Level 1 evidence, but . . ..

Dr. Bryan A. Cotton: As far as the Class 1 evidence that's out there, there is some evolving stuff as far as randomized control trials that are under way, but not selective for head injury. For head injuries, I would just refer you to the Lund group out of Sweden who use actually a combination of metoprolol and clonidine, which is quite similar to what we're giving in labetalol and propanolol groups. They've shown—both in adults and children—improved outcomes, lower ICPs, and better Glasgow outcome scores. So, I would just refer you to the Lund group for as far as randomized control trials.