Beta-Blockers in Isolated Blunt Head Injury

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BACKGROUND: The purpose of this study was to evaluate the effect of β-blockers on patients sustaining acute traumatic brain injury. Our hypothesis was that β-blocker exposure is associated with improved survival.

STUDY DESIGN: The trauma registry and the surgical ICU databases of an academic Level I trauma center were used to identify all patients sustaining blunt head injury requiring ICU admission from July 1998 to December 2005. Patients sustaining major associated injuries (Abbreviated Injury Score ≥ 4 in any body region other than the head) were excluded. Patient demographics, injury profile, Injury Severity Score, and β-blocker exposure were abstracted. The primary outcomes measure evaluated was in-hospital mortality.

RESULTS: During the 90-month study period, 1,156 patients with isolated head injury were admitted to the ICU. Of these, 203 (18%) received β-blockers and 953 (82%) did not. Patients receiving β-blockers were older (50 ± 21 years versus 38 ± 20 years, $p < 0.001$), had more frequent severe (Abbreviated Injury Score ≥ 4) head injury (54% versus 43%, $p < 0.01$), Glasgow Coma Scale ≤ 8 less often (37% versus 47%, $p = 0.01$), more skull fractures (20% versus 12%, $p < 0.01$), and underwent craniectomy more frequently (23% versus 4%, $p < 0.001$). Stepwise logistic regression identified β-blocker use as an independent protective factor for mortality (adjusted odds ratio: 0.54; 95% CI, 0.33 to 0.91; $p = 0.01$). On subgroup analysis, elderly patients (55 years or older) with severe head injury (Abbreviated Injury Score ≥ 4) had a mortality of 28% on β-blockers as compared with 60% when they did not receive them (odds ratio: 0.3; 96% CI, 0.1 to 0.6; $p = 0.001$).

CONCLUSIONS: Beta-blockade in patients with traumatic brain injury was independently associated with improved survival. Older patients with severe head injuries demonstrated the largest reduction in mortality with β-blockade. (J Am Coll Surg 2008;206:432–438. © 2008 by the American College of Surgeons)

Traumatic brain injury (TBI) is a major cause of death and neurologic disability after blunt trauma. At this time, very few evidence-based therapeutic options have been shown to affect outcomes in this patient population. The interplay between the neuroendocrine system and the injured brain has been well documented. A catecholamine surge occurs after traumatic brain injury and the elevated plasma and urine catecholamine levels correlate well with admission Glasgow Coma Scale (GCS), neurologic recovery as measured by GCS or Glasgow Outcome Score, survival, length of stay, and ventilator dependence.[1-4]

An animal study using a murine model of brain injury demonstrated that β-blockade results in improved neurologic function and histologic brain edema.[5] To date, two retrospective human studies have also demonstrated a protective effect of β-blockade in brain-injured patients.[6,7]

The primary objective of this study was to evaluate the effect of β-blockade on critically ill patients with isolated acute traumatic brain injury. Our hypothesis was that β-blockade exposure results in improved survival. The secondary objective of this study was to identify the subset of brain-injured patients who would benefit the most from β-blocker therapy.

Competing Interests Declared: None.

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Abbreviations and Acronyms

AIS = Abbreviated Injury Score
GCS = Glasgow Coma Scale
ISS = Injury Severity Score
NE = norepinephrine
TBI = traumatic brain injury

METHODS

The Los Angeles County + University of Southern California Medical Center is a high-volume, academic Level I trauma center. After Institutional Review Board approval, data from the trauma registry and the surgical ICU databases were retrospectively abstracted. All patients sustaining blunt head injury who required an ICU admission from July 1998 to December 2005 were identified. Patients sustaining major associated injuries, defined by an Abbreviated Injury Score (AIS) ≥ 4 in any body region other than the head, were excluded. Patients with a nonsurvivable head injury, defined as a head AIS = 6, were also excluded. Patient variables abstracted for the study included age, gender, GCS, admission vital signs, injury characteristics, AIS, Injury Severity Score (ISS), and β-blocker exposure. The primary outcome measure analyzed was in-hospital mortality.

Data were entered into a computerized spreadsheet and analyzed using SPSS 12.0 for Windows (SPSS, Inc). Summary data are presented as a raw percentage or mean $\pm$ standard deviation or median $\pm$ range. Statistical analysis was performed using a chi-square or Fisher's exact test for categorical variables and an unpaired Student's *t*-test or Mann-Whitney rank sum test for continuous variables. For the analysis, several continuous variables were analyzed as dichotomous variables using clinically relevant cut-points (age ≥ 55 years, systolic blood pressure < 90 mmHg, GCS ≤ 8, ISS ≥ 16).

Risk factors that had a p value less than 0.2 from bivariate analysis were selected for stepwise logistic regression to identify independent predictors of mortality. The adjusted odds ratios and 95% confidence intervals were derived.

To identify the subsets of patients who would benefit from β-blocker treatment, the study population was stratified using the main predictors for mortality identified in the multivariable analysis. The odds ratio for mortality between patients exposed and not exposed to β-blockers was derived for each stratum and compared using a chi-square or Fisher's exact test.

RESULTS

During the 90-month study period, 2,269 blunt trauma patients were admitted to the surgical intensive care unit; 1,368 (60%) of these had a head injury. After exclusion of 206 patients with severe associated injuries and 6 patients with a nonsurvivable head injury, 1,156 patients with isolated head injury were available for analysis (Fig. 1).

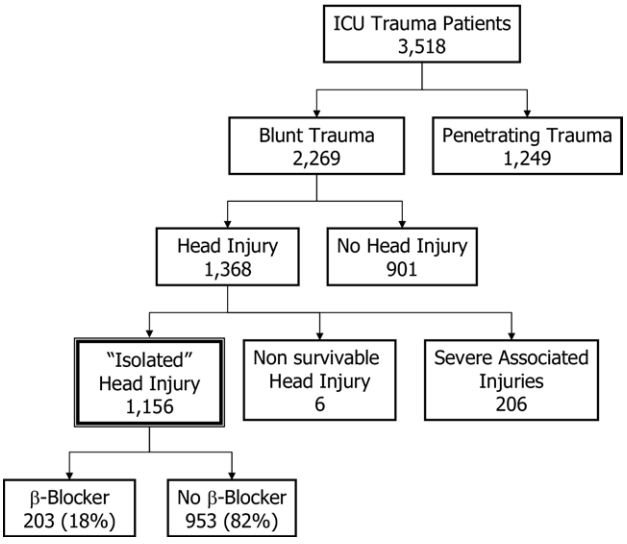

Figure 1. Outline of the study.

The study population was divided into two groups according to whether or not they received β-blockers during their ICU stay. Table 1 summarizes the clinical characteristics of the study population. Of the 1,156 patients, 203 (18%) received β-blockers and 953 (82%) did not. Patients receiving β-blockers were older (50 $\pm$ 21 years versus 38 $\pm$ 20 years, $p < 0.001$), had severe (AIS ≥ 4) head injury more frequently (54% versus 43%, $p < 0.01$), GCS ≤ 8 less often (37% versus 47%, $p = 0.01$), more skull fractures (20% versus 12%, $p < 0.01$), and underwent craniectomy more frequently (23% versus 4%, $p < 0.001$).

The unadjusted mortality for patients receiving β-blockers was lower than for patients not receiving the drug, but this did not reach statistical significance (17% versus 21%, $p = 0.183$).

Bivariate analysis identified 12 factors to be potentially associated with mortality ($p < 0.2$), including the use of β-blockers (Table 2). These factors were entered into a stepwise logistic regression model.

Stepwise logistic regression identified treatment with β-blockers to be an independent protective factor for mortality (adjusted odds ratio: 0.54; 95% CI, 0.33 to 0.91; $p = 0.01$). Table 3 summarizes the findings of the stepwise logistic regression.

After stratification of the study population using age and severity of head injury, elderly patients (≥ 55 years old) with severe head injury (AIS ≥ 4) who received β-blockers were found to have a mortality of 28% compared with 60%

Table 1. Comparison of Characteristics and Outcomes Between Patients Exposed and Not Exposed to Beta-Blockers

Characteristics	Total (n = 1,156)	Beta-blocker group (n = 203)	No beta-blocker group (n = 953)	p Value
Age, y, mean ± SD	40.2 ± 21.0	50.1 ± 21.1	38.1 ± 20.4	< 0.001
Age ≥ 55 y	24% (276/1,156)	43% (88/203)	20% (188/953)	< 0.001
Male gender	75% (863/1,156)	78% (158/203)	74% (705/203)	0.252
Glasgow Coma Scale ≤ 8	55% (634/1,153)	37% (74/200)	47% (445/953)	0.012
Systolic blood pressure < 90 mmHg	95% (1,089/1,144)	6% (11/200)	5% (44/944)	0.614
Head AIS ≥ 4	45% (517/1,156)	54% (109/203)	43% (408/953)	0.005
ISS mean ± SD	20.2 ± 9.9	20.6 ± 9.3	20.1 ± 10.0	0.534
ISS ≥ 16	66% (767/1,156)	69% (140/203)	66% (627/953)	0.385
Injury types				
Skull fracture (vault)	13% (153/1,156)	20% (40/203)	12% (113/953)	0.003
Basilar skull fracture	22% (248/1,156)	26% (53/203)	21% (195/953)	0.075
Subdural hematoma	22% (259/1,156)	27% (55/203)	21% (204/953)	0.078
Epidural hematoma	11% (132/1,156)	9% (19/203)	12% (113/953)	0.310
Subarachnoid hemorrhage	31% (358/1,156)	32% (64/203)	31% (294/953)	0.850
Craniectomy	7% (82/1,154)	23% (47/202)	4% (35/952)	< 0.001
Deaths	20% (233/1,156)	17% (34/203)	21% (199/953)	0.183
Median ICU LOS, d (range)	5(1–101)	7(1–57)	4(1–101)	< 0.001
Median hospital LOS, d (range)	10(1–173)	16(1–110)	9(1–173)	< 0.001

AIS, Abbreviated Injury Score; ISS, Injury Severity Score; LOS, length of stay.

if they did not (odds ratio: 0.3; 96% CI, 0.1 to 0.6; p = 0.001). When GCS is included in the stratification, the number of patients in each stratum is reduced and statistical significance is not reached. β-blockade results in a clinically significant decrease in mortality for patients with a GCS ≤ 8. For this group, mortality was 50% for patients in the β-blocker group versus 78% for the no β-blocker group (odds ratio: 0.43; 95% CI, 0.19 to 0.97; p = 0.1). Mortality odds ratios for each stratum are summarized in Table 4.

DISCUSSION

Traumatic brain injury (TBI) remains a major cause of death and neurologic disability. In the US it is estimated that more than 1 million emergency room contacts and 50,000 deaths are attributable to TBI every year.[8] The impact of TBI on society is amplified by the long-lasting residual effects of this injury. The Centers for Disease Control and Prevention estimates project greater than 5 million Americans are living with longterm disability as a result of TBI.[9] For these patients, very little has been demonstrated to significantly affect either mortality or neurologic outcome. β-adrenergic blockade in the head-injured patient population has the potential to exert a large clinical effect.

At this time, there is strong evidence to support a wide range of clinical indications for β-blockade. The importance of β-adrenergic blockade in surgical patients undergoing noncardiac surgery has been well established. It has been demonstrated to decrease perioperative myocardial ischemia, mortality, and the incidence of cardiac complications for up to 2 years postoperatively.[10,11] In cardiac surgery patients, β-blockade has been shown to result in a significant decrease in the incidence of postoperative neurologic complications.[12] In trauma patients, β-blockade is a standard initial management strategy for patients with a torn thoracic aorta and a standard-of-care definitive treatment option for certain patients with this injury. Beta-blockade has also been demonstrated to result in improved outcomes for patients who have sustained thermal injury.[13,14] In critically ill multisystem trauma patients with troponin I elevation, β-blockade has also been associated with a decrease in mortality.[15]

For trauma patients with acute brain injury, the potential therapeutic benefits of β-adrenergic blockade may be even greater. Recently, compelling animal data from a mouse brain injury model[5] and retrospective clinical human data[6,7] have become available that demonstrate both neurologic improvement and a survival advantage associated with β-blockade.

The neuroendocrine response to brain injury and nontraumatic intracranial hemorrhage has been studied for decades. In patients with nontraumatic subarachnoid hemorrhage, β-blockade has been demonstrated to result in both improved survival and neurologic outcomes.[16] In trauma patients, it has been clearly shown that after head injury, there is a sustained increase in sympathetic nervous system activity, as measured by both plasma and urinary catechol-

Table 2. Risk Factors for Mortality with a p Value < 0.2 that Were Included in the Multivariable Analysis

	Mortality			
Factors	**n**	**%**	**p Value**	**Odds ratio (95% CI)**
Age, y				
≥ 55	77/276	27.9	< 0.001	1.8 (1.3–2.5)
< 55	156/880	17.7		
Glasgow Coma Scale				
≤ 8	182/519	35.1	< 0.001	6.3 (4.5–8.8)
> 8	50/634	7.9		
Head Abbreviated Injury Score				
AIS < 4	29/639	4.5	< 0.001	13.7 (9.1–20.7)
AIS ≥ 4	204/517	39.5		
Injury Severity Score				
≥ 16	222/767	28.9	< 0.001	14.0 (7.5–26.0)
< 16	11/389	2.8		
Hypotension on admission				
Systolic blood pressure < 90 mmHg	30/55	54.5	< 0.001	5.4 (3.1–9.3)
Systolic blood pressure ≥ 90 mmHg	199/1,089	18.3		
Skull fracture (vault)				
Yes	45/153	29.4	0.002	1.8 (1.2–2.6)
No	188/1,003	18.7		
Basilar skull fracture				
Yes	74/248	29.8	< 0.001	2.0 (1.5–2.8)
No	159/908	17.5		
Subdural hematoma				
Yes	102/259	39.4	< 0.001	3.8 (2.8–5.2)
No	131/897	14.6		
Epidural hematoma				
Yes	47/132	35.6	< 0.001	2.5 (1.7–3.7)
No	186/1,024	18.2		
Subarachnoid hemorrhage				
Yes	125/358	34.9	< 0.001	3.4 (2.5–4.6)
No	108/798	13.5		
Craniectomy				
Yes	23/82	28.0	0.07	1.6 (1.0–2.7)
No	210/1,072	19.6		
Beta-blocker use				
Yes	34/203	16.7	0.183	0.8 (0.5–1.1)
No	199/953	20.9		

The p values were derived from two-tailed chi-square test or Fisher's exact test.

amine levels.[1-4,17] In patients with TBI undergoing plasma norepinephrine (NE) sampling, these abnormal levels were inversely proportional to the patient's GCS.[2,3] Patients who had normalization of their GCS after injury also had normalization of their NE levels; those who remained comatose had persistently elevated NE levels upward of seven times normal with blood pressure, heart rate, and temperature elevations proportional to these levels.[2] Not only have these catecholamine levels been shown to correlate with GCS, NE levels have also been shown to be effective outcome markers.[3,4] Plasma NE levels at 48 hours after TBI predicted GCS at 1 week, the Glasgow Outcome Score, survival, and in those who survived for greater than a week, the hospital length of stay and ventilator-dependent days.[4]

Based on this evidence, even in the early 1980s, the use of β-blockade for patients with traumatic brain injury was being raised as a potential therapeutic option.[1] In a placebo-controlled, double-blind trial using a murine model of TBI, propranolol-treated mice had significantly improved neurologic recovery and histologic brain edema as compared with mice receiving placebo.[5]

Table 3. Predictors of Mortality from Stepwise Logistic Regression

Step	Variable selected	R^2	Adjusted odds ratio (95% CI)	p Value
1	Head AIS ≥ 4	0.28	5.0 (2.9–8.6)	< 0.001
2	Glasgow Coma Scale ≤ 8	0.05	4.5 (2.9–6.9)	< 0.001
3	Age ≥ 55 y	0.04	3.7 (2.4–5.8)	< 0.001
4	Systolic blood pressure ≤ 90 mmHg	0.02	4.7 (2.3–9.4)	< 0.001
5	Subarachnoid hemorrhage	0.02	2.0 (1.4–2.8)	< 0.001
6	Basilar skull fracture	0.01	1.7 (1.2–2.6)	0.01
7	Beta-blocker use	0.01	0.5 (0.3–0.9)	0.01
8	ISS ≥ 16	0.01	2.6 (1.2–5.8)	0.02

AIS, Abbreviated Injury Score; ISS, Injury Severity Score.

In human trauma patients with TBI, two retrospective studies have recently been published.[6,7] In the first,[6] of 4,117 trauma patients admitted, 303 received β-blockers. After controlling for age, intubation status, GCS, ISS, and blood pressure, despite being older, more severely injured, and with a lower GCS, β-blocked patients had a decreased risk of death, with an adjusted odds ratio of 0.3 ($p < 0.001$). In the subset of head-injured patients with a GCS of 13 or less, β-blockade was associated with a significant improvement in survival, with an adjusted odds ratio of 0.2 ($p < 0.001$). In a second study of 420 patients with a head AIS ≥ 3 given β-blockers for 2 or more days, again, despite being older, more severely injured, and with a lower predicted survival, β-blockade significantly reduced mortality.[7]

Our study is the largest series to date examining β-adrenergic blockade in isolated TBI and provides further evidence to support the use of β-blockers in patients with acute head injury. Beta-blocker exposure in patients with isolated TBI was found to be independently associated with improved survival, with an adjusted odds ratio of 0.5 (CI, 0.3 to 0.9; $p = 0.01$). The subgroup analysis further identified elderly patients with severe (AIS ≥ 4) head injury as a high-priority target for further evaluation.

The exact mechanism for this protective effect has not been well delineated, but both local and systemic effects have been proposed. Locally, β-blockade may result in the attenuation of intracerebral posttraumatic catecholamine-induced vasospasm, decreasing the potential for local ischemia to occur. The brain parenchyma itself also has β-adrenoreceptors,[18] activation of which may act to decrease local brain tissue metabolism and oxygen consumption.[19,20] Systemically, β-blockade may exert its beneficial effects by protecting the end organs that are susceptible to

Table 4. Odds Ratio of Mortality Between Beta-Blocker and No Beta-Blocker Groups after Stratification Using the Main Predictors of Mortality

Head AIS	Age, y	GCS	Mortality			Odds ratio (95% CI)	p Value
			Group	n	%		
≥ 4	≥ 55	≤ 8	No beta-blocker	40/51	78	2.32 (1.02–10.57)	0.11
			Beta-blocker	5/10	50		
≥ 4	≥ 55	> 8	No beta-blocker	12/36	33	1.18 (0.87–1.59)	0.29
			Beta-blocker	6/28	21		
≥ 4	< 55	≤ 8	No beta-blocker	111/231	48	1.23 (0.96–1.57)	0.14
			Beta-blocker	17/47	36		
≥ 4	< 55	> 8	No beta-blocker	11/90	12	1.09 (0.97–1.23)	0.46
			Beta-blocker	1/22	5		
< 4	≥ 55	≤ 8	No beta-blocker	2/12	17	1.20 (0.93–1.56)	1.00
			Beta-blocker	0/3	0		
< 4	≥ 55	> 8	No beta-blocker	8/89	9	1.00 (0.89–1.12)	1.00
			Beta-blocker	4/45	9		
< 4	< 55	≤ 8	No beta-blocker	7/151	5	1.05 (1.01–1.09)	1.00
			Beta-blocker	0/14	0		
< 4	< 55	> 8	No beta-blocker	8/293	3	1.03 (1.01–1.05)	1.00
			Beta-blocker	0/31	0		

AIS, Abbreviated Injury Score; GCS, Glasgow Coma Scale.

damage from the brain injury–induced catecholamine surge. Because β-blockade has been demonstrated to be cardioprotective under a diverse set of clinical circumstances, one of the primary potential target organs is the heart. This is especially relevant in the setting of brain injury, because both rhythm disturbances and myocardial necrosis have been documented after head trauma.[21,22] In subarachnoid hemorrhage patients randomized to β-blockade versus placebo, postmortem examination demonstrated necrotic myocardial damage in placebo-treated nonsurvivors. In β-blocked nonsurvivors, there was no evidence of any myocardial damage, leading to the conclusion that β-blockade had a cardioprotective effect on catecholamine-induced myocardial necrosis.[23] In another prospective randomized study of β-blockade in acute head injury[24] using myocardial damage as the primary outcome measure, atenolol was found to reduce the likelihood of arrhythmias and cardiac necrosis seen at autopsy. Other organ systems in addition to the heart may also be affected. For example, β-blockade may also protect pulmonary function[25] and decrease the incidence of edema in the uninjured lung parenchyma.

Because of the retrospective design of our study, the indication for β-blockade, β-receptor selectivity, start date, duration of treatment, and titrated end points were not controlled for. These questions remain the major reason why further prospective, controlled evaluation is required before instituting β-blockade as a therapeutic option after brain injury.

In summary, after traumatic brain injury, there is an abnormal catecholamine surge that correlates to GCS, Glasgow Outcome Scale, and survival. A prospective randomized animal study and retrospective human data suggest that β-blockade may be protective, improving survival and neurologic outcomes. From our subgroup analysis, elderly patients with severe brain injury may benefit most from treatment. Although the exact mechanism remains unclear, there is sufficient evidence to support the further prospective evaluation of the role of β-blockade in this patient population. Specific questions to be addressed should include the indication for instituting therapy, timing, dosing end points, and the β-selectivity of the drug to be used to maximize the protective effects of this treatment.

Author Contributions

Study conception and design: Inaba, Teixeira, David, Chan, Beale, Rhee, Demetriades

Acquisition of data: Inaba, Teixeira, Salim, Brown, Browder

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Drafting of manuscript: Inaba, Teixeira, David, Chan

Critical revision: Inaba, Teixeira, David, Chan, Beale, Salim, Brown, Browder, Rhee, Demetriades

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