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ORIGINAL WORK

Association of Angiotensin-Converting Enzyme Inhibitors with Increased Mortality Among Patients with Isolated Severe Traumatic Brain Injury

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Abstract

Background: Traumatic brain injury (TBI) is associated with one-third of all deaths from trauma. Preinjury exposure to cardiovascular drugs may affect TBI outcomes. Angiotensin-converting enzyme inhibitors (ACEIs) exacerbate brain cell damage and worsen functional outcomes in the laboratory setting. β-blockers (BBs), however, appear to be associated with reduced mortality among patients with isolated TBI.

Objective: Examine the association between preinjury ACEI and BB use and clinical outcome among patients with isolated TBI.

Methods: A retrospective cohort study of patients age ≥ 40 years admitted to an academic level 1 trauma center with isolated TBI between January 2010 and December 2014 was performed. Isolated TBI was defined as a head Abbreviated Injury Scale (AIS) score ≥ 3, with chest, abdomen, and extremity AIS scores ≤ 2. Preinjury medication use was determined through chart review. All patients with concurrent BB use were initially excluded. In-hospital mortality was the primary measured outcome.

Results: Over the 5-year study period, 600 patients were identified with isolated TBI who were naive to BB use. There was significantly higher mortality ($P = .04$) among patients who received ACEI before injury (10 of 96; 10%) than among those who did not (25 of 504; 5%). A multivariate stepwise logistic regression analysis revealed a threefold increased risk of mortality in the ACEI cohort ($P < .001$), which was even greater than the twofold increased risk of mortality associated with an Injury Severity Score ≥ 16. A second analysis that included patients who received preinjury BBs ($n = 98$) demonstrated slightly reduced mortality in the ACEI cohort with only a twofold increased risk in multivariate analysis ($P = .05$).

Conclusions: Preinjury exposure to ACEIs is associated with an increase in mortality among patients with isolated TBI. This effect is ameliorated in patients who receive BBs, which provides evidence that this class of medications may provide a protective benefit.

Keywords: Angiotensin-converting enzyme inhibitor, β-Blockers, Isolated, Mortality, Traumatic brain injury

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Introduction

Traumatic brain injury (TBI) presents a significant health burden to the USA. There are nearly 1.7 million new patients with TBI annually, and this injury is associated with nearly one-third of all trauma-related deaths [1–3]. The estimated medical cost from TBI is reported to be as high as $79.1 billion annually [1, 4–6]. Despite advances in motor vehicle safety technology, sports-related protective equipment, and medical and surgical treatment of trauma patients, the incidence and socioeconomic burden of TBI in the USA have remained unchanged.

Various drugs have shown some promise in providing neuroprotection from TBI and may provide an avenue to decrease the impact of TBI in the USA [7]. Preinjury exposure to β-blockers (BBs) among patients with isolated severe TBI has been associated with decreased risk of mortality [8]. The hypothetical mechanism of BBs in mortality reduction is through decreasing secondary injury [8]. It has been postulated that this secondary cascade of events is the primary cause of the neurological deficits observed after TBI [7, 9]. Other authors have postulated that because of this delay, there may be a therapeutic window for BB treatment that improves outcome [7].

The kinin pathway has been implicated as a mediator of secondary injury in TBI patients [10, 11]. Because of the effect of the antihypertensive medication and angiotensin-converting enzyme inhibitors (ACEIs) on this pathway, it was believed that use of ACEIs may affect outcomes in this patient population. The treatment of TBI with ACEIs has been shown in animal models to exacerbate motor deficits and increase dark cell changes [12]. This effect has yet to be observed clinically. Through a single-center review of a trauma registry, we investigated the role of preinjury ACEI and BB use among patients with isolated severe TBI, with a primary measured outcome of mortality.

Study Methods

This study protocol was approved by the institutional review board at the University of Nevada, Las Vegas. Trauma patients 40 years of age or older with an isolated severe TBI who were admitted to an academic level 1 trauma center between January 1, 2010, and December 31, 2014, were retrospectively identified with use of the hospital's trauma database. A retrospective chart review was subsequently conducted.

Isolated severe TBI was defined as a head Abbreviated Injury Scale (AIS) score ≥ 3, with chest, abdomen, and extremity AIS scores ≤ 2. Although the head AIS includes intracranial, skull, neck, and cervical spine injuries, only patients with a head AIS score ≥ 3 due to intracranial injury were included. Patients with a brain injury and an AIS score of 6 were excluded because the primary injury in these cases is not survivable.

The data collected from both the trauma registry and the chart review included age, sex, ethnicity, Glasgow Coma Scale (GCS) on initial assessment, GCS on discharge date, systolic blood pressure (SBP) on initial assessment, Injury Severity Score (ISS), AIS score for all body regions, imaging findings, cardiovascular protective medication exposure before trauma, surgical procedures, additional injuries, intensive care unit days, hospital days, ventilator days, ventilator-free days, disposition, and mortality during inpatient hospitalization.

Statistical Methods

Two separate analyses were performed. The first analysis excluded patients with preinjury exposure to a BB, and the second analysis included these patients. Percentages and frequencies were used to describe demographic and clinical characteristics, and means and standard deviations (SDs) were applied to describe age and ISS. Chi-square tests were performed to compare demographic and clinical characteristics for patients with ACEI and patients without ACEI, and two-sample *t* tests were applied to compare age and ISS for patients with ACEI and patients without ACEI. Univariate logistic regression was used to identify the potential risk factors for mortality. Risk factors for mortality in a univariate analysis with P value < .2 were included in a multivariable analysis. A stepwise logistic regression model was used to identify significant predictors for mortality. The level of significance was set at $P < .05$. SAS version 9.4 for Microsoft Windows (SAS Institute, Inc) was applied for data analysis.

Results

No Preinjury BB Use

A total of 698 patients were identified with isolated severe TBI and met the study inclusion criteria. However, 98 of these patients were found to have preinjury exposure to BBs (including 28 patients with concurrent ACEI use) and were excluded from the first analysis.

Of the remaining 600 patients without preinjury BB use, a total of 96 patients (16%) used ACEI prior to injury. The mean age of ACEI-exposed patients was significantly higher (65.7 ± 11.5 years) than that of the nonexposed patients (58.7 ± 13.4 years; $P < .001$), and ACEI-exposed patients were more likely to be 55 years of age or older (79% vs. 52.4%; $P < .001$) (Table 1). Overall, 35 patients died (5.8%). ACEI exposure was associated with a significantly higher rate of mortality than nonexposure (10.4% vs. 5%; $P = .04$) (Table 2). Next, a univariate analysis was performed to determine the risk factors for mortality (Table 3). Age 55 years or older,

Table 1 Comparison of demographic and clinical characteristics between patients with and without angiotensin-converting enzyme inhibitor use who had isolated severe traumatic brain injury without preinjury β-blocker exposure

Demographic or clinical characteristic	All patients, % ($n = 600$)	Patients with ACEI use, % ($n = 96$)	Patients without ACEI use, % ($n = 504$)	*P* value
Age, years, mean (SD)	59.8 (13.4)	65.7 (11.5)	58.7 (13.4)	< .001
Age ≥ 55 years	56.7	79.2	52.4	< .001
Male sex	69.8	65.6	70.6	.33
GCS ≤ 8	12.0	9.4	12.5	.38
SBP < 90 mm Hg	3.5	5.2	3.2	.36
ISS, mean (SD)	15.4 (5.4)	15.1 (4.7)	15.5 (5.5)	.54
ISS ≥ 16	53.5	58.3	52.6	.30
Head AIS ≥ 4	47.2	47.9	47.0	.87
Epidural hematoma	5.8	5.2	6.0	.77
Subdural hematoma	36.8	36.5	36.9	.93
Subarachnoid hematoma	41.7	39.6	42.1	.65
Diffuse axonal injury	4.8	3.1	5.2	.60
Other injury	23.7	24.0	23.6	.94
Craniotomy	8.0	6.3	8.3	.49
Craniectomy	1.0	2.1	.8	.25
ICP monitoring	2.5	3.1	2.4	.72

Data are presented as percentage of patients unless otherwise indicated

ACEI angiotensin-converting enzyme inhibitor, *AIS* Abbreviated Injury Scale, *BB* β-blocker, *GCS* Glasgow Coma Scale, *ICP* intracranial pressure, *ISS* Injury Severity Score, *SBP* systolic blood pressure, and *SD* standard deviation

Table 2 Comparison of outcomes between patients with and without angiotensin-converting enzyme inhibitor use who had isolated severe traumatic brain injury without preinjury β-blocker exposure

Outcome	Total ($n = 600$)	Patients with ACEI use ($n = 96$)	Patients without ACEI use ($n = 504$)	*P* value
Mortality (%)	5.8	10.4	5.0	.04
HLOS (days)	7.6 (19.8)	6.9 (14.3)	7.7 (20.7)	.62
ICU LOS (days)	3.1 (6.3)	3.6 (9.2)	5.0 (5.5)	.57
ICU-free days	4.4 (17.1)	3.3 (6.5)	4.7 (18.5)	.19
Ventilator days	1.9 (6.3)	2.8 (10.9)	1.7 (4.9)	.32
Ventilator-free days	5.7 (18.1)	4.0 (5.7)	6.0 (19.6)	.06

Data are mean (SD) unless otherwise indicated

ACEI angiotensin-converting enzyme inhibitor, *HLOS* hospital length of stay, *ICU* intensive care unit, and *LOS* length of stay

GCS of 8 or less, SBP less than 90 mm Hg, ISS of 16 or greater, subdural hematoma, diffuse axonal injury, other cranial injury, craniotomy, and ACEI exposure were all found to be significant in a univariate analysis. These significant factors and all other factors that were associated with mortality ($P < .20$) were included in a multivariate analysis (Table 4). Following stepwise logistic regression, GCS of 8 or less, preinjury ACEI exposure, and ISS of 16 or greater were found to be significant predictors of mortality among patients without preinjury BB use.

Preinjury BB Use

In the second analysis, a univariate analysis was performed that included patients with preinjury BB exposure (Table 5). All risk factors for mortality that significantly varied in the univariate analysis ($P < .20$) were included in a multivariate stepwise logistic regression analysis (Table 6). GCS of 8 or less, ISS of 16 or greater, and ACEI exposure were again found to be significant predictors of mortality. Additionally, all of these predictors were associated with a decreased risk

Table 3 Risk factors for mortality among patients who had isolated severe traumatic brain injury without preinjury β-blocker exposure

Risk factor	Mortality, no. (%)	OR (95% CI)	*P* value
Age ≥ 55 years			
Yes	26/340 (7.7)	2.31 (1.06, 5.02)	.04
No	9/260 (3.5)		
Male sex			
Yes	25/419 (6.0)	1.09 (.51, 2.31)	.83
No	10/181 (5.5)		
GCS ≤ 8			
Yes	24/72 (33.3)	24.5 (10.8, 50.8)	< .001
No	11/528 (2.1)		
SBP < 90 mm Hg			
Yes	4/21 (19.0)	4.16 (1.32, 13.1)	.02
No	31/579 (5.6)		
ISS ≥ 16			
Yes	28/321 (8.7)	3.71 (1.59, 8.64)	.002
No	7/279 (2.5)		
Head AIS ≥ 4			
Yes	27/283 (9.5)	4.07 (1.82, 9.12)	< .001
No	8/317 (2.5)		
Epidural hematoma			
Yes	4/35 (11.4)	2.22 (.74, 6.7)	.16
No	31/565 (5.5)		
Subdural hematoma			
Yes	21/221 (9.5)	2.74 (1.36, 5.50)	.005
No	14/379 (3.7)		
Subarachnoid hemorrhage			
Yes	15/250 (6.0)	1.05 (.53, 2.10)	.87
No	20/350 (5.7)		
Diffuse axonal injury			
Yes	4/29 (13.8)	2.79 (.91, 8.51)	.07
No	31/571 (5.4)		
Other cranial injury			
Yes	2/142 (1.4)	.18 (.04, .78)	.02
No	33/458 (7.2)		
Craniotomy			
Yes	8/48 (16.7)		
No	27/552 (4.9)	.26 (.11, .60)	.002
Craniectomy			
Yes	0/6 (0)		
No	35/594 (5.9)	N/A	
ACEI			
Yes	10/96 (10.4)	2.23 (1.03, 4.81)	.04
No	25/504 (5.0)		
ICP monitoring			
Yes	2/15 (13.3)	.39 (.08, 1.79)	.07
No	33/585 (5.6)		

ACEI angiotensin-converting enzyme inhibitor, *AIS* Abbreviated Injury Scale, *CI* confidence interval, *GCS* Glasgow Coma Scale, *ICP* intracranial pressure, *ISS* Injury Severity Score, *N/A* not applicable, *OR* odds ratio, and *SBP* systolic blood pressure

of mortality among patients with preinjury BB exposure compared with patients without preinjury BB exposure.

Discussion

TBI is a major source of trauma-related morbidity and socioeconomic burden in the USA. Primary injury in a TBI includes the mechanical damage that occurs as a result of shearing, tearing, or stretching of neurons, axons, glial cells, and blood vessels [7, 13, 14]. Following the primary injury in TBI, additional damage occurs in a secondary phase because of neuronal hyperexcitability and resultant inflammation [15]. The secondary phase may evolve and persist over months after the initial insult. The secondary phase of TBI results in blood–brain barrier disruption, vasodilation, and edema, which can lead to elevated intracranial pressure, neuronal apoptosis, and neuronal necrosis [7, 9]. The majority of TBI-associated morbidity and disability results from this secondary injury cascade. To combat TBI-induced disability, it is critical to understand and prevent the devastating secondary injury cascade. The previous cerebral ischemia animal models have demonstrated improved outcomes through use of ACEIs and ganglionic blockade; however, it is not clear how these interventions may affect outcomes in TBI [16, 17]. This study was, to our knowledge, the first to clinically investigate preinjury ACEI exposure before a TBI and its potential effect on mortality.

Our study found preinjury ACEI exposure in patients with severe, isolated TBI to be a significant predictor of mortality. The risk of mortality was more than twofold greater among patients who had ACEI exposure before injury (10.4% vs. 5%). This association of increased risk of death was also seen when ACEI or angiotensin receptor II blockers were continued preoperatively for noncardiac surgeries [18]. One plausible explanation for this finding is that the secondary injury cascade is exacerbated by higher levels of the neuroinflammatory mediators substance P and bradykinin when angiotensin-converting enzyme is inhibited [12, 15, 19–22]. Bradykinin and substance P are potent mediators of secondary injury via neuroinflammation [10, 11]. ACEI potentiates the release of both by inhibiting angiotensin-converting enzyme, which inactivates both bradykinin and substance P [12, 15, 20]. This mechanism has even prompted the development of antagonists to attempt to block bradykinin effects, which have been shown in animal models to improve edema and neurological function following TBI [19, 23]. While this study does not prove the proposed mechanism, the results are consistent with exacerbation of the secondary phase of neuroinflammation.

Interestingly, the odds of mortality increased when all patients with concurrent BB use were excluded (odds ratio [OR], 3.66). A recent meta-analysis by Alali et al.

Table 4 Predictors of mortality using stepwise logistic regression among patients who had isolated severe traumatic brain injury excluding patients with preinjury β-blocker exposure

Step	Variable selected	Adjusted OR (95% CI)	*P* value
1	GCS ≤ 8	23.4 (10.27, 53.86)	< .001
2	ACEI use	3.66 (1.43, 9.39)	< .001
3	ISS ≥ 16	2.47 (1.02, 5.97)	.04

ACEI angiotensin-converting enzyme inhibitor, *CI* confidence interval, *GCS* Glasgow Coma Scale, *ISS* Injury Severity Score, and *OR* odds ratio

Table 5 Risk factors for mortality among patients who had isolated severe traumatic brain injury including patients with β-blocker exposure

Risk Factor	Mortality, no. (%)	OR (95% CI)	*P* Value
Age ≥ 55 years			
Yes	32/428 (7.5)	2.10 (1.02, 4.35)	.05
No	10/270 (3.7)		
GCS ≤ 8			
Yes	25/80 (31.3)	16.1 (8.18, 31.6)	<.001
No	17/618 (2.8)		
SBP < 90 mm Hg			
Yes	4/23 (17.4)	3.53 (1.14, 10.9)	.03
No	38/675 (5.6)		
ISS ≥ 16			
Yes	33/377 (8.8)	3.33 (1.57, 7.06)	.002
No	9/321 (2.8)		
Head AIS ≥ 4			
Yes	31/334 (9.3)	3.28 (1.62, 6.64)	.009
No	10/364 (3.0)		
Subdural hematoma			
Yes	24/257 (9.3)	2.42 (1.29, 4.55)	.006
No	18/441 (4.1)		
Diffuse axonal injury			
Yes	5/34 (14.7)	2.92 (1.07, 7.99)	.04
No	37/664 (5.6)		
Other cranial injury			
Yes	3/165 (1.8)	.23 (.07, .77)	.02
No	39/533 (7.3)		
Craniotomy			
Yes	11/58 (19.0)		
No	31/640 (4.8)	.22 (.1, .46)	<.001
Craniectomy			
Yes	0/7 (0)		
No	42/691 (6.1)	N/A	
ACEI use			
Yes	11/124 (8.9)	1.7 (.83, 3.49)	.14
No	31/574 (5.4)		

ACEI angiotensin-converting enzyme inhibitor, *AIS* Abbreviated Injury Scale, *CI* confidence interval, *GCS* Glasgow Coma Scale, *ISS* Injury Severity Score, *N/A* not applicable, *OR* odds ratio, and *SBP* systolic blood pressure

[24] analyzed 6240 patients in nine studies and found that in-hospital exposure to BBs significantly reduced in-hospital mortality. Additionally, Mohseni et al. [8] found the lack of preinjury BB exposure to be a predictor of mortality in a similar patient population. Studies examining subarachnoid hemorrhage patients have demonstrated the role of the adrenergic response following the initial insult [25–29]. Sympatholytic pharmacotherapy has proven beneficial in patients with subarachnoid hemorrhage through alteration of the adrenergic surge induced by the initial injury [28, 30, 31]. As is the case in patients with subarachnoid hemorrhage, BBs are thought to be protective in patients with TBI by decreasing the elevated adrenergic drive seen in severe head trauma, which results in secondary injury primarily via hypoperfusion [8]. Our findings support this conclusion, as preinjury ACEI, GCS of 8 or less, and ISS of 16 or greater were all found to be significant predictors of mortality. This effect was decreased in the patients with preinjury BB use (GCS ≤ 8: OR, 23.4 vs. 15.5; ISS ≥ 16: OR, 2.47 vs. 2.27).

The ACEI-exposed group was found to be older than the nonexposed group, with a mean age of 65.7 (± 11.5) years in the exposed cohort compared with 58.7 (± 13.4) years in the nonexposed cohort. In the univariate analyses for patients with and without BB exposure, age 55 years or older was found to be a significant predictor of mortality. These findings correlate with other TBI studies that have found an increase in mortality among older patients [32, 33]. In a large retrospective study performed in two level 1 trauma centers, TBI-induced mortality increased twofold in those older than 65 years of age [32]. Importantly, in neither final logistic regression was age of 55 years or greater a significant predictor of mortality.

As previously noted, in addition to preinjury ACEI exposure, GCS of 8 or less and ISS of 16 or greater were both found to be significant predictors of mortality after stepwise logistic regression in both analyses. GCS of 8 or less was found to have the strongest association with mortality. GCS has historically been used as a predictor of mortality. In a large study that included more than 7000 patients with head injury, GCS between 4 and 8 was found to be associated with a ninefold increase in mortality [34]. In our analyses, ISS of 16 or greater was found to increase mortality more than twofold, which was defined more than 20 years ago as an indicator of a major trauma [35, 36]. Similarly, a large Australian study that included more than 8000 patients found the mortality rate to be 15.1% in patients with an ISS greater than 24, 1.5% in patients with an ISS of 16 to 24, and 0% in patients with an ISS of 12 to 14 [37]. Interestingly, when patients with BB usage were excluded, the risk of mortality associated with preinjury ACEI exposure was greater than that

Table 6 Predictors of mortality using stepwise logistic regression among patients who had isolated severe traumatic brain injury including patients with β-blocker exposure

Step	Variable selected	Adjusted OR (95% CI)	*P* value
1	GCS ≤ 8	15.5 (7.67, 31.2)	< .001
2	ISS ≥ 16	2.37 (1.07, 5.27)	.03
3	ACEI use	2.27 (1.01, 5.09)	.05

ACEI angiotensin-converting enzyme inhibitor, *CI* confidence interval, *GCS* Glasgow Coma Scale, *ISS* Injury Severity Score, and *OR* odds ratio

associated with an ISS of 16 or greater, which suggests that the exacerbated secondary injury cascade caused by ACEI may be more important than the primary injury with regard to morbidity and mortality. It should be noted that head AIS of 4 to 5 and SBP less than 90 mm Hg were found to be predictors of mortality in both univariate analyses, and both factors have been associated with an increased risk of mortality in other studies [34, 36]. However, GCS of 8 or less, preinjury ACEI exposure, and ISS of 16 or greater were found to be much greater predictors of mortality than these factors.

Limitations

Limitations to our study include those seen in all retrospective cohort studies. A randomized controlled study with careful patient selection analyzing this question would offer stronger conclusions. Furthermore, our study did not evaluate causes of death for individual patients and could not control for medical comorbidities, including cardiopulmonary pathologies. Patients receiving dual antihypertensive medications presumably have more severe cardiovascular disease than those receiving a single medication; however, we found that patients with ACEI exposure and no concurrent use of BBs had a greater risk of mortality. This may illustrate that the increased mortality with ACEI exposure was not due to the inherent medical comorbidities but rather to a more robust secondary injury cascade.

Conclusions

Preinjury exposure to an ACEI is associated with an increase in mortality among patients with isolated severe TBI. This effect is ameliorated in those receiving BBs, which provides further evidence that this class of medications may provide a protective benefit. In patients with no BB exposure, ACEI use was a greater predictor of mortality than ISS of 16 or greater. This is remarkable considering that ISS of 16 or greater has been validated as a strong predictor of mortality. Additional studies to confirm these findings in patients with TBI are needed.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; AIS: Abbreviated Injury Scale; BB: β-Blocker; GCS: Glasgow Coma Scale; ISS: Injury Severity Score; OR: Odds ratio; SBP: Systolic blood pressure; TBI: Traumatic brain injury.

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Author Contributions

JSC performed data collection or management, data analysis, protocol/project development, and manuscript writing/editing. AJC contributed to protocol/project development and manuscript writing/editing. MD, JMA, JG, SB, CDM, and ACW performed manuscript writing/editing. LPH was involved in data collection or management. ML was involved in data analysis. JMZ performed manuscript writing/editing/approval. DRF performed protocol/project development and manuscript writing/editing. The authors confirm that authorship requirements have been met and the final manuscript was approved by all authors.

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Conflict of interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consent was waived on IRB approval and was not obtained because of the retrospective nature of the study with minimal risk to patients.

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