

# The Impact of Substance Abuse on Mortality in Patients With Severe Traumatic Brain Injury

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**Background:** Drug and alcohol use are common in neurotrauma patients. Despite growing methamphetamine use there are few studies of the impact of methamphetamine use on outcome after traumatic brain injury (TBI).

**Methods:** We conducted a retrospective review of 5-years of data from a trauma database. Inclusion criteria included severe TBI and diagnosis codes indicating head injury. The entire database was analyzed and then a subset of patients with complete toxicology data were examined separately. Primary outcome was mortality.

**Results:** Four hundred eighty-three patients were included. Toxicology re-

sults were available for 52.6% of patients. Alcohol, amphetamines, and cannabis were the most commonly detected substances. Overall mortality was 50.9%. When the group with complete tox screen data were analyzed, a toxicology screen that was positive for alcohol or amphetamine was associated with decreased mortality with an odds ratio of 0.23 (CI: 0.10–0.56,  $p = 0.001$ ) and 0.25 (CI: 0.08–0.79,  $p = 0.02$ ), respectively. When the subset of patients for whom toxicology data were available was analyzed the amphetamine-positive group was more likely to use cannabis and less likely to use alcohol.

**Conclusions:** We unexpectedly found alcohol and methamphetamine use to be associated with decreased mortality. Neurotoxic and possible neuroprotective mechanisms of these substances are discussed as well as possible interactions between cannabis and methamphetamine. The potential influence of psycho-social factors are also considered. Prospective studies are needed to further investigate the effects of drug and alcohol use on outcome after severe TBI.

**Key Words:** Traumatic brain injury, Methamphetamine, Alcohol, Outcome.

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Trauma is the fourth leading cause of death in the United States, and the leading cause of death and disability for people between the ages of 1 year and 45 years old. Most patients who die in the hospital after acute trauma die from their brain injuries.<sup>1</sup> There are approximately 1.5 million cases of traumatic brain injury (TBI) in the United States each year, and an estimated 50,000 deaths. Alcohol and illicit drug use have been identified as significant risk factors for traumatic injury. Estimates of illegal drug use have exceeded 30% in populations of patients with TBI.<sup>2</sup> In one study, 78% of patients had consumed some amount of alcohol or illicit drug before traumatic injury.<sup>3</sup>

Several studies have addressed the influence of ethanol consumption on acute and chronic aspects of recovery after TBI. Preinjury alcohol consumption has been associated with more severe focal injury on neuroimaging,<sup>4</sup> longer episodes of post-

traumatic amnesia,<sup>5</sup> increased levels of agitation, and increased length of hospital stay.<sup>6</sup> More long-term disabilities associated with preinjury alcohol use include decreased postinjury verbal learning and memory,<sup>7</sup> increased posttraumatic brain atrophy on magnetic resonance imaging, and deficits on tests of verbal performance and general memory function.<sup>8</sup>

There is less literature available exploring the impact of illicit drug use on TBI. Methamphetamine use is growing throughout the United States and is frequently seen in the same population that sustains TBI. In a recent study at our trauma center,<sup>9</sup> methamphetamine use was found in 27% of trauma patients and was associated with longer hospital stay and higher hospital charges. The synergistic effects of substance abuse and TBI have not been thoroughly investigated. The objective of the present study was to evaluate the effect of substance abuse on in hospital mortality at discharge in patients with severe TBI.

## METHODS

A retrospective review of the medical records and trauma database was approved by the Institutional Review Board at Queen's Medical Center, Honolulu, HI, a 500 bed Level II trauma center. Criteria for inclusion were admission to The Queen's Medical Center between 2001 and 2006, admission Glasgow Coma Scale (GCS) score of <9, mechanism of injury consistent with blunt trauma, and diagnosis codes indicating head injury. Patients who survived but spent fewer than 2 days in the intensive care unit (ICU) were excluded since intoxicated patients may have a lower initial GCS due to the effects of alcohol rather than underlying brain injury.

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**Table 1** Data Fields Queried

Age
Location at time of injury—specifically which island
Use of protective devices: helmets and seat belts
Scene vital signs and GCS (Glasgow Coma Scale) score
How patients were transported to QMC: air, ambulance, friend, or family
Toxicology screen (all drugs that are tested) and BAL (blood alcohol level)
ED vital signs and GCS score if available
Complications during hospitalization
Discharge GCS
Mortality
Location after discharge: home, SNF, RHOP, other
Medical record number (to assure no double entries)
Visit account number
Gender
Mechanism of injury
ISS (injury severity scale)
Transport time to QMC
Hospital length of stay
ICU length of stay

The trauma data registry system used at The Queen's Medical Center is Collector from Digital Innovations (Forest Hill, MD). Data fields used are listed in Table 1. The subset of patients for whom toxicology data were available was analyzed and comparisons made between those who had positive toxicology tests and those who had negative toxicology tests.

### Statistical Analysis

Fisher's exact test was used for count data, with odds ratios and 95% confidence intervals where appropriate. Student's *t* test and the Yuen-Welch robust test (as the latter is immune to differences from normality)<sup>10</sup> were used together for comparing continuous data between drug usage groups. Logistic regression was used for analysis of predictors of mortality. All computations were made in R version 2.6.0.<sup>11</sup>

### RESULTS

Between January of 2001 and December of 2006, 483 patients meeting the inclusion criteria were admitted to The Queen's Medical Center (Table 2). The mean age was 41.8 years and 74% of patients were men. The mean Injury Severity Scale (ISS) was 32.0 and the mean admission GCS was 4.3. Toxicology screening was performed on 52.6% of the sample and blood alcohol concentration was recorded for 52.8%. Alcohol, amphetamine, and cannabis were the most commonly detected substances after exclusion of benzodiazepines and opiates, which were likely administered by medical personnel. Overall mortality was 50.9%.

Predictors of in-hospital mortality are presented in Table 3. Older age, higher ISS, and lower GCS were all associated with higher mortality. When the subset of patients with toxicology data were analyzed, a toxicology screen that was positive for methamphetamine, cocaine, or marijuana was found to be associated with a lower mortality with odds ratios of 0.33 (95% CI:

**Table 2** Description of the Overall Sample (n = 483)

	Mean	SD
Age (yr)	41.8	23.1
GCS		
Scene	5.4	3.2
Admission	4.3	1.8
Gender		
Female	126	
Male	357	
ISS	32.0	13.1
ICU days	7.8	10.1
Hospital days	13.2	18.3
Mortality	246 (50.9%)	
Toxicology screen		
Amphetamine	47	9.7%
Benzodiazepine	111	23.0%
Narcotic	33	6.8%
Cannabis	35	7.3%
Cocaine	15	3.1%
Alcohol	331	68.5%
Polydrug	376	77.8%
Polydrug excluding alcohol	68	14.1%

**Table 3** Predictors of In-hospital Mortality

Variable	OR	95% CI	<i>p</i>
Age	1.04	1.00–1.07	0.033
ISS	1.04	0.99–1.08	0.117
GCS	0.67	0.49–0.90	0.009
Toxicology screen positive vs. negative	0.33	0.15–0.65	<0.001
Amphetamine positive	0.29	0.12–0.65	<0.001

OR, odds ratio; CI, confidence interval.

**Table 4** Subset Analysis of Patients With Toxicology Screen: Amphetamine Negative vs. Positive

	Amphetamine (–)	Amphetamine (+)	<i>p</i>
N	79	43	
Age (yr)	39 ± 21	35 ± 10	0.1
ISS	35 ± 14	31 ± 13.9	0.03
Systolic blood pressure (mm Hg)	135 ± 33	141 ± 35	0.44
Admission GCS	4.6 ± 2	4.9 ± 2	0.55
BAL	200 ± 117	102 ± 80	0.07

0.15–0.65). Forty-seven patients tested positive for methamphetamine although only 14 of these were positive for exclusively this drug. When the subset of patients who were positive for methamphetamine were compared with those with negative toxicology tests, (Table 4) the odds ratio for mortality was 0.29 with 95% CI 0.12 to 0.65. The methamphetamine-positive and methamphetamine-negative groups did not differ in age (39 vs. 35, *p* = 0.1), systolic blood pressure (135 vs. 141, *p* = 0.44), or GCS (4.8 vs. 5.2, *p* = 0.43). The methamphetamine-positive group did have a strong trend toward lower blood alcohol level (200 vs. 102, *p* = 0.07). ISS scores were also slightly lower in

**Table 5** Selected Predictors of Mortality: Results of Logistic Regression

	Estimate	Std. Error	Z Value	p
(Intercept)	0.168	0.615	0.273	0.7845
GCS	-0.389	0.100	-3.901	<0.0001
Age	0.049	0.013	3.620	0.0003
Amphetamine use	-1.193	0.459	0.459	0.0094

the methamphetamine-positive group (35 vs. 31,  $p = 0.03$ ). A bias analysis was performed to compare the 286 subjects without toxicology testing to the 366 subjects with complete toxicology data. Conventional  $t$  tests and Yuen-Welch tests were performed. Mean age was significantly higher in the group without toxicology data (43.7 vs. 35.7 years,  $p < 0.001$ ). ISS scores were not significantly different (28.2 vs. 27.0,  $p = 0.30$ ). Admission GCS was lower in the group not tested (mean 3 vs. 5,  $p < 0.01$ ). Mortality was significantly higher in the group without toxicology data (O.R. 2.7,  $p < 0.001$ ). Logistic regression analysis was performed to evaluate for independence of effects (Table 5). Amphetamine status, age, and GCS were each significant predictors of mortality. When amphetamine status was considered in addition to age and GCS amphetamine status remained a significant predictor (OR 0.30, CI 0.12–0.75,  $p = 0.009$ ).

## DISCUSSION

The findings in this study are consistent with the reported literature on TBI with respect to established predictors of mortality, such as older age, higher ISS score, and lower admission GCS score. However, the finding that substance abuse was associated with lower in-hospital mortality was unexpected. The statistical analysis controlled for age, ISS, and admission GCS. Logistic regression analysis supported this significant effect even when considering the contribution of age and GCS to mortality. The mean ICU length of stay was not significantly different for the two groups ( $p = 0.35$ ). This makes it unlikely that acute intoxication was the cause for decreased mental status on initial presentation.

Hypotension is a well-established predictor of poor outcome after TBI. Stimulants such as methamphetamine and cocaine are known to cause hemodynamic changes because of dopamine release including systemic hypertension. We compared the initial blood pressures recorded by the emergency response teams for the two groups to investigate whether patients who tested positive for methamphetamine were less likely to have hypotension. As initial systolic blood pressures were not significantly different in the two groups, hypotension is an unlikely explanation for the difference in mortality. We performed a bias analysis to compare those subjects with toxicology data to those without available data. This demonstrated that those not tested were significantly older, had lower admission GCS scores, and were more likely to die during their hospitalization. This suggests that our findings may not be generalizable to an older patient population.

Several authors have addressed the effects of alcohol consumption on TBI and have found both worsening and improvement of posttraumatic neural damage and clinical outcome. The acute effects of alcohol on cerebral blood flow (CBF) and metabolism have been studied in experimental models. In a swine model investigating the combined effects of alcohol and hemorrhagic shock before fluid percussion injury, Zink et al.<sup>12</sup> reported that alcohol was associated with decreased CBF and decreased cerebral perfusion pressure. In a clinical study, Alexander et al.<sup>13</sup> evaluated 80 patients with severe TBI, measuring CBF using Xenon CT within 36 hours after TBI, and outcome using the Glasgow Outcome Scale at three, 6 months and 12 months postinjury. Serum ethanol levels greater than 100 mg/dL were associated with increased incidence of low CBF (<30 mg/dL). However, alcohol consumption before injury did not affect mortality or outcome. In contrast, some authors have reported favorable metabolic or functional outcomes in experimental models of alcohol and TBI. Kelly et al.<sup>14</sup> reported elevated CBF and decreased hyperglycolysis with less uncoupling between glucose metabolism and CBF in a rat model using intraperitoneal ethanol injection followed by controlled cortical impact injury. Taylor et al.<sup>15</sup> reported a decreased febrile response after cortical impact injury in ethanol-fed rats. These ethanol-fed animals also showed decreased deficits in spatial learning as assessed with the Morris Water Maze.

Although alcohol has shown some neuroprotective effects, experimental studies have shown that methamphetamine is neurotoxic.<sup>16–18</sup> Clinical studies of active and abstinent methamphetamine users have demonstrated altered brain blood flow, glucose metabolism, and altered morphology.<sup>19–21</sup> Although oral  $D$ -amphetamine administration has been seen to decrease the cerebral metabolic rate of glucose in a dose-dependent fashion in schizophrenic subjects and controls,<sup>22</sup> no such change was found in a study of subjects with attention deficit hyperactivity disorder.<sup>23</sup> In a study of healthy volunteers,<sup>24</sup> global glucose did not change but regional glucose metabolism increased in the limbic, frontal, and cerebellar regions and decreased in the temporal lobes. One possible explanation for our contrasting findings may involve the interaction between methamphetamine use and marijuana use. In our subset analysis of patients with toxicology screens, (Table 4) the methamphetamine-positive cohort was more likely to also test positive for cannabis ( $p = 0.01$ ). Several authors have described alterations in cerebral metabolism,<sup>22,25,26</sup> and blood flow<sup>27,28</sup> as well as synergistic effects of methamphetamine and THC.<sup>29</sup> A recent review by Biegon<sup>30</sup> summarizes potential mechanism for cannabinoids as neuroprotective agents in TBI. In vitro and in vivo models suggest several potential mechanisms including decreased glutamatergic excitotoxicity, free radical scavenging, and decreased tumor necrosis factor- $\alpha$  activity. Furthermore, a multicenter, phase 2 trial<sup>31</sup> in patients with severe TBI showed decreased intracranial pressure in patients treated with Dexanabolol and a trend toward better outcome at 6 months postinjury.

Several limitations of this study should be noted. First, the current study involves retrospective analysis of prospectively collected data. There were also limited data available regarding the clinical course during the acute hospitalization. Other factors, such as lack of toxicology screening in all patients, intracranial pressure values, surgical treatment of patients after admission to the ICU, and detailed drug histories were not available. This made it impossible to distinguish chronic versus acute drug use. We also could not consider the timing or dose of drug used relative to the TBI event. Patients who tested negative for methamphetamine also could have had a history of methamphetamine use in the past. Previous studies have shown long-term methamphetamine use can cause alterations in CBF and metabolism and may affect outcome.<sup>20,22</sup> Acute toxicology screening would not identify these patients. These factors may all have influenced mortality in our patient population. One specific consideration involved the prevalence of withdrawal of life support. Withdrawal of life support in patients with severe TBI requires the involvement of family members who are willing to consider the patients' quality of life and act on their behalf to stop aggressive treatments. It is possible that patients who test positive for methamphetamine have less family involvement and may have a lower incidence of withdrawal of life support. Our findings in this study underscore the need to conduct prospective clinical research to study the acute effects of methamphetamine use on CBF and metabolism as well as psychosocial factors that may influence outcome after TBI.

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