Influence of Alcohol on Mortality in Traumatic Brain Injury

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Traumatic brain injury (TBI) represents a major public health problem. Each year, 1.4 million people sustain TBIs in the United States; 235,000 patients are hospitalized and 50,000 die. The leading cause of TBI in the general population is falls, where rates are highest among children ages 0 to 4 years and among adults ages 75 years or older. Falls are followed closely by motor-vehicle crashes and assaults as overall causes of TBI. However, motor-vehicle crashes result in the greatest number of TBI-related deaths and hospitalizations.

TBI injuries are extremely costly from a public health perspective because they require expenditures for hospital care, extended care, and other medical services, as well as the loss of productivity that can follow the permanent neurological consequences of TBI. For example, the Centers for Disease Control and Prevention estimated that at least 5.3 million patients have a long-term or lifelong need for help with activities of daily living because of TBI.2 As early as 1985, the annual economic burden of TBI in the United States was estimated at $37.8 billion,3 and during the past several years, it has increased to almost $60 billion annually.4 One source estimated the cost of acute care and rehabilitation for new cases of TBI at $9 to $10 billion annually in 1999.5 In addition, the psychosocial burden borne by families of individuals with TBI must be taken into account, even though it cannot be financially evaluated. Although not all of these figures are from the current decade, it is clear that TBI represents a prevalent and costly public health issue.

Alcohol contributes considerably to the morbidity and mortality of trauma patients, regardless of the type of injury suffered.6-9 Serum alcohol levels correlate closely with extent of injury.10-12 In 2006, alcohol intoxication was involved in 32% of fatal motor-vehicle crashes in the United States.13 Approximately half of the alcohol-related deaths in trauma occur in prehospital settings.14 Specifically in TBI, 35% to 81% of the injured patients are alcohol-intoxicated15,16 and 42% of TBI patients were heavy drinkers before injury.16 A study from the National Trauma Database found similar rates.17

In contrast to the strong correlation between alcohol and prehospital mortality in TBI victims, the effects of alcohol on the outcomes of injured patients surviving the field and admitted to the hospital is less clear. Some clinical studies seem to suggest, surprisingly, a beneficial effect of alcohol in injured patients with TBI. This review will analyze basic research in animal models and available clinical information to provide a realistic perspective on the effect of alcohol on outcomes of patients admitted to the hospital with a diagnosis of TBI. The investigational literature can be categorized into studies of the effects of low to moderate doses of alcohol in TBI animal models, investigations into the effects of high doses of alcohol in such models, and experiments directed at elucidating the mechanisms of such effects. We will consider each in turn before moving to the clinical literature.

EXPERIMENTAL STUDIES

No single experimental model of TBI can reproduce the clinical characteristics of TBI.18 Clinical TBI is complex, involving both focal and diffuse brain injuries. In addition, most patients have secondary insults that contribute to the intricate TBI picture. For example, systemic hemorrhage with hypotension can alter cerebral perfusion, as can intracranial bleeding that increases intracranial pressure and decreases cerebral perfusion despite the hypertension of Cushing reflex. Along with altered cerebral perfusion, changes in levels of inflammatory cytokines, differences in oxygenation, sepsis, and many other factors contribute to the complex global physiologic derangement observed after injury.

The experimental—clinical translation of knowledge can be limited by the size and anatomic complexity of the animal model. Most experimental TBI studies use rodents. Few studies have used sheep or pigs, perhaps because of financial or animal welfare considerations. The different brain geometry among diverse species is likely a confounding factor, and findings in animal studies might not translate in the same fashion to humans.19 The mechanism by
which TBI is created also varies among studies, and is necessarily more standardized and different from human TBI mechanisms. Three types of animal TBI model have been described: focal, diffuse, and combined focal and diffuse brain injury. In most clinical cases, the human brain suffers a combined diffuse and focal form of injury. Weight drop, fluid percussion, impact acceleration, or controlled cortical impact models have been created to replicate the characteristics of human TBI. These forces have been applied on the lateral cortex or over the midline. Each causes different cortical cellular pathophysiology that, to a variable extent, resembles the injury suffered by the human brain.

In addition, clinical studies generally focus on severe TBI, defined as a Glasgow Coma Score (GCS) \(<8\). In contrast, experimental studies cannot accurately replicate such severe brain injury because of the high resulting fatality rate, so most animal studies model less severe TBI. Anesthetic management also varies between clinical settings, in which propofol or benzodiazepines are commonly used after TBI, and experimental models, in which anesthesia is typically applied before TBI because of animal welfare considerations and, in particular, propofol or benzodiazepines are associated with the poorest outcomes.20 Clinical data suggest the potential importance of demographic variables in TBI outcomes, in a manner not necessarily consistent with animal data. Such factors as gender and age have been identified as important in clinical TBI. Although the clinical opinion is that women experience better outcomes than men,20 some research studies were not able to prove this. In one study, female patients with head injury had considerably worse intracerebral pressure reactivity and higher mortality than men.21 However, a meta-analysis yielded contradictory results with no clear conclusions on this subject.20 Although male rats exhibit better cognitive recovery than females rats,22 no gender differences were found in humans.19 Increased mortality is expected in older patients, probably because of associated comorbidities.23 Most animal studies use either healthy female or male rats with narrow age ranges. Such homogenous groups of animals cannot reflect the demographic, genetic, and clinical variability of humans injured in TBI trauma.

Differences in pharmacokinetics, dosing, or cell susceptibility to alcohol among models or species could also add to the complexity of the translation between experimental models and humans. Alcohol metabolism in the liver depends on the amount of alcohol dehydrogenase present. This varies among humans and has genetic determinants.24 Alcohol absorption and metabolism are influenced by ingested food and gender. Alcohol is 3 times more slowly absorbed if there is food in the stomach and women consuming similar amounts of alcohol as men are more susceptible to brain or heart muscle damage.26-28 Body weight also critically influences alcohol effects. For example, a 70-kg man would have to consume 3 drinks of alcohol to reach a blood concentration of 0.10% (100 mg/dL). A 100-kg man would have to consume 5 drinks to reach the same blood concentration. However, these metabolic features are common to humans and variation among species would also probably be expected.

Effects of low to moderate doses of alcohol in experimental TBI

Bearing such concerns in mind, numerous basic science studies have sought to define the effect of alcohol on the outcomes of TBI in rats or swine to establish experimental models that can generate hypotheses to be further tested in humans. Although published reports seem in conflict on first reading, additional analysis suggests that exposure to low doses of alcohol exerts qualitatively different results in TBI models than exposure to high-dose alcohol. We will consider first the results of studies in which alcohol was administered orally or intragastrically by gavage or injected intraperitoneally at low to moderate doses (<1 g/kg or 100 mg/dL, approximately 0.1%) (Table 1). Behavioral tests for characterization of motor or cognitive deficits,29-31 histopathology testing of neuronal layers,32 and various physiologic parameters33,34 were used to determine the outcomes in animals after administration of alcohol and experimental TBI in comparison with their respective controls.

Tureci and colleagues demonstrated less vacuolar degeneration in the pyramidal cell layer in rats with TBI in which alcohol was administered at low to moderate doses, and concluded that alcohol can have a neuroprotective role.32 Low-dose alcohol was associated with marked attenuation of immediate postinjury hyperglycolysis in rats, with more normal glucose metabolism and less reduction of cerebral blood flow in the injury penumbra over the contusion site.34 Alcohol pretreatment lowered cytokine levels in the cortex, hippocampus, and hypothalamus of rats, although serum corticosterone levels were higher after TBI induction with a low to moderate dose of alcohol compared with controls with corticosterone only.33 Both lower cytokine levels and higher corticosterone levels might contribute to alcohol neuroprotection. Less impairment of motor and

### Abbreviations and Acronyms

- GCS = Glasgow Coma Score
- TBI = traumatic brain injury
- NMDar = N-methyl-D-aspartic acid receptors
cognitive functions was found in rats that had been administered low to moderate doses of alcohol after TBI generation. At least some investigations suggest that low to moderate doses of alcohol can be neuroprotective in experimental animal models of TBI.

Effects of high doses of alcohol in experimental TBI

In contrast to studies mentioned here, some TBI investigators have administered higher alcohol doses, ie, >3 g/kg body or 200 mg/dL by the same techniques, exceeding 0.2% blood levels (Table 2). Respiratory impairment is one of the most adverse effects associated with use of high-dose alcohol in swine. Zink and colleagues reported increased lactic acid in the brain and decreased organ blood flow in intoxicated swine. The same author separately reported multiple hemodynamic changes, including decreased mean arterial pressure and cerebral blood flow after administering high-dose alcohol. Increased brain edema and negative effects on neurobehavioral function have been described in TBI rats receiving higher doses of alcohol as opposed to TBI rats exposed without alcohol.

Exploring the apparent contrast between the effects of low- and high-dose alcohol on animal TBI, some researchers have employed more than 1 experimental group, comparing high-dose alcohol with low and/or moderate-dose alcohol along with control animals not receiving alcohol. Yamakami and colleagues demonstrated substantially increased mortality and markedly worsened neurologic deficits in the high-dose alcohol group compared with rats receiving low or moderate doses of alcohol. Gottesfeld and colleagues similarly reported that levels of interleukin-1β or tumor necrosis factor—α in the cortex, hippocampus, or hypothalamus varied, depending on whether the experimental rats received low- or high-dose alcohol.

Kelly and colleagues observed that TBI-injured rats receiving low- and moderate-dose alcohol had considerably less severe behavioral outcomes compared with either rats without alcohol or rats receiving high-dose alcohol.

POTENTIAL MECHANISMS OF ALCOHOL PROTECTION IN TBI

Although high-dose alcohol can worsen TBI, low or moderate doses of alcohol can be neuroprotective. Various mechanisms have been suggested for this neuroprotective effect, including inhibition of N-methyl-D-aspartic acid receptors (NMDAr) or sympathetic response. We will review the extant data in support of these theories.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Animal model</th>
<th>Main findings</th>
</tr>
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<tbody>
<tr>
<td>Zink</td>
<td>1995</td>
<td>Swine</td>
<td>Impairment in respiratory control following TBI</td>
</tr>
<tr>
<td>Zink</td>
<td>1999</td>
<td>Swine</td>
<td>Increased in concentration of brain and cerebral venous blood lactate</td>
</tr>
<tr>
<td>Zink</td>
<td>1993</td>
<td>Swine</td>
<td>Increased hemodynamic (decreased mean arterial and cerebral perfusion pressure) and respiratory depression</td>
</tr>
<tr>
<td>Katada</td>
<td>In press</td>
<td>Rat</td>
<td>Increased volume of cytotoxic brain edema after TBI</td>
</tr>
<tr>
<td>Yamakami</td>
<td>1995</td>
<td>Rat</td>
<td>Significantly increased mortality</td>
</tr>
</tbody>
</table>

TBI, traumatic brain injury.
**Blunting of NMDAr**

One of the most postulated mechanisms of alcohol neuroprotection is blunting of the NMDAr. NMDAr overactivation increases levels of extracellular excitatory amino acids, glutamate, and aspartate. A major release of excitatory neurotransmitters is common after TBI and is believed to be a proximate cause of a series of neurochemical sequelae of cortical injury.\(^{40-44}\) This chain reaction was demonstrated to promote neuronal cell death through calcium influx, which activates Ca\(^{2+}\)-dependent enzymes that cause mitochondrial lysis.\(^{45-47}\) There is also evidence that the neuronal cell death occurs through sodium influx, which promotes massive cellular swelling.\(^{48,49}\)

This neurochemical reaction has been successfully counteracted using competitive or noncompetitive antagonists targeting the binding sites of the NMDAr. Numerous basic science studies have demonstrated that the pharmacologic blockade of NMDAr improves brain metabolic status, attenuates cortical damage, and overall limits neurological dysfunction after TBI.\(^{41,50-54}\)

However, clinical trials of different competitive or non-competitive NMDAr antagonists\(^{55-58}\) have been uniformly disappointing. None of these trials has shown any benefit for NMDAr blockade in intoxicated TBI patients. The most commonly invoked reason for this failure was the poor pharmacokinetics of these drugs and poor design of the trials.\(^{59-61}\) NMDAr antagonists also have adverse effects, including increase in blood pressure, hallucinations, and catatonia.\(^{62}\) These effects are encountered mainly with nonselective NMDAr antagonists and limit the dose that can be used clinically. Hardingham and colleagues showed that synaptic and extrasynaptic NMDAr elicit opposing effects in hippocampal neuron cultures.\(^{63}\) Their study established that stimulation of synaptic NMDAr is antia apoptotic, but extrasynaptic NMDAr stimulation causes loss of mitochondrial membrane potential and neuronal death. Development of selective antagonists for extrasynaptic NMDAr could prove useful in TBI in the future.

More recently, Ikonomidou and Turski\(^{61}\) have offered another explanation for the failure of these clinical trials, introducing the concept of a short neuroprotective window. All of the benefits described in animal models of TBI were obtained when administration of the NMDAr antagonists was conducted before or immediately after the TBI. In fact, neuroprotection is lost when NMDAr antagonists were started 7 to 10 hours after TBI.\(^{52}\) Overactivation of NMDAr after TBI is short-lived (<1 hour) and followed by a more chronic upturn of receptor function that lasts >7 days.\(^{44,65}\) Ikonomidou and Turski\(^{61}\) suggested that the NMDAr are overactivated immediately after TBI in experimental models, but only for a short period of time. It would therefore seem that the ideal system to provide neuroprotection against NMDAr overactivation in intoxicated TBI patients would be to administer the antagonists before or immediately after the TBI, when the antagonists appear most efficacious in animal studies.\(^{64}\) This is especially true because some published experimental studies oppose the neuroprotection concept behind the NMDAr blockage. They actually demonstrate that synaptic transmission mediated by NMDAr is essential for neuronal survival and that administration of NMDAr antagonists during the critical period after TBI, when neurodegeneration occurs, exacerbates the neuronal damage.\(^{56,67}\) Similarly to the NMDAr antagonists, alcohol acts by inhibiting the NMDAr synaptic current.\(^{68-72}\)

This short therapeutic time window might explain the failure of clinical trials of NMDAr antagonists. Infusion of NMDAr antagonists was typically started within 8 to 12 hours after TBI in human trials and continued for 4 to 6 days after the initial injury. NMDAr blockade was achieved beyond the NMDAr blockade therapeutic window with subsequent impact on the neurological outcomes. In conclusion, the short-window of overactivation of NMDAr theoretically explains why low-dose alcohol inhibition of NMDAr in the initial period after TBI could be neuroprotective because the alcohol is metabolized quickly, allowing the NMDAr to return to its normal physiologic function. This same concept might also explain negative outcomes in TBI with high-dose alcohol, because of the more prolonged metabolism of higher alcohol levels, proportionally to ingested amounts, in which case prolonged inhibition of NMDAr would be detrimental.

Conclusions can be drawn from experimental studies of alcohol impact on NMDAr and the neurophysiology of brain injury, along with data derived from clinical trials of NMDAr blockade. An alternative mode of treatment might administer NMDAr antagonists only in the immediate 1-hour period after TBI to block the receptor only in the short window of overactivation of NMDAr. At the same time, consideration should be offered for the extrasynaptic NMDAr activation concept and other pitfalls associated with use of NMDAr antagonists before additional clinical trials should be restarted.

**Alcohol blunting of the adrenergic response in TBI**

The sympathetic nervous system is central to the stress response to injury. An initial surge in catecholamine levels is common after TBI, followed by a prolonged hyperadrenergic state.\(^{73-78}\) The response of circulating hormonal levels correlates proportionally with the neurological impairment reflected by the admission GCS or Injury Severity Score.\(^{74-76}\) In a clinical study, Hamill and colleagues found that patients with severe brain injury (GCS 3 to 8) had a...
5-fold increase in plasma norepinephrine and epinephrine levels after TBI. In addition, catecholamine levels predicted the neurological outcomes and recovery in these patients. Patients who had an unchanged neurological status 1 week after the injury consistently showed markedly elevated plasma norepinephrine levels. Woolf and colleagues found that 12 of 15 patients with twice-normal norepinephrine levels and severe brain injuries (GCS 3 to 6) either failed to improve neurologically or died, and that norepinephrine and epinephrine levels correlated with the length of hospitalization. In a different study, Woolf and colleagues compared polytrauma patients with and without brain injuries and found that circulating norepinephrine levels correlated with the severity of injury in patients with brain injury only.

Studies in mice have investigated the adrenergic contribution to the neurological changes that occur after TBI using β-blockers. Using micro-PET imaging, Ley and colleagues demonstrated improved cerebral perfusion and decreased cerebral hypoxia in mice treated with propranolol compared with a placebo group. In a similar animal study, nonselective β-blockers lessened the volume of brain edema compared with placebo. Improved outcomes have been also reported in retrospective clinical studies with the use of β-blockers in TBI, with greatest effect in elderly and more severely injured patients. These studies provide Level III evidence that β-blockers improve mortality in injured patients with TBI.

There is good evidence that alcohol intoxication blunts the sympathetic surge that is observed after TBI because increased alcohol levels are associated with decreased circulating norepinephrine and epinephrine response and improved GCS scores in patients with TBI. However, only retrospective studies have addressed the potential beneficial effect of sympathetic blockade in TBI. The potential benefits of β-blockers in the prevention of TBI complications and death could be better defined by prospective studies in the future.

CLINICAL STUDIES OF THE EFFECT OF ALCOHOL IN TBI

There has recently been increased interest in research on the effects of alcohol in specific TBI populations, driven by a combination of attractive basic science data, the failure of most clinical trials, and the contradictory results of retrospective studies of mortality in alcohol-intoxicated patients with multiple injuries with or without TBI. It is important to distinguish between studies that examined mortality in patients with or without TBI and other associated injuries and studies that were limited to patients with TBI with or without associated injuries.

When the study population comprised traumatized patients who did not necessarily have TBI, various researchers have demonstrated increased, decreased, or no difference in mortality in intoxicated patients admitted to the hospital. For example, Luna and colleagues found a 4-fold increase in mortality in intoxicated compared with unintoxicated motorcyclists. In addition, the protective effect of the helmet was lost in intoxicated patients. Similarly, in a more heterogeneous population with polytrauma resulting from motor-vehicle crashes, falls, or sports injuries, Pories and colleagues reported increased mortality in intoxicated patients. In contrast, some researchers reported decreased mortality among intoxicated patients with any type of injury, not necessarily TBI. Plurad and colleagues found decreased mortality in victims of motor-vehicle crashes with high-dose compared with low-dose alcohol. Other researchers have also reported decreased mortality after alcohol intoxication with various mechanisms of injury, such as assaults, burns, or stabbing, resulting in a high preponderance of blunt over penetrating injuries, and again without necessarily including TBI.

In the setting of some reports of increased mortality and some of decreased mortality in intoxicated trauma patients, it is important to recognize that many investigators have found no statistically significant differences in mortality of alcohol-intoxicated injured patients in either direction. These studies included patients with any type of injury and not necessarily with TBI. For example, Jurkovich and colleagues performed a subgroup analysis based on time of death, ie, in the field, trauma bay, within 24 hours of admission, or after longer hospitalization. Although there were no evidence that alcohol affected mortality in these groups of patients, subgroup analysis based on mechanism of injury, magnitude of hemodynamic or inflammatory alterations, or type of TBI could be more revealing.

In contrast with these studies of patients with any type of injury, some researchers have aimed to test mortality in a specific cohort of patients with TBI without or with other associated injuries. Studies restricted to TBI patients still demonstrate some inconsistencies, but might be more readily understandable (Table 3). One of the first studies of the association between alcohol and mortality in TBI was published in 2004 by Alexander and colleagues. This study found no impact of alcohol levels at admission on mortality. However, the small sample size of this study might have obscured a significant difference between the patient groups, if present. Tien and colleagues in 2006 were the first to report significant differences in mortality in TBI patients, depending on alcohol levels. In this seminal study, the authors divided the patients into 3 groups based on admission alcohol levels. These groups were no
alcohol (0 mg/dL), low to moderate alcohol (<230 mg/dL), and high alcohol (>230 mg/dL). The low to moderate alcohol group exhibited better survival than the no-alcohol group. In contrast, compared with the same no-alcohol reference group, the high alcohol group demonstrated worse survival rates. O’Phelan and colleagues reported similar findings in 2008 in a more diverse population, including patients with substance abuse and alcohol intoxication.99

Shandro and colleagues100 found no statistically significant difference in mortality among patient groups with TBI in 2009, but the data did demonstrate a clear trend toward lower mortality in patients with higher alcohol levels.100

Salim and colleagues17,101 recently published 2 other important studies, 1 using data from the National Trauma Data Bank, and the other focusing on patients from a major trauma center. In each case, alcohol-intoxicated patients, regardless of blood levels, were compared with patients who tested negative for alcohol. Each study found lower mortality in intoxicated patients with TBI.17,101

Influence of pre-TBI alcohol on neuropsychological testing

Besides mortality and morbidity, neuropsychological outcomes have also been investigated in patients with TBI and prior alcohol use. Patients with alcohol abuse and/or alcohol dependence were followed for different periods of time after TBI and neuropsychological/cognitive outcomes were compared with those of sober patients with TBI. Most researchers who have studied individuals with alcohol abuse and alcohol dependence before TBI have found inferior performance on neuropsychological/cognitive testing in alcohol-intoxicated patients with TBI.102-105 In contrast, Lange and colleagues106 reported that sober patients with TBI performed more poorly in neuropsychological/cognitive testing than intoxicated patients. A key difference is that Lange and colleagues enrolled only alcohol-intoxicated patients, regardless of blood levels, and compared them to sober patients who were included in the study regardless of blood alcohol levels.

Table 3. Clinical Studies of the Impact of Alcohol Intoxication on Outcomes of Subsequent Traumatic Brain Injury

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Patients included</th>
<th>Patients excluded</th>
<th>Patient groups</th>
<th>Mortality outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander97</td>
<td>2004</td>
<td>80 42</td>
<td>108 58</td>
<td>3 groups based on blood alcohol levels: 0 mg/dL; 1–100 mg/dL; &gt;100 mg/dL</td>
<td>No difference in mortality among the 3 groups of patients</td>
</tr>
<tr>
<td>Tien98</td>
<td>2006</td>
<td>3,675 89.7</td>
<td>424 10.3</td>
<td>3 groups based on blood alcohol levels: 0 mg/dL; 0–230 mg/dL; &gt;230 mg/dL</td>
<td>Increased mortality in the &gt;230 mg/dL group when compared with 0-mg/dL group; decreased mortality in the 0–230-mg/dL group when compared with 0-mg/dL group</td>
</tr>
<tr>
<td>O’Phelan99</td>
<td>2008</td>
<td>255 52.8</td>
<td>228 47.2</td>
<td>2 groups: alcohol-negative or positive*</td>
<td>Decreased mortality in the alcohol-positive group</td>
</tr>
<tr>
<td>Salim101</td>
<td>2009</td>
<td>482 47</td>
<td>543 53</td>
<td>2 groups: alcohol-negative or positive</td>
<td>Decreased mortality in the alcohol-positive group</td>
</tr>
<tr>
<td>Salim17</td>
<td>2009</td>
<td>38,019 52.6</td>
<td>34,275 47.4</td>
<td>2 groups: alcohol-negative or positive</td>
<td>Decreased mortality in the alcohol-positive group</td>
</tr>
<tr>
<td>Shandro100†</td>
<td>2009</td>
<td>836 54.6</td>
<td>693 45.4</td>
<td>3 groups based on based alcohol levels: 0.1–100 mg/dL; 101–230 mg/dL; &gt;230 mg/dL</td>
<td>No significant difference in mortality among these groups, but a clear trend toward lower mortality in 101–230-mg/dL and &gt;230-mg/dL groups</td>
</tr>
</tbody>
</table>

All studies had a retrospective design and used Abbreviated Injury Score of ≥3 for head to select for severe traumatic brain injury. The number of patients included represents the final population used in the analysis. In these studies, patients were excluded because of missing data on blood alcohol levels.

*In addition to alcohol intoxication, the patients enrolled in this study were under the influence of other various substances (eg, methamphetamine, cocaine, or marijuana).

†The study by Shandro and colleagues did not demonstrate a statistical significant difference between the different groups of patients but did show a trend toward lower mortality in patients with higher alcohol levels.
intoxicated patients at the time of injury and without any history of alcohol dependence. It is important to separate these types of patients into different groups based on the presence of alcohol abuse or dependence because their outcomes can be dissimilar. Whether alcohol intoxication at the time of injury can mitigate the neurological effects of subsequent TBI remains to be determined. In contrast, such neurologic sequelae can promote self-medication with alcohol in TBI patients. Such patients might need alternative strategies to ameliorate their TBI if alcohol cessation is to be achieved.

**LIMITATIONS OF CLINICAL STUDIES**

Understanding the limitations of the clinical studies that have investigated the effects of alcohol on mortality in TBI patients is important to design more effective research in the future. Such clinical studies are unavoidably retrospective because prospective trials offering alcohol to an intervention group would probably be unethical unless strong evidence can be developed first for a protective effect. The same guidelines for control of confounding variables should be considered for medications or other potential treatments. For example, future research designs should take into consideration the potential neuroprotective effect of β-blockers.

One discrepancy among extant clinical studies is the definition of the study groups. Some researchers have ascertained only the presence or absence of blood alcohol, and others have categorized patients based on the magnitude of their blood alcohol levels. Future studies should incorporate these considerations in their design for the same purpose as stated here.

Another concern about the inclusion criteria for many previous studies is that some patients did not have blood alcohol levels measured at admission and therefore were excluded from analysis in most studies. The selection bias introduced by the exclusion of this type of data would likely be eliminated by prospective measurements of blood alcohol levels in injured patients. Trauma centers that have incorporated routine alcohol determination in injured patients into routine screening guidelines would be able to perform such a research study without this particular type of bias.

It is also important to distinguish acute alcohol intoxication from chronic alcoholism. Chronic alcoholism is associated with immunosuppression and increased risk of infection, particularly pneumonia because of impairment of lung cytokine production. Chronic alcoholism might be an important factor in mortality and morbidity of patients with TBI, which should be considered in these types of research. Serum levels of γ-glutamyltransferase closely correlate with chronic alcohol consumption and can be useful in differentiating chronic alcoholism from the trauma victim with acute intoxication.

Most clinical studies on the effects of pre-existing alcohol on TBI have used mortality as the primary endpoint. Other outcomes variables, including intensive care unit and hospital length of stay, ventilator days, or complications, have also been considered. Unfortunately, no specific functional neurological outcomes were addressed in these studies. This represents another opportunity for further research.

Another important limitation of these studies is the lack of analysis based on specific types of injuries. Blunt or penetrating injuries might have different outcomes in terms of morbidity and mortality that could be specific to each type. It is probably also important to seek specific outcomes patterns based on the location of the injury, ie, frontal, temporal, or occipital lobes. In addition, interplay with other associated injuries can obscure the influence of alcohol on TBI and should be carefully tracked in future studies.

**Alcohol consumption after TBI**

Patterns of alcohol consumption after TBI have recently received considerably more attention in the literature. In general, after TBI, alcohol drinking varies over time. Early in the recovery period, alcohol use tends to decline. Twenty to eighty percent of patients with previous alcohol abuse problems tend to stop abusing alcohol for at least a short period of time after TBI. However, many of these patients who initially overcome alcohol abuse after TBI then relapse into the alcohol abuse patterns of their preinjury period. Heavy drinking actually increases with time after TBI. In addition, it appears that a history of alcohol drinking before injury is a strong predictor of heavy drinking after TBI. Not unexpectedly, patients with less education tend to have higher relapse drinking rates. In contrast, higher alcohol levels on admission also can predict a decrease in drinking after TBI. A more severe TBI, as defined by initial GCS, seems to also predict decreased drinking after TBI. The last 2 variables might actually be covariates because a higher alcohol level is associated with more severe injuries in trauma patients. These findings could be explained by the psychological effect of the injury or limited finances of these patients. In addition, more of the patients with initially lower GCS would seem likely to need placement in extended care facilities, where alcohol availability would be limited.

The period of time during which these patients abstain from alcohol is short, varying from 1 month to 1 year after TBI. Secondary prevention programs would probably have the greatest success when implemented during this
opportunity window, as described by Bombardier and colleagues, especially because during this period of time patients frequently contemplate changing their alcohol habits.

Consumption of alcohol after TBI is associated with several complications. Patients are at increased risk of recurrent TBI when returning to their preinjury alcohol habits. Continuation of alcohol drinking after TBI is also associated with more atrophy of the cerebral cortex, development of post-traumatic seizures, and deterioration of behavioral functioning. Overall, data suggest that secondary prevention of subsequent complications resulting either directly from recurrent TBI or from effects of alcohol on a previously injured cortex should be implemented early after TBI.

Considerable progress has been made to elucidate the role of alcohol in TBI by both experimental and clinical studies. That the resulting data are somewhat contradictory is probably not surprising, considering the complexity of the pathophysiologic response that accompanies TBI and any other associated injuries. Secondary prevention of alcohol abuse after TBI is as important as primary prevention and should be emphasized in the first month after the injury. There is a substantial need for additional clinical and experimental research with regard to the mechanisms responsible for the neurophysiology of TBI. For clinical studies in particular, a systematic approach might be beneficial in which details about possible confounders are taken into account. Potential mechanisms of alcohol effects on TBI, including blockage of NMDAr and sympathetic surge, need to be investigated in detail to be able to identify new opportunities for treatments to decrease mortality and morbidity in clinical settings. In the interim, screening for alcohol intake in trauma patients, good clinical care to prevent TBI, and subsequent counseling about the dangers of additional alcohol intake are valuable tools available to the practicing trauma surgeon today.

**Author Contributions**

Study conception and design: Opreanu, Basson
Acquisition of data: Opreanu, Kuhn, Basson
Analysis and interpretation of data: Opreanu, Kuhn, Basson
Drafting of manuscript: Opreanu, Kuhn, Basson
Critical revision: Opreanu, Kuhn, Basson

**REFERENCES**


