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Review

Ethanol and isolated traumatic brain injury

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ABSTRACT

The aim of this systematic review was to determine whether ethanol is neuroprotective or associated with adverse effects in the context of traumatic brain injury (TBI). Approximately 30–60% of TBI patients are intoxicated with ethanol at the time of injury. We performed a systematic review of the literature using a combination of keywords for ethanol and TBI. Manuscripts were included if the population studied was human subjects with isolated moderate to severe TBI, acute ethanol intoxication was studied as an exposure variable and mortality reported as an outcome. The included studies were assessed for heterogeneity. A meta-analysis was performed and the pooled odds ratio (OR) for the association between ethanol and in-hospital mortality reported. There were seven studies eligible for analysis. A statistically significant association favouring reduced mortality with ethanol intoxication was found (OR 0.78; 95% confidence interval 0.73–0.83). Heterogeneity among selected studies was not statistically significant ($p = 0.25$). Following isolated moderate-severe TBI, ethanol intoxication was associated with reduced in-hospital mortality. The retrospective nature of the studies, varying definitions of brain injury, degree of intoxication and presence of potential confounders limits our confidence in this conclusion. Further research is recommended to explore the potential use of ethanol as a therapeutic strategy following TBI.

Introduction

It is well established that ethanol intoxication increases the risk of sustaining a traumatic brain injury (TBI) [1,2]. However, once an injury has occurred, reports are divided on whether ethanol exposure is beneficial or detrimental to outcomes.

In various animal trials, ethanol has been shown to be neurotoxic in conjunction with TBI, especially at high levels. In addition, ethanol has been shown to be associated with respiratory depression, apnoea and hypoxia [3–5], which may contribute to secondary insults following TBI. Raised intracranial pressures and acidaemia have also been reported as potential adverse effects of ethanol exposure [6–8].

Beneficial effects of ethanol have been previously postulated by various mechanisms. Low dose ethanol inhibition of N-methyl-D-aspartate (NMDA) receptors could be neuroprotective as potassium and calcium influx through NMDA receptor channels following TBI leads to neuronal excitotoxicity [9–13]. The systemic catecholamine surge following TBI which is associated with worse outcomes has been shown to be moderated by ethanol [14–16]. Aquaporin-4, implicated in the development of cerebral oedema following TBI, has also been shown to be suppressed by ethanol [17]. A further neuroprotective mechanism may be the reduction of hyperglycolysis associated with ethanol exposure following TBI [10]. Ethanol may lead to a decrease in body temperature and this may have a neuroprotective effect [18]. Finally, ethanol decreases conscious state and, thus, patients with mild head injury may present as deeply comatose and meet the criteria for severe TBI where assessment of TBI severity is made by clinical state rather than anatomical or CT scan features.

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Previous reviews analysing human studies on the topic have commented on the contradictory nature of conclusions [19,20]. The inclusion of all major trauma patients with multiple complex injuries may have contributed to the heterogeneity among studies. In this systematic review, we aimed to include studies of patients with isolated traumatic brain injury (iTBI). The exposure variable of interest was ethanol, regardless of reported level, while the outcome of interest was mortality, regardless of reported time.

Materials and methods

Information sources

Authors searched for English language articles in MEDLINE, PubMed, Cochrane library, Scopus, EMBASE, CINAHL, Expanded Academic ASAP, PsycINFO and International Pharmaceutical Abstracts for manuscripts included until March 2014. A combination of keywords and subject headings were used: "ethanol," "alcohol," "blood alcohol," "alcohol intoxication," "brain injury," "acute brain injury," "traumatic brain injury," and "TBI". Truncation was used in applicable databases. Keywords were matched to subject headings to expand the scope of the search. Reference lists of identified relevant studies were manually searched for further studies.

Study selection

Studies were included if they addressed isolated moderate–severe TBI among human subjects in the presence of acute ethanol intoxication and included mortality as an outcome. Specific exclusion criteria were studies that examined chronic alcohol ingestion, addressed mild TBI, included patients with polytrauma or other organ injury, assessed the effect of alcohol intoxication and addiction as an outcome measure following TBI, addressed neuropsychological outcome as a primary outcome, paediatric populations, non-English language, and case reports and letters. No randomized control trials on the topic were available. Principally, retrospective cohort studies were eligible for inclusion. The study characteristics are described in Table 1.

Data collection

We extracted demographic data on included patients and injury characteristics (Table 2). Definitions for isolated traumatic brain injury were varied and were also collected [21]. Definitions of TBI all incorporated the abbreviated injury scale (AIS), however, they varied on whether TBI was defined exclusively by head AIS or by whole body AIS. The comparison group for all studies was based on historical data extracted by retrospective reviews or chart or registry data. As a result, the framework for quality assessment described by Gilbert et al. was used (Table 3) [22].

Statistical analyses

The odds ratios (OR) for dichotomous outcomes from each study were pooled using the DerSimonian–Laird random effects model [23]. An OR value of greater than 1.00 indicated an association of ethanol and increased mortality and values below 1.00 indicated that ethanol was associated with improved outcomes. Heterogeneity was assessed using the chi-squared test and was reported on a Forest plot to assess whether the observed differences in results were compatible with chance alone. A low p value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance).

Table 1
Study characteristics including methodology, patient groups and traumatic brain injury definitions for inclusion in the meta-analysis

Author (year)	Methodology	Patient groups	Definition of TBI for study inclusion
Tien (2006) [27]	Retrospective analysis of trauma registry	Three groups based on BAL: 0 mg/dL, 1–230 mg/dL, >230 mg/dL	Head AIS of 4–5
Salim (2009) [35]	Retrospective analysis of trauma registry	Two groups: ethanol positive or negative	Head AIS $\geqslant$ 3, all other body regions AIS $\leqslant$ 3
Shandro (2009) [36]	Prospective observational cohort at 18 Level I trauma centres and 51 nontrauma centres	Four groups based on BAL: 0 mg/dL, 0–100 mg/dL, 100–230 mg/dL, $\geqslant$230 mg/dL	Head AIS $\geqslant$ 3
Talving (2010) [32]	Prospective observational cohort at a trauma centre	Two groups based on BAL: 0–80 mg/dL, >80 mg/dL	Head AIS $\geqslant$ 3, extracranial AIS $\leqslant$ 3
Berry (2010) [33]	Retrospective analysis of trauma databases from five Level I and eight Level II trauma centres	Two groups: ethanol positive or negative	Head AIS $\geqslant$ 3, all other body regions AIS $\leqslant$ 3
Berry (2011) [31]	Retrospective analysis of trauma databases from five Level I and eight Level II trauma centres	Four groups based on BAL: 0 mg/dL, 0–100 mg/dL, 100–230 mg/dL, $\geqslant$230 mg/dL	Head AIS $\geqslant$ 3, all other body regions AIS $\leqslant$ 3
Lustenberger (2011) [30]	Retrospective analysis of trauma database	Two groups: ethanol positive or negative	Head AIS $\geqslant$ 3, all other body regions AIS $\leqslant$ 3

AIS = abbreviated injury scale, BAL = blood alcohol level, TBI = traumatic brain injury.

Results

Of the 7962 articles initially identified, 256 were indicated for abstract review after title screening and then 40 were indicated for full text review after abstract review. After full text review a further 29 were excluded. A further three studies were excluded due to absolute mortality data not being reported [1,24,25]. One further study was excluded for not independently testing ethanol, instead a total toxicology report was performed and analysis done accordingly [26]. A total of seven studies were included in the review (Fig. 1).

The meta-analysis of the seven studies found a significant association between ethanol exposure and decreased in-hospital mortality (pooled OR 0.78; 95% confidence interval [CI] 0.73–0.83; Table 4). Any heterogeneity among studies was not statistically significant ($p = 0.252$; Fig. 2).

Definitions of TBI

In the earlier literature there is considerable variation in the definition of TBI. Injury consistent with a diagnosis of TBI and the initial Glasgow coma scale (GCS) have been used to define TBI with GCS 9–12 for moderate TBI and GCS < 9 for severe TBI [24–26]. More recently, Tien et al. incorporated the AIS as a measure of severity after TBI [27]. The AIS was developed by the Association for the Advancement of Automotive Medicine as a method of comparing the severity of injury among trauma patients