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Alcohol intoxication and post-burn complications

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1. ABSTRACT

Results from the studies discussed in this article suggest that alcohol (EtOH) intoxication is a major public health problem. While the effects of injury and EtOH intoxication independent of each other have been studied in detail, only few studies have evaluated the effect of a combined insult of EtOH intoxication and burn injury on host defense. An analysis of the studies conducted in the clinical setting suggests that intoxicated patients require frequent intubations, experience delayed wound healing and longer hospital stay. Furthermore, there is a greater risk of mortality in these patients compared to those who sustained injuries in the absence of EtOH intoxication. On the other hand, there are a few studies that do not support this notion. The results obtained in experimental models clearly suggest that acute EtOH intoxication before burn injury impairs host defense and increases susceptibility to infection. Additionally, experimental data from our laboratory also indicate that EtOH intoxication before burn injury suppresses intestinal immune defense, impairs gut barrier functions and increases bacterial growth. This results in increased bacterial translocation in EtOH and burn injury. In addition, a decrease in cardiac function is also reported following a combined insult of EtOH intoxication and burn injury. Altogether, these findings suggest that EtOH intoxication before burn injury diminishes host resistance resulting in increased susceptibility to infection. Moreover, the findings of a higher incidence of infectious complications in burn and trauma patients who sustained injury in the presence of EtOH compared to those in its absence suggest that EtOH intoxication at the time of injury is a risk factor. Therefore blood EtOH should be monitored in burn/trauma patients at the time of admission in the emergency room.

2. INTRODUCTION

Nearly one million burn injuries are reported every year within United States (www.ameriburn.org). Studies have shown that the post-injury pathogenesis is a complex and the outcome of the patients is influenced by multiple factors including age, therapeutic interventions, preclinical conditions, as well as the socio-economic background such as alcoholism and drug abuse. In this article, we will review studies dealing with the influence of alcohol (EtOH) intoxication on the epidemiology of burn and trauma injuries. In addition, findings obtained in rodent models of acute EtOH intoxication and burn injury are discussed.

3. EPIDEMIOLOGY OF ETOH INTOXICATION AND BURN/TRAUMA

More than 50% of burn patients are found positive for blood EtOH at the time of hospital admission (1-7). Furthermore, EtOH-related motor vehicle crashes continue to be a major public health problem (2, 7-9). Domestic violence involves EtOH intoxication in 70% of cases and 65% of gun shot wound victims are legally intoxicated at the time of injury (8). While these reports indicate a significant association between EtOH intoxication and burn/trauma, there are only few studies in the literature that has evaluated the role of EtOH intoxication in post injury pathogenesis. The findings from these studies suggest that patients who consumed EtOH prior to burn injury require longer hospital stay, exhibit higher rates of infection and are more likely to die than the patients who sustained burn injury in the absence of EtOH (2, 7, 8). In a recent study, McGwin *et al.* (6) have shown that half of the burn victims aged 18 years and older are intoxicated at the time of hospital admission. In a previous study, Haum *et al.*(10) enrolled 225 patients with nearly similar extent of total body surface area burn injury. Of the 225 patients, 70 were positive for blood EtOH on admission. These patients had significantly higher deaths (31.5%) compared to burn patients who were negative for blood EtOH (18.1%) at the time of hospital admission. Similarly in another study, Jones *et al.* (3) concluded that the intoxicated patients required significantly more intravenous antibiotics and longer hospitalizations. Furthermore, these authors noted that the intoxicated patients not only had significantly higher mortality (46%) compared to burn patients who were not intoxicated (13%) at the time of injury but these patients died of smaller burns (3). In yet another retrospective analysis, Grobmyer *et al.* (11) found that hypotension, and pneumonia were more common in the intoxicated group. They also had more intensive care unit admissions, ventilator days, operations, transfusions, and total hospital days. However, mortality was lower in intoxicated patients (7.1%) than patients in the control group (10.9%). While the studies performed by McGill *et al.* (5) support the suggestion that burn patients who sustained injury under the influence of EtOH exhibits higher mortality compared to the patients who have not consumed EtOH prior to injury.

With regard to other traumatic injuries, Rivara *et al.* (12) enrolled 2650 trauma patients aged 18 years or older admitted within 24 hours of injury. Of these 1250 (47%) were found positive for blood EtOH in the range of 10-552 mg/dL. Thal *et al.* (13) suggested that patients who consume EtOH before injury have higher incidence of shock, severity of injury and mortality. Gentilello *et al.* (14) enrolled 365 patients with penetrating abdominal trauma to determine the impact of acute versus chronic EtOH intoxication on post trauma complications. The results from this study suggested that acute rather than chronic abuse accounted for septic complications after trauma. In contrast, Jurkovitch *et al.* (15) concluded that chronic and not acute EtOH intoxication influences the outcome from trauma. Ward *et al.* (16) on the other hand did not establish the relationship between EtOH intoxication and injury complications. Rather their findings indicated that mortality was significantly lower in patients who were positive for blood EtOH level compared to those who have not consumed EtOH prior to injury. Despite the negative findings, Cornwell *et al.* (17) concluded that the EtOH intoxication remains the major co-morbid factor in trauma and thus should be considered as a risk factor in over all evaluation of trauma patients.

Altogether, these findings indicate that EtOH intoxication has significant impact on the epidemiology of injury. Whether EtOH intoxication influences post injury pathogenesis remains inconclusive, and thus more studies are needed to determine the role of EtOH intoxication in post injury pathogenesis. These studies are important particularly in view of the findings of higher incidence of infections and longer hospital stay of burn and trauma patients who sustain injury in the presence of EtOH compared to those in the absence of EtOH. Furthermore, studies are also needed to examine the actions of a single (acute) or binge EtOH intoxication as opposed to chronic EtOH abuse in dealing with acutely injured patients. This distinction becomes particularly important in burn and trauma patients as a significant population of these patients is acutely intoxicated (2, 5-8).

4. ETOH INTOXICATION AND POST-BURN COMPLICATIONS

4.1. Immune response

Several studies have shown that burn injury regardless of the prior EtOH intoxication result in a cascade of inflammatory response characterized by overwhelming production of tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-10 and prostaglandin E_2 (PGE_2) (7, 8, 18, 19). The other functions of the immune system, such as the capacity of macrophage to present antigen, ability of T cell to recognize antigen, T cell proliferation, IL-2 production and IL-2 receptor expression are substantially suppressed (7, 8, 18-23). The decrease in macrophage ability to present antigen, or T cell antigen recognition, activation, proliferation and IL-2 production could potentially contribute to a suppression of immunity during burn and trauma. This results in a decrease in host resistance and increased susceptibility to infection. Although burn-mediated initial release of cytokines or inflammatory mediators is the normal host response to injury, however if it remained unchecked, can lead to

Table 1. Impact of EtOH intoxication on immune status after burn injury

Relative to Burn or EtOH, Burn + EtOH exhibits	
Decreased delayed type hypersensitivity.	
Decreased splenic T cell:	
	Proliferation
	IL-2 production
	IFN-gamma production
Decreased intestinal T cell:	
	Proliferation
	IL-2 production
	IFN-gamma production
Increased intestinal permeability.	
Increased gut bacterial translocation.	
Increased susceptibility to infection.	

multiple organ dysfunction and multiple organ failure, which is the major cause of deaths in injured patients.

Similarly, EtOH abuse independent of burn injury is also associated with a decrease in macrophage antigen presenting ability, T cell proliferation and IL-2 production (24-27). In addition, a loss of immune cells from lymphoid organs is also reported in animals fed on EtOH (28, 29). The most destructive complication of EtOH abuse is the liver disease and liver failure. EtOH consumption enhances the influx of endotoxin from the gut into the circulation. As a result, Kupffer cells are primed or activated for enhanced production of reactive oxygen species, cytolytic proteases and proinflammatory cytokines and chemokines (30). Excessive production of these biologically active substances during EtOH consumption is expected to contribute to the pathogenesis of alcoholic liver disease. Altogether, EtOH, when abused chronically, has many deleterious effects on various organ functions and, indeed, the literature is replete with both clinical and experimental studies on the biologic actions of chronic EtOH intoxication. In contrast, there are relatively few studies that have specifically examined the actions of a single (acute) or binge EtOH intoxication especially in dealing with patients with acute illness.

In recent years, efforts have been directed to evaluate the impact of a combined insult of EtOH intoxication and burn injury on host defense (1, 2, 7). The findings from these ongoing studies suggest that acute EtOH intoxication before burn injury impaired delayed type hypersensitivity, produced a greater suppression of mitogen-induced splenic-lymphocyte proliferation, serum immunoglobulin levels and neutrophil chemotaxis (Table 1; (1, 2, 7). Furthermore, results from these studies also indicate that acute EtOH intoxication before burn injury enhances susceptibility to bacterial infection (31). These studies further add that macrophage-derived inflammatory mediators such as IL-6 play a role in decreased host resistance. In addition, there are evidences that corticosterone (CORT; the end glucocorticoids product of HPA-axis in rodents and an equivalent to cortisol in human), levels in circulation following EtOH intoxication and burn also play a role in shaping the immune response (2, 7).

Kawakami *et al.* (32) have shown that while the ingestion of a single dose of EtOH alone does not elevate CORT levels, a similar dose of EtOH given before burn injury augmented the serum CORT levels. Consistent with these studies, our recent findings suggest that a combined insult of EtOH intoxication and burn injury heightens the releases of CORT which in turn causes mesenteric lymph nodes (MLN) T cell suppression (33). In contrast, Faunce *et al.* (34) have shown a somewhat protective role of glucocorticoids following a combined insult of EtOH intoxication and burn injury. These authors (34) observed that while the individual insult of EtOH intoxication and burn injury results in increased CORT levels, a combination of the two insults (i.e., EtOH intoxication and burn injury) caused a decrease in CORT levels. They also showed that treatment of animals with CORT prevented the splenic T cell suppression following EtOH and burn injury. In many previous studies, elevated levels of CORT were shown to suppress both macrophage and T cell functions including IL-2 and IFN-gamma production (2, 7, 35, 36). Elevation in CORT levels following EtOH intoxication or injury is correlated with diminished macrophage and T cell functions (37-39). Furthermore, studies have also shown a direct relationship between elevated CORT levels and the depletion of T cells from thymus, spleen and intestinal lymphoid organs, mesenteric lymph nodes and Peyer's patches (28). Similarly a role of CORT in increased apoptosis following burn injury is supported in a previous study (40). In our study, we have not observed T cell apoptosis following a combined insult of EtOH intoxication and burn injury (33). Rather, our results indicate that inhibition of p-38 and ERK-1/2 is likely the component of T cell signaling cascade which plays a role in CORT-mediated T cell suppression following a combined insult of EtOH intoxication and burn injury (33). Although a definitive cause for the observed differences between our (33) and the study by Faunce *et al.* (34) is not known, factors such as the degree of burn or route of EtOH administration are likely to contribute to the observed differences in our results. In this regards, Faunce *et al.* (34) utilized a mouse model of 15% burn and intra-peritoneal EtOH injection, while in our studies rats were orally gavaged with EtOH and received a 25% burn injury (33). Altogether, these findings suggest that CORT levels tightly control the immune cell functions. Thus, any change in CORT levels including low or high is likely to affect the immune response.

4.2. Intestinal bacterial translocation

Intestinal bacteria are considered as the source of infection in many disease and injury conditions such as burn and trauma. Findings from several previous studies have shown that burn injury results in bacterial translocation in the first few days after injury (41-47). However, this process prolongs if the burn injury is superimposed with additional stress factors such as burn wound sepsis, smoke inhalation, manipulation of intestinal flora, fluid resuscitation and endotoxin challenge (1, 46, 48-53). Similarly, EtOH consumption independent of burn is also associated with an increase in bacterial translocation (39, 54-56). Few studies have determined bacterial translocation in the event the two insults, EtOH intoxication and burn, combined together. In one such attempt by Napolitano *et al.* (57), rats were fed on EtOH for 14 days and then given a 30% total body surface area burn injury. Bacterial translocation was determined four

days after burn injury. Results from this study show that rats receiving combined insult of EtOH and burn injury exhibit significant increase in bacterial translocation compared to the rats receiving either EtOH intoxication and burn injury alone (57). In consistent with these findings, results obtained in our laboratory showed that EtOH intoxication four hours before burn injury significantly increases bacterial translocation (58, 59). Thus EtOH intoxication before injury may have a synergistic affect on bacterial translocation. While the mechanism by which EtOH intoxication combined with burn injury increases bacterial translocation remains to be established, recently we examined the intestinal immunity and barrier function.

Intestinal immune cells are primarily distributed in four major lymphoid organs 1) Peyer's patches, 2) lymphoid cells of the lamina propria, 3) intraepithelial lymphocytes, and 4) mesenteric lymph nodes. Peyer's patches are small opaque pouches scattered throughout the small intestine. They contain T and B cells, dendritic cells and macrophages. In addition PP have specialized epithelial cells called "M" cells. M cells are considered the gateway for entry of enteric bacteria and other luminal antigens (60, 61). M cells are highly selective and do not allow entry of microbes under normal conditions. However, their unique glycosylation and adhesion-molecule patterns can be utilized by many microbes (60-63) such as *S. typhimurium* which can trigger massive cytoskeletal rearrangement of M cells, promoting its engulfment (61, 63). The role for M cells in subsequent process of bacterial translocation and in the development of immune response is not clearly defined. However, pathogens that cross gut epithelial barrier through M cells directly encounter macrophage and dendritic cells, which are present in intraepithelial pockets under M cells. Thus both dendritic cells and macrophages are likely to play a role in bacterial transport from gut to the MLN and from MLN to the systemic circulation. In addition, the second major interface for absorption of soluble antigens from the lumen of the gastrointestinal tract is a columnar epithelial cell layer that contains large number of T cells commonly called intraepithelial (IE) lymphocytes. The majority of IE lymphocytes are T cell, with an approximately equal frequency of $CD3^+$ cells expressing gamma/delta or alpha/beta TCR heterodimeric chains. Both gamma/delta and alpha/beta T cells are helpful in the defense against the initial phase of bacterial translocation during the passage of bacteria from the intestinal lumen across the mucosal epithelium to the lamina propria. Lamina propria T cells are primarily $CD4^+$ cells which express alpha/beta TCR. A few indigenous bacteria continuously translocate to MLN, but because of intact PP and MLN immune cell functions, these bacteria do not survive and MLN from healthy animals remain relatively sterile. More recently, we examined whether EtOH intoxication before burn injury modulates intestinal immune defense. The findings from these studies (1, 33, 58, 59, 64) suggest that acute EtOH intoxication before burn injury results in a significant suppression in intestinal lymphoid organs PP and MLN T cell proliferation, and IL-2 production. Our results as summarized in Table 1 suggest that although there was a decrease in proliferation of PP and MLN T cells following burn injury alone, the suppression was greater in the group of animals receiving combined insult of EtOH and burn injuries (1, 33, 58, 59, 64). The suppression of T cell proliferation was accompanied by a significant decrease in IFN-? production. Furthermore, we found that depletion of T cells in healthy rats resulted in increased bacterial accumulation in MLN. Similar depletion of T cells in EtOH and burn injured rats further enhanced bacterial accumulation in MLN and in other distant organs including spleen and blood (58). These results support earlier studies by Sibley and Jerrells (65) in which they have shown that the loss of lymphoid cells after chronic EtOH abuse diminishes host resistance to enteric pathogens. Owens and Berg (66) noted spontaneous gut bacterial translocation to MLN, spleen and liver in athymic (nu/nu) mice, whereas no translocation was noticed in heterozygous (nu/+) or nude (+/+) mice grafted with thymus. Furthermore, findings from multiple studies have shown that depletion of $CD4^+$ and $CD8^+$ T cells resulted in increased bacterial translocation (58, 67). On the other hand the adoptive transfer of T cells provides protection against bacterial infections (67-69). Together, these findings support the suggestion that T cell-mediated immunity is critical in the defense against enteric bacteria.

In addition to altered intestinal T cell function, findings from our laboratory also suggest that the combined insult of EtOH intoxication and burn injury increases intestinal permeability. We found that the transfer of lactulose and mannitol from the intestine into circulation was several fold higher in EtOH and burn injured rats as compared to that observed in rats receiving either burn or sham injury alone (58, 59). Furthermore, lactulose and mannitol transfer occurs in EtOH and burn injured rats as early as 30 min after infusion as compared to burn alone group in which the transfer was evident only at end of the experimental procedure (90 min). This observation supports the notion that damage in EtOH and burn injured rats is more severe compared to the group receiving burn injury in the absence of EtOH. There was no demonstrable change in the morphology of intestine following EtOH and burn injury (58, 70). This is in contrast to a previous study in which, Napolitano *et al.* (57) have shown intestinal damage in rats receiving combined EtOH and burn injury. The differences in these findings could be due to the fact that rats in our studies received single dose of EtOH four hours before burn injury, whereas rats were gavaged daily for 14 days before burn injury in the studies reported by Napolitano *et al.* (57). While these finding suggest that alterations in intestinal immunity and barrier function may contribute to increased bacterial translocation following EtOH intoxication and burn injury, the mechanism for impaired intestinal immunity and barrier function following a combined insult of EtOH intoxication and burn injury remains to be established.

4.3. Cardiac function

There are two phases of cardiovascular response to burn injury (71, 72). The first or initial hypovolemic phase immediately follows the injury and is characterized by decreased blood flow to tissues and organs. This initial phase is followed by a hypermetabolic phase and is characterized by increased blood flow to the tissues and organs. Lorente *et al.* (71) found that burn patients have a hemodynamic profile similar to that of other trauma

patients. They observed that burn injury results in marked systemic and pulmonary vasoconstriction and low oxygen delivery and consumption. Their findings further suggested that as compared to survivors, non-survivors showed more systemic acidosis, lower cardiac index, more systemic hypotension and pulmonary hypertension, higher right and left filling pressures, lower oxygen delivery and consumption, higher oxygen extraction and higher pulmonary and systemic vascular resistance index. Similarly, in sheep model of combined burn (40% TBSA) and smoke inhalation, Sakurai *et al.* showed a biphasic hemodynamic response (72). In addition to the biphasic response, many studies have shown a decrease in blood flow to ileum, colon, pancreas and spleen following burn injury (72-75). These findings further indicate that the recovery from initial low perfusion state in these organs was considerably delayed. Furthermore, hemodynamic response to burn injury was found to be dependent on the size of burn area. In this regard, Carter *et al.* (73) did not observe differences in intestinal and hepatic blood flow after 20 % TBSA burn injury. Similarly studies of Ferguson *et al.* (76) did not show significant differences in liver and intestinal blood flow following burn injury. With regard to EtOH intoxication, studies have shown that both acute and chronic EtOH intoxication result in altered hemodynamic responses following injury (77-81). In our study, we did not observe a significant effect of burn injury on hemodynamic responses. In contrast hemodynamic responses were significantly altered when burn injury was combined with prior EtOH intoxication (82). These results support previous findings of Carter el al. (73) suggesting that mild burn injury may not produce hemodynamic alterations. However, if the mild injury is superimposed with additional stress factors, it produces alterations in cardiac functions and organ blood flow similar to those observed in experimental models of severe injury (83). We observed that cardiac output and blood flow in the liver and small intestine were significantly lower in EtOH and burn-injured rats compared with sham-injured rats and rats subjected to burn injury in the absence of prior EtOH ingestion. Similar to cardiac output and blood flow, oxygen delivery was significantly lower in liver and small intestine after EtOH and burn injury compared to rats receiving either insult alone. In contrast, oxygen extraction and consumption was significantly increased in both the organs. The deficit in oxygen delivery in the face of increased oxygen extraction and consumption are likely to add to hypoxic insult to liver and intestine. Several studies have shown that the post-ischemic gut creates an inflammatory environment that provokes multiple organ failure (74, 79, 84-86). Wang *et al.* (87) have shown that depressed hemodynamics and blood flow result in development of the immunosuppressive responses observed following trauma hemorrhage. Furthermore, the intestinal hypoperfusion following burn injury may lead to increased permeability and bacterial translocation (75, 86-88). In conclusion, our results indicate that a combined insult of EtOH and burn injury causes a decrease in blood flow and oxygen delivery to liver and intestine. Such decreases in blood flow and oxygen delivery may cause hypoxic insult to liver and intestine. While a hypoxic insult to liver would result in release of pro-inflammatory mediators, a similar insult to intestine will perturb both intestinal immune cell and barrier functions. Thus, results from these studies suggest that reduced splanchnic blood flow and oxygen delivery may contribute to impaired intestinal immune and barrier function following EtOH and burn injury.

5. CONCLUSION AND FUTURE RECOMMENDATIONS

Altogether, these studies suggest that EtOH intoxication has significant impact on the epidemiology of injury. However, whether EtOH intoxication influences post injury pathogenesis remains inconclusive, and therefore more studies are needed to determine the role of EtOH intoxication in post injury pathogenesis. Results obtained from the experimental studies suggest that acute EtOH intoxication prior to burn injury results in greater decrease in host defense. These studies further suggest that EtOH intoxication before burn injury impairs intestinal immune and barrier functions leading to increased intestinal bacterial translocation. In addition, a decrease in cardiac function is also reported following a combined insult of EtOH intoxication and burn injury. Altogether, these findings suggest that EtOH intoxication before burn injury diminishes host resistance resulting in increased susceptibility to infection. One potential cause for the conflicting reports from the patient studies could be due to the fact that patient studies were performed in more of a heterogeneous population. It is likely that the factors such as age, gender preclinical manifestation and triage criteria may have may have confounded the impact of EtOH intoxication in those studies. Therefore, more planned studies are needed to determine the role of EtOH in the clinical setting. These studies should be performed by enrolling patients of similar age and injury. Furthermore, studies both in clinical and experimental settings should also be planned to evaluate if EtOH intoxication influences the outcome in less severely injured patients. These studies would help in designing more specific therapeutic interventions in the treatment of burn and trauma patients who sustained injuries under the influence of EtOH intoxication.

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