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Substance Use and the Systemic Inflammatory Response Syndrome (SIRS) Following Trauma

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ABSTRACT

The purpose of this research was to evaluate the effect of substance use on the occurrence of systemic inflammatory response syndrome (SIRS) and severity following trauma. A total of 600 charts from a level 1 trauma center were screened (N = 246). Patients positive for ethyl alcohol had more occurrences of SIRS ($P = .005$) and more severe SIRS than other substance users ($P = .0008$). Patients positive for cannabis had less severe SIRS than other substance users ($P = .02$). Substance users could be at increased risk for poor SIRS-related outcomes (sepsis, organ failure) following trauma. Clinicians can use this information to identify high-risk patients early and tailor treatment strategies.

KEY WORDS

Ethanol, Cannabis, Inflammation, Trauma, Wounds and Injuries

Trauma, defined as acute, life-threatening injuries, is the leading cause of morbidity and mortality for persons between 15 and 44 years of age and accounts for more years of potential life lost than both heart disease and cancer.[1] In 2008, more than 13 million adults aged 20 to 49 years were injured, and nearly 87,000 were killed.[2]

Substance use is a common precursor to trauma[3] and has been positively correlated to increased infection and mortality following trauma.[4,5] Greater than two-thirds of patients injured in motor vehicle crashes have tested positive for single or multiple substances.[6] Testing trauma patients for substance use on admission to the hospital is recommended by the American Medical Association.[7] A recent survey showed that 75% of trauma surgeons comply with this recommendation.[8] Despite this availability of screening data, the influence of substance use on systemic inflammatory response syndrome (SIRS) following trauma is under-reported in the literature.

Systemic inflammatory response syndrome is a severe proinflammatory response that can develop within minutes of trauma.[9] A balanced systemic inflammatory response aids in recovery and maintains homeostasis.[10] However, a severely imbalanced response in either direction (increased or decreased) has been associated with poor outcomes. Increases in SIRS severity have been correlated with multiple organ failure. This response can also trigger a severe compensatory anti-inflammatory response known as CARS.[11-14] It can result in immune suppression with increased vulnerability to infection and sepsis.[12-14] Similarly, preexisting immune suppression prior to trauma can result in decreased SIRS severity, which can also increase the risk for infection and sepsis.

Importantly, trauma morbidity and mortality following hospital admission have been linked to poor outcomes that originate from SIRS, including infection, sepsis, and multiple organ failure.[9,14] These outcomes have been reported to have mortality rates as high as 80%.[14]

Evidence supports a potential association between substance use and SIRS following trauma, but there is a paucity of data that show direct comparisons between these variables. Existing comparisons between inflammatory biomarkers and substance use have shown alterations in the inflammatory response following trauma.[15-17] The purpose of this research was to evaluate the effect of substance use on SIRS occurrence and severity following trauma.

METHODS

A retrospective chart review was conducted of patients seen between 1998 and 2007 at a level 1 trauma center in the southeastern United States. This trauma center receives approximately 1400 trauma patients from a 2-state regional catchment area annually. All charts were identified from the trauma registry database. A trauma registry database is a requirement of all designated trauma centers and contains demographic and injury-related data on patients evaluated at these institutions.[18]

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Inclusion criteria were (1) age between 18 and 44 years, based on age ranges in the Centers for Disease Control Web-based injury statistics system[1]; (2) moderate to severe trauma defined by an injury severity score (ISS) 15 or more[19]; and admission to the intensive care unit (ICU) for 24 hours or more. Exclusion criteria were (1) treatment with blood or blood products; (2) presence of spinal cord injury; (3) history of comorbidities with potential to affect immune function and/or inflammatory response such as autoimmune diseases, cancer, HIV/AIDS, and/or history of organ transplant[20]; (4) regular use of nonsteriodal anti-inflammatory drugs; and/or (5) missing data associated with primary study variables. Permission to conduct this study was obtained from the local institutional review board.

The occurrence and severity of SIRS were assessed on admission to the ICU using the SIRS score.[21] The SIRS score incorporates 4 criteria: (1) temperature greater than 38°C or less 36°C; (2) heart rate greater than 90 beats per minute; (3) respiratory rate greater than 20 per minute (or $PaCO_2$ >32 mm/Hg); (4) white blood cell count greater than 12 000 or less than 4000 cells/dL. One point was assigned for each criterion that was met. Possible scores ranged from 0 to 4. A score of 0 or 1 defined "No" SIRS occurrence. A score of 2, 3, or 4 defined "Yes" SIRS occurrence. A score of 2 was defined as "mild" severity, 3 was "moderate," and 4 was "severe" SIRS. Data were also collected for complications, defined as "yes/no" for documentation of the following outcomes: died, infection, sepsis, and organ failure, including acute respiratory distress syndrome.

Substance use was assessed from laboratory values recorded in the chart at the time of admission to the emergency department and from self-report (tobacco use). In addition to tobacco, substance use variables were ethyl alcohol, marijuana, cocaine, benzodiazepines, and opiates. A substance use category of "other" included 8 additional substances including barbiturates, amphetamines, "acid," and spray paint. Ethyl alcohol was tested from serum. Other substances were tested from urine. A positive result for ethyl alcohol use was serum concentration of greater than 10 mg/dL. A positive result for marijuana use was presence of the marijuana metabolite, tetrahydrocannabinol, which can be detected up to 30 days after smoking marijuana. A positive result for cocaine was presence of cocaine metabolites in the urine. Benzodiazepines were detected directly from urine samples. Cocaine can be detected in the urine from 1 to 3 days. Short acting benzodiazepines can be detected from 1 to 3 days, while longer acting benzodiazepines can be detected for up to 30 days.[22]

Trauma severity was measured by using the ISS. This score is the accepted standard for measuring degree of injury in trauma populations, because it objectively describes injury severity regardless of injury mechanism. The trauma registry database software calculates the score by assigning different statistical weights to injuries based on the region of the body in which the injuries occur. If multiple injuries occur in the same body region, the most severe injury for that body region was scored. The sum of the squared values for the three most injured body systems comprised the final ISS. Scores range from 1 to 75. Scores of 15 or greater were associated with moderate to severe trauma.[19,23,24]

Sample charts were selected using the trauma registry database. All charts that met both inclusion and exclusion criteria were included. Of 600 charts screened, 101 (18%) were excluded for blood transfusions and 108 (20%) were excluded for missing data. Forty-one charts (7%) were excluded because of spinal cord injury, while 50 (9%) were excluded for a stay of less than 24 hours in the ICU. Six charts (1%) were excluded for comorbidities that affect systemic inflammatory response. A total of 246 charts were included in the final sample. Following sample selection, data for all study variables were collected and entered directly into a data entry spreadsheet developed by the principal investigator.

Descriptive statistics were calculated for each variable of interest. The chi-square test was used to assess the relationship between dichotomous outcome variables and dichotomous predictor variables. Fisher exact test or Fisher–Freeman-Halton test was used where applicable for small cell counts. The Wilcoxon–Mann-Whitney test was used to assess the relationship between ordinal outcome variables and dichotomous predictor variables. Significance level was set at $P \leq .05$. SAS statistical software was used for all analyses (Version 9.1, SAS Institute Inc, Cary, North Carolina).

RESULTS

Demographics

Of the 246 subjects represented in the final sample, 72% (n = 178) were male (Table 1). The mean age was 29 (SD = 7.9) years. A majority of the sample were employed (66% [n = 152]) and 76% (n = 182) were unmarried. The mean ISS was 22 (SD = 7.1; range = 16-59) representing moderate injury severity. Mechanism of injury data was available for 230 subjects. Motor vehicle crashes were the most common mechanism of injury (85% [n = 197]), followed by falls (7% [n = 16]), blunt assaults (5% [n = 11]), gunshot wounds (2% [n = 4]), and other (<1% [n = 2]).

Substance Use

Tobacco use (smoking) data were available for 227 subjects. Slightly more than half reported smoking tobacco (52% [n = 118]). Most patients were positive for substance use (58% [n = 144]). Ethyl alcohol was the most commonly used substance (n = 97), followed by marijuana (n = 50), cocaine (n = 36), benzodiazepines (n = 20), and opiates (n = 16). The mean ethyl alcohol level was 154 mg/dL (SD = 81.4 mg/dL, range = 10-341 mg/dL).

TABLE 1 Frequency of Demographic, Substance Use, and Injury Factors for SIRS

Variables	No SIRS	Mild SIRS (Score 0 or 1)	Moderate SIRS (Score 2)	Severe SIRS (Score 3)	Total (Score 4)
Number (%)	53 (22)	75 (30)	92 (37)	26 (10)	246 (100)
Gender[a]					
Male	38 (21)	47 (27)	75 (42)	18 (10)	178 (72)
Female	18 (26)	27 (40)	16 (24)	7 (10)	68 (28)
Age[a]					
Mean ± SD	30 (7.7)	27.5 (7.8)	26 (8.0)	30 (8.4)	29 (8.1)
Range	18–43	18–43	18–44	19–44	18–44
No substance use	24 (24)	31 (30)	35 (34)	12 (12)	102 (42)
Substance use	32 (22)	43 (30)	56 (39)	13 (9)	144 (58)
Ethyl alcohol[a]	15 (15)	25 (26)	49 (51)	8 (8)	97 (39)
Range, mg/dL	49-275	10-341	10-283	23-300	10-341
Median, mg/dL	118	154	175	150	152
Marijuana[a]	15 (30)	18 (36)	13 (26)	4 (8)	50 (20)
Cocaine	10 (28)	9 (25)	12 (33)	5 (14)	36 (15)
Benzodiazapines	3 (15)	7 (35)	7 (35)	3 (15)	20 (8)
Opiates	1 (7)	6 (43)	5 (36)	2 (14)	14 (6)
Other	4 (50)	2 (25)	1 (12.5)	1 (12.5)	8 (3)
Injury severity score					
Median	22	22	22	26	22
Range	16-45	16-43	16-50	17-59	16-59
(*n* = x)	53	73	87	25	238

Abbreviation: SIRS, systemic inflammatory response syndrome.

[a]Significant at the .05 level.

There were significantly more SIRS occurrences among ethyl alcohol users ($P = .005$ [Table 2]). Eighty-two of 97 or 85% of these patients had SIRS, whereas 15% did not have SIRS. Alcohol users also had significantly *increased* SIRS severity compared to other substance users ($P = .0008$ [Table 3]). Marijuana users had significantly *decreased* SIRS severity ($P = .02$) compared to other substance users (Table 3). There were no other significant results for SIRS compared to any other substance, including tobacco. However, a significant proportion of benzodiazepine users (55% [n = 11]) experienced a complication ($P = .01$), the most common of which was infection ($P = .05$).

DISCUSSION

Alcohol

This research showed a significant association between ethyl alcohol use and increased SIRS occurrence and severity following trauma. The present data are consistent with results from studies that show relationships between ethyl alcohol use and biomarkers of systemic inflammatory response, including increased cytokine levels and white blood cell counts. In their study of acute ethyl alcohol intoxication in a pig model of traumatic hemorrhage, Woodman and colleagues[25] reported that neutrophil counts were increased with for up to 24 hours after insult. Similarly, Colantoni and colleagues[26] reported higher levels of the proinflammatory cytokine IL-6 in mice that had been given ethyl alcohol. This is consistent with two human studies of chronic alcohol use in noninjury settings in which IL-6 and other proinflammatory cytokines were increased, including IL-1β, IL-12, TNFα, and granulocyte-colony stimulating factor.[27,28] Collectively these results have been confirmed by recently published reviews of similar studies, which concluded that ethyl alcohol ingestion

TABLE 2 Chi-Square Test Results for Substance Use and SIRS Occurrence

Predictor Variable Substance	Outcome Variable SIRS Occurrence
Alcohol	0.0051[a]
Cocaine	0.3545
Tetrahydrocannabinol	0.1016
Benzodiazepines	0.5654[b]
Opiates	0.1940[b]
Other	0.0732[b]

Abbreviation: SIRS, systemic inflammatory response syndrome.

[a]Significant at the .05 level.

[b]Fisher exact test or Fisher-Freeman-Halton test was used because of small cell counts.

increased proinflammatory mediators, susceptibility to pathogenic invasion, and the incidence of both organ failure and infection following trauma.[17,29,30]

Marijuana

In contrast to the *increased* SIRS occurrence and severity found with ethyl alcohol, positive marijuana use correlated significantly with *decreased* SIRS severity, supporting reports of the anti-inflammatory effects of cannabinoids. This is clinically important, because decreased SIRS severity has been associated with increased risk for infection and sepsis.[14]

The term "cannabinoids" collectively refers to all marijuana metabolites, including tetrahydrocannabinol or THC, the metabolite used to detect marijuana use in toxicology reports. Evidence shows that the anti-inflammatory properties of some cannabinoids are many times stronger than aspirin.[31] These effects are so strong that some have suggested cannabinoids could be used for treatment of severe proinflammatory conditions,[32] which may explain the decreased SIRS severity in association with marijuana use found in this study.

The mechanism responsible for these effects is unclear, though some studies have shown that cannabinoids may suppress inflammation directly by decreasing serum concentrations of proinflammatory cytokines IL-1β, IL-6, IL-12, and TNFα—biomarkers that have been linked with SIRS.[14,33] Cannabinoids may also suppress inflammation indirectly through their anxiolytic properties.[31] Anxiolytics reduce anxiety.[34] Acute anxiety associated with trauma increases white blood cell count and also increases body temperature.[35-38] The presence of cannabinoids prior to trauma may limit postinjury anxiety, thereby inhibiting increases in white blood cell count and body temperature, both of which are indicators of SIRS. Cannabinoids are absorbed by fatty tissue and released back into the vascular circulation in detectable levels for up to 4 weeks.[31] This supports the assertion that if a patient tests positive for marijuana, plasma concentrations are high enough to produce both the analgesic and anxiolytic effects of marijuana, potentially decreasing SIRS severity and increasing risk for infection and sepsis.

TABLE 3 Wilcoxon–Mann-Whitney Test Results for Substance Use and SIRS Severity

Predictor Variable Substance	Outcome Variable SIRS Severity
Alcohol	0.0008[a]
Cocaine	0.8973
Tetrahydrocannabinol	0.0244[a]
Benzodiazepines	0.4877
Opiates	0.4072
Other	0.1311

Abbreviation: SIRS, systemic inflammatory response syndrome.

[a]Significant at the .05 level

Implications for Practice and Research

This study is the only one known to us, which assessed the relationship between marijuana use and SIRS following trauma. It is one of very few that assessed relationships between ethyl alcohol use and SIRS. Thus, it addresses an important gap in the literature regarding the effect of substance use on acute outcomes of trauma. Because substance use is an established contributor to trauma, more research is needed to guide clinicians on how to assess for increased risk of poor outcomes of inflammatory origin such as infection, sepsis, and organ failure in this population. Suggestions for future research include validation studies with larger sample sizes and studies to establish whether or not study findings translate into increased risk of poor outcomes in ethyl alcohol users and marijuana users.

When nurses and other health care providers know which populations are at increased risk for complications, practice can be adjusted accordingly. Possible practice changes include increased vigilance using the SIRS score as a bedside assessment tool, earlier identification of problems, and earlier treatments.[39]

LIMITATIONS

This research has several limitations, including the retrospective design and associated inherent flaws with collection of data from secondary databases. Generalizability of study results is limited to trauma populations in the

Southeastern United States. When assessed in combination, analysis of polysubstance use yielded counts too small from which to conclude significant results. Studies with larger populations of polysubstance use should be conducted.

Another limitation is the existence of differences between the time from injury and the time to ICU admission, when the SIRS score was measured. Ideally, SIRS should be measured at a consistent point in time following injury. Measurement of SIRS is dependent, however, on a complete set of vital signs and on concurrently measured laboratory values for white blood cell count. Because of these limitations, injury researchers have measured SIRS on admission to the emergency department,[40] on admission to the ICU,[41] and on the second and third postinjury day.[42]

CONCLUSIONS

The significant relationships identified for ethyl alcohol and marijuana users suggest that these patients may be at higher risk for poor trauma outcomes that are associated with SIRS. Because of increased SIRS severity, trauma patients who test positive for ethyl alcohol on admission may be at risk for multiple organ failure. Furthermore, because increased SIRS severity can result in a severe compensatory anti-inflammatory response followed by immune suppression, these patients may also be at increased risk for infection and sepsis. Likewise, trauma patients who test positive for marijuana may also be at risk for infection and sepsis because of decreased SIRS severity and associated immune suppression. Health care providers should take these factors into consideration when tailoring postinjury treatment for these populations. More research is needed to assess differences in SIRS-related outcomes in trauma patients who use substances.

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