American Journal of Emergency Medicine 34 (2016) 250–253

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Respiratory depression in the intoxicated trauma patient: are opioids to blame?☆,☆☆

Eleni Shenk [a], Cassie A. Barton [a,*], Nathan D. Mah [a], Ran Ran, MD [b], Robert G. Hendrickson, MD [b], Jennifer Watters, MD [c]

[a] Department of Pharmacy, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239
[b] Department of Emergency Medicine, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239
[c] Department of Trauma, Critical Care and Acute Care Surgery, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR, 97239

ARTICLE INFO

Article history:
Received 4 September 2015
Received in revised form 29 October 2015
Accepted 30 October 2015

ABSTRACT

Providing effective pain management to acutely intoxicated trauma patients represents a challenge of balancing appropriate pain management with the risk of potential respiratory depression from opioid administration. The objective of this study was to quantify the incidence of respiratory depression in trauma patients acutely intoxicated with ethanol who received opioids as compared with those who did not and identify potential risk factors for respiratory depression in this population. Retrospective medical record review was conducted for subjects identified via the trauma registry who were admitted as a trauma activation and had a detectable serum ethanol level upon admission. Risk factors and characteristics compared included demographics, Injury Severity Score, Glasgow Coma Score, serum ethanol level upon arrival, urine drug screen results, incidence of respiratory depression, and opioid and other sedative medication use. A total of 233 patients were included (78.5% male). Patients who received opioids were more likely to have a higher Injury Severity Score and initial pain score on admission as compared with those who did not receive opioids. Blood ethanol content was higher in patients who did not receive opioids (0.205 vs 0.237 mg/dL, $P = .015$). Patients who did not receive opioids were more likely to be intubated within 4 hours of admission (1.7% vs 12.1%, $P = .02$). Opioid administration was not associated with increased risk of respiratory depression (19.7% vs 22.4%, $P = .606$). Increased cumulative fentanyl dose was associated with increased risk of respiratory depression. Increased cumulative fentanyl dose, but not opioid administration alone, was found to be a risk factor for respiratory depression.

1. Introduction

Recognition of inadequate pain management has prompted efforts across many disciplines to increase appropriate treatment of acute pain in the hospital setting. Effective pain management has been shown to be important for multiple reasons, including patient satisfaction, earlier mobilization, shortened hospital stay, and reduced costs [1–4]. Although it may not be possible to eliminate all pain, a substantial effort should be made to minimize the incidence and severity of acute pain.

Adequate assessment of pain is complex in nonintoxicated patients, and ethanol intoxication only further complicates pain assessment and determining appropriate treatments. With 31% to 70% of trauma patients presenting with detectable serum alcohol concentrations, this scenario occurs often [5–8]. Trauma patients have a need for effective pain control, but known or suspected intoxication may lead some providers to withhold the use of opioid therapy. Reasons for withholding pain medication include being unable to appropriately assess the patient's pain, the potential for variable perceptions of pain, unawareness of the patient's pain tolerance, and the risk of serious adverse effects such as respiratory depression. Intoxicated trauma patients are at particular risk for undertreated pain and for the negative outcomes that providers are attempting to prevent [4,9].

There are limited data evaluating the interaction between ethanol and opioid medications. The combination is known to cause respiratory depression due to additive central nervous system depressive effects, but data evaluating the risk of respiratory depression in intoxicated trauma patients receiving opioid therapy are lacking [4,10]. The purpose of this study is to determine the rate of respiratory depression seen in intoxicated trauma patients who receive opioids for pain management as compared with those who do not receive opioids.

☆ Conflicts of interest and source of funding: No authors have declared conflicts of interest. No funding was provided for this study.
☆☆ Meetings at which this article will be presented: The Society of Critical Care Medicine, Critical Care Congress, Orlando, FL, February 2016.
* Corresponding author at: 3181 SW Sam Jackson Park Rd, Mail Code: CR 9-4, Portland, OR, 97239-3098. Tel.: +1 503 494 8007; fax: +1 503 494 5094.
E-mail addresses: elenikin@gmail.coma (E. Shenk), bartonc@ohsu.edu (C.A. Barton), mahn@ohsu.edu (N.D. Mah), ran@ohsu.edu (R. Ran), hendriro@ohsu.edu (R.G. Hendrickson), wattersj@ohsu.edu (J. Watters).

http://dx.doi.org/10.1016/j.ajem.2015.10.053
0735-6757/

2. Methods

From November 2013 to June 2014, all patients 18 years or older who had a detectable blood ethanol level and were admitted as a trauma activation to the emergency department (ED) of a single university-affiliated level 1 trauma center were included in this retrospective cohort study. A *detectable blood ethanol level* was defined as greater than or equal to 10 mg/dL. Patients were excluded if endotracheal intubation was performed before admission or if the patients had a severe allergic reaction to opioids, were pregnant, met the definition for respiratory depression at admission, were transferred from an outside hospital, or were intubated for reasons other than respiratory depression. This study was approved by the institutional review board.

The primary outcome variable was to evaluate the incidence of respiratory depression in intoxicated trauma patients who were administered opioids as compared with those who were not administered opioid therapy. The secondary outcome was to evaluate risk factors for respiratory depression, specifically looking at fentanyl equivalent dose, blood ethanol content, and midazolam equivalent dose.

Eligible patients were identified via an institutional trauma database, and subject inclusion and exclusion criteria were applied through extensive medical record review. Demographic information, treatment characteristics, and opioid use were gathered from the trauma database and electronic health records. Included patients were separated into 2 groups; the treatment group included those who were administered opioids within 4 hours of ED admission or before endotracheal intubation, and the comparator group consisted of those who were not administered opioids within this time frame.

Respiratory depression was defined as the presence of at least 1 of the following criteria: respiratory rate <10 breaths per minute, oxygen saturation <90% requiring supplemental oxygen, need for endotracheal intubation, and use of naloxone within 4 hours of ED admission.

All opioid doses were converted to fentanyl equivalent doses. The conversion was done using the Hopkins Opioid Program [11]. All doses of benzodiazepines were converted to midazolam equivalent doses. The conversion factor used for converting between midazolam and lorazepam was 3:1 [12].

Data were analyzed using IBM SPSS Statistics 22 Software with a defined significance a priori as $P < .05$ by 2-tailed asymptotic or exact tests. A cross-tabulation and χ^2 test with continuity correction was used to assess the association between trauma patients who received opioids and trauma patients with respiratory depression. χ^2 with continuity correction was also used to test the significance of ordinal data. All continuous variables were first tested for normality. Normally distributed continuous variables were analyzed by independent-samples *t* test. Nonparametric variables were analyzed with Mann-Whitney *U* test. Binary logistic regression was used to measure the effects of fentanyl equivalent opiate dosing, blood ethanol content, and midazolam equivalent benzodiazepine dosing on the incidence of respiratory depression in trauma patients who received opiates, either within 4 hours of presentation to the ED or before intubation.

3. Results

The trauma database identified 268 adult trauma patients admitted with a detectable serum ethanol concentration in the study period. Nineteen patients were excluded for intubation before admission. Of the patients in the treatment group, 2 were excluded for documentation of severe opioid allergies, 3 for intubation due to aggression rather than respiratory depression, and 2 who were treated with hydromorphone infusions, but the electronic health records did not specify the exact dosage received during the measured time frame. Of the patients in the comparator group, 7 were excluded for documentation of severe opioid allergies and 2 for intubation due to aggression. A total of 117 patients were included in the treatment group and 116 patients in the comparator group.

Table 1
Baseline demographics

Characteristic	Treatment group (n = 117)	Comparator group (n = 116)	*P* value
Age, y	44 (15)	42 (18)	.204
Male, n (%)[a]	88 (75.2)	95 (81.9)	.216
GCS [a]	15 (14-15)	15 (14-15)	.014
ISS score[a]	9 (4-14)	5 (1-10)	.001
Initial pain score[a]	8 (6-9)	3 (0-5)	<.001
Blood alcohol content, mg/dL	0.205 (0.09)	0.237 (0.104)	.015

[a] Median (interquartile range).

Baseline demographics of included patients are listed in Table 1. The treatment group was more likely to have a higher Injury Severity Scale score (ISS), have a higher initial pain score on admission, and be admitted to the ward from the ED as compared with the comparator group (Table 2). Thirty-five patients (29.9%) required supplemental oxygen in the treatment group and 17 patients (14.7%) in the comparator group. Patients in the comparator group were more likely to require endotracheal intubation ($P = .02$) (Table 2). The most common mechanism of injury for both groups was motor vehicle accident. Twenty-three patients (9.9%, n = 10 in treatment group, n = 13 in comparator group) had a positive urine drug screen, with the most common exposures being opiates, amphetamines, cannabinoids, and benzodiazepines. There was not a statistically significant difference in either the rate of positive urine drug screen or any substance between the 2 groups.

Forty-nine patients (21.0%) experienced respiratory depression. Of these patients, 23 (46.9%) were administered opioids. There was no statistically significant difference between the 2 groups in regard to respiratory depression and administration of opioids (Table 3). Cumulative fentanyl dose was associated with statistically significant increase in respiratory depression (Figure) (Table 4).

4. Discussion

Given the high prevalence of ethanol intoxication in trauma patients, surprisingly little data are available regarding the risk of respiratory depression in intoxicated trauma patients requiring opioid therapy. Traumatic injuries are known to cause severe pain, and opioids should be administered in adequate doses to relieve patient suffering and reduce trauma-related stress responses [13]. The fear of respiratory depression from opioid administration can be compounded by the presence of

Table 2
Treatment characteristics

Characteristic [mean (±SD)][a]	Treatment group (n = 117)	Comparator group (n = 116)	*P* value
Respiratory rate	14 (4)	13 (3)	.144
Use of supplemental O_2	20%	24%	.591
Use of naloxone	0%	2.5%	.081
Endotracheal intubation, n (%)	2 (1.7)	14 (12.1)	.02
Use of benzodiazepines	20%	24%	.410
Midazolam equivalent dose, mg	0.7 (1.7)	1.1 (2.7)	.154
Use of antipsychotics	0%	7.8%	.002
ED LOS, h	4.4 (3.1)	4.8 (3.3)	.319
ICU admission from ED	38%	28%	.106
Ward admission from ED	26%	10%	.002
ICU LOS, d	1 (3.6)	1 (3.1)	.935
Ward LOS, d	1.9 (2.8)	0.8 (3.1)	.007
Mortality, n (%)	1 (0.8)	2 (1.7)	.558
Fentanyl equivalent dose (μg)[b]	117 (50-200)	0	.000

ICU, intensive care unit; LOS, length of stay.
[a] Unless otherwise noted.
[b] Median (interquartile range).