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Opioid dependency is independently associated with inferior clinical outcomes after trauma

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ABSTRACT

Introduction: Increased use of opioids has led to higher rates of overdose and hospital admissions. Studies in trauma populations have focused on outcomes associated with acute intoxications rather than addiction. We hypothesize that clinical outcomes after injury would be inferior for opioid-dependent patients compared to opioid-naïve patients.

Methods: We identified all opioid-dependent adult patients admitted to an academic level I trauma center in 2016 with an Injury Severity Score (ISS) ≥ 5. Patients were further categorized by their pattern of opioid dependency into prescription abuse, illicit abuse, or chronic pain subgroups. Outcome measures included length of stay (LOS), major complications, mortality, non-home discharge, ventilator days, and readmissions. Regression models were adjusted for patient demographics, insurance, ISS, and comorbidities.

Results: Of the 1450 patients who met the inclusion criteria, 18% were opioid-dependent. Among opioid-dependent patients, 30%, 27%, and 43% were prescription abuse, illicit abuse, and chronic pain patients, respectively. Compared to opioid-naïve (non-users) patients, opioid-dependent patients had longer LOS, more ventilator days, more non-home discharges, and higher readmission rates. Subgroup analysis revealed significant differences among all cohorts when compared to non-users in LOS, non-home discharge, readmissions, and major complications. Opioid dependency was not associated with mortality.

Conclusion: Opioid dependency was detected in 18% of trauma patients and was independently associated with inferior outcomes. The impact of opioid dependency affects each opioid subgroup differently with all cohorts demonstrating increased 30-day readmissions. Opioid dependent patients may be targeted for risk interventions to reduce LOS, non-home discharge, complications and readmissions.

Background

Over the past two decades, the rate of prescription opioid abuse in the United States has increased significantly, spurring legislation to create prescription drug-monitoring databases [1,2]. A steady increase in opioid-related mortality has been observed between 2002 and 2013 [1]. Recent trends also indicate a rise in opioid prescribing from 2007 to 2010 but a leveling between 2010 and 2012 as medical specialties began reducing opioid use [3]. In 2012, 36.5% of prescriptions written in surgery specialties were for opioids, one of the highest opioid prescribing rates across medical specialties [3]. Despite increased utilization of opioids, the prevalence of pain among patients in the United States has not changed [4].

Patients with opioid dependency encompass a highly variable group, including those who misuse prescription opioids, those who abuse non-prescription opioids (predominantly heroin), and those who use opioids to manage chronic pain [5,6]. Long-term opioid prescriptions for chronic pain treatment remains controversial, particularly due to concerns regarding lack of efficacy and the rise in opioid-related fatalities [7,8]. Both Cron et al. and Waljee et al. recently demonstrated that opioid-dependent patients undergoing elective abdominal surgery exhibited higher hospital costs, longer hospital length of stay (LOS), and more readmissions compared to their opioid-naïve counterparts [9,10]. No distinctions were made

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among the different types of opioid-dependent patients. Research investigating the clinical outcomes of opioid-dependent trauma patients, who represent a unique population given the association between substance abuse and traumatic injury, remains limited [11]. Studies that investigate opioid use in trauma populations have commonly focused on acute intoxications or postoperative misuse rather than long-term addiction [11,12].

Our retrospective study characterized the different patterns of opioid use and assessed the impact of opioid dependency on clinical outcomes in a trauma population at a Level I trauma center. We hypothesized that opioid-dependent trauma patients would have inferior outcomes compared to opioid-naïve patients.

Methods

Study population

This study was reviewed and approved by Institutional Review Board at Yale University. A retrospective chart review from a single academic center, this study included all adult patients age 18 or older with an Injury Severity Score (ISS) greater than 5 admitted to an academic Level I trauma center between January 2016 and December 2016 (n = 1466). An ISS of 5 was selected because in patients with minimal and minor injuries, opioid use likely does not significantly interact with the injury and impact outcome. Patients were identified from the trauma registry (Traumabase, Clinical Data Management, Denver CO) which includes patient demographics, hospital length of stay, description of injury and surgical interventions required, complications, comorbidities, as well as clinical outcome measures. Patients who died in the emergency room were excluded from the sample (n = 16), leaving a final study population of 1450 patients.

Opioid dependency

Opioid-dependent patients were identified through retrospective chart review of physician, social work, nursing notes, and telephone encounters prior to the patient's trauma admission. All patient's charts at our institution included a standardized report from social work, where social workers met with all trauma patients and documented opioid abuse in a standardized fashion. Urine toxicology screens were not used to identify opioid-dependent patients because many patients were given pain control medications either on the way to the hospital or in the ED because of their injuries. The criteria used to determine opioid dependency and opioid-dependent subgroups (Prescription abuse, Illicit abuse, Chronic pain use) are shown in Fig. 1. We defined prescription abuse patients as any intentional misuse of prescription opioids in the three months prior to their trauma admission. Illicit abuse patients were patients with a history of non-prescription opioid use (predominantly heroin) in the previous three months prior to their trauma admission and chronic pain patients were defined as patients who were prescribed narcotics at least once a month over the course of three months for a chronic pain condition prior to their trauma admission. Prescription opioid use was also verified through the Connecticut Prescription Monitoring Program (www.ct.gov/dcp/pmp) by examining the number of controlled substance prescribers, dispensers, and dispensations as well as the name of each controlled substance prescribed. Patients who exhibited characteristics of one or more subgroups were assigned to the subgroup most recently exhibited by the patient prior to the patient's date of trauma injury and admission. Any patient without a history of opioid use at the time of admission was categorized as opioid-naïve.

Outcome measures

The primary outcome measure was hospital length of stay. Secondary outcome measures included number of ventilator days, non-home discharges, 30-day hospital readmissions, major complications, and 30-day mortality. Non-home discharges were defined as discharge destinations that included rehabilitation facilities, skilled nursing facilities, jails, or psychiatric hospitals. Major complications were recorded as a binary variable indicating the presence of one or more of the following complications: urinary tract infection, catheter associated urinary tract infection, wound infection, acute respiratory distress syndrome, acute respiratory failure, myocardial infarction, cardiac arrest, arrhythmia, pneumonia, aspiration pneumonia, ventilator-associated pneumonia, cerebrovascular accident, surgical site infection, extremity compartment syndrome, coagulopathy, GI bleed, severe sepsis, thromobocytopenia, shock, unplanned return to the operating room, unplanned admission to the intensive care unit, unplanned intubation, acute renal failure, in-hospital fall, gastrointestinal obstruction, seizures, pulmonary embolism, deep vein thrombosis, and delirium.

Statistical analysis

Statistical analysis was performed using SPSS version 24 (IBM SPSS Statistics, Armonk, NY). We compared clinical characteristics between opioid-naïve and opioid-dependent cohorts, as well as between the opioid-naïve cohort and each opioid-dependent subgroup. A Chi-square test or Fisher's exact test was used to analyze differences in categorical clinical variables. An independent samples *t*-test was used to evaluated normally distributed variables, such as age, BMI, and time to readmissions. The Kruskal-Wallis test was used to evaluate skewed continuous clinical variables, including LOS and ventilator days. Multivariable regression was performed to evaluate the association of opioid

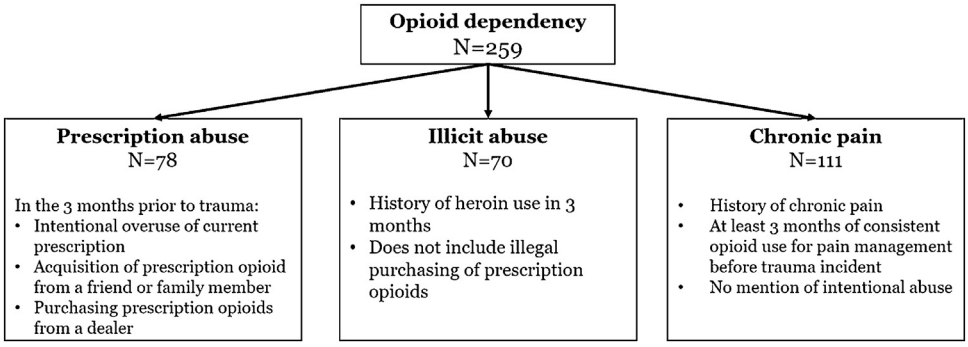

Fig. 1. Sub-classification of opioid dependent patients.

dependency on clinical outcomes after adjusting for confounding variables. To mitigate the effect of overdispersion on LOS and ventilator days data, a negative binomial with log link model was created. The means-adjusted LOS was also calculated. Binary logistic regression was performed to analyze non-home discharges, readmissions, major complications, and mortality. Analysis of ventilator days was limited only to the 174 patients who required ventilation. All models were adjusted for the following potential confounding variables: age, gender, race (white, black, other), injury severity score (fitted as a categorical term with ranges 5–8, 9–14, and >15), insurance status (private, Medicaid, Medicare, other), and comorbidities, including alcoholism, smoking, diabetes, hypertension, coronary artery disease, cerebrovascular accident, congestive heart failure, obesity, bleeding disorder, respiratory disease, cirrhosis, renal disease, and steroid use. Comorbidities were defined as a binary term, which would take a positive value if any of the listed comorbidities were present. Two-sided p values less than 0.05 were considered to be statistically significant.

Results

The prevalence of opioid dependency in our trauma population was 18% (n = 259). Opioid-dependent patients were younger and were prescribed more controlled substances than their opioid-naïve counterparts (non-users) (Table 1). Opioid-dependent patients (users) were more likely to be white, have Medicaid insurance, be smokers, and have a higher shock index. 27% (n = 71) used methadone to manage opioid dependency. When stratified into subgroups, significant differences in the clinical characteristics among subgroups were observed (Table 2). Notably, chronic pain patients were older, more likely to be female and have Medicare than other opioid-dependent subgroups. Illicit abuse patients were more likely to be non-white, smoke, use methadone and have Medicaid. Prescription abuse patients significantly more likely to have private insurance and 35% (n = 27) use methadone to manage their opioid dependency. Opioid-naïve patients had significantly fewer controlled drug prescriptions compared to opioid-dependent patients. The primary substances used by opioid-naïve patients included benzodiazepines and zolpidem.

The unadjusted median hospital LOS was 4 days (2–7 days) for non-users and 5 days (2–8 days; p = 0.01) for users. Prescription abuse, illicit abuse, and chronic pain patients had a median LOS of 4 days (2–8 days; p = 0.52), 5.5 days (2–9 days; p = 0.02), and 5 days (3–8 days; p = 0.03), respectively. Multivariable negative binomial regression analysis demonstrated that opioid dependency was associated with a significantly increased LOS, particularly among illicit abuse patients (Table 3). The means-adjusted LOS for non-users and users were 5.7 days versus 7.4 days, respectively. When we evaluated the effect of concomitant alcohol abuse with opioid dependency, patients with both substance use disorders had an increased mean-adjusted LOS of 10.1 days.

A total of 138 (12%) non-users and 36 (14%) users required mechanical ventilation. Opioid dependency was not associated with a change in unadjusted median ventilator days (p = 0.56). Multivariable negative binomial regression analysis demonstrated that opioid dependency was associated with an increase in ventilator days (Table 3). The means-adjusted ventilator days for non-users vs. users were 4.7 days versus 7.8 days, respectively. Unadjusted non-home discharge rates were not significantly different between the groups. Multivariable regression analysis of non-home discharges demonstrated that opioid dependency was associated with an increase in non-home discharges (Odds ratio [OR] 1.47; 95% CI:1.03, 2.11, p < 0.05). Prescription abuse status was associated with the greatest increase in non-home discharges (Table 3).

The unadjusted mortality rate was significantly greater at 5% (n = 14) in users compared to 3% (n = 34) in non-users (p = 0.04). The prescription abuse cohort was the only subgroup to have a statistically significant increase in mortality compared to non-users (8% [n = 6] versus 3% [n = 34], p = 0.026). Although not significant, multivariable regression analysis demonstrated that opioid dependent patients had a mortality odds ratio of 1.8 (Table 3). The unadjusted major complications rate was 1.3-fold higher in users compared to non-users (41% [n = 105] versus 31% [n = 369]; p = 0.003). Both prescription abuse (45% [n = 35] versus 31% [n = 369]; p = 0.02) and chronic pain (44% [n = 49] versus 31% [n = 369]; p = 0.003) subgroups demonstrated increased major complications rates compared to that of non-users. On multivariable regression, only prescription abuse was significantly

Table 1
Clinical characteristics of opioid-naïve and opioid-dependent patients.

		Opioid-naïve (n = 1191)		Opioid-dependent (n = 259)		
Age, mean (SD)		54 (19)		51 (16)		p < 0.001
Male		714	60%	165	64%	p = 0.262
Race						p = 0.021
	White	821	69%	196	76%	
	Black	175	15%	38	15%	
	Other	195	16%	25	10%	
Insurance						
	Private	443	37%	44	17%	p < 0.001
	Medicare	458	39%	83	32%	
	Medicaid	339	29%	151	58%	
	Other	102	9%	19	7%	
Number of controlled substance prescriptions, mean		8 (13)		34 (32)		p < 0.001
Body mass index, mean (SD)		28 (7)		28 (7)		p = 0.942
Injury severity score						p = 0.016
	5–8	332	28%	95	37%	
	9–14	603	51%	111	43%	
	>=15	256	22%	53	21%	
Smoker		280	24%	126	48%	p < 0.001
Alcoholism		232	20%	84	32%	p < 0.001
Shock index, mean (SD)		0.66 (0.20)		0.70 (0.20)		p < 0.001
Glasgow coma scale						p = 0.516
	3–7	51	5%	9	4%	
	8–11	21	2.0%	7	3%	
	12–15	1056	94%	227	93%	

Table 2
Clinical characteristics of opioid-dependent subgroups.

		Opioid dependency subgroups						P value*
		Prescription abuse(n = 78)		Illicit abuse (n = 70)		Chronic pain use(n = 111)		
Age, mean (SD)		47 (15)		40 (13)		61 (13)		p < 0.001
Male		57	73%	54	77%	54	49%	p < 0.001
Race	White	65	83%	47	67%	84	76%	p = 0.08
	Black	9	12%	9	13%	20	18%	
	Other	4	5%	14	20%	7	6%	
Insurance	Private	18	23%	8	11%	18	16%	p < 0.001
	Medicare	17	22%	5	7%	61	55%	
	Medicaid	50	64%	57	81%	44	40%	
	Other	7	9%	4	6%	8	7%	
Number of prescriptions, mean (SD)		36 (39)		16 (19)		42 (28)		p < 0.001
Body mass index, mean (SD)		29 (8)		27 (6)		29 (7)		p = 0.565
Injury severity score	5–8	28	36%	28	40%	39	35%	p = 0.043
	9–14	31	40%	25	36%	55	50%	
	>=15	19	24%	17	24%	17	15%	
Smoker		41	53%	53	76%	32	29%	p < 0.001
Alcoholism		28	36%	32	46%	24	22%	p < 0.001
Methadone use		27	35%	44	63%	0	0%	p < 0.001
Shock index, mean		0.71 (0.24)		0.73 (0.18)		0.68 (0.18)		p < 0.001
Glasgow score	3–7	5	7%	1	1%	3	3%	p = 0.651
	8–11	2	3%	2	2%	3	3%	
	12–15	64	90%	65	96%	98	94%	

Table 3
Multivariable comparison of clinical outcomes by opioid dependency and opioid-dependent subgroups.

	Length of stay *% longer*	Ventilator days *% longer*	Non-home discharges *odds ratio*	Readmissions *odds ratio*	Major Complications *odds ratio*	Mortality *odds ratio*
Opioid-naïve (n = 1191)	0 (Ref)	0 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Opioid-dependent (n = 259)	23% (6%, 42%)**	69% (1%, 181%)*	1.5 (1.0, 2.1)*	2.9 (1.9, 4.6)**	1.3 (0.9, 1.9)	1.8 (0.6, 5.2)
Prescription abuse (n = 78)	17% (−9%, 51%)	98% (−5%, 313%)	2.4 (1.3, 4.5)**	2.6 (1.2, 5.6)*	2.1 (1.2, 3.8)*	1.8 (0.4, 9.5)
Illicit abuse (n = 70)	44% (11%, 87%)**	10% (−59%, 196%)	1.8 (0.9, 3.4)	2.9 (1.3, 6.6)*	0.8 (0.4, 1.6)	1.0 (0.1, 9.9)
Chronic pain use (n = 111)	15% (−6%, 41%)	71% (−19%. 262%)	1.0 (0.6,1.6)	3.1 (1.8, 5.4)**	1.3 (0.8, 2.1)	2.2 (0.6, 8.3)

* P < 0.05.
** P < 0.01.

associated with an increased major complications rate (OR 2.09; 95% CI: 1.15, 3.77; p < 0.05) (Table 3).

Unplanned readmissions were significantly more common at 17% (n = 43) in users compared to 6% (n = 72) in non-users (p = 0.001). In particular, the chronic pain subgroup demonstrated marked increase in unadjusted readmissions compared to that of non-users (22% [n = 24] versus 6% [n = 72]; p = 0.001). On multivariable regression, all opioid subgroups were significantly associated with increased risk of readmissions (Table 3). We observed a trend for lower mean time to readmission for opioid-dependent patients compared to that of opioid-naïve patients (10 days [9 days] versus 12 days [10 days]; p = 0.136). Reasons for readmissions included infection, cardiovascular, neurological, respiratory, substance abuse, fever, pain, gastrointestinal disorder, surgical complication, fall, metabolic disorder, and others. Infections were the most common reason for readmission in all patient populations. No differences in reason for readmission between opioid-naïve and opioid-dependent patients were observed expect that opioid-dependent patients had a significantly higher rate of readmission for alcohol withdrawal (p = 0.03).

A subgroup analysis compared outcomes of methadone users (n = 71) to non-methadone opioid users (n = 188). No statsitically significant differences in LOS, ventilator days, non-home discharges, mortality, readmissions, or major complications were observed.

Discussion

While numerous studies have chronicled the growing opioid epidemic in the United States, current understanding of the impact opioid dependency has on trauma and surgical outcomes remains limited. This study demonstrates that 18% of patients were dependent on opioids prior to their trauma admission. This corroborates the results from recent studies of trauma populations which report the prevalence of opioid use from 16% to 20% [13,14]. In comparison, the prevalence of opioid use among the adult population in the United States is estimated to be approximately 5% [15]. Unlike in prior studies that demonstrated opioid users were older and more likely to be female, patients in our opioid-dependent cohort are significantly younger and are more likely to be male. The primary factor contributing to this disparity is our inclusion of illicit abuse patients within our sample. Prior studies have not examined illicit users, who are significantly younger and significantly more likely to be male. This finding underscores the importance of understanding distinct patterns of opioid use and their associations with unique patient populations.

Increased hospital LOS was significantly associated with opioid dependency, particularly among illicit abuse patients. Cron et al. provides a number of reasons explaining why opioid use may lead to increased LOS [10]. Poor and complex management of pain in

opioid-dependent patients, because of increased opioid tolerance or opioid-induced hyperalgesia, is the most likely cause for increased LOS. Other possible factors leading to increased LOS opioid-induced impairment of the gastrointestinal system and immune systems as well as the lengthier nature of processes of care in opioid-dependent patients [10,16,17]. We also observed that concomitant alcohol abuse with opioid dependency was associated with a further increase in LOS, suggesting that multiple substance use disorders may exponentiate the effect on clinical outcomes. Despite the increased LOS, concomitant alcohol and opioid use did not worsen other outcomes. These findings may be due to time required to address alcohol withdrawal symptoms.

In addition to LOS, opioid dependency significantly increased ventilator days, non-home discharges, major complications, and hospital readmissions. The impact of opioid dependency affects each opioid subgroup differently. All opioid subgroups were associated with significantly increased risk of readmissions. Opioid-dependent patients were more likely to be readmitted for alcohol withdrawal and have fewer days in between consecutive readmissions. This may have implications for trauma centers with respect to readmissions penalties should Medicare and other insurers expand penalty programs to trauma.

In a 2015 study of preexisting opioid use in trauma patients, Pandaya et al. elucidated the mechanisms of trauma injury associated with opioid use as well as determined that head, abdomen, and lower extremity injuries among opioid users were associated with greater LOS compared to that of opioid-naïve patients. While this study examined the effect of preinjury opioids on specific types of injuries, it did not distinguish among different types of opioid misuse [13]. To the best of our knowledge, our study is the first to assess the impact of multiple patterns of opioid dependency on a wide range of clinical outcomes in a trauma population. The variable demographics and impact on outcomes based on our classification of opioid misuse is important as it will allow for more targeted interventions to prevent the negative impact on outcomes. While our findings indicate that opioid-dependent patients represent a spectrum of opioid use, more research is needed to design targeted screening tools and risk interventions for specific opioid-dependent populations within trauma centers.

Our study is subject to several limitations. As a retrospective single institution study, these results may not be representative across different trauma centers and geographic regions. Information regarding opioid use from the patient's chart is frequently dependent on the accuracy of family-reported or self-reported data. We attempted to maximize the accuracy of the patient chart by cross referencing patients to those listed in the state prescription drug monitoring database. However, as of 2016, 97% of prescribers and only 40% of pharmacies participate in the drug monitoring database, and the database does not capture illicit abuse [18]. Therefore, not all patients could have their opioid use verified through this program. Furthermore, we are unable to accurately determine the exact indication, dose, duration, and schedule of opioid use due to lack of detailed information regarding opioid use in the outpatient setting. Access to this information may expand our understanding of the patterns of opioid use among trauma patients. In addition, our analysis on mortality was based on data from 48 patients, a smaller n than was present in other outcome variables. Therefore, although these results were non-significant, the mortality differences observed may not be neglibible. Finally, the outcomes identified in this study are dependent on events occurring within our health system. Readmissions and management of complications may have occurred in centers outside our hospital network.

In conclusion, this study sought to characterize the different patterns of opioid use and to investigate the impact of opioid dependency on clinical outcomes in trauma patients. Preoperative opioid use is highly prevalent among trauma patients and is significantly associated with increased LOS, ventilator days, non-home discharges, major complications and readmissions. These findings may allow for more targeted screening approaches, risk assessments, and interventions among opioid patients presenting to trauma centers.

Conflicts of interest

None.

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None.

Author contribution

W.H. and K.S. designed the study. W.H., C.M., S.L., and W.C. performed the data collection. W.H. and K.S. performed the data analysis. W.H., K.S., R.B., and K.D. interpreted the data. W.H. and K.S. drafted the manuscript. W.H., C.M., K.S., R.B., K.D., provided critical revisions.

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