

## Original Article

# The contribution of opiate analgesics to the development of infectious complications in trauma patients

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**Abstract:** Trauma-related pain is a natural consequence of injury and its surgical management; however, the relationship between opiates and complications in trauma patients is unknown. To study this a retrospective chart review of selected subjects following traumatic injury with admission to the SICU for > 3 days was performed, and opiate administration data was collected for the first 3 days of admission. Associated data from each subject's chart was also collected. Analysis of the data revealed that increased opiate intake after admission to the SICU was associated with significantly increased SICU and hospital LOS independent of injury severity. This increase in LOS was independent of mechanical ventilation in the moderate ISS group. Infectious complications were also more prevalent in the moderate ISS group with higher opiate use. These findings suggest that increased doses of opiate analgesics in trauma patients may contribute to an increased overall LOS and associated infectious complications. Analgesic regimes that minimize opiate intake, while still providing adequate pain relief, may be advantageous in reducing LOS, complications and reduce hospitalization costs.

**Keywords:** Pain, mechanical ventilation, analgesia, LOS, infection, ICU

## Introduction

Trauma-related pain is a natural consequence of injury and can be compounded by the numerous diagnostic and therapeutic procedures or even evoked by daily care, such as mobilization, positioning, and wound care. Adequate postoperative pain control is an important part of routine care and nearly all intensive care patients receive some kind of intravenous analgesia. Opiate analgesics (i.e., morphine and other opiate derivatives) are the preferred treatment modality for the management of patients' pain associated with major trauma, surgical trauma, burn injury and cancer [1, 2].

Analgesic medications in combination with sedatives routinely used in trauma patients provide two main benefits; they reduce discomfort, pain and anxiety related to the injury itself and allow tolerance of uncomfortable surgical procedures [3]. When poorly managed, pain may lead to unnecessarily increased stress respons-

es (tachycardia, increased oxygen consumption, hypercoagulability, immunosuppression, hypermetabolism), may delay recovery, increase medical costs, reduce the speed of post-surgical rehabilitation and possibly lead to the development of chronic pain [4, 5]. A variety of intravenous and oral opiates with different analgesic potencies, time to action, and duration are available. These oral opiates include morphine, fentanyl, hydrocodone, hydromorphone, and tramadol.

Opiate derivatives have excellent analgesic action, but their use is not without consequences as opiate use can be accompanied by adverse drug events (ADEs). Their overuse can lead to potential complications that include excessive sedation, constipation, nausea/vomiting, infection and increased mortality [6, 7]. Recently, several studies of routine post-op patients (exclusive of trauma) reported increased hospital length of stay (LOS) and hospitalization costs associated with opiate-related

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ADEs [8, 9]. Sullivan et al. showed that, in a burn patient population, there was a significant increase in the dose of opiates used, which in turn required higher volumes of fluid to be administered [10]. This association might be due to the hemodynamic consequences derived from higher opiate doses. Experimental studies also suggest that morphine contributes to the development of coagulation disorders such as disseminated intravascular coagulation [11], a significant clinical problem in the polytrauma patient. These findings support the concept that therapeutic opiates might adversely affect outcomes following injury [6]. While considered necessary to address pain, if true, this would indicate that adjunctive and innovative measures for pain control might be considered to minimize overall complications. Indeed, the length of time a patient stays in the ICU after a traumatic injury directly correlates with a higher risk of developing an ICU-acquired infection and an associated increase in morbidity and mortality logically follows.

A major concern is the relationship between opiates and complications of an immunological nature. Previous studies have clearly demonstrated that opiates can compromise the immune response [6, 12] and increase susceptibility to infection [13, 14]. Opiates are a primary analgesic used in trauma patients however; the relationship between opiate use and the development of such immune related and other types of complications in trauma patients is unknown. Our study herein was a retrospective chart review designed to examine the relationship between opiate use following trauma, length of stay and the development of infectious and non-infectious complications.

### Materials and methods

#### *Study population*

This was a single-center, retrospective study based on the hospital trauma registry of patients aged 18 years and older admitted after injury to University Hospital (San Antonio, TX), a Level I Trauma Center, over a four-year period (2006 to 2009). The study was approved by the Institutional Review Board of The University of Texas Health Science Center at San Antonio, with waiver of consent. The University of Texas Health Science Center at San Antonio is an academic tertiary referral

center for traumatic injuries sustained in Southwest Texas.

#### *Data collection*

For the purpose of this study we collected demographic data (age, gender, previous opiate use), Injury Severity Score (ISS), type of injury (blunt vs. penetrating) and specific injury patterns (TBI, facial fracture, long bone fracture, pelvic fracture), Glasgow coma scale (GCS) at admission, dates of surgical ICU admission and discharge, date of initiation and length of mechanical ventilation, and hospital length of stay (LOS). All adult patients admitted to the University Hospital with at least 3 days stay in the SICU and no radiologic evidence of traumatic brain injury were eligible for participation in this retrospective study. Patients receiving epidural analgesia were excluded from the study as well patients with a documented history of chronic opiate use.

Outcomes of interest were total amount of opiates delivered in the initial 24 and 72 hours after admission to the SICU, and SICU LOS and hospital LOS. Opiate administration was recorded as any drug product given that contained morphine, codeine, fentanyl, hydromorphone, hydrocodone, or methadone. For statistical analysis, it was necessary to express the opiate analgesic using a common metric equivalent because of the varying relative potency. Each opiate analgesic was translated into units of opiate equivalents (OE) where 10 mg of morphine sulfate administered intravenously equals 1 OE as previously described [15].

From an initial query of the trauma database, 2154 patients were identified. Given that the data had to be collected manually from each subject's chart, a random cohort of 516 subjects was selected using a random number generator. Traumatic brain injury excluded 296 and an additional 21 subjects were excluded because of epidural analgesia use. Also, 19 subjects were excluded for varied reasons (6 subjects' data was misfiled, 4 subjects had chronic opiate intake, 2 subjects were quadriplegic, and 7 had no recorded data). This left a total of 180 subjects who were enrolled into the initial phase of the study (**Figure 1**). In a second phase of the study an additional 116 subjects were enrolled using the same criteria with an intermediate ISS of 10-14 to further evaluate

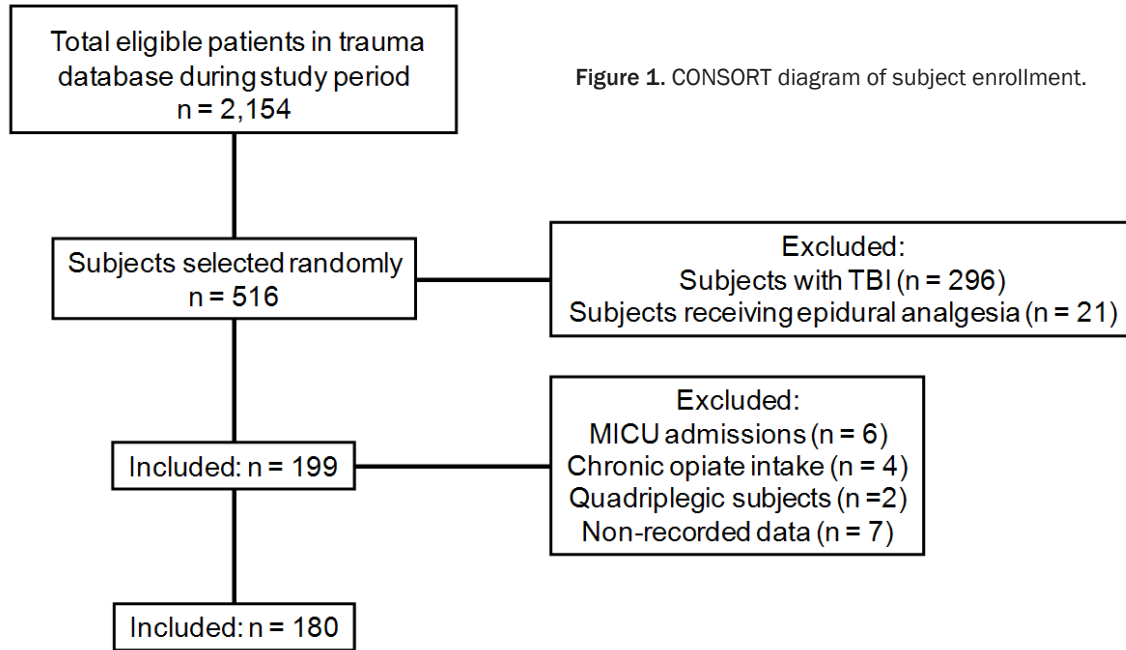


Figure 1. CONSORT diagram of subject enrollment.

Table 1. Demographics (n = 180)

Characteristic	Mean ± SD	Median	Range
Age	44.2 ± 19.5	43.5	17 to 94
ISS	18.7 ± 11.7	17	1 to 66
GCS	12.2 ± 4.6	15	3 to 15
Opioids 0 to 24 hours	100.6 ± 113.3	58.2	0 to 690
Opioids 0 to 72 hours	299 ± 340.1	165.1	11.7 to 1841
ICU length of stay (days)	8.4 ± 8.5	5	3 to 49
Hospital length of stay (days)	18.5 ± 17.9	12	3 to 121

Results

Clinical characteristics and length of stay (LOS)

The age for our study group was 44.2 ± 19.5 years (Table 1) who were predominantly men (65%); ISS was 18.7 ± 11.7. Blunt trauma was the prevalent injury type (86%) and 45% of the subjects were mechanically ventilated.

the relationship between opiates and infectious complications.

Statistical analysis

Continuously distributed outcomes were summarized with mean and standard deviation. Unadjusted contrasts were carried out with a Wilcoxon test. The significance of the relation between LOS and opiate dose was assessed with linear models of LOS in terms of opiate equivalent dose, expressed as the logarithm of the 24 hour dose +1, ISS and admission GCS and the opiate equivalent dose by ISS and the opiate equivalent dose by GCS interaction. All statistical testing was two-sided with a significance level of 5%. SAS Version 9.2 for Windows was used for analysis and R was used for graphics.

ICU LOS was compared by mechanical ventilation, facial fractures, rib fractures, pelvic fractures, long bone fractures, surgical procedure event, type of injury (blunt vs. penetrating), correlations between ICU LOS and ISS, and opiate use during the initial 24 and 72 hours after admission were examined (Table 2). ICU LOS was increased in patients who received mechanical ventilation [mechanical ventilation: 11.5 ± 10.6, no mechanical ventilation: 5.9 ± 5.2, P < 0.001] and ICU LOS was correlated with ISS (correlation = 0.25, P = 0.001), opiates used in the first day (correlation = 0.26, P = 0.001), and opiates used in the first 3 days (correlation = 0.36, P < 0.001). ICU LOS varied significantly with 24 hour and 72 hour opiate intake after adjusting for ISS (Figure 2); the proportion of variance explained by the model was

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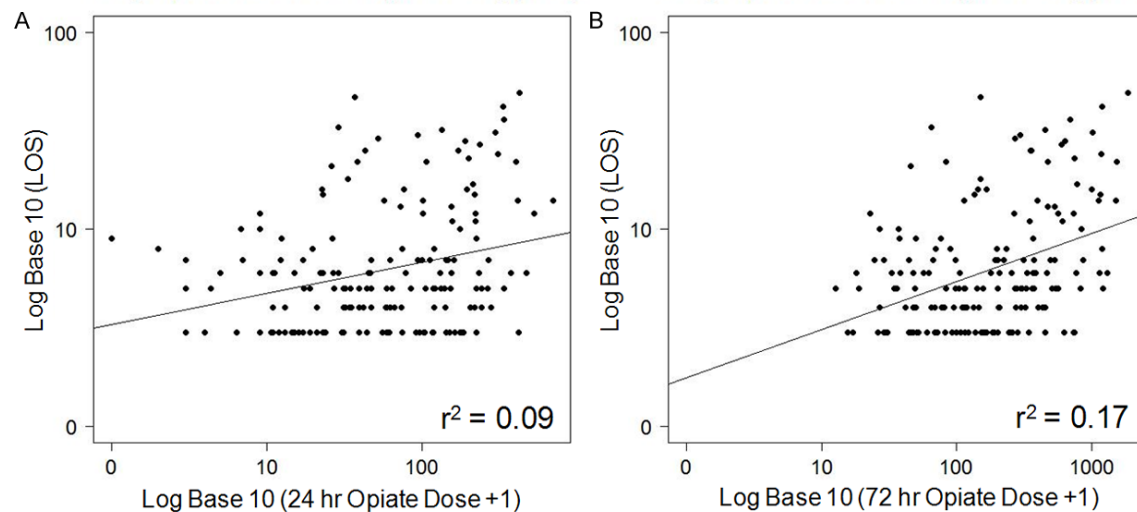
**Table 2.** Relationships between ICU length of stay (LOS) and clinical characteristics

Clinical characteristic	ICU LOS (n, mean $\pm$ SD)				P-value <sup>1</sup>
	Absent		Present		
Mechanical ventilation	99	5.9 $\pm$ 5.2	81	11.5 $\pm$ 10.6	< 0.001
Facial fracture	147	8.6 $\pm$ 8.6	33	7.4 $\pm$ 8.1	0.32
Rib fracture	97	8.6 $\pm$ 9.0	83	8.2 $\pm$ 7.9	0.99
Pelvic fracture	140	8.5 $\pm$ 9.0	40	8.0 $\pm$ 6.6	0.76
Long bone fracture	111	8.2 $\pm$ 8.7	69	8.7 $\pm$ 8.3	0.17
Surgery	69	7.1 $\pm$ 6.3	111	9.2 $\pm$ 9.6	0.08
Blunt injury	25	8.0 $\pm$ 7.9	155	11.2 $\pm$ 11.7	0.36

Clinical characteristic	Mean $\pm$ SD	Correlation	P-value <sup>2</sup>
Opiates 1 day	101 $\pm$ 113	0.26	0.001
Opiates 3 day	299 $\pm$ 340	0.36	< 0.001

<sup>1</sup>Wilcoxon test; <sup>2</sup>For testing correlation equals zero.



**Figure 2.** ICU length of stay (LOS) and opiate use. A. ICU LOS correlation with day 1 opiate intake after adjustment for ISS ( $P < 0.001$ ); B. ICU LOS correlation with 3 day opiate intake after adjustment for ISS ( $P < 0.001$ ). Both length of stay and opiate intake are in log units base 10. 1 was added to opiate intake prior to log transformation as described in the Materials and Methods.

0.09 for opiate intake in the first 24 hours and 0.17 for opiate intake in the first 72 hours.

Hospital LOS was compared by level of binary clinical characteristics and correlations between hospital LOS and ISS, and opiate use during the initial 24 and 72 hours after admission was examined (**Table 3**). Hospital LOS was increased in patients who received mechanical ventilation [mechanical ventilation:  $24.4 \pm 22.7$ , no mechanical ventilation:  $13.6 \pm 10.6$ ,  $P <$

$0.001$ ], experienced long bone fracture [long bone fracture:  $23.6 \pm 19.2$ , no long bone fracture:  $15.3 \pm 16.3$ ,  $P < 0.001$ ], and underwent an operation [surgery:  $22.3 \pm 20.7$ , no surgery:  $12.4 \pm 9.5$ ,  $P < 0.001$ ]. Additionally, hospital LOS was correlated with ISS (correlation = 0.20,  $P = 0.006$ ), opiates used on the first ICU day (correlation = 0.22,  $P = 0.003$ ), and opiates used in the first 3 days (correlation = 0.32,  $P < 0.001$ ). Hospital LOS varied significantly with 24 hour and 72 hour opiate dose after adjust-

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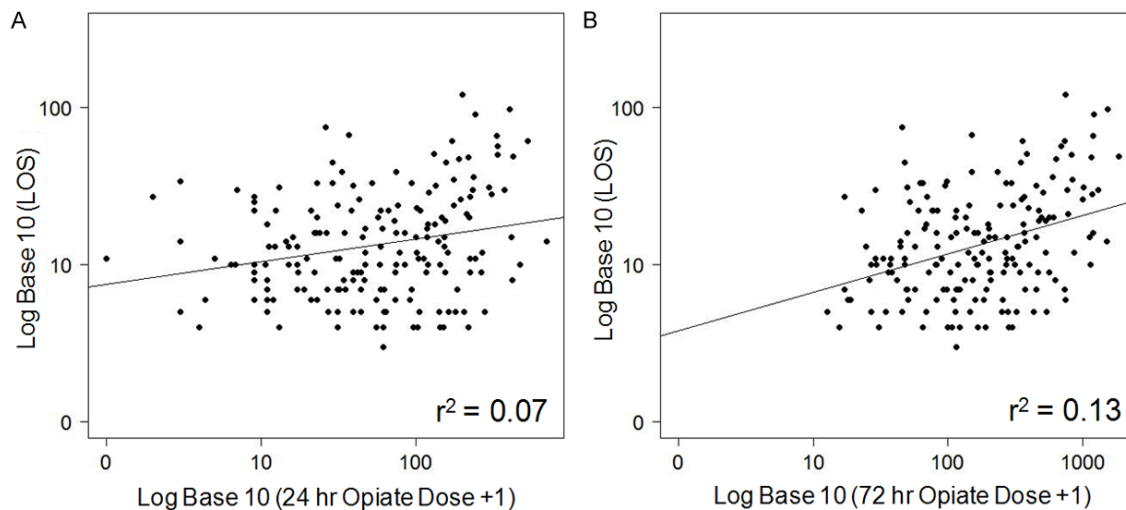
**Table 3.** Relationship between hospital length of stay (LOS) and clinical characteristics

A. Mean changes in hospital LOS with levels of binary characteristics (absent, present)					
Clinical characteristic	Hospital LOS (n, mean $\pm$ SD)				P-value <sup>1</sup>
	Absent		Present		
Mechanical ventilation	99	13.6 $\pm$ 10.6	81	24.4 $\pm$ 22.7	< 0.001
Facial fracture	147	18.5 $\pm$ 18.2	33	18.5 $\pm$ 16.6	0.830
Rib fracture	97	20 $\pm$ 20.5	83	16.7 $\pm$ 14.2	0.730
Pelvic fracture	140	18.4 $\pm$ 18.3	40	18.9 $\pm$ 16.7	0.220
Long bone fracture	111	15.3 $\pm$ 16.3	69	23.6 $\pm$ 19.2	< 0.001
Surgery	69	12.4 $\pm$ 9.5	111	22.3 $\pm$ 20.7	< 0.001
Blunt injury	25	16.7 $\pm$ 14.0	155	29.3 $\pm$ 31.3	0.220

B. Correlations with hospital LOS			
Clinical characteristic	Mean $\pm$ SD	Correlation	P-value <sup>2</sup>
ISS	19 $\pm$ 12	0.20	0.006
Opiates 1 day	101 $\pm$ 113	0.22	0.003
Opiates 3 day	299 $\pm$ 340	0.32	< 0.001

<sup>1</sup>Wilcoxon test; <sup>2</sup>For testing correlation equals zero.



**Figure 3.** Hospital length of stay (LOS) and opiate use. A. LOS correlation with day 1 opiate intake after adjustment for ISS ( $P = 0.0002$ ); B. LOS correlation with 3 day opiate intake after adjustment for ISS ( $P < 0.001$ ). Both length of stay and opiate intake are in log units base 10. 1 was added to opiate intake prior to log transformation as described in the Materials and Methods.

ing for ISS (**Figure 3**); the proportion of variance explained by the model was 0.07 for opiate intake in the first 24 hours and 0.13 for opiate intake in the first 72 hours.

### Opiate intake and LOS

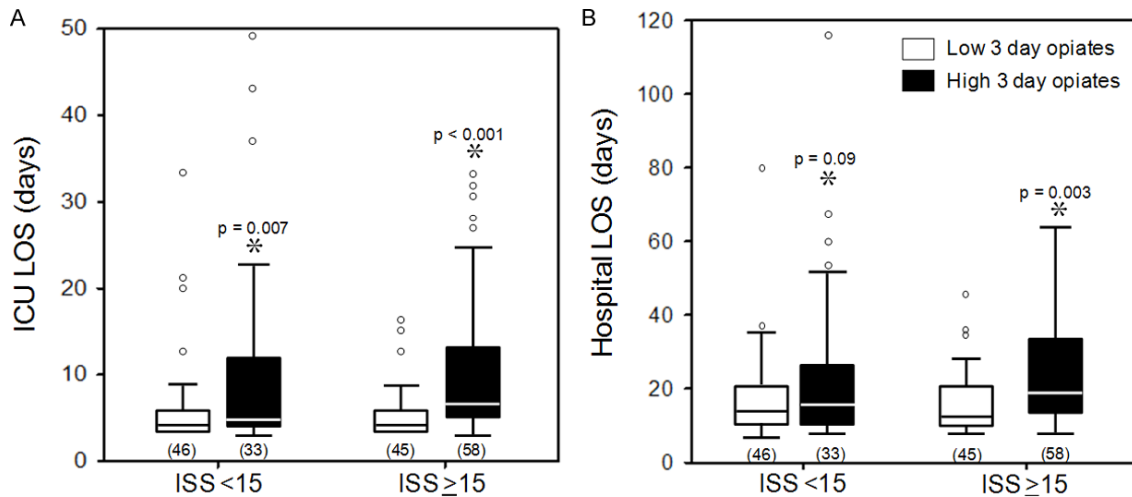
We stratified the entire cohort to those with ISS < 15 and those with ISS  $\geq$  15, dichotomized 3 day opiates to Low ( $\leq$  170 mg/dl) and High (> 170 mg/dl) and compared the opiate groups

with regard to ICU and hospital LOS by strata of ISS (**Figure 4**). Among those with ISS  $\geq$  15, subjects in the High opiate intake stayed between 1 and 3 days more in the ICU ( $P < 0.001$ ) and 6 days longer in the hospital ( $P = 0.003$ ) when compared with the Low opiate intake.

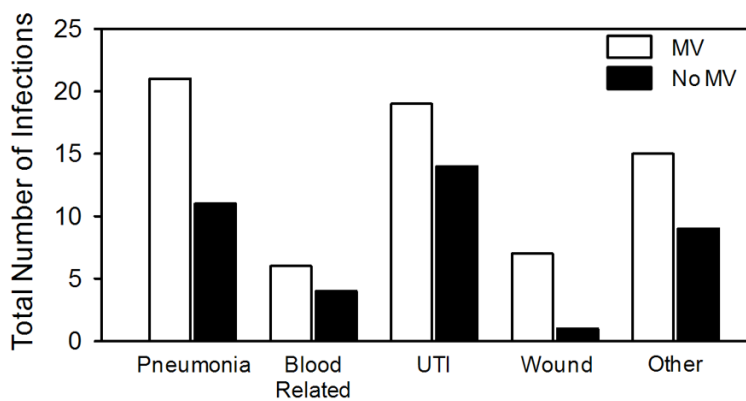
### Opiate intake and infectious complications

In order to more critically evaluate infectious complications specifically, subjects were strati-

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**Figure 4.** Relationship between LOS, opiate use and injury severity. Subjects were stratified based on injury severity (ISS) and LOS and opiate use (low and high) compared. A. ICU LOS; B. Hospital LOS. Data are expressed as median with the 25 and 75 percentiles in original units and *P*-values are based on a linear model of the log transformed LOS. The numbers in the parenthesis represent the number of subjects per group. \**P* < 0.05 as compared with respective low 3 day opiate group.



**Figure 5.** Infections in mechanically ventilated and non-mechanically ventilated patients. Infections were evaluated in 179 trauma patients with regard to mechanical ventilation (MV) and infection type [pneumonia, blood related infections, urinary tract (UTI), wound or other].

ified into three equally sized groups based on injury severity score (ISS < 10, ISS from 10-24, and ISS > 24). These groups parallel the clinical stratification of patients representing those with mild, moderate, and severe injuries. Intra-group comparisons were conducted by dividing the group into those patients that had “high” opiate usage and those that had “low” opiate usage. For comparison “high” and “low” were deemed to be those patients within the group that used more or less opiates than the mean of the group. Analyses conducted involved com-

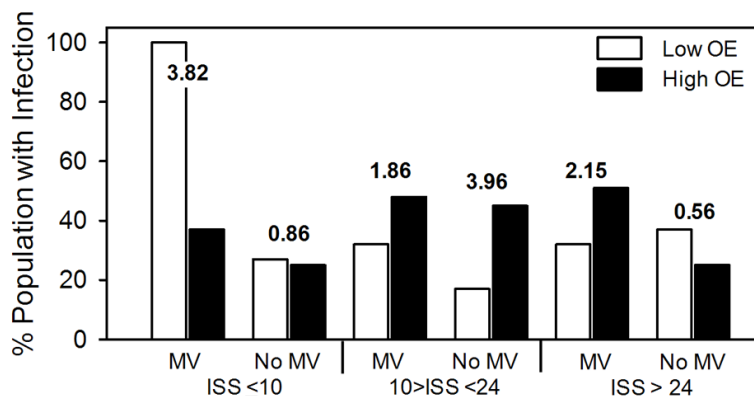
paring infection rate, length of stay, and mechanical ventilator usage.

Further analyses were performed on the intermediate ISS group (ISS of 10-14) by adding an additional 116 randomly selected subjects specific to this group. It is speculated that this group is the most clinically relevant where interventions could make the most difference on length of stay given the intermediate degree of injury. The same inclusion and exclusion criteria were utilized when selecting these additional 116 sub-

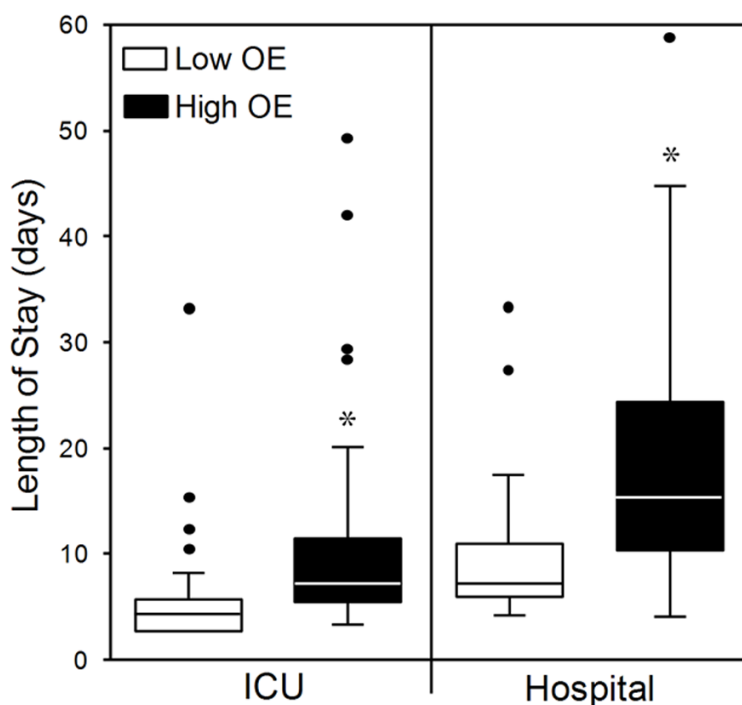
jects. All documented infections were confirmed by culture results. The various classifications of the infections between those subjects with and without mechanical ventilation are displayed in **Figure 5**. The subjects that were mechanically ventilated had a higher rate of pneumonia, bacteremia, urinary tract infection, and wound infection.

The rate of infection in those subjects who required high versus low opiate dosages stratified for mechanical ventilation, and injury sever-

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**Figure 6.** Infection rates in mechanically ventilated and non-mechanically ventilated patients. Infection rates were evaluated in 179 trauma patients with regard to mechanical ventilation (MV) ISS score (ISS < 10, ISS > 10, but < 24 and ISS > 24) and opiate use [low opiate equivalents (OE), and high OE] as described in the Materials and Methods. The odds ratios comparing the low OE and high OE groups are shown.



**Figure 7.** Impact of opiate intake on LOS in the intermediate ISS group. ICU and hospital LOS were compared in the intermediate ISS group (ISS > 10, but < 24) with regard to OE intake during the first 3 days after admission. Data are expressed as median with the 25 and 75 percentiles. \*P < 0.001 as compared with the respective Low OE group.

ity score is displayed in **Figure 6**. Each injury severity group was compared separately stratifying for the use of a mechanical ventilator and then comparing the infection rate in those with

high versus low opiate usage. The presence of mechanical ventilation increased the infection rate in those with a low ISS and those with a high ISS. However, in the group with an intermediate ISS, opiate intake had a significant impact on infection rate after correction for mechanical ventilation. Specifically, those with an intermediate injury who did not receive mechanical ventilation had an odds ratio of 3.958 for infection if given an increased dose of opiates over the first 72 hours of admission.

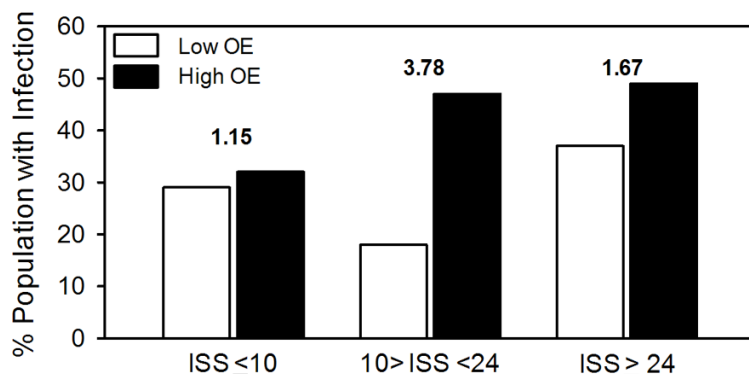
Finally, the intermediate injury group (ISS 10-24) was studied in depth to examine correlation between length of stay and opiate usage at 72 hours (**Figure 7**). The main reason that the middle ISS group was examined in depth was not only that it was the group of subjects who clinically represented the patients where the most impact could be made with different care strategies, but also that the data showed that this group had the greatest difference in infection rate between high and low opiate usage. The odds ratio for infection in the moderate injury group when given a high opiate regiment was 3.78. The other injury severity groups did not display this correlation. The findings are displayed in **Figure 8**.

### Discussion

After initial stabilization, the key components of major trauma include resuscitation, specific injury treatment and

appropriate pain control. Pain and the inability to treat it increases endogenous catecholamine activity, may delay recovery, lead to a prolonged hospital stay, and increase medical

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**Figure 8.** Relationship between infection rates, ISS score and opiate use. Infection rates were evaluated in 179 trauma patients with regard to OE intake during the first 3 days after admission and ISS score (ISS < 10, ISS > 10, but < 24 and ISS > 24) as described in the Materials and Methods. The odds ratios comparing the low OE and high OE groups are shown.

costs [4]. Our results show that the amount of opiate analgesia administered during the first 3 days positively correlated with ICU and hospital length of stay in trauma patients admitted to the ICU and that this correlation was independent of injury severity. This has potential implications for clinicians, as opiate analgesia forms the cornerstone of pain control in the ICU.

Sedative and analgesic practices vary in ICUs around the world, with some physicians opting to use opiates for the “double effect” of analgesia and sedation, thereby reducing the need for benzodiazepines or propofol [16]. In fact, fentanyl or remifentanyl infusion may be used for its sedative properties in addition to its analgesic indication. This practice leads to differences in duration of mechanical ventilation as reported by Breen et al., supporting the concept that specific opiates have particularly good profiles and desirable side effects [17].

Oderda et al [8, 9], showed the effect of opioid-related adverse drug events in terms of length of stay and total hospital costs in a non-acute setting of surgical patients. Our results, however, show a greater effect on ICU and hospital days than those generally reported in a non-ICU surgical service. While a routine surgical patient might have a half day longer hospital LOS as a consequence of developing an opiate-related adverse drug event, our data shows an increased LOS of up to 6 days with high opiate intake when compared with a similarly injured group of patients who received less opiates. Although in our analysis we did not account for

specific adverse drug events, the variability explained by our final model ( $R^2 = 0.16$ ) was in the range ( $R^2 = 0.15-0.34$ ) reported by other authors [18, 19]. An increased ICU length of stay with increased ICU intake suggests that opiate-related consequences have a proportionally higher effect given the critical condition of this patient population with dysfunctional drug metabolism, altered volume of distribution, opiate pharmacokinetic changes and possible interactions with exogenous factors (multiple medication interactions). Indeed, prolonged ICU stay and mechanical ventilation are well-known risk factors for ICU-acquired infections [20]. Increased cost is also a critical aspect to be considered, when expenses are particularly higher in this type of service.

Over the past decade, the implementation of evidence-based measures as standard of care (aggressive resuscitation, source control of infection, antibiotics) has shown to improve survival. A well-recognized area of outcome improvement is early recovery and reduced ICU and hospital stay. Some of the causative factors for post-trauma morbidity and mortality may be in part related to therapeutic regimes employed in the treatment of such patients. In this regard, efforts should be focused on the development of pain management protocols that might combine opiate and non-opiate medications and/or complementary non-pharmacologic interventions. For compassionate and rational ICU care, pain must be addressed and minimized through effective treatments and modalities. The use of opiates is the current and most likely future foundation of such treatments, but we have shown that higher doses are associated with poorer overall outcomes, suggesting that alternative strategies might be developed and considered should a threshold be reached. Such strategies would reduce overall opiate intake and the risk of side effects and consider patient dependent factor (previous renal or hepatic dysfunction, previous medications), active illness (sepsis, injuries, MODS) and possible medication interactions. Such innovations might include opiate rotation,



based on the assumption of incomplete cross-tolerance between different opiates, which has been a previously proposed strategy that may allow for improved pain control while controlling for adverse effects and decreasing overall opiate dose [21]. Another would be increased use of moderate sedation for painful procedures. Despite the potential benefit of certain principles of pain management, its applicability to surgical critically-ill patients should be based on well-controlled investigations. In this regard, further research is warranted in a retrospective and prospective design to determine susceptible patient populations at higher risk of developing complications related to the use of opiates. Additionally, based on a particular pharmacodynamic and pharmacokinetic profile of a specific opiate analgesic, guides of administration might be implemented along with further research to develop molecules with minimal side effects and interactions.

While length of stay is a marker for complications, it is more important to examine specific complications in depth in order to determine the role that complications play in additional hospital and ICU days. The increased infection rate in those subjects with an ISS of 10 to 24 is very important. Those patients with an ISS of < 10 can be considered minimally injured and should have a relatively short hospital stay. Those subjects with an ISS > 24 are by definition severely injured, and a prolonged hospital stay is not unexpected. However, this intermediately injured group represents a population where intervention may very well determine the length of stay. We show that the length of stay of those in this group is associated with an increased opiate usage. There is no causation shown in this study, as it is a retrospective review; however, it raises the issue of pain control regimes in moderately injured individuals. A reliance on opiate analgesia may contribute to increased length of stay in a group of subjects that would otherwise be able to leave the hospital earlier if not for an infection or other complication. Importantly, these findings need to be validated in a randomized controlled trial comparing pain regimens with differing levels of opiate usage.

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### Disclosure of conflict of interest

None.

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