Impact of age, sex and route of administration on adverse events after opioid treatment in the emergency department: A retrospective study

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BACKGROUND: The efficacy of opioids for acute pain relief in the emergency department (ED) is well recognized, but treatment with opioids is associated with adverse events ranging from minor discomforts to life-threatening events.
OBJECTIVE: To assess the impact of age, sex and route of administration on the incidence of adverse events due to opioid administration in the ED.
METHODS: Real-time archived data were analyzed retrospectively in a tertiary care urban hospital. All consecutive patients (≥16 years of age) who were assigned to an ED bed and received an opioid between March 2008 and December 2012 were included. Adverse events were defined as: nausea/vomiting (minor); systolic blood pressure (SBP) <90 mmHg, oxygen saturation (Sat) <92% and respiration rate <10 breaths/min (major) within 2 h of the first opioid doses.
RESULTS: In the study period, 31,742 patients were treated with opioids. The mean (± SD) age was 55.8±20.5 years, and 53% were female. The overall incidence of adverse events was 12.0% (95% CI 11.6% to 12.4%): 5.9% (95% CI 5.6% to 6.2%) experienced nausea/vomiting, 2.4% (95% CI 2.2% to 2.6%) SBP <90 mmHg, 4.7% (95% CI 4.5% to 4.9%) Sat that dropped to <92% and 0.09% respiration rate <10 breaths/min. After controlling for confounding factors, these adverse events were associated with: female sex (more nausea/vomiting, more SBP <90 mmHg, less Sat <92%); age ≥65 years (less nausea/vomiting, more SBP <90 mmHg, more Sat <92%); and route of administration (intravenous > subcutaneous > oral).
CONCLUSIONS: The incidence of adverse events associated with opioid administration in the ED is generally low and is associated with age, sex and route of administration.

Key Words: *Adverse events; Age effect; Emergency department; Sex; Opioid*

Les effets de l'âge, du sexe et de la voie d'administration sur les effets indésirables après un traitement aux opioïdes à la salle d'urgence : une étude rétrospective

HISTORIQUE : L'efficacité des opioïdes pour soulager la douleur aiguë à la salle d'urgence ne fait aucun doute, mais elle s'associe à des effets indésirables oscillant entre des malaises mineurs et des problèmes potentiellement mortel.
OBJECTIF : Évaluer les effets de l'âge, du sexe et de la voie d'administration sur l'incidence des effets indésirables causées par les opioïdes à l'urgence.
MÉTHODOLOGIE : Les chercheurs ont procédé à l'analyse rétrospective des données archivées en temps réel dans un hôpital de soins tertiaires en milieu urbain. Tous les patients consécutifs (16 ans ou plus) sur civière à l'urgence et qui ont reçu un opioïde entre mars 2008 et décembre 2012 en faisaient partie. Les effets indésirables étaient définies comme des nausées ou des vomissements (mineure), une tension artérielle systolique (TAS) inférieure à 90 mmHg, une saturation en oxygène (Sat) inférieure à 92 % et une fréquence respiratoire inférieure à dix respirations à la minute (majeure) dans les deux heures suivant les premières doses d'opioïdes.
RÉSULTATS : Pendant la période de l'étude, 31 742 patients ont reçu des opioïdes. Ils avaient un âge moyen (± ÉT) de 55,8±20,5 ans et 53 % étaient des femmes. L'incidence globale de effets indésirables était de 12,0 % (95 % IC 11,6 % à 12,4 %). Ainsi, 5,9 % (95 % IC 5,6 % à 6,2 %) ont souffert de nausées et de vomissements, 2,4 % (95 % IC 2,2 % à 2,6 %) d'une TAS inférieure à 90 mmHg, 4,7 % (95 % IC 4,5 % à 4,9 %) d'une Sat qui avait chuté à moins de 92 % et 0,09 % d'une fréquence respiratoire inférieure à dix respirations à la minute. Après contrôle des facteurs de confusion, ces effets indésirables s'associaient au sexe féminin (plus de nausées et de vomissements, plus de TAS < 90 mmHg, moins de Sat < 92 %), à un âge de 65 ans ou plus (moins de nausées et de vomissements, plus de TAS < 90 mmHg, plus de Sat < 92 %) et à la voie d'administration (voie intraveineuse > voie sous-cutanée > voie orale).
CONCLUSIONS : L'incidence de effets indésirables associées aux opioïdes à l'urgence est généralement faible et s'associe à l'âge, au sexe et à la voie d'administration.

Opioids, especially morphine, are medications of choice for emergency department (ED) patients with acute pain (1,2). The efficacy of opioids in acute pain relief in EDs is well recognized but is associated with adverse events, such as dizziness, nausea and/or vomiting, sedation, oxygen desaturation, delirium, hypotension and pruritus (3). The short-term incidence of these adverse events in EDs ranges from 4% to 46% because study samples are small and adverse event reporting is highly variable (4).

Several factors appear to be linked with opioid-induced adverse events. Women report more nausea/vomiting (5-8), older patients are more at risk of respiratory depression (8) and repeated opioid doses are associated with more adverse events (9-11). The intravenous (IV) route is also generally associated with more adverse events than the intramuscular and subcutaneous (SC) routes (8). Although the safety and efficacy of IV opioid administration have been frequently investigated (2,12-16), no study has specifically compared the effects of different routes of opioid administration in the ED on the frequency and severity of adverse events.

The objective of the present study was to ascertain, in a large cohort of ED patients, the incidence of adverse events after opioid exposure and their relationship to route of administration, sex and age. We hypothesized that the IV route would elicit more adverse events in general than the SC, intramuscular and oral (PO) routes, that women would experience more nausea/vomiting than men, and that patients

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TABLE 1
Hospital and patient characteristics for the entire sample (n=31,742)

Characteristic	
Emergency department bed patients per year, n	25,107
Age, years	
<65	64.3
≥65	35.7
Sex	
Male	47.5
Female	52.5
Triage priority	
High (1 or 2)	44.9
Low (3, 4 or 5)	55.1
Type of arrival	
Walk-in	47.3
Ambulance	52.7
Route of administration	
Intravenous	52.8
Subcutaneous	9.1
Oral	38.1
Coanalgesia	41.0
Disposition after emergency department	
Discharged	47.0
Admitted	53.0
Visit duration, h, median (Q25–Q75)	15.8 (8.4–26.2)

Data presented as % unless otherwise indicated. Q Quartile

≥65 years of age would experience greater oxygen saturation (Sat) declines compared with younger subjects.

METHODS

Study design and setting

Real-time, archived data from a computerized system used in the ED of a tertiary, academic, urban hospital with an annual census of approximately 60,000 ED visits were retrospectively analyzed. This computerized system includes demographic data, triage information as well as pertinent data collected by nurses during ED visits, such as medication prescribed (type, route of administration and time of treatment), observations relative to side effects or adverse events from medication administration and subsequent evaluations of vital signs. All data were collected in real time and were time-stamped. The study was approved by the institutional ethics review board.

Selection of participants

All consecutive patients ≥16 years of age assigned to an ED bed and who received an opioid treatment between March 2008 and December 2012 were selected. To ensure sufficient data for statistical comparisons, the search was restricted to the most common opioid/route of administration combinations, which represented at least 90% of all opioid treatments given in the ED. To eliminate possible medication or route of administration interaction effects, patients who received more than one type of opioid or route of administration during the study period were excluded from the final analysis. For example, patients who received two types of opioids PO or the same opioid PO and IV were excluded. Patients who received opioids for palliative care, pregnant women (due to physiological differences) and patients transferred from or to another hospital (who may have received an opioid treatment before the initial recorded opioid dose) were also excluded.

Data collection and outcome

Sex, age, triage level (high = 1 or 2 versus low = 3, 4 or 5), means of arrival (walk-in or ambulance), time of arrival at and release from the ED, disposition (admitted or discharged), comorbidities, history of asthma or chronic obstructive pulmonary disease (COPD), coanalgesia (nonopioids) before opioid administration, benzodiazepine use before opioid administration, tachycardia (heart rate >100 beats/min) and fever (oral temperature >37.8°C) before opioid administration, and vital signs before and 2 h after opioid administration were extracted from the database.

For equivalent comparisons between opioid/route combinations, the initial cumulative doses that patients received was computed as a morphine equipotent parenteral (MEP) dose of 1 mg: 1 MEP equals 1 mg of parenteral morphine, 3 mg of oral morphine, 2 mg of oral oxycodone, 0.01 mg of parenteral fentanyl, 0.15 mg of parenteral hydromorphone and 0.75 mg of oral hydromorphone (17).

The primary outcome was the presence of one or more adverse events within 2 h of the first opioid dose; these events are defined in the present study as adverse events. As in previous studies, nausea/vomiting was considered a minor adverse event, and systolic blood pressure (SBP) <90 mmHg, Sat <92% and respiration rate (RR) <10 breaths/min were considered to be major adverse events. Global adverse events refers to minor and major adverse events combined. These adverse events were retained because they are the most clinically significant. Information regarding delirium or level of sedation in the database used in the present study was not sufficiently reliable to be reported, and desaturation was used as a surrogate for sedation. To be identified, these adverse events had to be absent before the opioid administration and occur within 2 h after initial opioid doses. Whether patients with adverse events differed with regard to ED length of stay or rate of hospital admissions compared with patients without adverse events was also evaluated.

Statistical analysis

One-way ANOVAs were used to compare the effects of eight opioid/route combinations on vital signs. Univariate associations between adverse events and patient/treatment characteristics were assessed using χ^2 tests and *t* tests for independent groups. Because of the large sample size, Cohen's effect sizes (ESs) are reported instead of significance level. To interpret the importance of different ESs, Cohen designated 0.1 as small, 0.3 as medium, and 0.5 as large from χ^2 and Mann-Whitney U-test analyses; 0.2 as small, 0.5 as medium and 0.8 as large from *t* test analyses, and 0.10 as small, 0.25 as medium and 0.40 as large from one-way ANOVAs. Multivariate logistic regression analyses examined the unique contribution of sex, age, route of administration and type of opioid to each adverse event, controlling for confounding factors: MEP, coanalgesia, benzodiazepine use, number of comorbidities, history of asthma or COPD, tachycardia or fever. The logistic regression results are reported with ORs (higher risk if >1 and lower risk if <1) and associated 95% CIs. The alpha level was set at 0.01 for ORs. All data were analyzed using SPSS version 20 (IBM Corporation, USA).

RESULTS

The eight most common opioid/route combinations, which included 98% of all opioid treatments given in our ED, were: morphine/IV (30.1%), oxycodone/PO (27.2%), fentanyl/IV (20.7%), hydromorphone/PO (6.4%), morphine/SC (5.6%), morphine/PO (3.7%), hydromorphone/SC (3.2%) and hydromorphone/IV (1.1%). During the targeted study period, 32,623 patients received one of the eight combinations. Some patients (2.7%) were excluded because they received multiple types of opioid treatment during the study period or met other exclusion criteria, leaving a total of 31,742 patients eligible for final analysis. Patient characteristics are summarized in Table 1. The mean patient age was 55.8±20.5 years, and 53% were female. More than one-half of patients received IV treatments (mainly morphine and fentanyl). Oxycodone was the medication used most often, through the PO route of administration. Table 2 displays the vital signs before (ie, the measurement closest to) opioid administration as a function of the eight opioid/route combinations. Before opioid administration, vital signs were clinically similar for all opioid/route combinations (with small ESs ranging from 0.10 to 0.14). The incidence of RR

TABLE 2
Vital signs before opioid administration for the eight opioid/route combinations

Opioid/route combination	Heart rate, beats/min	Systolic blood pressure, mmHg	Oxygen saturation, %	Respiratory rate, breaths/min
Morphine/intravenous	81.3±16.6	135.2±21.8	97.5±1.9	17.8±3.3
Oxycodone/oral	80.0±15.3	133.3±21.7	97.2±2.0	17.2±2.6
Fentanyl/intravenous	84.9±20.0	129.3±24.5	97.7±2.3	18.1±3.9
Hydromorphone/oral	82.1±16.1	132.1±21.6	96.8±2.1	17.4±2.7
Morphine/subcutaneous	83.9±17.7	131.1±22.6	96.8±2.5	18.2±3.7
Morphine/oral	80.6±15.3	132.7±20.9	96.9±2.1	17.3±2.6
Hydromorphone/subcutaneous	84.8±17.8	130.6±21.0	97.1±2.2	17.7±2.9
Hydromorphone/intravenous	83.5±17.1	133.0±21.5	97.5±1.9	17.9±3.3
Effect size	0.11	0.10	0.12	0.14

Data presented as mean ± SD unless otherwise indicated. Effect size was calculated by one-way ANOVAs

TABLE 3
Incidence of adverse events according to patient and treatment characteristics

	Nausea/vomiting		SBP <90 mmHg		Saturation <92%		Major adverse events		Global adverse events	
Variable	**%**	**ES**	**%**	**ES**	**%**	**ES**	**%**	**ES**	**%**	**ES**
Overall (n=31,742)	5.9		2.4		4.7		6.7		12.0	
Sex										
Male	5.0	0.04	2.3	<0.001	5.3	0.03	7.3	0.02	11.6	0.01
Female	6.8		2.4		4.1		6.2		12.3	
Age, years										
<65	6.7	0.05	2.2	0.01	4.0	0.04	6.0	0.04	12.0	0.002
≥65	4.5		2.6		5.8		8.0		11.9	
Opioid dose, MEP, mean ± SD										
With adverse event	7.1±4.5	0.44*	7.7±6.3	0.46*	7.6±4.9	0.53*	7.6±5.3	0.53*	7.4±5.0	0.51*
Without adverse events	5.2±4.1		5.3±4.1		5.2±4.1		5.2±4.0		5.1±4.0	
Comorbidity										
0	6.5	0.03	3.3	0.04	4.1	0.03	7.0	0.02	12.7	0.01
1	6.7		1.9		4.3		5.9		12.0	
>1	5.2		2.0		5.2		7.0		11.5	
History of asthma or COPD										
Yes	4.6	0.02	2.6	0.005	5.1	0.007	7.4	0.009	11.6	0.004
No	6.1		2.3		4.6		6.6		12.0	
Coanalgesia										
Yes	4.8	0.04	1.5	0.05	3.4	0.05	4.8	0.06	9.2	0.07
No	6.6		3.0		5.5		8.1		13.9	
With benzodiazepine										
Yes	11.3	0.09	3.1	0.02	5.6	0.02	8.3	0.02	18.5	0.08
No	5.1		2.2		4.5		6.5		11.0	
With tachycardia										
Yes	6.4	0.008	4.5	0.06	5.3	0.01	9.3	0.04	14.8	0.04
No	5.8		2.0		4.5		6.3		11.5	
With fever										
Yes	4.3	0.02	2.8	0.008	5.0	0.004	7.4	0.008	11.2	0.007
No	6.0		2.3		4.6		6.7		12.0	
Administration route										
Oral	2.4	0.12	0.6	0.10	1.2	0.14	1.8	0.17	4.0	0.21
Subcutaneous	5.7		1.7		2.6		4.1		9.3	
Intravenous	8.5		3.7		7.5		10.7		18.2	
Opioid type										
Oxycodone	2.5	0.10	0.7	0.13	1.2	0.12	1.8	0.15	4.1	0.17
Fentanyl	7.2		6.1		6.5		11.7		18.0	
Morphine	7.9		1.9		6.6		8.3		15.4	
Hydromorphone	4.5		1.0		2.8		3.7		7.9	

**Effect size (ES) calculated by* t *test; other ESs were calculated by* χ^2 *test. COPD Chronic obstructive pulmonary disease; MEP Morphine equipotent parenteral dose*

<10 breaths/min was negligible (0.09%) and, therefore, was not reported in subsequent analyses.

The overall incidence of adverse events was generally low: 5.9% (95% CI 5.6% to 6.2%) of patients experienced nausea/vomiting, 2.4% (95% CI 2.2% to 2.6%) SBP <90 mmHg, 4.7% (95% CI 4.5% to 4.9%) Sat <92% and 12.0% (95% CI 11.6% to 12.4%) reported at least one of these three adverse events. Table 3 reports associations between each adverse event and sex, age, administration route, opioid

TABLE 4
Adjusted OR (95% CI) of adverse events according to patient and treatment characteristics

Variables	Nausea/vomiting	SBP <90 mmHg	Saturation <92%	Major adverse events	Global adverse events
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	**1.62 (1.46–1.78)**	**1.27 (1.09–1.48)**	**0.82 (0.74–0.92)**	0.95 (0.86–1.04)	**1.25 (1.16–1.34)**
Age, years					
<65	Reference	Reference	Reference	Reference	Reference
≥65	**0.82 (0.73–0.92)**	**1.65 (1.39–1.96)**	**2.04 (1.81–2.31)**	**1.93 (1.74–2.14)**	**1.34 (1.24–1.46)**
Opioid dose (for each 5 MEP increase)	**1.25 (1.24–1.26)**	**1.31 (1.29–1.32)**	**1.37 (1.36–1.38)**	**1.38 (1.36–1.40)**	**1.37 (1.36–1.38)**
Comorbidity					
0	Reference	Reference	Reference	Reference	Reference
1	1.08 (0.95–1.23)	**0.66 (0.53–0.81)**	1.09 (0.93–1.28)	0.91 (0.79–1.03)	1.00 (0.91–1.11)
>1	0.98 (0.87–1.11)	**0.62 (0.51–0.75)**	**1.32 (1.14–1.52)**	1.04 (0.92–1.17)	1.01 (0.92–1.11)
History of asthma or COPD					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.83 (0.69–1.00)	**1.41 (1.10–1.80)**	1.15 (0.97–0.1.38)	**1.23 (1.06–1.43)**	1.07 (0.94–1.21)
Coanalgesia					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.98 (0.89–1.09)	0.86 (0.72–1.04)	0.91 (0.81–1.03)	0.90 (0.82–1.00)	0.94 (0.87–1.02)
With benzodiazepine					
No	Reference	Reference	Reference	Reference	Reference
Yes	**2.22 (1.98–2.48)**	1.26 (1.00–1.53)	1.16 (1.00–1.34)	**1.18 (1.05–1.34)**	**1.71 (1.57–1.88)**
With tachycardia					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.00 (0.87–1.14)	**1.83 (1.54–2.17)**	1.05 (0.91–1.22)	**1.31 (1.17–1.47)**	**1.17 (1.07–1.29)**
With fever					
No	Reference	Reference	Reference	Reference	Reference
Yes	**0.67 (0.54–0.84)**	1.21 (0.90–1.61)	1.11 (0.89–1.38)	1.13 (0.94–1.35)	0.90 (0.77–1.04)
Administration route					
Oral	Reference	Reference	Reference	Reference	Reference
Subcutaneous	**2.44 (1.81–3.30)**	**2.56 (1.43–4.58)**	**1.90 (1.28–2.83)**	**2.07 (1.48–2.89)**	**2.23 (1.77–2.81)**
Intravenous	**4.21 (3.12–5.67)**	**3.39 (1.90–6.06)**	**7.30 (5.04–10.58)**	**6.10 (4.43–8.39)**	**5.18 (4.13–6.49)**
Opioid type					
Morphine	Reference	Reference	Reference	Reference	Reference
Fentanyl	**0.80 (0.71–0.91)**	**2.50 (2.10–2.97)**	**0.73 (0.64–0.83)**	1.07 (0.96–1.18)	0.96 (0.88–1.04)
Hydromorphone	1.19 (0.96–1.48)	0.90 (0.59–1.39)	1.15 (0.88–1.50)	1.09 (0.86–1.38)	1.15 (0.97–1.36)
Oxycodone	1.43 (1.00–1.96)	1.34 (0.73–2.48)	1.19 (0.79–1.79)	1.27 (0.90–1.80)	**1.35 (1.06–1.71)**

n=31,742 for all logistic regressions. Reference: level used as the basis to calculate the OR. Bolded values indicate P<0.01. COPD Chronic obstructive pulmonary disease; MEP Morphine equipotent parenteral dose

type and confounding factors. The effect of dose was significant for all adverse events; patients with adverse events received a mean MEP dose that was 1.5 times higher than that of patients without adverse events. Administration route and opioid type were associated with adverse events; ESs ranged from 0.10 to 0.21. However, significant ESs with opioid type were expected; this is likely attributable to the unique administration route for certain opioids (ie, oxycodone is only available PO).

After controlling for confounding factors, adverse events were associated with female sex (more nausea/vomiting, more SBP <90 mmHg, fewer Sat <92% events) and age ≥65 years (more SBP <90 mmHg, more Sat <92%, fewer nausea/vomiting events). The IV route was linked with higher rates of all adverse events, the SC route with moderate rates, and the PO route with fewer overall rates (Table 4). Higher opioid doses were generally associated with more adverse events, a history of asthma or COPD with more SBP decreases, previous benzodiazepine administration with generally more nausea/vomiting events and tachycardia with more declines in SBP. Fentanyl was coupled with fewer nausea/vomiting events, more SBP <90 mmHg events and fewer Sat <92% events than morphine. Oxycodone was linked to adverse events in general (mainly due to a trend in nausea/vomiting events), but not to a specific adverse event.

Associations between specific adverse events and length of stay at ED or hospital admission are reported in Table 5. Median length of stay did not appear to differ in patients with or without adverse events. A higher hospital admission rate was observed for patients with SBP <90 mmHg; however, the effect size was small.

DISCUSSION

The incidence of nausea/vomiting, SBP <90 mmHg or Sat <92% events after opioid administration in the ED was generally low (12%), but it was clearly associated with age, sex, dose and administration route. Our hypothesis – that the IV administration route produces more adverse events than the SC/PO routes – was confirmed, as observed by others (8). Moreover, the administration route is the most prominent factor influencing adverse events, with the IV route presenting a fourfold increase in the odds of producing nausea/vomiting or a SBP decline and a sevenfold increase in desaturation induction compared with the PO route. Our results show that the SC route has higher ORs (ranging from 1.9 to 2.6) for eliciting adverse events than the PO route.

We have also confirmed findings from previous studies with much smaller sample sizes: women have more nausea/vomiting events than men, patients ≥65 years of age have more oxygen desaturation events

than younger subjects (5-8), and higher opioid doses are associated with more adverse events, but this appears to be less significant than the effect of administration route (9-11). Women appear to report more intense, numerous and frequent physical symptoms compared with men. This could be explained by an innate difference in somatic and visceral perception (18). The findings that patients ≥65 years of age have more oxygen desaturation events could be explained by pharmacokinetic and pharmacodynamic changes associated with age (8). Also interesting is the fact that older patients appear to be less affected by nausea/vomiting than younger patients and that women appear to be less prone to desaturation than men.

The very low incidence of RR <10 breaths/min events was surprising because RR is believed to decrease before a drop in oxygen saturation. This could be explained by the fact that nurses were more aware of oxygen desaturation compared with RR and, while they provide oxygen to patients, they may have neglected to document their RR.

Contrary to our expectations, nonopioid coanalgesia with opioid administration did not significantly reduce the risk of adverse events. A potential explanation could be the low concomitant use of nonopioid coanalgesia in our study population. However, benzodiazepine use before opioid administration appears to slightly increase the risk of adverse events. Finally, a history of asthma or COPD and tachycardia before opioid administration tends to augment the odds of SBP <90 mmHg events.

Fentanyl is usually believed to produce fewer SBP declines (19,20). The present findings could be explained by the retrospective design of our study; patients were not randomly assigned to receive a specific opioid and, thus, fentanyl (being recognized as having less impact on blood pressure) could have been used for patients at risk for significantly decreased SBP and morphine could have been administered to more hemodynamically stable patients. Although we excluded all patients with SBP <90 mmHg events before administration of opioids in our definition of adverse events, the mean level of SBP immediately preceding opioid administration was slightly lower in patients receiving fentanyl IV than in patients receiving morphine (129.3 mmHg versus 134.3 mmHg; difference = 5.0 [95% CI 4.3 to 5.7]).

Contrary to the results of other studies (21), adverse events observed in our patients did not appear to impact ED length of stay, but they were associated with a higher percentage of hospital admissions, especially for patients with SBP <90 mmHg events after opioid treatment. However, the ESs were small and we are unable to determine whether all hospital admissions were directly related to adverse events. To our knowledge, this is the first time that adverse events associated with opioids have been associated with higher rate of hospital admissions. In a meta-analysis of prospective studies, Lazarou et al (21) demonstrated that adverse events (not specifically related to opioid treatment) were a significant cause of hospital admissions, and Davies et al (22) showed that opioids were frequently associated with adverse events in hospitalized patients. Kongkaew et al (23), however, could not implicate opioids as a significant source of adverse events and hospital admission.

TABLE 5
Impact of adverse events on length of stay and hospital admission

Adverse events	Presence	Absence	Effect sizes
Median length of stay, h (25th–75th quartile)			
Nausea/vomiting	15.3 (8.6–24.2)	15.8 (8.4–26.3)	0.008*
SBP <90 mmHg	12.8 (5.7–24.7)	15.8 (8.4–26.2)	0.03*
Oxygen saturation <92%	16.3 (9.2–27.0)	15.7 (8.3–26.2)	0.01*
Major adverse events	15.6 (8.1–26.2)	15.8 (8.4–26.2)	0.006*
Global adverse events	15.5 (8.4–25.3)	15.8 (8.4–26.3)	0.009*
Percent of hospital admission			
Nausea/vomiting	50.2	53.1	0.01
SBP <90 mmHg	72.5	52.5	0.06
Oxygen saturation <92%	60.1	52.6	0.03
Major adverse events	63.5	52.2	0.06
Global adverse events	57.1	52.4	0.03

**Effect sizes were calculated by the Mann-Whitney U-test. SBP Systolic blood pressure*

Our study had potential limitations. Nausea/vomiting events were documented from a text search of nurses' notes in the database. Though extensive text inclusion and exclusion criteria were used, some nausea/vomiting adverse events could have been missed. Additionally, it is possible that nurses omitted or forgot to report these adverse events because of their intense workload. However, database accuracy depends on personnel who enter data, and nurses as well as physicians are well aware of the importance of accurate and detailed charts. A formal survey in our hospital revealed that nurses always reported major adverse events (data not included). Furthermore, our retrospective study may have underestimated the rate of adverse events compared with a prospective study in which a research assistant would systematically ask a list of questions pertaining to adverse events. Finally, data on sleep apnea and obesity, which are factors that could impact the prevalence of oxygen desaturation, were not available in our database.

CONCLUSION

The present large retrospective study showed that the incidence of adverse events related to ED opioid treatment is generally low and is associated with age, sex and route of administration. This is in accordance with previous literature; however, large prospective studies on adverse events associated with opioid use and their impact are needed to confirm these results.

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