Effectiveness of Sublingual Buprenorphine for Pain Control in the ICU

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OBJECTIVES: The objective of this study was to compare pain control and opioid consumption in critically ill patients who were treated with buprenorphine sublingual or oxycodone oral/enteral during ICU admission.

DESIGN: This was a retrospective, parallel, cohort study.

SETTING: General medical or surgical ICUs of a quaternary, urban hospital in Sydney, NSW, Australia.

PATIENTS: Data were obtained for all patients admitted to two general medical or surgical ICU from January 2019 to January 2023. Patients were grouped as those who received buprenorphine sublingual versus oxycodone oral/enteral.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Pain control was compared between a propensity score matched cohort of patients who received buprenorphine versus oxycodone. The primary outcome was the probability of significant pain. A significant pain score was defined as greater than or equal to 4 on the 0–10 Numeric Rating Scale or greater than or equal to 6 on the Behavioral Pain Scale. The study cohort included 1,070 patients (288 buprenorphine and 782 oxycodone). After propensity score matching, there were 288 patients in each group. The mean age of the matched cohort was 64 ± 16 years, 295 (51%) were male, and 359 (62%) had a surgical admission. The median probability of significant pain was 0.16 with buprenorphine and 0.17 with oxycodone (median difference, 0.01; 95% CI, −0.02 to 0.04; $p = 0.50$). Median opioid consumption in oral morphine milligram equivalents (MMEs) was 65 with buprenorphine and 70 with oxycodone (median difference, −1 mg; 95% CI, −10 to 10 mg; $p = 0.73$). Median MME per ICU day was 22 with buprenorphine and 22 with oxycodone (median difference, 1 mg; 95% CI, −2 to 5 mg; $p = 0.38$).

CONCLUSIONS: Buprenorphine sublingual is as effective as oxycodone oral/enteral with regard to pain control and opioid consumption in the ICU. Buprenorphine sublingual is an appropriate option for patients in the ICU who are unable to take oral/enteral medications.

KEY WORDS: analgesia; buprenorphine; critical care; narcotics; opioid analgesics; pain

Most patients in the ICU have moderate-severe pain at rest, upon movement, and during procedures (1). International guidelines for pain in the critically ill provide recommendations for the use of analgesics (1). Opioids remain the mainstay of pain management in most ICU settings and are usually administered IV to enable rapid titration. When possible, patients in the ICU with functioning gastrointestinal tracts may be transitioned from IV to enterally administered opioids. This is to facilitate transition of patients out of the ICU and is part of the ICU liberation bundle (2). The opioid used via enteral administration is predominantly oxycodone (3). However, absorption via the gastrointestinal is highly variable in the critically

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KEY POINTS

Question: Is there a difference in pain control and opioid consumption in critically ill patients who were treated with buprenorphine sublingual or oxycodone oral/enteral during ICU admission.

Finding: In this retrospective, parallel, cohort study, the probability of significant pain was 0.16 with buprenorphine sublingual and 0.17 with oxycodone oral/enteral, which was not significantly different.

Meaning: Buprenorphine sublingual is as effective as oxycodone oral/enteral with regard to pain control in the ICU and is an appropriate option for patients who are unable to take oral/enteral medications.

ill. This is because of altered gastrointestinal perfusion, changes in gastric pH, drug interactions, and altered gastrointestinal motility (4). The latter effect may be mediated by opioids, which may decrease gastrointestinal absorption (5). Thus, alternative approaches to enteral opioids need to be investigated.

Buprenorphine sublingual has some theoretical advantages compared with traditional enterally or orally administered opioids in the critically ill. It is absorbed from the sublingual mucosa, bypassing gastrointestinal tract related absorption barriers (6). It is classified as partial mu-opioid receptor agonist and a kappa receptor antagonist (7). Opioid-induced hyperalgesia is potentiated by the interaction of dynorphins with kappa opioid receptors, which is mitigated by buprenorphine (8–10). However, the effectiveness of buprenorphine sublingual for pain in the in the ICU is unknown. There are no comparative effectiveness studies evaluating buprenorphine sublingual compared with traditional opioids such as oxycodone for pain control in the ICU.

The objective of this study was to compare pain control and opioid consumption in critically ill patients who were treated with buprenorphine sublingual or oxycodone oral/enteral during ICU admission.

MATERIALS AND METHODS

Ethics/Institutional Review Board

The study was approved by the Sydney Local Health District hospital ethics committee prior to data acquisition (Approval No. 2022/ETH02592; Date: 14 December 2022; Title: Effectiveness of Sublingual Buprenorphine for Pain Control in the ICU). All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Study Design

This was a retrospective, parallel, cohort study. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies was followed for all aspects of the study (11). Study design was constructed to emulate a pragmatic clinical trial. This included the selection of patients and matching to minimize bias between groups. The groups for comparison were ICU patients who received buprenorphine sublingual or oxycodone oral/enteral for pain control.

Setting

The study was conducted in a 950 bed, quaternary, urban hospital in Sydney, NSW, Australia. The hospital has a cardiac ICU, neurologic ICU, and two general medical/surgical ICUs. The general medical/surgical ICUs combined have a total of 30 beds, which were included in this study. The ICU has an electronic medical record system (Philips IntelliSpace Critical Care and Anesthesia) (12). The system contains all data used for the study, including demographics, medications, clinical notes, laboratory parameters, and assessments. The ICU also maintains the Australian New Zealand Intensive Care Society Adult Patient Database (ANZICS APD) that is embedded within the electronic medical record (13). The ICU pain management protocol does not specify the use of buprenorphine sublingual or oxycodone oral/enteral. With the exception of a few conditions, the selection of analgesics is based on clinician discretion. ICU physicians and pain specialists are involved with prescribing analgesics. The decision to use buprenorphine sublingual is often based on whether patients are unable to tolerate opioids via the gastrointestinal tract. However, based on the views of the clinician investigators, there was equipoise for using both options in general. The transition from IV to oral or buprenorphine sublingual is based on physicians' discretion and may be initiated during

mechanical ventilation. Pain is assessed in the ICU using a 0–10 verbal Numeric Rating Scale (NRS) for communicative patients or using the Behavioral Pain Scale (BPS) for noncommunicative patients (14). Level of agitation or sedation is assessed using the Richmond Agitation-Sedation Scale (RASS).

Participants

Data were acquired for all patients admitted to the general medical/surgical ICUs from January 1, 2019, to discharged before January 1, 2023. Adult patients (age ≥ 18 yr) were included if they received buprenorphine sublingual or oxycodone oral/enteral during ICU stay. Patients from the neurologic or cardiovascular ICUs were not included. Patients were excluded if they had less than 10 pain scores recorded, received both buprenorphine and oxycodone, an epidural, or transdermal form of buprenorphine, or initiated the intervention greater than 72 hours from ICU admission. The latter criterion was to emulate a clinical trial where upon enrollment the drug would be initiated within a few days of ICU admission.

Variables

Data acquired included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III score, diagnosis (categorized as medical or surgical using the APACHE III nonoperative and operative diagnosis codes) (13), pertinent past medical history prior to hospitalization (opioid use or pain condition, anxiety, depression, and metastatic cancer), mechanical ventilation, renal replacement therapy (RRT), extracorporeal membrane oxygenation, analgesics used (opioid and nonopioids), pain scores (NRS and BPS), sedatives used, RASS scores, occurrence of opioid withdrawal syndrome (OWS), hyperalgesia, ICU length of stay, and death in ICU.

Data Sources and Definitions

All data were obtained via electronic queries from the electronic medical record system (12, 13). The accuracy of the query system has been validated manually against the medical records. While most data were coded, past medical history, occurrence of OWS, and hyperalgesia was queried using text searches of notes. Data were also obtained from the ANZICS APD at the institution. The following definitions were used similar to a previous investigation (15): 1) probability of significant pain: number of pain scores with significant pain divided by the total number of pain scores. A significant pain score is defined as greater than or equal to 4 on the 0–10 NRS or greater than or equal to 6 on the BPS (16). These cutoffs are the thresholds for providing pain management interventions and are defined as moderate or higher-level pain (16). The BPS does not distinguish between scores above this threshold (i.e., moderate vs severe) in terms of pain severity (14). 2) Oral morphine milligram equivalents (MMEs): This was calculated as the cumulative dose used in the ICU and per ICU day to adjust for potential differences in ICU length of stay. This calculation used the equianalgesic ratios from the Australian and New Zealand College of Anaesthetists (17). RASS scores were categorized as normal (–2 to +1), low (< –2), and high (> +1). Probability of RASS within each category was evaluated.

Outcomes

The primary outcome was the probability of significant pain during ICU admission. Secondary outcomes included: 1) opioid consumption during ICU stay measured as MME; 2) duration of mechanical ventilation (calculated in the subset who were mechanically ventilated); and 3) duration of ICU stay. Exploratory outcomes were proportion of patients who had RASS scores that deviated from goal ranges, and ICU mortality.

Study Size

Based on a prior study using the transdermal formulation of buprenorphine and the same outcome measure (15), we estimated that the probability of significant pain to be 0.25 (i.e., number of significant pain scores divided by the total number of pain scores). Assuming a difference in probability of 0.10 with buprenorphine sublingual and using a common SD of 0.3, two-sided alpha of 0.05, and power of 80%, we estimated that 143 patients would be required in each group (286 total). However, there is uncertainty regarding what is considered to be a clinically important effect size and the SD that we may observe. Thus, all patients were included during the study time frame.

Data Analyses

Propensity score matching (1:1 nearest neighbor) was used to match buprenorphine and oxycodone groups. Propensity scores were calculated via logistic regression based on baseline variables. The overlap of the distribution of propensity scores between groups was evaluated visually. A good balance was considered to be a standardized mean difference (SMD) for each variable of less than 0.1 (18). The primary and secondary outcomes were compared using the Wilcoxon rank-sum test as they were not normally distributed and reported as medians. The 95% CIs of the median of differences were calculated using the Hodges-Lehmann estimator (19). Analyses were conducted using STATA software (Version 15; StataCorp, College Station, TX) or R software (Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). The "MatchIt" package in R (Version 4.5.3, Standford, CA) was used for propensity score analysis.

Sensitivity Analyses

Two sensitivity analyses were conducted: 1) Doubly robust analysis of the primary outcome measure. A multivariable analysis in the propensity matched cohort adjusting for all propensity matched variables to account for any residual confounding. 2) Doubly robust analysis of a using modified primary outcome of a median pain score. The NRS ranges from 0 to 10 and the BPS ranges from 3 to 12. The BPS was normalized to 0–10 by reducing the score by 2 points. Except a score of 3 was converted to 0, as this represents no pain on both scales. The median value for each patient was then used as an outcome in the model. A multivariable regression was conducted similar to the first sensitivity analysis.

Subgroup Analyses

A multivariable regression was conducted in the following subgroups of the propensity matched cohort: surgical versus nonsurgical patients, opioid history versus no opioid history, and patients who received mechanical ventilation versus no mechanical ventilation. Opioid requirements as MME were also reported in these subgroups.

RESULTS

Cohort

There were 2,247 patients who received buprenorphine or oxycodone during the study time period. Of these, 1,070 met selection criteria (288 buprenorphine and 782 oxycodone). After propensity score matching, there were 288 patients in each group. **Figure 1** is a flow diagram of the cohort selection. The mean age of the matched cohort was 64 ± 16 years, 295 (51%) were male, 359 (62%) had a surgical diagnosis, mean APACHE III score was 61 ± 23, 217 (37%) received mechanical ventilation, and 130 (23%) had a history of opioid use prior to hospitalization. Before matching, the buprenorphine group appeared to be older, higher APACHE III score, more likely to have a surgical diagnosis, metastatic cancer, receive RRT, and mechanical ventilation (**Table 1**). After matching all variables were balanced and had a SMD less than 0.1 (Table 1; and **Appendix Fig. 1S**, http://links.lww.com/CCM/H414). The distribution of propensity scores showed complete overlap (**Appendix Fig. 2S**, http://links.lww.com/CCM/H414). The baseline comparisons between groups before and after propensity score matching are in Table 1.

Buprenorphine was initiated a median of 33 hours (interquartile range [IQR], 17–45 hr) after ICU admission, with an initial dose of 0.2 mg (IQR, 0.2–0.2 mg), cumulative number of doses of 3 (IQR, 2–6), and cumulative dose of 0.8 mg (IQR, 0.4–1.6 mg). Oxycodone was initiated a median of 22 hours (IQR, 9–41 hr) after ICU admission, with an initial dose of 5 mg (IQR, 5–5 mg), cumulative number of doses of 4 (IQR, 2–6), and cumulative dose of 20 mg (IQR, 10–40 mg) (**Table 1S**, http://links.lww.com/CCM/H414). The type of opioid and nonopioid analgesics used are reported in **Table 2S** (http://links.lww.com/CCM/H414). All analgesics used were similar in both groups. The most common nonopioid analgesic was acetaminophen, which was used in 76% of patients in the buprenorphine group and 73% of patients in the oxycodone group. Pregabalin was used in 4% of patients in the buprenorphine group and 9% of patients in the oxycodone group. Other analgesics used included celecoxib, diclofenac, ibuprofen, meloxicam, and gabapentin, which were each used in less than 3% of patients. The type of sedatives used are reported in **Table 3S** (http://links.lww.com/CCM/H414). All sedatives used were similar in both groups.

Outcomes

The median probability of significant pain was 0.16 with buprenorphine and 0.17 with oxycodone (median difference, 0.01; 95% CI, –0.02 to 0.04; $p = 0.50$) (**Table 2**). This is depicted for each day of ICU stay in **Figure 2**. Median

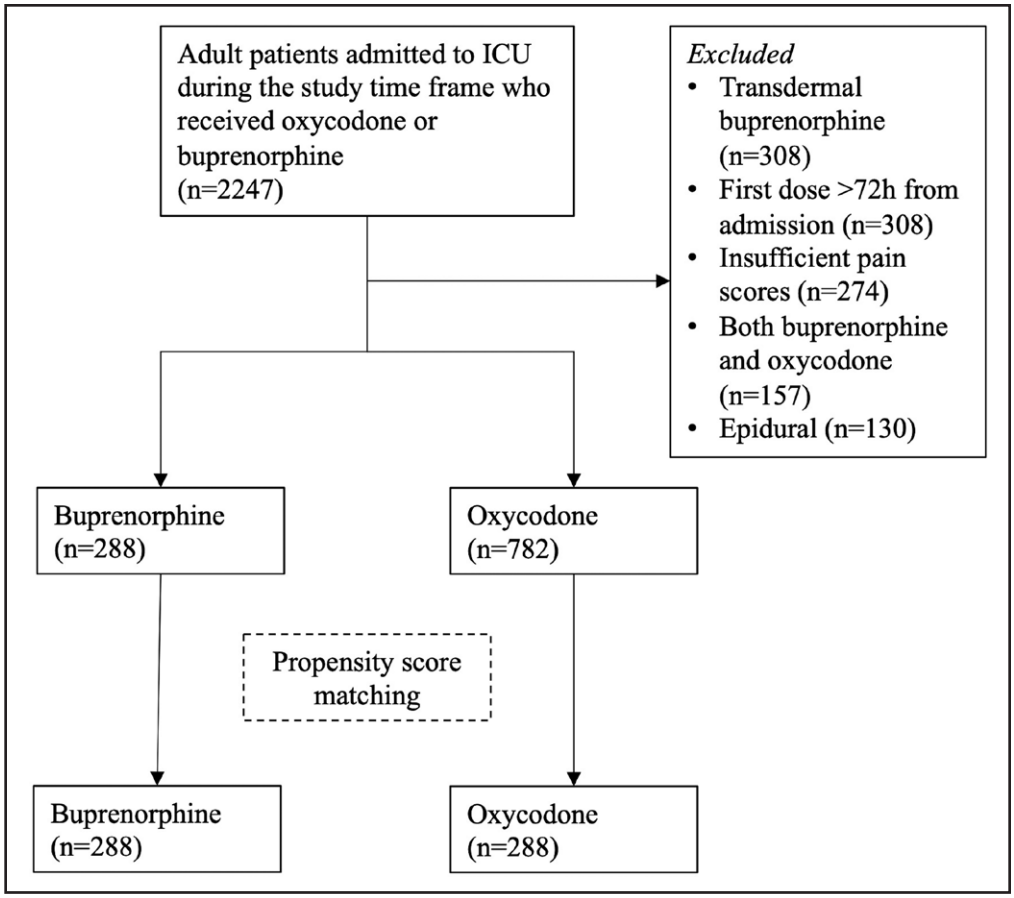

Figure 1. Flow diagram of patient selection.

MME was 65 mg with buprenorphine and 70 mg with oxycodone (median difference, −1 mg; 95% CI, −10 to 10 mg; $p = 0.73$). Median MME per ICU day was 22 mg with buprenorphine and 22 mg with oxycodone (median difference, 1 mg; 95% CI, −2 to 5 mg; $p = 0.38$). Median ventilator days was 0.6 with buprenorphine and 0.7 with oxycodone (median difference, 0.0 mg; 95% CI, −0.1 to 0.2 mg; $p = 0.71$). Median ICU length of stay was 3.4 days with buprenorphine and 3.3 days with oxycodone (median difference, −0.2 d; 95% CI, −0.6 to 0.0 d; $p = 0.10$). In terms of exploratory outcomes, the proportion who died in ICU were similar between buprenorphine 5% ($n = 13$) versus oxycodone 6% ($n = 18$). Similarly, the probability of RASS scores that were high, low or within range were similar between groups (**Table 4S**, http://links.lww.com/CCM/H414). No cases of OWS or hyperalgesia were identified in the study cohort.

Sensitivity and Subgroup Analyses

The sensitivity analyses using doubly robust multivariable adjustment in the propensity matched cohort were consistent with the main results (**Table 5S**, http://links.lww.com/CCM/H414). The subgroup analysis in surgical or nonsurgical, mechanical ventilation versus no mechanical ventilation, opioid history versus no opioid history also did not show a significant difference between buprenorphine and oxycodone (**Tables 6S** and **7S**, http://links.lww.com/CCM/H414).

DISCUSSION

The key finding of this study was that buprenorphine sublingual appeared to be a suitable alternative to oxycodone oral/enteral for pain control in the ICU when patients are transitioned from IV therapy to facilitate ICU discharge. Buprenorphine sublingual can be considered, especially if the gastrointestinal route is not a feasible option for patients. This occurs often in the ICU due to both anatomical and physiologic considerations, where oral/enteral absorption would be insufficient, or if this route of administration is contraindicated.

The groups were well balanced with regard to baseline variables after propensity score matching. Also, other opioids and nonopioids used in the cohort were similar minimizing bias due to the effect of other medications. In addition, our sensitivity analyses helped reduce any residual confounding, which strengthens the results. The results were also similar across subgroups of surgical versus nonsurgical, mechanically ventilated versus no mechanical ventilation, and patients with opioid history versus no opioid history. Thus, there is unlikely to be heterogeneity of effect based on subpopulations.

There are theoretical benefits of using buprenorphine compared with other traditional opioids. Buprenorphine is classified as partial mu-opioid

TABLE 1.
Baseline Comparisons

Characteristic	Full Cohort			Propensity Matched Cohort		
	BUP, *n* = 288, *n* (%)	OXY, *n* = 782, *n* (%)	SMD	BUP, *n* = 288, *n* (%)	OXY, *n* = 288, *n* (%)	SMD
Age (yr)[a]	63.8 (14.9)	57.2 (18.0)	0.44	63.8 (14.9)	63.6 (16.1)	0.01
Sex (male)	151 (52.4)	438 (56.0)	0.07	151 (52.4)	144 (50.0)	0.05
Acute Physiology and Chronic Health Evaluation III[a]	60.7 (20.8)	52.8 (22.7)	0.38	60.7 (20.8)	61.0 (24.0)	0.01
Base pain[a,b]	0.24 (0.28)	0.30 (0.29)	0.22	0.24 (0.28)	0.25 (0.27)	0.04
Base opioid[a,c]	59.4 (83.5)	47.8 (71.8)	0.14	59.4 (83.5)	56.6 (73.7)	0.03
Surgical diagnosis[d]	179 (62.2)	335 (42.8)	0.40	179 (62.2)	180 (62.5)	0.01
Metastatic cancer	28 (9.7)	47 (6.0)	0.13	28 (9.7)	32 (11.1)	0.05
Opioid history	67 (23.3)	179 (22.9)	0.01	67 (23.3)	63 (21.9)	0.03
Anxiety	16 (5.6)	35 (4.5)	0.05	16 (5.6)	13 (4.5)	0.05
Depression	24 (8.3)	53 (6.8)	0.06	24 (8.3)	19 (6.6)	0.06
Renal replacement therapy	23 (8.0)	29 (3.7)	0.16	23 (8.0)	23 (8.0)	0.00
Mechanical ventilation	112 (38.9)	166 (21.2)	0.36	112 (38.9)	105 (36.5)	0.05
Extracorporeal membrane oxygenation	1 (0.4)	1 (0.1)	0.04	1 (0.4)	1 (0.4)	0.00

BUP = sublingual buprenorphine, OXY = oral oxycodone, SMD = standardized mean difference.

[a]Mean (SD).

[b]Probability of significant pain during first 24 hr of ICU stay.

[c]Opioid use during first 24 hr of ICU stay measured in oral morphine milligram equivalents.

[d]Acute Physiology and Chronic Health Evaluation III postoperative diagnosis.

TABLE 2.
Study Outcomes

Outcome	Buprenorphine, *n* = 288, Median (IQR)	Oxycodone, *n* = 288, Median (IQR)	Median Difference[c] (95% CI)	*p*
Primary outcome				
Probability of significant pain[a]	0.16 (0.06–0.39)	0.17 (0.07–0.39)	0.01 (–0.02 to 0.04)	0.50
Secondary outcomes				
Opioid consumption[b]				
ICU total	65 (25–200)	70 (30–201)	–1 (–10 to 10)	0.73
Per ICU day	22 (8–50)	22 (10–58)	1 (–2 to 5)	0.38
Ventilator days	0.6 (0.4–1.4)	0.7 (0.4–1.3)	0.0 (–0.1 to 0.2)	0.71
ICU days	3.4 (2.5–5.1)	3.3 (2.2–4.7)	–0.2 (–0.6 to 0.0)	0.10

IQR = interquartile range.

[a]Defined as the number of pain scores with significant pain divided by the total number of pain scores. Significant pain is defined as pain score greater than or equal to 4 on 0–10 Numeric Rating Scale or ≥ 6 on the Behavioral Pain Scale.

[b]Oral morphine milligram equivalents.

[c]Median difference is not the same as difference of the medians.

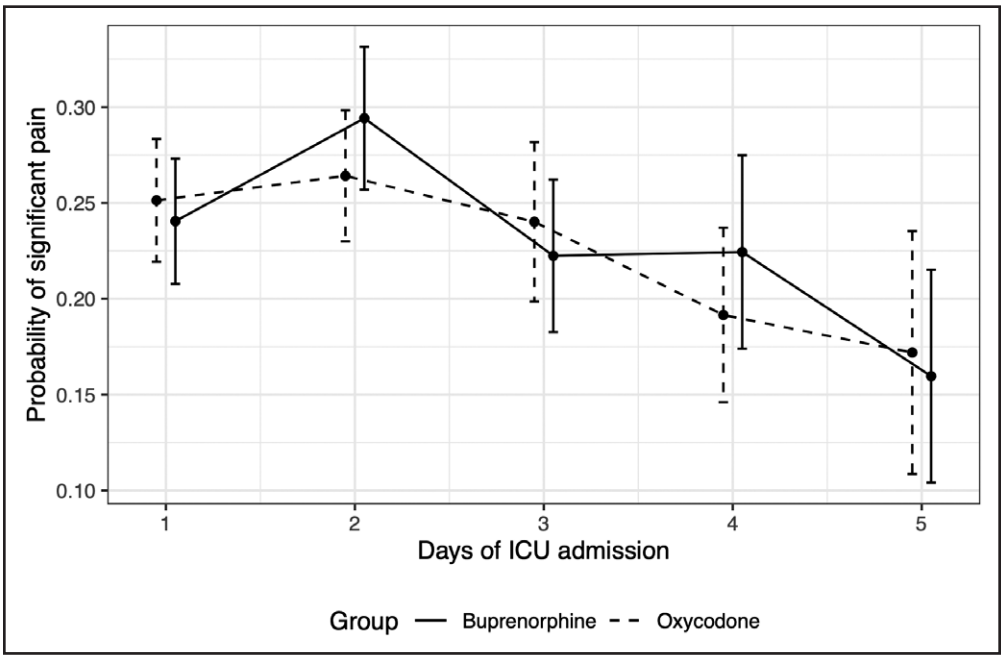

Figure 2. Probability of significant pain. Point estimate for each day is mean probability with 95% CI. Reported up to day 5 as this is the upper quartile based on ICU length of stay.

receptor agonist and is a kappa receptor antagonist (7). However, this classification as a partial agonist based on in vitro effects on receptors is a mischaracterization as it has shown to have similar maximal analgesic effects in humans compared with opioids that are full-agonists (20, 21). It blocks the effect of dynorphins on kappa opioid receptors, and binds to Toll-like receptors, mitigating the development of hyperalgesia (8–10). In patients with hyperalgesia, we would have expected a higher consumption of opioids. However, the results showed similar opioid consumption in both groups. No hyperalgesia was identified in this study.

This is the first study evaluating the use of buprenorphine sublingual in critically ill patients. Thus, there was no basis to juxtapose these findings to previous investigations. There was a previous observational study (n = 375) evaluating the use of transdermal buprenorphine in ICU patients who had undergone major gastrointestinal and genitourinary surgeries, which did not show a benefit compared with not using transdermal buprenorphine (15). In the aforementioned study, oxycodone use was possible in both groups and was not a comparison of buprenorphine versus oxycodone. Nonetheless, the use of sustained release opioid formulations such as transdermal buprenorphine for acute pain are not ideal and may only be considered in certain circumstances (22). While the primary analysis of our study did not show an improvement of pain with buprenorphine sublingual, it is assuring that it provided similar analgesia to oxycodone oral/enteral with a trend that favored buprenorphine sublingual. At a minimum, the findings support that buprenorphine sublingual can be considered when the gastrointestinal tract is not functional in the ICU setting.

Opioid-related adverse drug events (ORADEs) of buprenorphine sublingual are similar to other opioids. In a systematic review of 28 randomized controlled trials, there was no significant difference between buprenorphine and morphine with regard to respiratory depression, sedation, nausea, vomiting, dizziness, and hypotension (23). Pruritus was lower with buprenorphine (odds ratio, 0.31; 95% CI, 0.12–0.84). However, pruritus is known to be higher with morphine compared with other opioids. We were unable to assess many of these ORADEs retrospectively in the context of the ICU. However, effects on respiratory and CNS depression can be assessed by measurement of ventilator duration and RASS scores, which was similar between groups in our study. Another potential adverse effect upon initiation of buprenorphine sublingual is the occurrence of OWS, especially in those patients who are opioid dependent or transitioning from long-acting opioids or methadone. The precipitation of OWS in ICU patients due to buprenorphine sublingual is unknown. In our study, we did not identify any cases of OWS. Buprenorphine sublingual is routinely used in our ICU in the postoperative setting and OWS has not been an issue as confirmed by the results of our study. However, we acknowledge that this is dependent on the identification and documentation of OWS in the medical record.

The study is limited because of its observational design. Although we used propensity score matching, there is the possibility for residual confounding. It is possible that there are unknown variables that remain unbalanced. However, we accounted for this

with a doubly robust estimation. The cohort consisted of 214 individual diagnoses and represents a heterogeneous population. However, these circumstances are common for most ICU research. Diagnoses were categorized based on surgical or not as an attempt to group patients. Ideally, the cohort would consist of only one diagnosis to determine effectiveness of treatment interventions or matching by diagnosis. This was not possible in our investigation. It is possible that some patient populations would benefit more than others. The majority of patients in the study were surgical. However, there the results were consistent in the surgical and nonsurgical subgroups. It is also unclear how much buprenorphine sublingual and oxycodone oral/enteral exposure would be needed in each group to show a difference in outcomes. In this study, each group received a median of three to four doses, which may not have been sufficient. It was not possible to accurately obtain history of chronic pain. As an alternative, the baseline variable of opioid history was used, which was more accurately documented. A history of opioid use was also considered to be more directly relevant. We were unable to quantify the amount of preexisting opioid use, which may have been beneficial to determine if buprenorphine sublingual would be more beneficial in those with higher prior opioid use. The use of opioids after ICU and hospital discharge could not be reported and our analysis is restricted to the ICU setting. Occurrence of delirium could not be reported as assessment is not routinely documented in our ICU.

CONCLUSIONS

Buprenorphine sublingual was as effective as oxycodone oral/enteral with regard to pain control and opioid consumption in the ICU. Buprenorphine sublingual is an appropriate option for pain control in the ICU for patients who are unable to take oral/enteral medications.

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