OBSERVATIONAL STUDY

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Effectiveness of Transdermal Buprenorphine for Pain Control in the ICU After Major Surgical Procedures

Asad E. Patanwala, PharmD, MPH[1,2]

Benjamin Moran, MBBS, BMedSci (Hons), MMedStats[3,4]

Charlotte Johnstone, MBChB[5]

Heike Koelzow, MD[6]

Jonathan Penm, BPharm (Hons), PhD[1,7]

OBJECTIVES: Transdermal buprenorphine (TBUP) may be useful for postoperative pain after major surgery, when pain is expected to be severe and sustained. The objective of this study was to compare pain control and opioid consumption in critically ill postoperative patients who were treated with TBUP or not during ICU admission.

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

SETTING: ICU of a quaternary, urban hospital in Sydney, Australia.

PATIENTS: Data were obtained for all patients admitted to the ICU from January 2019 to July 2021 after major gastrointestinal (GI) or genitourinary (GU) surgery.

INTERVENTIONS: TBUP or non-TBUP.

MEASUREMENTS AND MAIN RESULTS: Pain control was compared between patients who received TBUP and those who did not receive TBUP. 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. Inverse probability of treatment weighting was used to adjust for baseline differences. The cohort included 376 patients, with 224 (60%) in the control group and 152 (40%) in the TBUP group. The mean age was 60 ± 14 years, 202 (54%) were male, mean Acute Physiology and Chronic Health Evaluation III score was 44 ± 13, and 147 (39%) received mechanical ventilation. After adjustment, the median probability of significant pain was 0.25 with control and 0.30 with TBUP (median difference, 0.02; 95% CI, 0.04–0.11; $p = 0.44$). The median opioid consumption (oral morphine milligram equivalents) per day was 5.7 mg with control and 10.1 mg with TBUP (median difference, 0.4 mg; 95% CI, −0.4 to 3.7 mg; $p = 0.31$).

CONCLUSIONS: In patients who are admitted to the ICU after major GI or GU procedures, the use of TBUP in the ICU was not associated with improved pain control or opioid consumption compared with those who did not receive TBUP.

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

Most patients in the ICU experience moderate-to-severe pain (1). The management of pain is complex in this setting. Although opioids are used first line, multimodal therapy is recommended to improve patient outcomes (2). Buprenorphine is an atypical opioid that binds to all classes of opioid receptors. It is a partial agonist with high affinity to μ-opioid receptors, inverse agonist of δ-opioid receptors, and antagonist of κ-opioid receptors (3). By blocking the interaction of dynorphins with κ-opioid receptors, it may reduce the development of opioid tolerance and opioid-induced hyperalgesia in the critically ill (4). This may improve pain control and reduce opioid consumption.

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Buprenorphine is available in a transdermal formulation, which is indicated for chronic pain. However, there is interest in the use of transdermal buprenorphine (TBUP) for acute postoperative pain, especially when there is an expectation for severe and sustained pain after major surgical procedures (5, 6). Although there is a sublingual formulation of buprenorphine available for break through pain, the rationale for use of TBUP is to provide a stable background level of analgesia. This is controversial, as sustained-release opioids are not recommended for acute pain control (7, 8). However, in one national position statement, an exception is considered with wording acknowledging that sustained-release opioids may be useful for prolonged pain states on an individualized and temporary basis in the postoperative or posttraumatic setting (7). In a systematic review that included nine clinicals, the use of TBUP for acute postoperative pain was associated with improved pain control in six trials and decreased opioid consumption in five trials (5). The studies were small, were heterogeneous, and had a high or unclear risk for bias. In addition, the use of TBUP has not been evaluated in the critically ill.

The objective of this study was to compare pain control and opioid consumption in critically ill postoperative patients who were treated with TBUP or not 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 commencement (Approval 2021/ETH00632).

Study Design

This was a retrospective, parallel, cohort study. All reporting was followed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies (9).

Setting

The study was conducted in a 950-bed, quaternary, urban hospital in Sydney, Australia. The hospital has a 55-bed ICU that has a mix of general medical, surgical, neurologic, and cardiac patients. The ICU has an electronic medical record system (Philips IntelliSpace Critical Care and Anesthesia) (10). The system contains all data used for the study, including medications, 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 (11). The ICU pain management protocol does not specify the use of TBUP. The prescribing of TBUP in the ICU is based on physician preference. TBUP is specified as part of the institutional guideline for the management of pain in patients undergoing pelvic exenteration surgery. These patients are admitted to the ICU postoperatively. Selection of analgesics and sedatives for patients in general is based on clinician discretion. 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 (12).

Participants

Data were obtained for all patients admitted to the ICU from January 1, 2019, and discharged before July 1, 2021. Patients admitted after major gastrointestinal (GI) or genitourinary (GU) surgery were included (list of specific procedures are in **eTables 1** and **2**, http://links.lww.com/CCX/A954). Patients with less than 2 scores within the first 24 hours of ICU admission or less than 2 scores 24 hours post TBUP initiation were excluded. Thus, each patient had at least 4 pain measurements during their ICU stay. A 24-hour window was used after TBUP initiation because of a delayed time to onset of effect. Quantifiable concentrations are achieved after 17 hours (13). The timing of pain scores used for comparisons between control and TBUP is further illustrated in the **eFigure 1** (http://links.lww.com/CCX/A954). Patients were excluded if the initiation of TBUP was delayed (>96 hr) or were using TBUP chronically prior to ICU admission. This latter criterion did not apply to patients admitted after pelvic exenteration, as TBUP may be initiated in the immediate preoperative phase per hospital protocol.

Variables

Data collected included demographics, Acute Physiology and Chronic Health Evaluation (APACHE) III score, diagnosis procedure, pertinent past medical history, use of mechanical ventilation, use of vasopressors or inotropes, epidural use, analgesics used,

sedatives used, pain scores (NRS and BPS), Richmond Agitation Sedation Scale (RASS) scores, ICU length of stay, days of mechanical ventilation, or death. Diagnoses procedures were grouped by organ system as classified in the ANZICS APD (i.e., GI or GU) (11). Past medical history that we considered pertinent in terms of pain control was history of opioid use, depression, anxiety, chronic pain, and metastatic cancer.

Data Sources

All data were obtained via electronic queries from the electronic medical record system (10, 11). The accuracy of the query system has been checked manually against the medical records.

Outcomes

The primary outcome was the probability of significant pain scores during ICU admission. This is defined as the number of significant pain scores 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 (14). These cutoffs were used as these are the thresholds for providing pain management interventions and are defined as moderate or higher level pain (14). The BPS does not distinguish between scores above this threshold in terms of pain management (12). The time-period of measure was from 24 hours after ICU admission to ICU discharge. The first 24 hours was not included in the primary outcome as it was used for baseline calculations in the propensity score analysis. This is further illustrated in eFigure 1 (http://links.lww.com/CCX/A954). Secondary outcomes included: 1) total oral morphine milligram equivalents (OMMEs) administered during ICU stay (and per day). Equianalgesic ratios were used as recommended by the Australian and New Zealand College of Anaesthetists (15), 2) duration of mechanical ventilation including all episodes during ICU stay if a patient was extubated and reintubated (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.

Inverse Probability of Treatment Weighting

Propensity scores were calculated, which was defined as the conditional probability that the participant was treated with TBUP given baseline covariates (16). Propensity scores were estimated using a logistic regression model using the following baseline variables: age, sex, APACHE III score, diagnosis subcode (i.e., specific surgical procedure), vasopressor or inotrope use, mechanical ventilation, past medical history (opioid history, pain condition, anxiety, depression, and metastatic cancer), epidural use, opioid use in first 24 hours, and baseline pain. Baseline pain was defined as the probability of scores in the first 24 hours of ICU admission that were significant pain (≥4 on the 0–10 NRS or ≥6 on the BPS). The propensity score was used to calculate stabilized inverse probability of treatment weights (IPTW) (17). Thus, bias was reduced by using IPTW to conduct adjusted analyses. Baseline covariates were considered balanced if standardized differences were less than 0.1 (16).

Study Size

Based on preliminary data from our institution, we estimated that the probability of significant pain to be 0.2 (i.e., number of significant pain scores divided by the total number of pain scores). Assuming a reduction in probability from 0.2 to 0.1 with TBUP 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).

Data Analyses

Baseline and outcome variables were compared between the control and TBUP groups using unadjusted and adjusted analyses. Categorical variables were compared using the Fisher exact test, and continuous variables were compared using an unpaired Student *t* test or Wilcoxon rank-sum test as appropriate. Continuous outcomes were not normally distributed. Thus, they were reported as medians. The 95% CIs of the median of differences were calculated using the Hodges-Lehmann estimator (18). All adjusted analyses were conducted using IPTW. Analyses were conducted using the STATA software (Version 15, College Station, TX) and R software (Version 4.0.3, Vienna, Austria).

Sensitivity Analyses

Four sensitivity analyses were conducted: 1) Trimmed: the sample was trimmed by removing extreme propensity

scores to ensure overlap between groups. Observations were removed if propensity score percentile was less than 1% in the TBUP group and more than 99% in the control group. 2) Modified baseline: the 24-hour period immediately prior to TBUP initiation was used for calculation of baseline pain rather than the first 24 hours of ICU admission. This modified baseline was used in the TBUP group for propensity score and IPTW calculations. 3) Outcomes as covariates: opioid consumption (i.e., oral morphine equivalents), ICU length of stay, and ventilator days were treated as covariates in a linear regression model using IPTW. Although we considered these to be outcomes rather than confounders, they could be the latter in some circumstances. 4) Dose stratified: linear regression model using IPTW with stratification by TBUP dose to determine the effect of dosing.

RESULTS

Cohort

The cohort included 376 patients, with 224 (60%) in the control group and 152 (40%) in the TBUP group. **Figure 1** is a flow diagram of the cohort selection. The mean age was 60 ± 14 years, 202 (54%) were male, and mean APACHE III score was 44 ± 13. The reason for ICU admission was GI surgeries for neoplasms (n = 159; 42%) or GU surgeries (n = 217; 58%). There were 147 (39%) who received mechanical ventilation and 157 (42%) who received a vasopressor or inotrope. The median time to initiation of TBUP after ICU admission was 25 hours (interquartile range [IQR], 14–59 hr). The initial dose of TBUP was 5 μg/hr (n = 52/152; 34%), 10 μg/hr (n = 82/152; 54%), 20 μg/hr (n = 11/152; 7%), or 40 μg/hr (n = 7/152; 5%). Most patients (n = 121/152; 80%) did not have any dose changes. Specific changes in dose are in **eTable 3** (http://links.lww.com/CCX/A954). Prior to IPTW adjustment, the TBUP group was younger with higher severity of illness (Table 1). The latter is based on higher APACHE III score, mechanical ventilation, vasopressor/inotrope use, and opioid use in the first 24 hours of ICU admission. The TBUP group was also more likely to have GU rather than GI surgeries, prior opioid use, and metastatic cancer. After IPTW adjustment, all baseline variables were balanced (Table 1 and eTable 2, http://links.lww.com/CCX/A954) and with all standardized differences being less than 0.1 (**eFig. 2**, http://links.lww.com/CCX/A954). Nonopioid analgesic and sedative use is in Table 2.

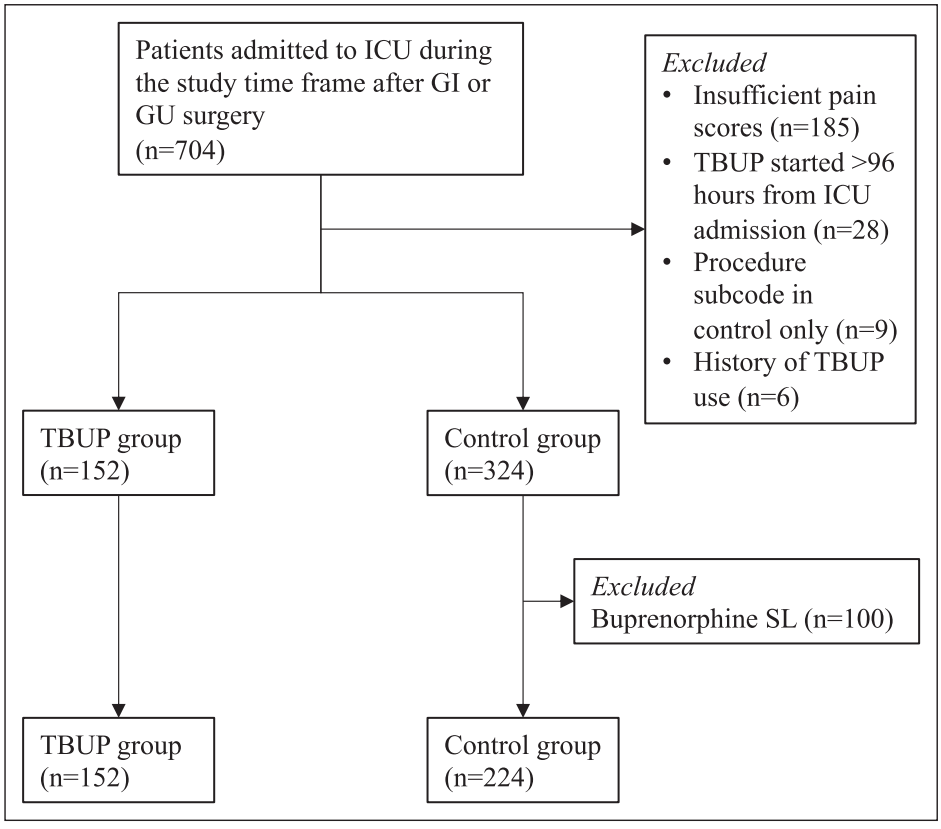

Figure 1. Flow diagram of patient selection. GI = gastrointestinal, GU = genitourinary, SL = sublingual, TBUP = transdermal buprenorphine.

Outcomes

The median probability of significant pain was 0.25 with control and 0.30 with TBUP (median difference, 0.02; 95% CI, –0.04 to 0.11; p = 0.44). The median OMME used per day was 5.7 mg with control and 10.1 mg with TBUP (median difference, 0.4 mg; 95% CI, –0.4 to 3.7 mg; p = 0.31). However, as ICU length of stay was greater in the TBUP group, total OMME was higher in the TBUP group (Table 3). Median ICU length of stay was 3.0 versus 4.8 days in the control and TBUP groups,

TABLE 1.
Baseline Characteristics

Characteristic	Unadjusted[a]			Adjusted[a]		
	Control, *n* = 224	TBUP, *n* = 152	*p*	Control, *n* = 224	TBUP, *n* = 152	*p*
Demographics and severity of illness						
Age (yr)[b]	63 ± 13	57 ± 14	< 0.01	60 ± 13	59 ± 14	0.65
Sex (male)	53	55	0.67	56	52	0.51
Apache III[b]	45 ± 14	42 ± 12	0.05	43 ± 13	43 ± 13	0.99
Baseline pain[b,c]	0.24 ± 0.30	0.26 ± 0.29	0.43	0.25 ± 0.30	0.26 ± 0.28	0.95
Opioids in first 24 hr[d]	33 ± 61	75 ± 93	< 0.01	52 ± 74	50 ± 84	0.85
Vasopressor or inotrope	30	59	< 0.01	43	47	0.51
Mechanical ventilation	27	57	< 0.01	41	41	> 0.99
Epidural	8	7	> 0.99	7	8	0.62
Diagnosis/surgery						
Gastrointestinal surgery[e,f]	57	20	< 0.01	40	38	0.73
Genitourinary surgery[f,g]	43	80	< 0.01	60	62	0.73
Pertinent medical history						
Opioid history	12	29	< 0.01	20	21	0.88
Pain history	5	4	> 0.99	4	3	0.69
Anxiety	2	1	0.71	2	1	0.84
Depression	5	3	0.42	3	3	0.78
Metastatic cancer	13	26	< 0.01	17	19	0.58

TBUP = transdermal buprenorphine.
[a]Categorical values are reported in percent and rounded to the nearest integer.
[b]Mean ± SD.
[c]Mean probability of scores with significant pain in first 24 hr of ICU admission. Significant pain is defined as pain score greater than or equal to 4 on 0–10 numeric rating scale or greater than or equal to 6 on the behavioral pain scale.
[d]Oral morphine milligram equivalents.
[e]Gastrointestinal surgery for neoplasm.
[f]Specific surgeries listed in eTable 1 (http://links.lww.com/CCX/A954).
[g]Genitourinary surgery.

TABLE 2.
Nonopioids and Sedatives

Medication	Unadjusted[a]			Adjusted[a]		
	Control, *n* = 224	TBUP, *n* = 152	*p*	Control, *n* = 224	TBUP, *n* = 152	*p*
Nonopioid analgesics						
Acetaminophen	77.7	88.8	0.03	84.5	81.2	0.56
Ibuprofen	0	0.7	0.40	0	0.7	0.20
Gabapentin	0.5	0.7	> 0.99	0.3	0.4	0.79
Pregabalin	3.1	8.9	0.03	3.1	6.2	0.18
Sedatives						
Propofol	26.8	58.6	< 0.01	40.1	41.2	0.96
Midazolam	1.8	4.0	0.21	1.6	3.2	0.34
Lorazepam	0.5	1.3	0.57	0.3	1.8	0.11
Dexmedetomidine	0.5	0	> 0.99	1.7	0	0.42
Ketamine	10.7	19.7	0.02	17.4	14.8	0.58

[a]Values are reported in percent.

TABLE 3.
Outcomes

Outcome	Unadjusted Analysis			
	Control, $n = 224$, Median	TBUP, $n = 152$, Median	Median Difference[a] (95% CI)	p
Primary outcome				
Probability of significant pain[b]	0.29	0.39	0.10 (0.04–0.17)	< 0.01
Secondary outcomes				
Opioid consumption[c]				
Per ICU-day	3.2	19.4	7.0 (2.9–13.1)	< 0.01
Total	10	82	50 (30–74)	< 0.01
Days of ICU stay	2.9	4.9	1.8 (1.3–2.1)	< 0.01
Ventilator days[d]	0.5	0.5	0 (–0.1 to 0.1)	0.93
Adjusted analysis				
Primary outcome				
Probability of significant pain[b]	0.25	0.30	0.02 (–0.04 to 0.11)	0.44
Secondary outcomes				
Opioid consumption[c]				
Per ICU-day	5.7	10.1	0.4 (–0.4 to 3.7)	0.31
Total	20.0	54.5	8.0 (0–33.0)	0.03
Days of ICU stay	3.0	4.8	1.3 (0.9–2.0)	< 0.01
Ventilator days[d]	0.5	0.5	0 (–0.1 to 0.1)	0.47

TBUP = transdermal buprenorphine.
[a]Median difference is not the same as difference between medians.
[b]Defined for each patient 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 greater than or equal to 6 on the behavioral pain scale.
[c]Oral morphine milligram equivalents.
[d]Subset of 167 patients who received mechanical ventilation.

respectively (difference, 1.3 d; 95% CI, 0.9–2.0 d; $p < 0.01$). In the subset of patients who were mechanically ventilated, the duration of mechanical ventilation was similar between the groups. Additional details are reported in Table 3. Only one patient in the cohort died in the ICU, who was in the control group. Comparison of RASS scores is in **eTable 4** (http://links.lww.com/CCX/A954).

Sensitivity Analyses

In the four sensitivity analyses for the primary outcome, the direction of effect did not change to favor TBUP. TBUP did not improve pain compared with control. The sensitivity analyses are reported in Table 4.

DISCUSSION

The key finding of this study was that the use of TBUP in the postoperative critically ill patient did not improve pain control compared with non-TBUP treatment modalities. Although a previous systematic review has identified nine previous clinical trials investigating TBUP for postoperative pain, none focused on the critically ill patient population (5). The studies were also small without sample size calculations and with sample sizes ranging from 45 to 96 patients. The studies involved heterogeneous populations that included spine surgery, abdominal surgery, hysterectomy, myomectomy, hip surgery, and hallux valgus corrections. Our study is the largest, adequately powered to show clinically meaningful differences, and can

TABLE 4.
Sensitivity Analyses

Outcome	Control[a]	TBUP[a]	Median Difference (95% CI)	*p*
Trimmed[a]	0.25	0.25	0 (−0.05 to 0.10)	0.58
Modified baseline[b]	0.25	0.30	0.02 (−0.04 to 0.12)	0.44
Outcome	**Control[a]**	**TBUP[a]**	**Coefficient (95% CI)**	***p***
Outcomes as covariates[c]	NA	NA	0.06 (−0.09 to 0.20)	0.45
Dose stratified[d]				
No TBUP	NA	NA	Reference	
Dose 5 µg/h	NA	NA	0.01 (−0.11 to 0.13)	0.87
Dose 10 µg/h or more	NA	NA	0.09 (−0.01 to 0.19)	0.08

NA= not available, TBUP = transdermal buprenorphine.
[a]Values represent the primary outcome, which is the mean probability of pain scores with significant pain. Significant pain is defined as pain score greater than or equal to 4 on 0–10 numeric rating scale or greater than or equal to 6 on the behavioral pain scale. Those with propensity scores less than 1st percentile in the TBUP group or greater than 99th percentile in control group removed.
[b]Baseline pain scores used for TBUP that were in the 24 hr prior to TBUP initiation instead of first 24 hr of ICU admission.
[c]Regression analysis adjusting for opioid consumption, length of ICU stay, and ventilator days.
[d]Regression analysis to determine effect of dose.

be extrapolated to patients undergoing major GI or GU procedures requiring ICU admission.

The control groups in the previous studies have also been different, and the effect of TBUP on pain has been variable. Control groups included placebo, nonsteroidal anti-inflammatory medications (NSAIDs) (celecoxib, parecoxib, and flurbiprofen), tramadol, or transdermal fentanyl. The use of cyclooxygenase-1-selective NSAIDs is not routinely recommended in the critically ill, and the role of cyclooxygenase-2-selective NSAIDs is unclear (2). In our study, less than 1% of the sample received an NSAID. Instead, we had more concurrent use of acetaminophen, agents for neuropathic pain (gabapentin and pregabalin), and ketamine, which is more consistent with guidelines and what is expected to be used in the ICU. The use of adjunctive nonopioids was balanced between the groups. As ours is the first study in the critically ill, there is no additional basis for meaningful comparisons to previous findings. One consideration is that previous studies in noncritically ill populations initiated TBUP 6–48 hours prior to surgery, whereas in our study, TBUP was initiated postoperatively. Although we only included pain scores after 24 hours of TBUP initiation to account for onset of effect, it is possible that the peak effect of TBUP takes longer. This could potentially explain the difference in findings between the studies.

The primary outcome of this study enabled the utilization of pain measures that are meant for both communicative and noncommunicative patients. Patients may transition between these states throughout ICU admission. In the context of the critically ill, all measures should be incorporated to provide a complete picture of pain control. One of the challenges is that the NRS is an ordinal scale from 0 to 10 and the BPS from 3 to 12. There is no well accepted conversion between these scales. In addition, self-reported and BPS cannot be used interchangeably because of a lack of correlation (19). However, both scales have well accepted thresholds for providing pain management interventions (≥4 on the 0–10 NRS or ≥6 on the BPS) (14). Thus, our primary outcome (i.e., significant pain) was defined by incorporating these thresholds and combining the pain measures. This was also deemed to be most clinically relevant because values exceeding these limits could trigger an intervention with both scales (14).

As guidelines have recommended, the use of long-acting or sustained-release opioids should not be routinely used in the postoperative setting (7, 8). The use of such opioid formulations has known risks associated with continued use and tolerance. For example, without adequate follow-up structures in place, it is possible that TBUP initiated in the ICU could be continued long term. Thus, the potential benefits of TBUP in this setting need to be viewed carefully from the context of these risks.

Even if TBUP is considered, it should be in consultation with pain specialists in a narrow patient population.

The study has a few important limitations. First, although the groups were well balanced after IPTW adjustment, it is unlikely that all confounding was eliminated. For example, the increased opioid use and length of ICU stay in the TBUP group are indicative of residual selection bias. Thus, it would be inappropriate to conclude that TBUP caused these effects. Only a randomized trial would eliminate such bias. Nonetheless, our sensitivity analyses supported that TBUP did not improve pain control.

Second, there is no universally accepted measure that captures the pain experience in the ICU. Although pain is assessed using scales such as NRS and BPS, they may be taken at different times, clustered during certain periods, confounded by medication use, or difficult to combine into a single summary measure, the latter being because of different scales (0–10 vs 3–12) and lack of correlation (19). We chose to use the probability of significant pain as our primary measure as it enabled us to combine the NRS and BPS, was clinically relevant, was easy to interpret by clinicians, and has been defined in clinical guidelines (14). However, we acknowledge that there may be other summary measures that could have been used.

Third, different doses of TBUP were used ranging from 5 to 40 μg/hr. The doses were also modified during ICU stay in some patients. Ideally, we would have investigated the same dose in all patients. We tried to overcome this by evaluating the effect of dose in a regression analysis, which did not change our conclusions. In addition, patients were initiated on TBUP at different times. We were somewhat flexible in the time-period cutoff (i.e., allowed up to 96 hr) used for patient inclusion.

Fourth, although we captured and incorporated the use of epidurals to balance the groups, we were not able to capture the use of other local anesthetic procedures. For example, preperitoneal use of local anesthetic infusions may be used for a few GI or GU surgeries. However, it is unlikely that incorporating this variable would change our findings as the groups were balanced within each specific procedure.

Fifth, we did not evaluate safety outcomes such as drug-induced adverse events. Identification of such events was not possible retrospectively.

Sixth, the study should not be generalized to other populations beyond those with GI surgeries for neoplasm or GU surgeries.

CONCLUSIONS

In adult patients who are admitted to the ICU after major GI or GU procedures, the use of TBUP in the ICU was not associated with improved pain control compared with those who did not receive TBUP. The use of TBUP in these circumstances should be assessed in a future clinical trial.

1 *Faculty of Medicine and Health, School of Pharmacy, The University of Sydney, Sydney, NSW, Australia.*

2 *Department of Pharmacy, Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

3 *Department of Intensive Care, Gosford Hospital, Gosford, NSW, Australia.*

4 *Department of Anaesthesia and Pain Management, Gosford Hospital, Gosford, NSW, Australia.*

5 *Department of Anaesthesia, Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

6 *Department of Intensive Care, Royal Prince Alfred Hospital, Camperdown, NSW, Australia.*

7 *Department of Pharmacy, Prince of Wales Hospital, Randwick, NSW, Australia.*

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For information regarding this article, E-mail: asad.patanwala@sydney.edu.au

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