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Buccal Buprenorphine for Postoperative Analgesia After Major Orthopedic Surgery: Results of a Retrospective Cohort

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Background: Opioids remain in common use for postoperative pain management after orthopedic surgery. Buprenorphine (BUP) is a partial agonist opioid best known as a lifesaving medication for opioid use disorder. Although extensively studied for acute pain management with at least the efficacy as full agonist opioids (FAO) and a superior safety profile, it is rarely used for this purpose in contemporary practice.

Objectives: To assess feasibility of inpatient administration of buccal BUP, in addition to usual analgesic care, and conduct an exploratory analysis of pain outcomes in an orthopedic surgery population, including a subset who received twice-daily buccal BUP.

Study Design: Retrospective cohort.

Setting: Veterans Health Administration.

Methods: A cohort of patients were treated with buccal BUP perioperatively at the discretion of the anesthesiologist. We subsequently undertook a retrospective chart review of 35 recent orthopedic cases at our institution over several months, including the subset who received buccal BUP, aiming to assess the feasibility of its use and make a preliminary assessment of pain outcomes.

Results: Our review found that perioperative buccal BUP was feasible within a population of largely opioid-naïve patients undergoing major orthopedic surgery. Pain outcomes were similar between the groups receiving BUP, in addition to usual care, and those not receiving BUP in addition to usual care.

Limitations: This is a retrospective review and lacks a randomization process and size to address bias and confounding. The largely homogenous patient population further limits generalizability. As such, no conclusions, generalizable or otherwise, should be made about any of the observed results.

Conclusions: To our knowledge, the buccal formulation of BUP, which received US Food and Drug Administration approval for chronic pain management in 2015, has not been studied for acute pain management. In a population undergoing total joint arthroplasty, buccal BUP was readily accepted by patients and nursing staff, resulted in pain and opioid consumption outcomes similar to the usual care, was compatible with FAO, and resulted in no safety concerns. Given its expected safety advantages over FAO, BUP deserves further consideration and study as an opioid analgesic within a multimodal analgesic regimen.

Key words: Buprenorphine, buccal, belbuca, acute pain, postoperative pain, opioid

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BACKGROUND

Ten percent of opioid prescriptions and almost 22% of opioid initiations are by surgeons (1,2). Unfortunately, this high rate confers a high risk for opioid complications, including overdose and opioid use disorder (OUD) following surgery. New, persistent postoperative opioid use after surgery is approximately 6% across a wide range of minor and major surgeries (3). In the year after surgery, odds of opioid overdose increased by almost 7 times that of matched controls (4).

Orthopedic surgeries present a particularly challenging environment for pain management, and opioids continue to be relied upon for both intraoperative management and postoperative analgesia in orthopedic patients. In addition to the ubiquitous use of full agonist opioids (FAO) intraoperatively, patients receive a total mean oral oxycodone dose of 50 mg in the early postoperative period after lateral total hip arthroplasty (THA) (5). Another study (6) found that over an average 2-day length of stay (LOS) after THA, patients receive approximately 60 mg total inpatient oral oxycodone. Musculoskeletal conditions in general result in nearly 75% of new opioid prescriptions for non-cancer pain, and total knee arthroplasty (TKA) and THA are the top surgical procedures associated with new opioid use (7). Claims data of dispensed opioid prescriptions across > 1 million surgical procedures across ages 18 to 64 years found that knee arthroplasty resulted in the greatest mean morphine equivalents dispensed (8). Persistent postoperative opioid use was found to be 21% in a TKA cohort (9). Meanwhile, a quarter of patients experience persistent postoperative pain after TKA (10).

Buprenorphine (BUP), a partial mu opioid receptor agonist, has become an essential medication for OUD and is increasingly used for chronic pain. Evidence for its efficacy in acute pain management is, however, well established. BUP demonstrates a full agonist effect for analgesia without a ceiling effect for analgesia across an analgesic dose range from 0.05 to 0.6 mg intravenous (IV) (11,12). In a randomized study of 200 patients undergoing TKA, Londhe et al (14) examined the safety and efficacy of the lowest commercially available transdermal BUP strength (13) (5 mcg/h) vs alternating acetaminophen and tramadol, and found that patients in the BUP group reported improved pain scores at rest and with movement, greater satisfaction, and less postoperative nausea and vomiting. A meta-analysis (15) focusing exclusively on postoperative pain across a range of surgeries and inclusive of 58 randomized trials comparing BUP to any comparator opioid, found BUP to result in significant reductions in pain intensity (Hedges's g = -0.36, 95% CI = -0.59 to -0.14, $P < 0.001$) and reduced likelihood of receiving rescue analgesia requirements (odds ratio = 0.40, 95% CI = 0.26 to 0.63, $P < 0.001$). Included studies investigated intramuscular, IV, sublingual (SL), and transdermal BUP formulations.

Despite these promising findings, its use for acute perioperative pain is dwarfed compared to that of FAO. In response to the recognized harms of FAO, the plausible safety benefits offered by BUP, and the demonstrated efficacy of BUP for acute perioperative pain management, including in orthopedic populations, we began adding BUP to our established multimodal analgesia regimen in TKA and THA in the Connecticut Veterans Affairs Health Care System. The IV BUP dose that has a labeled indication for acute pain management, 0.3 mg, is approximately bioequivalent to 1 mg SL and 450 mcg buccal, based on 30% and 55% bioavailabilities, respectively (16,17). As IV BUP is nonformulary and we were unable to exactly split a 2 mg SL dose to 1 mg, we opted for the approximately bioequivalent buccal dose of 450 mcg.

Buccal BUP's pharmacokinetics match well with most surgeries and support this approach. A dose given in the preoperative holding area achieves onset in 20 minutes, typically around the induction of anesthesia and certainly prior to incision, and achieves max concentration at 2 hours, typically prior to emergence and the experience of pain (18). We elected a twice-daily dosing schedule as recommended by the buccal BUP package insert (17).

We subsequently conducted a review of a series of patients who recently underwent one of these surgeries, including the subset who received perioperative buccal BUP. The aims of this retrospective review were to assess basic feasibility outcomes, including patient and nursing acceptance, and conduct an exploratory analysis of possible pain and opioid consumption effects and associations. While we do report on pain outcomes, our project is exploratory and not meant as a definitive study for these pain and opioid outcomes.

METHODS

We assessed the analgesia management and pain outcomes of 35 recent orthopedic surgery patients who underwent primary THA or TKA at the Connecticut Veterans Affairs Health Care System, a subset of whom received buccal BUP as part of a multimodal analgesia

strategy. This review was approved as a quality project (protocol number 1809019-1) by our hospital research office.

Buccal BUP Program

A short online training module, "Buccal Buprenorphine (Belbuca®) Use and Administration," was created and deployed to postanesthesia care unit (PACU) and floor nursing to provide basic background information and administration tips. Patients received anesthesia care at the discretion of the assigned anesthesiologist. The BUP group most often (10 of 14 cases) shared a common anesthesiologist (TH), who added buccal BUP to a multimodal pain regimen for total joint arthroplasty patients. It was thus the assignment of a shared common anesthesiologist rather than any patient factor that determined administration of BUP. In general, the mainstay anesthetic management at our institution for both THA and TKA consists of a bupivacaine spinal anesthetic with propofol sedation. All TKA patients receive a single-shot adductor canal block with 0.5% ropivacaine. We do not offer peripheral regional blocks for THA. Routine nursing pain assessments using the Numeric Rating Scale (NRS-11), postoperative analgesia order sets, and vital sign assessments were all according to the usual hospital practices and protocols performed. Surgical management was directed by the same attending surgeon for all cases.

Inpatient analgesic management was per the preexisting standard order set prescribed by the orthopedic surgery service after all hip and knee arthroplasties, including those receiving BUP. Specifically, inpatients received standing oral acetaminophen (975 mg Q6H), IV ketorolac as needed (15 mg Q8H, if pain unrelieved by acetaminophen), oral oxycodone as needed for severe pain (10 mg Q4H, NRS-11 8-10/10), oral oxycodone as needed for moderate pain (5 mg Q4H, NRS-11 5-7/10), and IV morphine as needed for breakthrough pain (4 mg Q6H, if pain unrelieved by oxycodone and ketorolac). While outside the scope of our data collection here, standard discharge analgesic medications are standing acetaminophen (1 g Q6H) for 2 weeks and then as needed, meloxicam (7.5 mg BID), aspirin (325 mg daily for 5 weeks, for deep venous thrombosis prophylaxis), and oxycodone as needed (5-10 mg Q6H for 2 weeks).

In the twice-daily BUP group, buccal BUP was initiated in the preoperative holding area and continued twice-daily (0600, 1800) per standing orders throughout the admission, with hold parameters typical of other perioperative opioid order sets with respect to respiratory depression and sedation (e.g., "do not administer if respiratory rate is less than 10 and Richmond Agitation and Sedation Scale is -2 or lower").

Data Extraction and Management

Data collection consisted of a retrospective review of patient medical records captured on the Computerized Patient Record System for patients who recently underwent either THA or TKA. Anesthesia preoperative notes, intraoperative electronic charting from Innovian® (Draeger, Telford, PA) accessed via VistA Imaging (San Carlos, CA), and medication administration logging provided the necessary deidentified information about comorbidities, intraoperative medications, and inpatient postoperative course.

We abstracted the following anonymized data: NRS-11 0-10, analgesics administered during admission, American Society of Anesthesiologists physical status, anesthetic type (spinal vs general), surgical procedure, surgical or anesthetic complications, lengths of stay in PACU and overall, PACU antiemetic treatment, and PACU naloxone administration. We recorded established risk factors for poor acute postoperative pain control, including younger age, female gender, smoking status, anxiety, depression, sleep difficulties, obesity, preoperative pain, and preoperative analgesic use (19). For simplicity, we established thresholds of age $\leq$ 40 years and body mass index $\geq$ 30 for these continuous risk factors.

We noted any feedback from patients and perioperative providers that could inform buccal BUP's feasibility. We assessed completion rates of the training module. We noted whether any BUP doses were held. We conducted a preliminary assessment of costs.

Data Analysis

Oral morphine milligram equivalent (OME) calculations of FAO were made using a standard opioid equianalgesic dosing table available at openanesthesia.org (20). As there is no accepted equianalgesic conversion between the partial agonist opioid BUP and FAO (21), BUP is not included in the OME calculation. Student's t tests were used to compare continuous variables (e.g., pain scores, opioid consumption) and Fisher's exact test was used for dichotomous variables.

RESULTS

Buccal BUP was readily accepted by all patients to whom it was offered. No concerns were identified from

perioperative providers. There were no noted difficulties with acceptability, deficient training, logistics, or with the buccal administration. Over 90% of nurses completed the assigned training module within 45 days of the assignment. No BUP doses were held. Pricing estimates within the Veterans Health Administration suggest an approximately $6 cost for a 450 mcg buccal film (22).

Our review included 35 patients. Fourteen patients received BUP, eleven of which received twice-daily standing 450 mcg buccal BUP beginning in the preoperative holding area and extending throughout the inpatient stay. In the one-time BUP group, buccal BUP was administered in the preoperative holding area and was not continued due to omission of the necessary order by the attending anesthesiologist rather than because of perceived intolerance. All patients who received BUP had an uncomplicated PACU recovery. All patients prescribed twice-daily buccal BUP received all doses as prescribed and responded appropriately to FAO administered for breakthrough pain. We discovered no adverse events related to BUP administration from PACU nursing, floor nursing, or from the surgical team.

Baseline characteristics were similar. Patients receiving buccal BUP had on average more risk factors for acute postoperative pain, but not significantly so. A higher percentage of patients in the BUP groups underwent TKA (91% in twice-daily, 100% in single dose) compared with the no BUP group (67%). We identified no significant difference in postoperative pain scores or opioid consumption. There was a significantly longer LOS in the BUP-treated group. Demographic data are found in Table 1, clinical characteristics and pain and opioid consumption outcomes in Table 2, and adverse effect and safety outcomes in Table 3. We conducted a further analysis comparing pain and opioid consumption outcomes restricted to the TKA populations, finding reduced floor pain scores and OME, without statistical significance (Table 4).

Two patients who received a single dose of BUP were unique in key respects. The first was a man undergoing TKA who wished to avoid opioids due to a history of severe OUD in sustained remission. He understood the strong likelihood he would need FAO postoperatively, was familiar with BUP, recognized from prior experience its relative lack of euphorigenic effect, and accepted a 300 mcg dose in the preoperative area. A 300 mcg was chosen as it was the only dose available at the time. The only other postoperative analgesic for this patient was 975 mg oral acetaminophen Q6H. His maximum pain score was 3/10 and he required no other opioids during his admission.

The second was a woman with multiple (4) risk factors for poorly controlled acute postoperative pain, also undergoing knee arthroplasty. She had escalating pain on postoperative day one despite increasing doses of oral oxycodone, IV hydromorphone, and IV morphine. Pain deescalated only after 450 mcg buccal BUP was given on the evening of postoperative day one. We did not include her pain and opioid consumption in the tables due to the unusual circumstance of BUP applied for rescue analgesia well into her postoperative course, distinctly different than the preoperative dosing for the other 3 single dose patients. She was discharged on postoperative day 2 with an outpatient prescription for 300 mcg twice-daily buccal BUP and had an uneventful postdischarge course.

DISCUSSION

Perioperative twice-daily buccal BUP administration, together with standard-of-care multimodal analgesia, including FAO, in patients undergoing TKA and THA, was acceptable to both patients and perioperative clinicians. We identified no safety concerns. Despite having more risk factors for poorly controlled acute postoperative pain and a higher percentage of TKA cases, a surgery associated with more severe pain than THA, the BUP-treated group had similar pain levels and opioid consumption as the other group. Comparisons involving only TKA showed on average reduced pain and opioid consumption in the BUP-treated group during the admission.

When opioids are needed for acute pain management, BUP is expected to result in important harm reductions, including reduced respiratory depression and abuse potential. A benchmark experimental study (23) on respiratory depression found that "buprenorphine causes limited respiratory depression with a ceiling effect at higher doses, while fentanyl causes dose-dependent respiratory depression with apnoea at high dose levels." Specifically, minute ventilation leveled out at 50% baseline in the BUP group despite dose escalation. Buccal doses up to the maximum available dose of 900 mcg were indistinguishable from placebo in respiratory depressant effect (24), and SL doses up to 32 mg reduced respiratory rate by only 4 breaths per minute (25). A background BUP infusion was found to be protective against fentanyl-induced respiratory depression in both opioid-naïve and tolerant patients (26). Intriguingly, BUP has been shown to be a safe, ef-

Table 1. Baseline demographic and clinical characteristics.

	No BUP (n = 21)	**BUP x 1 (n = 3)**	**BUP BID (n = 11)**	***P* value: No BUP vs BUP x 1**	***P* value: No BUP vs BUP BID**
Age – y	69.9 (SD = 9.0)	70.7 (9.0) (SD = 7.7)	72.3 (SD = 6.7)	0.89	0.44
ASA Physical Status	3.1 (SD = 0.30)	3.0 (SD = 0.00)	2.82 (SD = 0.60)	0.60	0.09
	n (%)	n (%)	n (%)		
Race					
White	18 (85.7)	3 (100)	8 (72.7)	1	0.39
Black	2 (9.5)	0 (0)	1 (9.1)	1	1
Other	1 (4.8)	0 (0)	2 (18.2)	1	0.27
Female Sex	1 (4.8)	0 (0)	2 (18.2)	1	0.27
Smoker	13 (61.9)	0 (0)	3 (27.3)	0.08	0.14
Anxiety	2 (9.5)	0 (0)	2 (18.2)	1	0.59
Depression	5 (23.8)	1 (33)	2 (18.2)	1	1
Sleep Difficulties	0 (0)	0 (0)	0 (0)	-	-
BMI ≥ 30	13 (61.9)	1 (33)	9 (81.8)	0.55	0.43
Home Opioids	3 (14.3)	1 (33)	0 (0)	0.44	0.53

Abbreviations: y, year; ASA, American Society of Anesthesiologists; BUP, buprenorphine; BMI, body mass index; BID, twice-daily (0600, 1800). Percentages were compared using Fisher's exact test.

Table 2. Clinical characteristics and outcome variables by group.

	No BUP (n = 21)	**BUP x 1 (n = 3)**	**BUP BID (n = 11)**	***P* value: No BUP vs BUP x 1**	***P* value: No BUP vs BUP BID**
	n (%)	n (%)	n (%)		
Type of Surgery					
TKA	14 (66.7)	3 (100)	10 (90.9)	0.53	0.21
THA	7 (33.3)	0 (0)	1 (9.1)		
Anesthetic Technique					
Spinal	16 (76.2)	2 (67)	8 (72.7)	1	1
General	5 (23.8)	1 (33)	3 (27.3)		
	Mean (SD)	Mean (SD)	Mean (SD)		
Surgery Time	104.5 (18.9)	98.3 (12.7)	106.9 (17.8)	0.60	0.73
Mean Total Acute Pain Risk Factors	1.8 (1.1)	2.3 (2.1)	2.4 (1.3)	0.45	0.17
Mean PACU Pain Score	1.8 (2.3)	1.4 (2.4)	2.1 (2.3)	0.74	0.76
PACU OME (mg)	16.6 (24.2)	25 (43.3)	10.4 (10.6)	0.61	0.42
Floor Mean Pain Scores	4.9 (1.7)	3.8 (1.2)	4.1 (1.4)	0.32	0.22
Floor OME (mg)	49.2 (31.1)	40 (35.4)	42.2 (39.9)	0.64	0.59
Total OME (mg)	78 (42.2)	82 (83.1)	62.2 (43.9)	0.89	0.33
LOS (d)	2.2 (0.4)	2 (0)	2.5 (0.5)	0.43	0.04
PACU recovery time (min)	197 (118)	213 (134)	167 (71)	0.84	0.44

Abbreviations: d, day; mg, milligram; BUP, buprenorphine; OME, oral morphine equivalent; LOS, length of stay; min, minute; TKA, total knee arthroplasty; THA, total hip arthroplasty; PACU, postanesthesia care unit; BID, twice-daily (0600, 1800). Based on independent t tests for continuous measures and Fisher's exact tests for categorical measures.

Table 3. Adverse effect and safety outcomes.

	No BUP (n = 21)	BUP x 1 (n = 3)	BUP BID (n = 11)	*P* value: No BUP vs BUP x 1	*P* value: No BUP vs BUP BID
	n (%)	n (%)	n (%)		
PACU antiemesis	2 (9.5)	1 (33)	1 (9.1)	0.34	1
PACU naloxone	0 (0)	0 (0)	0 (0)	-	-
Death < 30 d of surgery	0 (0)	0 (0)	0 (0)	-	-
Readmission < 30 d of discharge	0 (0)	0 (0)	0 (0)	-	-

Abbreviations: BUP, buprenorphine; d, day; PACU, postanesthesia care unit; BID, twice-daily (0600, 1800).

Table 4. Clinical characteristics and outcome variables by group, restricted to total knee arthroplasty.

	No BUP (n = 14)	BUP x 1 (n = 3)	BUP BID (n =10)	*P* value: No BUP vs BUP x 1	*P* value: No BUP vs BUP BID
	n (%)	n (%)	n (%)		
Type of Surgery					
TKA	14 (100)	3 (100)	10 (100)		
Anesthetic Technique					
Spinal	12 (85.7)	2 (67)	7 (70.0)	0.46	0.61
General	2 (14.3)	1 (33)	3 (30.0)		
	Mean (SD)	Mean (SD)	Mean (SD)		
Surgery Time	101.1 (16.6)	98.3 (12.7)	107.1 (18.8)	0.79	0.42
Mean Total Acute Pain Risk Factors	1.9 (1.2)	2.3 (2.1)	2.3 (1.3)	0.65	0.48
Mean PACU Pain Score	1.3 (1.8)	1.4 (2.4)	1.8 (2.1)	0.93	0.54
PACU OME (mg)	13.5 (24.7)	25 (43.3)	8.7 (9.4)	0.53	0.56
Floor Mean Pain Scores	5.2 (1.4)	3.8 (1.2)	4.1 (1.5)	0.13	0.07
Floor OME (mg)	52.2 (30.9)	40 (35.4)	41.9 (42.1)	0.55	0.50
Total OME (mg)	85.9 (40.6)	82 (83.1)	57.7 (43.5)	0.90	0.12
LOS (d)	2.1 (0.4)	2 (0)	2.5 (0.5)	0.52	0.06
PACU recovery time (min)	202.5 (119.9)	212.7 (133.8)	160.5 (71.7)	0.90	0.34

Abbreviations: d, day; mg, milligram; BUP, buprenorphine; TKA, total knee arthroplasty; LOS, length of stay; OME, oral morphine equivalent; min, minute; PACU, postanesthesia care unit; BID, twice-daily (0600, 1800). Based on independent t tests for continuous measures and Fisher's exact tests for categorical measures.

fective, and rapid alternative to naloxone in overdosed opioid-tolerant patients (27).

Abuse potential is also less with BUP. One survey (28) of approximately 1,600 persons who use drugs found that only 1% reported nonprescription use. These findings are supported by the early research on BUP's abuse potential compared with other opioids, which found that while the positive reinforcing aspects of opioids (e.g., euphoria) are present they are relatively less, and that the negative reinforcing effects (e.g., physiologic dependence, withdrawal syndrome) are much less (29). They are also consistent with the US Drug Enforcement Agency's classification of BUP as a Schedule III drug, in contrast to Schedule II opioids typically employed perioperatively, and with new recommendations by large health care organizations to consider BUP in patients on daily opioid therapy in the chronic pain context, due in part to reduced euphoriant effects (30).

Limitations

This project has many limitations. This is not a randomized trial and lacks size to address bias and confounding. As such no conclusions, generalizable or otherwise, should be made about any of the observed results. Future prospective research may determine whether perioperative buccal BUP improves pain outcomes and reduces opioid adverse effects.

CONCLUSIONS

To our knowledge, the buccal formulation of BUP, which received US Food and Drug Administration approval for chronic pain management in 2015, has not been studied for acute pain management. In a largely homogeneous population of predominately opioid-naïve patients undergoing total joint arthroplasty, buccal BUP was readily accepted by patients and nursing staff, resulted

in pain and opioid consumption outcomes similar to the usual care, was compatible with FAO, and resulted in no safety concerns. Given its expected safety advantages over FAO, BUP deserves further consideration and study as an opioid analgesic within a multimodal analgesic regimen.

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