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

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Background: Opioids are widely used in the management of acute postoperative pain after thoracic surgery. Buprenorphine (BUP), though discovered as an analgesic, with robust evidence supporting its efficacy for this purpose, and possessing important safety advantages compared with commonly used full agonist opioids, is currently rarely used for acute pain management.

Objectives: To assess feasibility of implementing buccal BUP as part of a multimodal analgesia strategy, and to conduct an exploratory comparison of pain outcomes between patients receiving buccal BUP in addition to standard postoperative pain management, and patients receiving standard postoperative pain management alone.

Study Design: Retrospective cohort.

Setting: Veterans Health Administration.

Methods: In this single-center, retrospective cohort study of patients undergoing minimally invasive lung surgery, we assessed feasibility of buccal BUP administration for perioperative pain management, and conducted an exploratory analysis of pain outcomes in 29 patients, a subset of which received perioperative buccal BUP.

Results: Buccal BUP is feasible, safe, and is associated with improved pain outcomes after thoracic surgery.

Limitations: This retrospective review within a relatively homogenous population lacks a randomization process and size to address bias and confounding. Further study is needed to confirm any identified associations. We did not assess long-term outcomes, such as function and persistent opioid use.

Conclusions: We are not aware of prior study of the buccal formulation of BUP for acute pain management. In this retrospective cohort study of largely opioid-naive patients undergoing thoracic surgery, buccal BUP was feasible, safe, and was associated with reduced pain postoperatively.

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

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BACKGROUND

Thoracic surgery is broadly acknowledged to be among the most painful types of operations (1). Surgical trauma to the chest wall and pleura result in a complex pain pathophysiology involving somatic, visceral, and often neuropathic mechanisms, which are always exacerbated by the necessary mechanics of breathing and often by the presence of chest tubes (1). A significant effort has been made to better address acute postoperative pain, including within increasingly adopted enhanced recovery after surgery pathways, a key aim of which is to reduce reliance on opioids through implementation of a multimodal analgesia strategy (2).

Despite these advances and an appreciation of the well-known harms of opioids, the perioperative period remains high risk for opioid adverse effects. Nearly half of patients who undergo common surgical procedures are dispensed a postoperative opioid prescription and over 20% of all opioid initiations are by surgeons (3,4). In the first year after surgery, opioid overdose occurred in 0.7% vs 0.1% in matched controls (odds ratio 6.71), and a new diagnosis of opioid use disorder (OUD) was made in 0.8% (5). After thoracic surgery, patients typically require a 30 mg morphine equivalent daily dose (6), almost 95% are discharged on oral opioids, a third experience persistent pain, and 38% persistent opioid use (7).

Buprenorphine's (BUP's) original role as an analgesic has been eclipsed by its lifesaving role as a medication for OUD. However, there is robust evidence supporting its efficacy in treating acute pain. Over 70 randomized controlled trials (RCTs) have compared BUP to other opioids for acute pain management (8). A recent meta-analysis (9), including 58 RCTs comparing BUP, at a mean dose of 0.76 mg sublingual (SL), to any comparator opioid for postoperative pain in adults, found that BUP significantly reduced pain and rescue analgesia requirements, and resulted in a mean 8.5-hour duration of analgesia. A study (10) comparing BUP to morphine in a thoracic surgery population found a higher risk of rescue analgesia in the morphine group and more reduction in acute pain scores in the BUP group. At one-month follow-up, there was less hyperalgesia in the BUP group.

Given the established evidence base, beginning in April 2023, buccal BUP was made available for perioperative administration at the discretion of the anesthesiologist. Our aims in undertaking this retrospective review were to assess buccal BUP's feasibility and to conduct a preliminary analysis of outcome data to lay the groundwork for future study.

METHODS

Buccal BUP Program

A 10-slide online training module, "Buccal Buprenorphine (Belbuca) Use and Administration," was created and deployed to postanesthesia care unit (PACU) and surgical intensive care unit (ICU) nursing to provide basic background information and administration tips. Patients underwent usual standard of care deemed appropriate by the anesthesiologist and surgeon. The BUP group shared a common anesthesiologist (author ACP), who routinely administers BUP to thoracic surgery patients. Nursing pain assessments, postoperative analgesia order sets, and vital sign assessments were all according to the usual practices and protocols, including for patients receiving BUP. The typical anesthetic was general anesthesia with sevoflurane, supplemented with intravenous (IV) fentanyl and/or hydromorphone in the no BUP group, and with no additional opioid in the BUP group. Intraoperative acetaminophen, ketorolac, and dexmedetomidine administration varied by provider.

Postoperatively, all patients were monitored in the PACU and received as-needed full agonist opioids (FAO). After PACU recovery, all patients were transitioned to the ICU with a standardized multimodal analgesia order set, including standing gabapentin, acetaminophen, and ketorolac with as-needed oxycodone, morphine, and hydromorphone. Patients who were continued on buccal BUP postoperatively received it in addition to the aforementioned standard orders.

A 450 mcg buccal dose was chosen as it is approximately bioequivalent to the mean dose identified in the above meta-analysis (0.76 mg SL) and to the IV dose with a labeled indication for acute pain, 0.3 mg (11,12). When developing this project, IV buprenorphine was non-formulary in our healthcare system, resulting in the need for to use alternate formulations without a labeled indication for acute pain. We opted for a twice-daily (0600 and 1800) dosing strategy to maintain consistency with the buccal BUP package insert recommendation for chronic pain management (12).

Data Extraction and Management

We retrospectively assessed pain management and associated outcomes of 29 consecutive patients who underwent thoracic surgery in the Connecticut Veterans Affairs Health Care System between April 2023 and February 2024. We abstracted the following anonymized

data: Numeric Rating Scale (NRS-11) pain scores 0-10, analgesics administered during admission, American Society of Anesthesiologists Physical Status, surgical procedure, surgical or anesthetic complications, length of stay in the PACU, and overall PACU antiemetic treatment and PACU naloxone administration, death within 30 days, and readmission within 30 days of discharge. 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 (13).

Data collection consisted of reviewing patient electronic medical records on a computerized patient record system. Anesthesia preoperative notes, intraoperative charting on Vista Imaging (San Carlos, CA), and medication administration logging provided the necessary de-identified information about comorbidities, home medications, intraoperative medications, and inpatient postoperative course.

Oral morphine milligram equivalents (OME) calculations of FAO were made using equianalgesic conversion with a widely used online anesthesiology reference (14). As there is no accepted equianalgesic conversion between the partial agonist opioid BUP and FAO (15), BUP was not included in the OME calculation. Continuous measures were compared between groups using analysis of variance followed by post-hoc, pairwise group comparisons. Categorical outcomes were compared by Fisher's exact test.

Regarding feasibility outcomes, we noted any feedback from patients, surgeons, anesthesiologists, and nursing. We queried completion rates of the assigned training module. We noted whether any ordered BUP doses were held. We conducted a preliminary assessment of costs. This project (protocol number 1777795-1) was approved as a quality project by our hospital research office.

RESULTS

Buccal BUP was readily accepted by patients. We identified no concerns from surgery, anesthesia, or nursing. In particular, there were no noted difficulties with acceptability, training needs, logistics, or buccal administration. There was a > 90% completion rate of the assigned training module within 45 days. No ordered BUP doses were held. Our review of publicly available pricing within the Veterans Health Administration estimates the cost of a 450 mcg buccal film at approximately $6 (16).

Our retrospective chart review included 29 patients, of which 14 received BUP. Seven patients received a single dose of buccal BUP preoperatively, and 7 received twice-daily buccal BUP starting preoperatively and continued throughout the admission. Baseline characteristics are found in Table 1, pain and opioid consumption outcomes in Table 2, and adverse effect and safety outcomes in Table 3. Figure 1 displays mean pain scores by day. Patients receiving buccal BUP reported, on average, lower NRS-11 pain scores and required lower OME in the PACU and throughout admission. Average pain scores were significantly lower on postoperative days 1 and 2.

DISCUSSION

Buccal BUP, together with the usual multimodal analgesia including FAO, was readily accepted by both patients and clinicians, was operationally feasible, and resulted in no safety concerns. Treatment with BUP was associated with lower pain scores and reduced FAO compared to the usual care group, both in PACU and ICU. Patients who received twice-daily BUP throughout their admission had a greater reduction in pain scores.

BUP's relative safety, in terms of respiratory depression and abuse potential, further argues for its consideration as a first-line opioid analgesic. While BUP may cause respiratory depression, the evidence suggests it is of less clinical concern than FAO-induced respiratory depression (17-19), and in an experimental setting is protective against fentanyl-induced respiratory depression (20). Another significant advantage of BUP is reduced abuse potential (21,22). The buccal formulation has advantageous pharmacokinetics for most surgeries, achieving onset in 20 minutes and max concentration at 2 hours (23). Moreover, nonparenteral formulations are inherently safer and are consistent with best practices to avoid IV opioids whenever possible (24).

An important consideration regarding postoperative opioid harms is cost. At approximately $6, 450 mcg buccal film is significantly greater than the cost of an oxycodone tablet. However, persistent postoperative opioid consumption costs $2,500 over 6 months postoperatively, with $200 excess cost per month continuing indefinitely thereafter (25). Additionally, the economic burden of OUD and fatal opioid overdose was estimated to be $1.02 trillion in 2017 (26). It is plausible that BUP would result in a net savings compared with FAO, given its lower abuse potential, expected reduction in

Table 1. Baseline demographic and clinical characteristics. For the continuous risk factors for poorly controlled acute postoperative pain, age, and BMI, we established thresholds of age ≤ 40 years and BMI ≥ 30.

	No BUP (n = 15)	BUP x 1 (n = 7)	BUP BID (n = 7)	No BUP vs BUP x 1 *P* value	No BUP vs BUP BID *P* value
Age - y	69.1 (SD = 8.7)	66.3 (SD = 5.9)	69.3 (SD = 8.7)	0.45	0.97
ASA physical status	2.9 (SD = 0.26)	3.0 (SD = 0)	2.9 (SD = 0.4)	0.51	0.58
	n (%)	**n (%)**	**n (%)**		
Race					
White	12 (80)	6 (86)	5 (71)	1	1
Black	3 (20)	1 (14)	1 (14)	1	1
Other	0 (0)	0 (0)	2 (29)	-	0.09
Female gender	1 (7)	0 (0)	0 (0)	1	1
Smoker	7 (47)	4 (57)	3 (43)	1	1
Anxiety	3 (20)	0 (0)	0 (0)	0.52	0.52
Depression	1 (7)	0 (0)	0 (0)	1	1
Sleep difficulties	0 (0)	0 (0)	0 (0)	-	-
BMI ≥ 30	0 (0)	3 (43)	4 (57)	0.02	0.005
Home opioids	1 (7)	1 (14)	1 (14)	1	1
Type of Surgery					
Wedge resection	7 (47)	7 (100)	2 (29)	0.02	0.65
Segmentectomy	2 (13)	0 (0)	2 (29)*	1	0.56
Lobectomy	5 (33)	0 (0)	4 (57)*	0.13	0.38
Other	1 (7)	0 (0)	1 (14)	1	1
Intraoperative Analgesic					
Dexmedetomidine infusion	8 (53)	7 (100)	7 (100)	0.051	0.051
Acetaminophen	12 (80)	4 (57)	4 (57)	0.33	0.33
Ketorolac	2 (13)	0 (0)	0 (0)	1	1
Surgery time (min)	291.3 (SD = 121.1)	191.6 (SD = 49.9)	295 (SD = 134.2)	0.051	0.98

Abbreviations: ASA = American Society of Anesthesiologists, BUP = buprenorphine, BMI = body mass index, BID = twice-daily, y = year, min = minute. *One patient received both a lobectomy and wedge resection.

persistent postoperative consumption and associated health care expenditures, and potential for reduced respiratory depression and overdose.

Limitations

Our retrospective review in this thoracic surgery cohort is a quality assessment within a relatively homogenous population and lacks a randomization process and size to address bias and confounding. Further study is needed to confirm any identified associations. We captured only acute inpatient outcomes; future research is required to inform whether BUP has potential to improve long-term outcomes, such as function and persistent opioid use.

CONCLUSIONS

We are not aware of any literature describing the application of the buccal formulation of BUP for acute pain management. In this retrospective cohort study of largely opioid-naive patients undergoing thoracic surgery, buccal BUP was feasible, safe, and was associated with reduced pain postoperatively.

Table 2. Pain and opioid consumption outcomes by group.

	No BUP (n = 15)	BUP x1 (n = 7)	BUP BID (n = 7)	No BUP vs BUP x1 *P* value	No BUP vs BUP BID *P* value
	Mean (SD)	Mean (SD)	Mean (SD)		
Total acute pain risk factors	1.13 (0.74)	1.14 (0.9)	1.13 (0.83)	0.98	0.37
PACU pain score	2.9 (2.6)	0.4 (0.8)	2.2 (2.9)	0.024	0.62
PACU OME	14.9 (24.2)	4.9 (11.2)	7.8 (10.1)	0.31	0.50
PACU recovery time (min)	118.5 (45.8)	139 (32.3)	102 (13.3)	0.30	0.40
Pain Score					
POD 0	3.6 (1.6)	1.5 (1.7)	2.2 (1.9)	0.018	0.12
POD 1	3.7 (1.5)	2.5 (1.4)	2.1 (1.9)	0.08	0.044
POD 2	3.5 (1.3)	1.8 (1.4)	1.7 (2.3)	0.032	0.050
POD 3	2.7 (1.6)	0.7 (0.8)	1.6 (2.7)	0.13	0.30
OME					
Total	120.6 (101.5)	39 (51.1)	74.1 (98.8)	0.06	0.33
OME POD 0	23 (19.5)	12 (26.8)	11.2 (15.5)	0.29	0.18
OME POD 1	41.5 (31.3)	11.4 (14.2)	27.4 (38.4)	0.027	0.38
OME POD 2	34.6 (25.7)	13.1 (26.3)	21.6 (37.7)	0.17	0.41
OME POD 3	21.1 (26.8)	5.6 (11.3)	18.6 (32.5)	0.29	0.87
LOS (d)	5.6 (3.2)	3.1 (1.1)	5.6 (3.9)	0.06	0.99

Abbreviations: BUP = buprenorphine, POD = postoperative day, OME = oral morphine equivalent, min = minute, PACU = postanesthesia care unit, LOS = length of stay, BID = twice-daily, d = day.

Table 3. Adverse effect and safety outcomes by group.

	No BUP (n = 15)	BUP x 1 (n = 7)	BUP BID (n = 7)	No BUP vs BUP x 1 *P* value	No BUP vs BUP BID *P* value
PACU ondansetron	1 (6.7%)	0 (0%)	0 (0%)	1	1
PACU naloxone	0 (0%)	0 (0%)	0 (0%)	-	-
Death within 30 days of surgery	0 (0%)	0 (0%)	1 (14%)*	-	0.32
Readmission within 30 days of discharge	0 (0%)	0 (0%)	0 (0%)	-	-

Abbreviations: BUP = buprenorphine, PACU = postanesthesia care unit, BID = twice daily. *Unrelated to pain management.

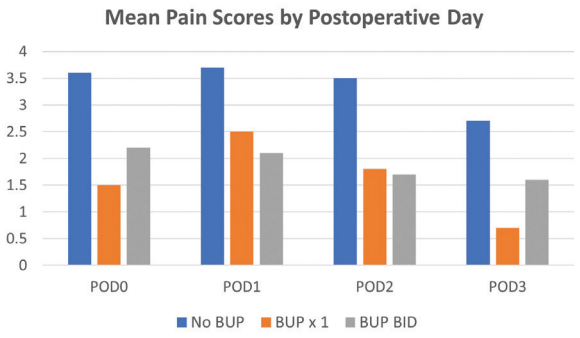

Fig. 1. Mean pain scores by postoperative day.
BUP = buprenorphine, POD = postoperative day, BID = twice-daily.

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