Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Issue 2, Page No: 172-182

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Multimodal Analgesia with Butorphanol vs Sufentanil via PCIA: A Retrospective Propensity-Matched Analysis

Claire Dupont[1]*, Julien Martin[1]

[1]Department of Pharmacy Practice and Therapeutic Care, Faculty of Pharmacy, University of Bordeaux, Bordeaux, France.

***E-mail** ✉ claire.dupont@gmail.com

Received: 04 October 2025; **Revised:** 09 December 2025; **Accepted:** 11 December 2025

ABSTRACT

We assessed the effectiveness and tolerability of butorphanol as part of a multimodal analgesic approach together with dexmedetomidine and ketorolac administered via patient-controlled intravenous analgesia (PCIA) following hepatobiliary procedures, using sufentanil as the comparator. Follow-up information after surgery was gathered retrospectively for individuals who underwent hepatobiliary operations at Henan Provincial People's Hospital from March 2018 through June 2021. Cases were assigned to either a butorphanol-based regimen (group B) or a sufentanil-based regimen (group S), depending on the intravenous controlled analgesia protocol received postoperatively. Propensity score matching (PSM) was applied to balance baseline variables and operative characteristics between the two cohorts. Initial screening identified 3437 patients; after PSM, the matched sample comprised 1816 individuals, with 908 allocated to the butorphanol cohort and 908 to the sufentanil cohort. Relative to group S, group B exhibited a reduced rate of moderate-to-severe pain on both the first day after surgery and the second day after surgery, whether assessed during rest (3.2% vs 10.9%, $P < 0.001$; 1.2% vs 4.6%, $P < 0.001$) or during activity (7.0% vs 18.9%, $P < 0.001$; 2.6% vs 8.7%, $P < 0.001$). Those administered butorphanol required a smaller amount of morphine (50 mg vs 120 mg, $P < 0.001$). The frequency of bolus demands on the analgesic pump was notably lower in group B compared with group S (1 vs 2, $P < 0.001$). The duration of postoperative hospitalization was shorter in group B (11d vs 12d, $P = 0.017$). The proportion of patients who developed vomiting after surgery was also lower in group B (1.4% vs 3.0%, $P = 0.025$) than in group S. Conversely, dizziness was encountered more often in group B (0.9% vs 0.1%, $P = 0.019$). In contrast to sufentanil, incorporating butorphanol into multimodal analgesia coupled with dexmedetomidine and ketorolac through PCIA improved postoperative pain control following hepatobiliary surgery, was associated with a decrease in opioid use, and led to a reduction in postoperative length of hospital stay.

Keywords: Patient-controlled intravenous analgesia, Butorphanol, Sufentanil, Propensity score matching

How to Cite This Article: Dupont C, Martin J. Multimodal Analgesia with Butorphanol vs Sufentanil via PCIA: A Retrospective Propensity-Matched Analysis. Ann Pharm Pract Pharmacother. 2025;5(2):172-82. https://doi.org/10.51847/4sC4lDrzSc

Introduction

Acute discomfort in the period immediately following surgery remains a prevalent difficulty for those recovering from hepatobiliary operations [1, 2]. Inadequately managed pain contributes to heightened sympathetic drive, diminished immune function, greater strain on cardiovascular and respiratory systems, delayed restoration of gastrointestinal motility, and negative psychological states [3, 4]. Without adequate early intervention, acute nociceptive input may trigger peripheral and central sensitization processes, ultimately transitioning into persistent postsurgical pain [5-7]. Consequently, delivering sufficient postoperative analgesia is a fundamental requirement, forming a central tenet of Enhanced Recovery After Surgery (ERAS) protocols [8, 9]. Since the nature of pain after hepatobiliary procedures is multifactorial and distinct from that seen in other surgical contexts, a multimodal analgesic strategy incorporating agents that act on complementary nociceptive pathways is advocated as the ideal approach for abdominal surgery [10, 11].

Accumulating data reflect mounting enthusiasm for innovative modalities, among them intrathecal morphine, truncal fascial plane blocks, and newer pharmacological options such as esketamine and 5-HT3-receptor antagonists [2, 12-16]. Still, opioid agents continue to be the foundation of perioperative pain therapy because of their strong, fast-acting systemic effects [17]. However, they concurrently carry a substantial burden of opioid-attributable adverse events, including delayed respiratory compromise, nausea with vomiting, urinary retention, pruritus, vertigo, and others [4]. Tactics that curtail opioid usage while maximizing patient wellbeing and convalescence are therefore a priority.

Butorphanol, which possesses both agonist and antagonist properties at opioid receptors, has lately gained broad application for managing postoperative pain. It principally engages κ receptors situated on presynaptic and postsynaptic nerve membranes throughout the central nervous system. Inhibition of adenylyl cyclase reduces intracellular cyclic adenosine monophosphate levels. It lowers protein kinase phosphorylation, thereby suppressing glutamate release and decreasing the excitability of downstream neurons, which yields its analgesic action. At the κ-opioid receptor, butorphanol acts as a partial agonist in the G protein signaling cascade, while functioning as a full agonist in the β-arrestin recruitment pathway [18].

In comparison with agents that purely stimulate μ-receptors, butorphanol provides superior relief of visceral pain and is accompanied by fewer opioid-typical side effects and less propensity for dependence [18-21]. It has additionally been demonstrated to attenuate emergence agitation and lessen postoperative shivering [22, 23]. Real-world experience with dual-drug pairings—combining butorphanol with either ketorolac or dexmedetomidine via PCIA—has become well recognized in recent years. Whether the triple combination of butorphanol with both ketorolac and dexmedetomidine in a multimodal analgesic protocol confers distinct advantages, along with its respective side-effect profile, remains to be confirmed by large-scale clinical investigation [24]. The present retrospective analysis was designed to explore the efficacy and safety of butorphanol combined with dexmedetomidine and ketorolac as a multimodal pain strategy after hepatobiliary operations, compared with sufentanil.

Materials and Methods

Approval for the present investigation was obtained from the Ethics Committee of Henan Provincial People's Hospital [Ethics approval number: (2019) lun shen (102)], a tertiary-level academic institution situated in central China. Because the research employed a retrospective framework and drew upon anonymized records, the ethics committee waived the requirement for written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki, and the presentation of this cohort analysis conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [25]. Every piece of data underwent analysis in a fully anonymized fashion.

Digital health records belonging to patients who received general anesthesia for hepatobiliary operations and were placed on PCIA from March 2018 through June 2021 were compiled. Subjects were excluded if any of the following applied: clinical documentation was incomplete; opioids had been used chronically before surgery (for at least three months); hepatic or renal function was compromised; or postoperative surveillance data covering the initial 72 hours after surgery were missing. Based on the specific opioid loaded into the analgesic pump, the cohort was split into two arms: a sufentanil arm (group S) and a butorphanol arm (group B).

Anesthesia and analgesia techniques

The anesthetic regimen delivered to both arms followed the institution's standard perioperative protocols. Once the patient entered the operating theatre, a peripheral intravenous line was placed, and standard monitoring was commenced (encompassing NIBP, ECG, SPO2, and ETCO2). Preoxygenation with 100% oxygen was carried out for three minutes, after which induction of general anesthesia was achieved through intravenous administration of propofol together with sufentanil [26, 27]. Placement of a tracheal tube or laryngeal mask was facilitated by rocuronium or cis-atracurium. Throughout the surgical procedure, a combined intravenous-inhalational maintenance technique employing propofol, remifentanil, and sevoflurane was titrated to keep the BIS within the 40-60 range, and consistent muscle relaxation was maintained with intermittent intravenous boluses of cisatracurium [28, 29]. Upon completion of the operation, residual neuromuscular block was reversed with neostigmine and atropine. The airway device was removed once full emergence from anesthesia was confirmed. Every subject received PCIA to manage postsurgical discomfort. The formulation contained in the electronic

pump was prepared by combining the following: a single opioid (either sufentanil at 1.5~2.0ug/kg or butorphanol at 8~12mg) along with dexmedetomidine 1~1.5ug/kg, ketorolac 240~360mg, and tropisetron 10~15mg, diluted to a final volume of 100mL. The pump was programmed to deliver a continuous background infusion of 2 mL/hr and to allow a patient-initiated bolus of 2 mL, with a lockout period set at 15 minutes. The choice between sufentanil and butorphanol was left to the discretion and familiarity of the attending anesthesiologist. The PCIA device was stopped in the event of hypoventilation (defined as a respiratory rate below 10 breaths per minute) or hypoxia (indicated by SPO2 falling below 88% while supplemental oxygen was delivered via nasal cannula at 5 L/min). A specialized acute pain service (APS) team, having received dedicated training, performed daily ward rounds each morning (spanning 8:00 a.m. to 10:00 a.m.) on the first, second, and third days after surgery (referred to as POD1, POD2, and POD3, respectively). Pain intensity was quantified using a Visual Analogue Scale (VAS), where 0 mm represented the absence of pain and 100 mm represented the worst pain the patient could imagine; ratings were obtained at rest and during provoked movement (elicited by taking a deep breath or coughing forcefully 3 times). Pain episodes classified as moderate-to-severe (VAS $\geq$ 4) were separately logged [30]. Additionally, opioid-attributable untoward events—namely, nausea, vomiting, dizziness, and urinary retention—were documented.

The data elements collected encompassed: (1) preoperative descriptors: age, sex, body weight, ASA physical status grade, smoking status, alcohol intake history, and coexisting conditions (hypertension, diabetes, coronary heart disease); (2) intraoperative descriptors: surgical modality (open or laparoscopic), anesthetic modality (general anesthesia supplemented by a nerve block versus general anesthesia as a standalone technique), operative time, total volume of intraoperative fluid administered, estimated blood loss, urine output, and allogeneic blood transfusion; (3) postoperative descriptors: VAS pain ratings during movement and at rest on POD1, POD2, and POD3, number of bolus demands registered by the analgesic pump, opioid-related adverse phenomena (nausea, vomiting, dizziness, and urinary retention), and total duration of postoperative hospitalization. The quantities of sufentanil and butorphanol delivered through PCIA were transformed into morphine-equivalent doses [31, 32].

Statistical analysis

All statistical computations were performed using IBM SPSS Statistics (version 26.0, Chicago, USA). Categorical variables are summarized as counts and corresponding percentages, whereas continuous variables are reported as mean ± standard deviation or median with interquartile range (IQR). Normality of data distributions was assessed using the Shapiro–Wilk test. For continuous measures, comparisons were drawn using the unpaired Student's t-test when the data conformed to a normal distribution, or the Mann–Whitney U-test when they did not. Categorical endpoints were assessed via the $\chi 2$ test or Fisher's exact test, depending on appropriateness. Since the dataset for this retrospective review was already fixed in size, the number of eligible records could not be modified; accordingly, a post hoc statistical power estimation was undertaken rather than an a priori sample size determination. To attenuate biases introduced by confounding variables, propensity score matching (PSM) was executed through a multivariable logistic regression framework applying a 1:1 pairing ratio, with matching factors encompassing age, sex, ASA status, comorbidities, surgical modality, anesthetic modality, operative time, total intraoperative fluid volume, estimated blood loss, urine output, and blood transfusion, using a caliper distance of 0.02. Subgroup analyses stratified by surgical and anesthetic modality were performed for the primary endpoint (incidence of moderate-to-severe pain within 72 hours after surgery) to probe treatment responses across distinct subpopulations. A two-tailed significance threshold of 0.05 was adopted for every statistical comparison.

Results and Discussion

Screening of our institutional records identified 5987 patients who underwent hepatobiliary operations **(Figure 1).** From this starting population, we excluded individuals with missing baseline data (n=2108), those with a history of preoperative opioid intake (n = 350), those exhibiting hepatic or renal compromise (n = 14), and those lacking complete follow-up records covering the first 72 postoperative hours (n = 78). The remaining 3437 subjects were then allocated to two cohorts: one receiving sufentanil (n = 913) and the other receiving butorphanol (n = 2524). **Table 1** presents a side-by-side summary of demographic features and intraoperative details before matching. Several parameters—namely, diabetes, coronary arterial disease, operative technique, length of surgery, total intraoperative fluids administered, intraoperative transfusion, urine volume, and estimated blood loss—

showed statistically meaningful between-group differences ($P < 0.05$). After propensity score matching, the two cohorts achieved satisfactory balance across all baseline and intraoperative variables **(Table 2).**

Table 1. Baseline characteristics and intraoperative information before PSM.

Characteristic	P-value	Sufentanil group (n = 913)	Butorphanol group (n = 2524)
Sex (male/female)	0.352	509/404	1362/1162
Age (years)	0.858	57.33 ± 14.69	57.43 ± 13.76
Body weight (kg)	0.600	64.44 ± 12.72	64.69 ± 12.09
ASA physical status	0.266		
• Class I		27 (2.96%)	75 (2.97%)
• Class II		690 (75.58%)	1958 (77.58%)
• Class III		194 (21.25%)	490 (19.41%)
• Class IV		2 (0.22%)	1 (0.04%)
Hypertension	0.890	135 (14.8%)	378 (15.0%)
Diabetes mellitus	0.010	109 (11.9%)	227 (9.0%)
Coronary artery disease	0.038	37 (4.1%)	148 (5.8%)
Smoking history	0.177	323 (35.4%)	829 (32.8%)
Alcohol use history	0.728	286 (31.3%)	775 (30.7%)
Type of surgery	< 0.001		
• Open surgery		601 (65.8%)	1205 (47.7%)
• Laparoscopic surgery		312 (34.2%)	1319 (52.3%)
Anesthesia type (GA + nerve block)	0.644	811 (88.8%)	2256 (89.4%)
Duration of surgery (min), median (IQR)	< 0.001	210 (145, 297.5)	180 (115, 260)
Total intraoperative fluid (mL), median (IQR)	< 0.001	2500 (1500, 3500)	2000 (1250, 3000)
Blood transfusion	0.039	188 (20.6%)	442 (17.5%)
Urine output (mL), median (IQR)	< 0.001	400 (200, 600)	300 (100, 500)
Blood loss (mL), median (IQR)	< 0.001	200 (50, 300)	100 (20, 200)

Note: Figures are presented as n (%), mean (SD), or median (IQR). Abbreviations: PSM = propensity score matching; CAD = coronary arterial disease; SD = standard deviation; GA = general anesthesia; IQR = interquartile range.

Table 2. Baseline characteristics and intraoperative information after PSM.

Clinical characteristic	P-value	Sufentanil group (n = 908)	Butorphanol group (n = 908)
Sex (male/female)	0.603	506/402	517/391
Age (years)	0.827	57.34 ± 14.72	57.19 ± 13.19
Body weight (kg)	0.360	64.39 ± 12.70	64.92 ± 11.98
ASA physical status	0.853		
• Class I		27 (3.0%)	24 (2.6%)
• Class II		689 (75.9%)	701 (77.2%)
• Class III		190 (20.9%)	182 (20.0%)
• Class IV		2 (0.2%)	1 (0.1%)
Hypertension	0.646	133 (14.6%)	140 (15.4%)
Diabetes mellitus	0.320	106 (11.7%)	120 (13.2%)
Coronary artery disease	0.312	37 (4.1%)	46 (5.1%)
Smoking history	0.694	321 (35.4%)	313 (34.5%)
Alcohol consumption history	0.761	285 (31.4%)	279 (30.7%)
Type of surgery	0.921		
• Open surgery		596 (65.6%)	598 (65.9%)
• Laparoscopic surgery		312 (34.4%)	310 (34.1%)
Anesthesia type (GA + nerve block)	0.493	807 (88.9%)	816 (89.9%)
Duration of surgery (min), median (IQR)	0.149	210 (145, 295)	205 (130, 290)

Total fluid administered (mL), median (IQR)	0.262	2500 (1500, 3500)	2500 (1500, 3337.5)
Blood transfusion	0.236	187 (20.6%)	167 (18.4%)
Urine output (mL), median (IQR)	0.951	400 (200, 600)	300 (200, 600)
Intraoperative blood loss (mL), median (IQR)	0.131	200 (50, 300)	200 (50, 300)

Note: Figures are presented as n (%), mean (SD), or median (IQR). Abbreviations: PSM = propensity score matching; CAD = coronary arterial disease; SD = standard deviation; GA = general anesthesia; IQR = interquartile range.

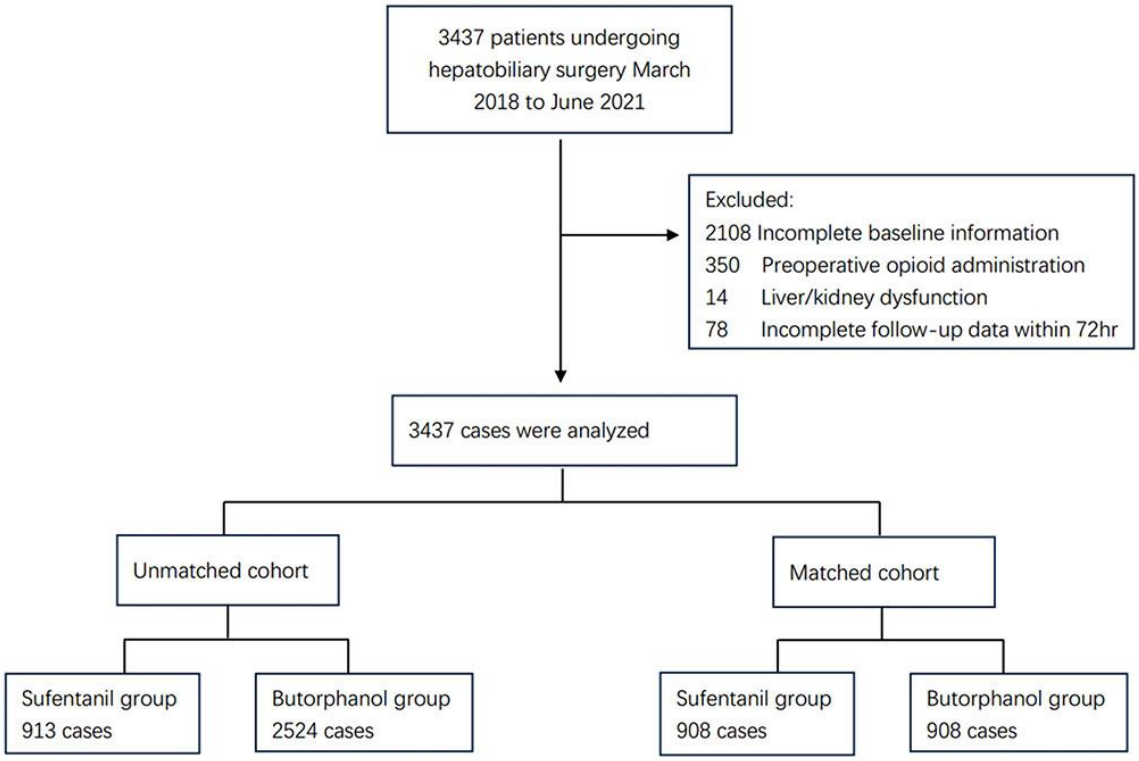

Figure 1. Flow diagram of the study.

Primary outcome

When measured against the sufentanil cohort, the butorphanol cohort demonstrated a reduced rate of moderate-to-severe pain on both POD1 and POD2, evident under resting conditions (3.2% vs 10.9%, P < 0.001; 1.2% vs 4.6%, P < 0.001) as well as under movement conditions (7.0% vs 18.9%, P < 0.001; 2.6% vs 8.7%, P < 0.001). By POD3, the two cohorts no longer differed significantly in the occurrence of moderate-to-severe pain, either at rest (7.2% vs 6.3%, P = 0.453) or during movement (11.9% vs 10.0%, P = 0.202); this pattern is depicted in **Figure 2.** The butorphanol cohort likewise recorded markedly lower VAS scores on POD1 and POD2, both at rest and upon movement (P < 0.05), though by POD3 this discrepancy had resolved (P > 0.05), as documented in **Table 3.**

Table 3. VAS pain scores within 72 hours after surgery.

	P	Sufentanil (n = 908)	Butorphanol (n = 908)
POD1 at rest	< 0.001	1 (0, 2)	0 (0, 1)
POD1 at movement	< 0.001	2 (1, 3)	2 (1, 3)
POD2 at rest	< 0.001	0 (0, 1)	0 (0, 1)
POD2 at movement	< 0.001	2 (0, 3)	1 (0, 2)
POD3 at rest	0.168	0 (0, 1)	0 (0, 1)
POD3 at movement	0.229	2 (0, 3)	1 (1, 2)

Note: Figures are presented as median (IQR). Abbreviations: POD = postoperative day; IQR = interquartile range.

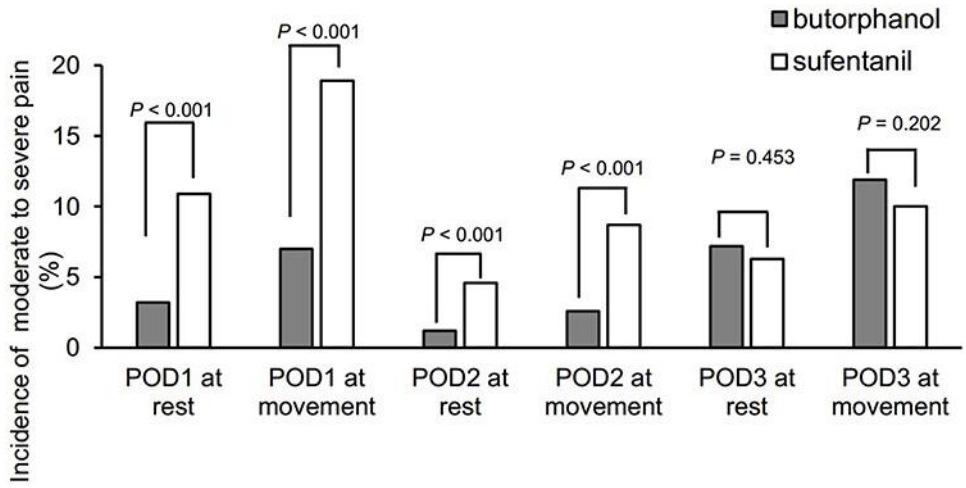

Figure 2. Incidence of moderate to severe pain during movement and at rest within 72 hours after surgery.

Secondary outcome

As displayed in **Table 4**, subjects assigned to butorphanol required a smaller total morphine-equivalent dose (50mg vs 120 mg, P < 0.001). Regarding adverse events, the two cohorts did not differ significantly in the frequency of nausea or urinary retention during the first 72 hours following surgery (P > 0.05). Postoperative vomiting occurred less often in the butorphanol cohort (1.4% vs 3.0%; P = 0.025) than in the sufentanil cohort. In contrast, dizziness was encountered more frequently among those who received butorphanol (0.9% vs 0.1%, P = 0.019). The butorphanol cohort also registered a significantly lower total number of bolus requests, along with a reduced rate of repeated bolus attempts (defined as exceeding 5 demands) (P < 0.05). Additionally, the length of postoperative hospitalization was significantly shorter in the butorphanol cohort than in its counterpart (11d vs 12d, P = 0.017).

Table 4. Secondary outcomes.

Outcome variable	P-value	Sufentanil group (n = 908)	Butorphanol group (n = 908)
Morphine consumption (mg), median (IQR)	< 0.001	120 (99, 150)	50 (40, 50)
Adverse reactions			
Nausea	0.075	34 (3.7%)	21 (2.3%)
Vomiting	0.025	27 (3.0%)	13 (1.4%)
Dizziness	0.019	1 (0.1%)	8 (0.9%)
Urinary retention	0.157	2 (0.2%)	0 (0%)
Analgesic pump bolus attempts, median (IQR)	< 0.001	2 (1, 5)	1 (0, 3)
Patients with multiple bolus attempts	< 0.001	214 (23.6%)	94 (10.4%)
Postoperative hospital stay (days), median (IQR)	0.017	12 (8, 15)	11 (7, 15)

Note: Figures are presented as n (%) or median (IQR). Abbreviations: mg = milligram; IQR = interquartile range.

Subgroup analysis

Findings from the subgroup assessment demonstrated that the principal conclusions held steady for the primary endpoint (VAS ≥ 4) across the entire 72-hour postoperative period, regardless of whether patients had undergone laparoscopic or open procedures (P > 0.05). That said, the advantage conferred by butorphanol was no longer detectable on POD2 in the subset of individuals whose anesthetic management consisted solely of general anesthesia, independent of the pain assessment context (at rest, 1.1% vs 4.0%, P = 0.423; during movement, 3.3% vs 7.9%, P = 0.163), in contradistinction to those whose care involved general anesthesia supplemented by a nerve block.

The data from this investigation indicate that postoperative delivery of butorphanol in combination with dexmedetomidine and ketorolac via PCIA was associated with lower VAS pain scores and a reduced prevalence of moderate-to-severe discomfort within the first 48 hours after surgery, compared with sufentanil. In addition,

individuals in the butorphanol arm had a shorter inpatient stay and a lower rate of vomiting. Counterbalancing these advantages, however, a higher proportion of patients in the butorphanol arm encountered dizziness.

A thorough appreciation of the physiological and pathophysiological dimensions of pain is indispensable for achieving effective pain management. The harmful stimuli encountered during hepatobiliary operations arise chiefly from several sources: the discharge of inflammatory mediators consequent to localized tissue disruption and the triggering of nociceptive sensory endings, direct insult to peripheral nerve fibers, visceral discomfort elicited by intraoperative traction on internal organs, distension of the peritoneal lining during laparoscopy, stretching of the diaphragm, and inadequate blood supply to the viscera [33, 34]. During the early hours following surgery, somatic pain may considerably outweigh visceral pain on account of the surgically removed structure (such as the gallbladder). As the initial somatic component recedes, however, visceral pain escalates due to irritation and inflammation of the parietal peritoneum [35, 36]. It follows that, to deliver optimal postoperative analgesia, each of these contributing elements must be addressed to intercept the propagation of afferent nociceptive signaling.

As precision surgery and minimally invasive methodologies continue to evolve, laparoscopic techniques are increasingly used in hepatobiliary procedures. This trend can mitigate the severity of incisional pain to a certain degree [37]. Peripheral nerve blockade, which alleviates wound-related pain by halting the somatic conduction of noxious input, has likewise gained wider acceptance in recent years due to its favorable safety profile and proven efficacy. Where visceral pain is concerned, opioids, along with other centrally mediated analgesics, may offer more pronounced benefits. Classical opioids, of which sufentanil is representative, deliver robust pain-relieving effects and have long been regarded as the cornerstone of postoperative pain therapy. As a highly selective agonist of the μ receptor, sufentanil activates opioid receptors located not only within pain-modulating pathways but also throughout the respiratory apparatus, the gastrointestinal tract, the urinary system, and elsewhere, consequently precipitating respiratory depression, nausea and vomiting, urinary retention, pruritus, and various other untoward effects. Butorphanol is a laboratory-synthesized opioid with mixed agonist-antagonist properties; it exerts its analgesic action predominantly by stimulating κ receptors, while displaying antagonist or partial agonist activity at μ receptors and minimal interaction with δ receptors [18]. Analogous to conventional opioids like sufentanil, butorphanol suppresses the onward relay of noxious signals within the dorsal horn of the spinal cord and mobilizes the descending pain-inhibitory pathway that extends from the midbrain through the rostral ventromedial medulla (RVM) to the spinal dorsal horn, thereby producing its analgesic effect. Moreover, unlike agents that act solely as μ-receptor agonists, butorphanol demonstrates greater potency against visceral pain. It carries a lower burden of adverse effects such as nausea, vomiting, dizziness, and respiratory compromise [19, 20].

The mitigation of postsurgical discomfort enhances the healthcare experience and promotes swifter postoperative convalescence. Simultaneously, shortening hospitalization duration facilitates more rapid bed turnover, enhances the efficiency of medical resource allocation, and curtails costs borne by society and the economy. In the present analysis, most observed effects persisted unchanged in subgroup analyses, regardless of operative approach (open versus laparoscopic), indicating that the superior analgesic performance of butorphanol was reproducible across distinct surgical populations. That said, in the subset of patients whose anesthetic management consisted of general anesthesia administered without a concurrent nerve block, no discernible intergroup difference emerged on POD2. A conceivable interpretation is that butorphanol, when used as an adjunct with local anesthetic agents, may contribute to a synergistic pain-relieving action mediated by κ receptors in the spinal cord [38]. If butorphanol is infused intravenously as a sole agent, this heightened analgesic benefit fails to materialize.

Our findings imply that the use of butorphanol was associated with enhanced pain regulation and a shorter postoperative inpatient stay, observations that align broadly with previously published reports. The work by Du *et al*. [39] revealed that, among women undergoing laparoscopic hysterectomy, the pairing of dexmedetomidine with butorphanol administered through PCIA effectively diminished both the postoperative pain score and the frequency of postoperative nausea and vomiting, while simultaneously boosting patient satisfaction. Bearing in mind that opioid consumption is climbing steadily and excessively on a global scale, strategies that strike a balance between attaining satisfactory analgesia and minimizing opioid exposure constitute investigational imperatives [40, 41]. Our study established that butorphanol combined with nonsteroidal anti-inflammatory drugs (NSAIDs) and dexmedetomidine yielded a reduction in the morphine-equivalent dose. Earlier research demonstrated that in patients recovering from abdominal hysterectomy, butorphanol co-administered with morphine through PCIA was capable of delivering a superior analgesic response and greater patient satisfaction than morphine monotherapy [42]. It also curbed morphine requirements and lessened the frequency of side effects, including nausea, vomiting,

dizziness, drowsiness, and the like. Beyond this, butorphanol attenuated the postoperative hyperalgesic state induced by remifentanil. Kong *et al.* [43] reported that, in subjects undergoing laparoscopic cholecystectomy, a continuous intraoperative infusion of low-dose butorphanol can lower postoperative VAS scores and reduce the demand for fentanyl both in the PACU and on the surgical ward, compared with the exclusive use of remifentanil. Beyond the broadly adopted minimally invasive surgical approaches and truncal nerve blockade techniques that form components of the multimodal analgesic strategy at our institution, we additionally employed other opioid-sparing pharmacological agents, specifically ketorolac and dexmedetomidine. Serving as a foundational class within the three-step analgesic ladder, NSAIDs function by blocking cyclooxygenase (COX), thereby disrupting arachidonic acid metabolism and curtailing prostaglandin synthesis (PGs); this mechanism accounts for their antipyretic, analgesic, and anti-inflammatory properties. When co-administered with opioids, a synergistic interaction emerges, facilitating opioid dose reduction, amelioration of postoperative inflammatory pain, and attenuation of opioid-related untoward effects [44]. Dexmedetomidine represents a highly selective agonist at α2-adrenergic receptors. Its analgesic mechanisms are multifaceted, primarily operating through α2 adrenergic receptors in the dorsal horn of the spinal cord, where it suppresses norepinephrine release via a negative feedback loop and interrupts pain signal propagation [45]. In contemporary practice, dexmedetomidine has gained widespread application when combined with other sedative and analgesic compounds for PCIA [46, 47]. Beyond its analgesic properties, dexmedetomidine also possesses the capacity to diminish the stress response, ameliorate delirium, and reduce postoperative shivering [48-50]. Taken together, each of these analgesic components engages distinct molecular targets along the pain transmission pathway, collectively contributing to an elevated pain perception threshold, diminished nociceptive receptor activation, and reduced or even prevented central and peripheral sensitization, ultimately yielding additive or synergistic pain-relieving effects [51-53].

Several limitations warrant acknowledgment in the present study. Although a 1:1 propensity score-matching procedure was implemented to equilibrate baseline characteristics between the two cohorts, substantial attrition in the butorphanol arm during the matching process may have introduced bias into the findings; consequently, these results ought to be interpreted with circumspection. Second, the electronic database captured information solely from the early postoperative window, and extended surveillance encompassing chronic postsurgical pain was not undertaken. Furthermore, the analgesic pump delivered not only opioids but also nonsteroidal analgesics alongside dexmedetomidine, suggesting that the inherent pharmacodynamic interactions among these agents, along with other covariates and unmeasured confounders, may have shaped the observed outcomes. Accordingly, a prospective, randomized, controlled investigation with a sufficiently large sample size is warranted to more definitively explore optimal butorphanol dosing and its ideal pairing with other analgesic agents within multimodal analgesic protocols.

Conclusion

Relative to sufentanil, the incorporation of butorphanol into a multimodal analgesic regimen combined with dexmedetomidine and ketorolac administered via PCIA yielded enhanced pain relief following hepatobiliary surgery, accompanied by decreased opioid requirements and a shorter postoperative inpatient stay. Further prospective, large-scale investigations are needed to substantiate the effectiveness and safety profile of butorphanol within postoperative multimodal analgesia.

Acknowledgments: This work was supported by the Key Project of Provincial and Ministerial Cooperation of Medical Science and Technology Project of Henan Province (SBGJ202102008).

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Kim HC, Song Y, Lee JS, Kim SH, Lee JH, Park SY, et al. Comparison of pharmacologic therapies alone versus operative techniques in combination with pharmacologic therapies for postoperative analgesia in

patients undergoing laparoscopic cholecystectomy: a randomized controlled trial. Int J Surg. 2022;104:106763.
2. Bhushan S, Huang X, Su X, Luo L, Xiao Z. Ultrasound-guided erector spinae plane block for postoperative analgesia in patients after liver surgery: a systematic review and meta-analysis on randomized comparative studies. Int J Surg. 2022;103:106689.
3. Kehlet H. Postoperative pain, analgesia, and recovery-bedfellows that cannot be ignored. Pain. 2018;159(Suppl 1):S11-6.
4. Pirie K, Traer E, Finniss D, Myles PS, Riedel B. Current approaches to acute postoperative pain management after major abdominal surgery: a narrative review and future directions. Br J Anaesth. 2022;129(3):378-93.
5. Pak DJ, Yong RJ, Kaye AD, Urman RD. Chronification of pain: mechanisms, current understanding, and clinical implications. Curr Pain Headache Rep. 2018;22(2):9.
6. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.
7. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537-46.
8. Memtsoudis SG, Fiasconaro M, Soffin EM, Liu J, Wilson LA, Poeran J, et al. Enhanced recovery after surgery components and perioperative outcomes: a nationwide observational study. Br J Anaesth. 2020;124(5):638-47.
9. Nimmo SM, Foo ITH, Paterson HM. Enhanced recovery after surgery: pain management. J Surg Oncol. 2017;116(5):583-91.
10. Sjövall S, Kokki M, Kokki H. Laparoscopic surgery: a narrative review of pharmacotherapy in pain management. Drugs. 2015;75(16):1867-89.
11. Liu S, Peng P, Hu Y, Zhang Y, Wang Y, Chen X, et al. The effectiveness and safety of intravenous dexmedetomidine of different concentrations combined with butorphanol for post-caesarean section analgesia: a randomized controlled trial. Drug Des Devel Ther. 2021;15:689-98.
12. Abdelaziz DH, Boraii S, Cheema E, Mansour NO, Elnaem MH, Salem MA, et al. The intraperitoneal ondansetron for postoperative pain management following laparoscopic cholecystectomy: a proof-of-concept, double-blind, placebo-controlled trial. Biomed Pharmacother. 2021;140:111725.
13. Pirie K, Doane MA, Riedel B, Myles PS. Analgesia for major laparoscopic abdominal surgery: a randomised feasibility trial using intrathecal morphine. Anaesthesia. 2022;77(4):428-37.
14. Desai N, El-Boghdadly K, Albrecht E. Epidural vs transversus abdominis plane block for abdominal surgery: a systematic review, meta-analysis and trial sequential analysis. Anaesthesia. 2021;76(1):101-17.
15. Yu JM, Tao QY, He Y, Liu D, Niu JY, Zhang Y. Opioid-free anesthesia for pain relief after laparoscopic cholecystectomy: a prospective randomized controlled trial. J Pain Res. 2023;16:3625-32.
16. Xie M, Liang Y, Deng Y, Li T. Effect of S-ketamine on postoperative pain in adults post-abdominal surgery: a systematic review and meta-analysis. Pain Physician. 2023;26(4):327-35.
17. Adams TJ, Aljohani DM, Forget P. Perioperative opioids: a narrative review contextualising new avenues to improve prescribing. Br J Anaesth. 2023;130(6):709-18.
18. Ji J, Lin W, Vrudhula A, Zhang H, Yang F, Wang Y, et al. Molecular interaction between butorphanol and κ-opioid receptor. Anesth Analg. 2020;131(3):935-42.
19. Rivière PJ. Peripheral kappa-opioid agonists for visceral pain. Br J Pharmacol. 2004;141(8):1331-4.
20. Hoskin PJ, Hanks GW. Opioid agonist-antagonist drugs in acute and chronic pain states. Drugs. 1991;41(3):326-44.
21. Lv S, Sun D, Li J, Yang L, Sun Z, Feng Y. Anesthetic effect of different doses of butorphanol in patients undergoing gastroscopy and colonoscopy. BMC Surg. 2021;21(1):266.
22. Zhang X, Qi S, Lin Z, Wang H, Li Y, Chen J, et al. Pre-operative administration of butorphanol mitigates emergence agitation in patients undergoing functional endoscopic sinus surgery: a randomized controlled clinical trial. Front Psychiatry. 2022;13:1090149.
23. Wang Y, Zhao K, Wu N, Liu X, Zhang H, Chen L, et al. Effect of different doses of butorphanol on postoperative shivering in elderly patients: a randomized, double-blind, placebo-controlled trial. Drug Des Devel Ther. 2023;17:839-49.
24. Zhu Z, Zhang W. Efficacy and safety of butorphanol use in patient-controlled analgesia: a meta-analysis. Evid Based Complement Alternat Med. 2021;2021:5530441.

25. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24.
26. Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: physiologic basis, benefits, and potential risks. Anesth Analg. 2017;124(2):507-17.
27. Jaber S, De Jong A, Schaefer MS, Futier E, Paugam-Burtz C, Molinari N, et al. Preoxygenation with standard facemask combining apnoeic oxygenation using high-flow nasal cannula versus standard facemask alone in patients with and without obesity: the OPTIMASK international study. Ann Intensive Care. 2023;13(1):26.
28. Lu Z, Wang Q, Sun X, Zhang Y, Li H, Chen W, et al. Transcutaneous electrical acupoint stimulation before surgery reduces chronic pain after mastectomy: a randomized clinical trial. J Clin Anesth. 2021;74:110453.
29. Lu Z, Zheng H, Chen Z, Wang Q, Sun X, Li Y, et al. Effect of etomidate vs propofol for total intravenous anesthesia on major postoperative complications in older patients: a randomized clinical trial. JAMA Surg. 2022;157(10):888-95.
30. Xu Y, Ye M, Liu F, Wang H, Zhang Y, Li X, et al. Efficacy of prolonged intravenous lidocaine infusion for postoperative movement-evoked pain following hepatectomy: a double-blinded, randomised, placebo-controlled trial. Br J Anaesth. 2023;131(1):113-21.
31. Anderson R, Saiers JH, Abram S, Schlicht C. Accuracy in equianalgesic dosing: conversion dilemmas. J Pain Symptom Manage. 2001;21(5):397-406.
32. De Iaco F, Mannaioni G, Serra S, Bianchi M, Berti M, Fanelli G, et al. Equianalgesia, opioid switch and opioid association in different clinical settings: a narrative review. Eur Rev Med Pharmacol Sci. 2022;26(6):2000-17.
33. Li Y, Dou Z, Yang L, Wang Q, Ni J, Ma J. Oxycodone versus other opioid analgesics after laparoscopic surgery: a meta-analysis. Eur J Med Res. 2021;26(1):4.
34. Wills VL, Hunt DR. Pain after laparoscopic cholecystectomy. Br J Surg. 2000;87(3):273-84.
35. Boezaart AP, Smith CR, Chembrovich S, Leonardi C, Botha CB, Venter R, et al. Visceral versus somatic pain: an educational review of anatomy and clinical implications. Reg Anesth Pain Med. 2021;46(7):629-36.
36. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90(3):261-9.
37. Mansour NO, Boraii S, Elnaem MH, Abdelaziz DH, Salem MA, Cheema E, et al. Evaluation of preoperative duloxetine use for postoperative analgesia following laparoscopic cholecystectomy: a randomized controlled trial. Front Pharmacol. 2022;13:944392.
38. Fu H, Fu Y, Xu X, Gao Y. Ultrasound-guided rectus sheath block combined with butorphanol for single-incision laparoscopic cholecystectomy: what is the optimal dose of ropivacaine? J Pain Res. 2020;13:2609-15.
39. Du J, Li JW, Jin J, Shi CX, Ma JH. Intraoperative and postoperative infusion of dexmedetomidine combined with intravenous butorphanol patient-controlled analgesia following total hysterectomy under laparoscopy. Exp Ther Med. 2018;16(5):4063-9.
40. Allen ML, Kim CC, Braat S, Bellomo R, Pilcher D, Story D, et al. Post-discharge opioid use and handling in surgical patients: a multicentre prospective cohort study. Anaesth Intensive Care. 2020;48(1):36-42.
41. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348:g1251.
42. Wang F, Shen X, Liu Y, Xu S, Guo X. Continuous infusion of butorphanol combined with intravenous morphine patient-controlled analgesia after total abdominal hysterectomy: a randomized, double-blind controlled trial. Eur J Anaesthesiol. 2009;26(1):28-34.
43. Kong M, Yang L, Li J, Wang Y, Zhang H, Liu X, et al. Low-dose butorphanol alleviates remifentanil-induced hyperalgesia in patients undergoing laparoscopic cholecystectomy. J Clin Anesth. 2016;34:41-5.
44. Zhang Z, Xu H, Zhang Y, Li W, Yang Y, Han T, et al. Nonsteroidal anti-inflammatory drugs for postoperative pain control after lumbar spine surgery: a meta-analysis of randomized controlled trials. J Clin Anesth. 2017;43:84-9.
45. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, et al. Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) protocols for postoperative pain. Curr Pain Headache Rep. 2020;24(5):21.
46. Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anaesth. 2009;102(1):117-22.

47. Gao Y, Deng X, Yuan H, Leng Y, Zhang T, Xu X, et al. Patient-controlled intravenous analgesia with combination of dexmedetomidine and sufentanil in patients after abdominal operation: a prospective, randomized, controlled, blinded, multicenter clinical study. Clin J Pain. 2018;34(2):155-61.
48. Duan X, Coburn M, Rossaint R, Sanders RD, Van Waesberghe J, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomized controlled trials. Br J Anaesth. 2018;121(2):384-97.
49. Liu ZX, Xu FY, Liang X, Zhou M, Wu L, Wu J, et al. Efficacy of dexmedetomidine on postoperative shivering: a meta-analysis of clinical trials. Can J Anaesth. 2015;62(7):816-29.
50. Miao M, Xu Y, Li B, Chang E, Zhang L, Zhang J. Intravenous administration of dexmedetomidine and quality of recovery after elective surgery in adult patients: a meta-analysis of randomized controlled trials. J Clin Anesth. 2020;65:109849.
51. White PF. Expanding role of multimodal analgesia in facilitating recovery after surgery: from fast-tracking to enhanced recovery. J Clin Anesth. 2019;55:105-7.
52. Dunkman WJ, Manning MW. Enhanced recovery after surgery and multimodal strategies for analgesia. Surg Clin North Am. 2018;98(6):1171-84.
53. Zhang H, Yang YT, Jiang LL, Xu XD, Zhang JQ, Zhang LZ. Risk factors for moderate-to-severe acute pain after hepatobiliary and pancreatic surgery: a single-center retrospective study. BMC Anesthesiol. 2023;23:In Press.