Review Article

Efficacy and safety of sublingual buprenorphine in managing acute postoperative pain – A systematic review

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Abstract

Sublingual (SL) buprenorphine has been used as a modality of managing acute postoperative pain in many studies. This systematic review aimed to investigate the safety and efficacy of SL buprenorphine as an analgesic for various surgeries. After registering the protocol with PROSPERO, we searched PubMed, Cochrane Library, and Ovid databases with relevant keywords. The primary outcomes were 24-hour pain scores, and the secondary outcomes were postoperative nausea and vomiting, sedation scores, pruritus, rescue analgesia, and urinary retention. The risk of bias scale was used to identify the quality of evidence. From the 103 articles identified, four randomized-controlled trials fulfilled the inclusion criteria for qualitative analysis. The overall risk of bias was low. Most of the studies showed that the use of SL buprenorphine led to either better or comparable pain scores when compared to a control group with lesser or tolerable adverse events. There was a lot of heterogeneity across the studies in this systematic review in terms of the type of surgery performed, the comparison groups, doses of buprenorphine, and the outcomes that were assessed. Therefore, a quantitative meta-analysis was not performed. The results of this systematic review should be interpreted with caution due to heterogeneity in the methodology. Adequately powered studies with robust methodology should investigate the safety and efficacy of SL buprenorphine when used for postoperative analgesia.

Keywords: Acute pain, buprenorphine, postoperative, sublingual

Introduction

Acute postoperative pain is a common problem faced by patients undergoing surgical procedures. Adequate management of postoperative pain is crucial for the patient's comfort, improvement of functional outcomes, and reduction in the risk of complications. Poorly managed postoperative pain can lead to chronic postsurgical pain.[1] Pain management strategies have evolved, and various pharmacologic and non-pharmacologic approaches have been used to address this issue.[2]

Sublingual (SL) buprenorphine is a mode of administration for opioid pain management, which has been gaining popularity in recent years. Buprenorphine is a semi-synthetic opioid agonist–antagonist with a unique pharmacological profile that makes it an attractive option for the management of acute postoperative pain. Unlike traditional opioids, buprenorphine has a ceiling effect on its analgesic efficacy, beyond which further increases in dose do not result in increased pain relief. This property reduces the risk of overdose and respiratory

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depression associated with traditional opioids. In addition, buprenorphine has a lower potential for abuse and dependence and a lower risk of withdrawal compared to other opioids.[3,4] Several clinical trials have evaluated the efficacy and safety of SL buprenorphine in the management of acute pain.[5-9] The advantages of using SL buprenorphine, such as the ease of administration, lower risk of overdose, and lesser chance of respiratory depression, make it a useful opioid for postoperative use. To date, there has been no qualitative systematic review or quantitative meta-analysis performed to assess the efficacy and safety of SL buprenorphine as an analgesic in surgical patients.

This systematic review aimed to investigate the efficacy and safety of SL buprenorphine when used for providing perioperative analgesia in patients undergoing various surgeries by comparing it with placebo or any other analgesic modalities.

Material and Methods

This systematic review was registered prospectively with the International Prospective Register of Systematic Reviews: PROSPERO (-Fill it--) and reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[10] The relevant keywords were found in databases from January 2000 to January 2023. PubMed/MEDLINE, Ovid, Cochrane Library (CENTRAL), and clinicaltrials.gov databases were searched from the year 2000 till January 2023. The following search terms were used for searching various databases: "Acute pain" OR "Postoperative pain" AND "Buprenorphine" AND "Sublingual" AND "Surgery." Supplementary File 1 contains the complete search method for all databases.

The database findings were carefully examined for randomized controlled trials (RCTs) comparing SL buprenorphine to a placebo or any other premedication. Two authors independently reviewed the titles and abstracts, and duplicates were deleted. The final studies included were chosen after careful deliberation by both authors, who also read the entire texts. A third author resolved any disagreements and inconsistencies. Each reviewer extracted data separately using a specified manner. The finalized articles were evaluated in terms of study features and outcomes. The data collected included the author's name, publication year, study design, number of participants, nationality, age, type of surgical intervention, buprenorphine dose and frequency of usage, and information about the comparison group (placebo or another premedication).

Participants (inclusion and exclusion criteria)

RCTs in which SL buprenorphine was compared with either a placebo or another medication in patients undergoing various surgeries were included. No other route of administration other than SL [e.g., intravenous (IV), transdermal, intrathecal, or epidural] was entertained. Studies in which there were no control groups, case reports/series, editorials, review articles, or conference abstracts were excluded. Studies in which SL buprenorphine was used for pain due to non-surgical causes (renal colic, metastatic pain) were excluded. Studies in which patients were opioid-dependent and SL buprenorphine was used for postoperative pain were also excluded.

Intervention and comparators

The intervention under investigation was the use of SL buprenorphine, which was compared with either a placebo or any other premedication such as benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDs), and alpha-2 agonists in patients undergoing various surgeries.

Outcomes: primary and secondary

Primary outcomes were pain scores at rest and movement in the first 24 hours. The secondary outcomes were 24-hour opioid consumption, time to first analgesia, patients requiring rescue analgesia, adverse events such as postoperative nausea/vomiting (PONV), patient satisfaction, adverse events such as drowsiness, respiratory depression, and length of hospital stay.

Methodological quality assessment

To assess the methodologic quality and risk of bias of the included RCTs, the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was employed. For bias assessment, six categories were considered: bias due to randomization, bias due to deviation from intended intervention, bias due to missing data, bias due to outcome measurement, bias due to reported result selection, and overall bias.[11]

Data extraction

The publications' reference data, populations, and outcomes were retrieved and placed into pre-planned tables. The two authors (— and —) extracted data systematically. The data collection form was pilot-tested before being deployed. We collected information on the study design, number of arms, primary outcome, participant demographics, sample size, surgical procedures, and experimental intervention (dose and frequency of SL buprenorphine). As a dichotomous outcome, the existence or absence of a therapeutic or unfavorable effect was retrieved. For continuous data, we computed means and standard deviations (SDs). If not mentioned otherwise, the SDs were obtained from confidence intervals (CIs) or *P* values relating to mean variances between the two groups. If certain outcome details are represented in graphs and not in numbers, the corresponding authors were contacted to retrieve details.

Results

Description of the studies

Results of the literature search

In the search of various databases, we came across 103 citations. The PRISMA flowchart is displayed in Figure 1. We identified 103 articles by searching the abovementioned databases and registries. After removing duplicates and articles that were not relevant, we identified 21 articles for scrutiny. A total of nine studies were considered eligible. From these, five studies were excluded (review articles: 2, unrelated primary and secondary outcomes: 3). Finally, we included four studies that included 306 patients for analysis (154 in the SL buprenorphine group and 152 in the control group).[12-15] The population, intervention, control characteristics of the studies, and outcomes that were considered are listed in Table 1.

The retrospective cohort study by Heldreich *et al.* in which they compared data of 146 patients undergoing major abdominal surgery who received either SL buprenorphine or oral oxycodone for postoperative analgesia was excluded as it was a retrospective cohort study.[16]

Risk of bias

The risk of bias within the trials according to RoB 2 is depicted in Figure 2. The summary plot of the quality assessment is shown in Figure 3. The bias from the randomization process was low in all four studies.[12-15] Bias due to deviations from intended interventions (allocation concealment) was low in three studies[12-14] and high in one study.[15] Bias arising due to missing outcome data was low in one study[13] and had no information in the other three studies.[12,14,15] Bias in the measurement of outcome was low in all four studies.[12-15] Bias arising due to the selection of reported results was low in all four studies.[12-15] The overall bias was low in all four included studies.[12-15]

Outcomes studied

The details of primary and secondary outcomes studies are presented in Table 1.

Primary outcomes

Postoperative pain scores were reported by four studies (154 in the SL buprenorphine group and 152 in the control group).[12-15] In the study by Soltani *et al.*, pain scores in the first 12 hours were significantly higher in the morphine group than in the SL buprenorphine group, with a mean score of 2.5 ($P < 0.001$).[12] A total of 19 patients received rescue analgesic IV pethidine compared to eight patients in the SL buprenorphine group. The results of the study by Norozi *et al.* revealed that continued VAS score for 24

Table 1: Shows details of the studies, comparators, primary and secondary outcomes, and conclusions

Authors/ year	Country	Type of Study	Surgery	Number of patients	Comparator	Dose of SL buprenorphine	Primary outcome	Secondary outcome	Conclusions
Soltani *et al.*[12]/2015	Iran	RCT	Closed Reduction Orthopedic Surgery	90 (45 in each group)	0.2 mg/kg morphine IV	4.5 μg/kg (maximum 1 mg)	To compare the analgesic efficacy of SL buprenorphine with a single dose of intravenous morphine	Pruritus, nausea, vomiting, urinary retention, level of sedation, and consciousness	In comparison to IV morphine, SL buprenorphine administration before anesthesia induction in closed reduction orthopedic surgery can result in improved postoperative pain control.
Norozi *et al.*[13]/2021	Iran	RCT	Open Cholecystectomy	80 (40 in each group)	Fentanyl PCA	0.4 mg	Comparison of pain scores postoperatively till 24 hours	Nausea, vomiting, and sedation	Because of its safety profile, low cost, and ease of administration, SL buprenorphine is an effective medication for patients to relieve postoperative pain after open cholecystectomy.
Kiabi *et al.*[14]/2021	Iran	RCT	Lumbar discectomy	78 (39 in each group)	Placebo	2 mg	Comparison of pain scores at different periods in the first 24 hours	Nausea, vomiting, and pruritus	In the treatment of postoperative pain after lumbar discectomy, SL buprenorphine is an effective and low-dose medication and has a simpler route of administration.
Dokku *et al.*[15]/2023	India	RCT	Mastectomy	58 patients (30 in the buprenorphine group and 28 in the control group)	1.5 mg/kg tramadol IV	0.2 mg	Comparison of pain scores at rest and movement at different periods up to 24 hours postoperatively	Nausea, vomiting, sedation scores, and rescue analgesia requirements	Over the first 24 hours following a mastectomy, the analgesic efficacy of SL buprenorphine appears to be comparable to IV tramadol at rest and movement. Yet, in terms of simplicity of administration, SL buprenorphine scores over tramadol.

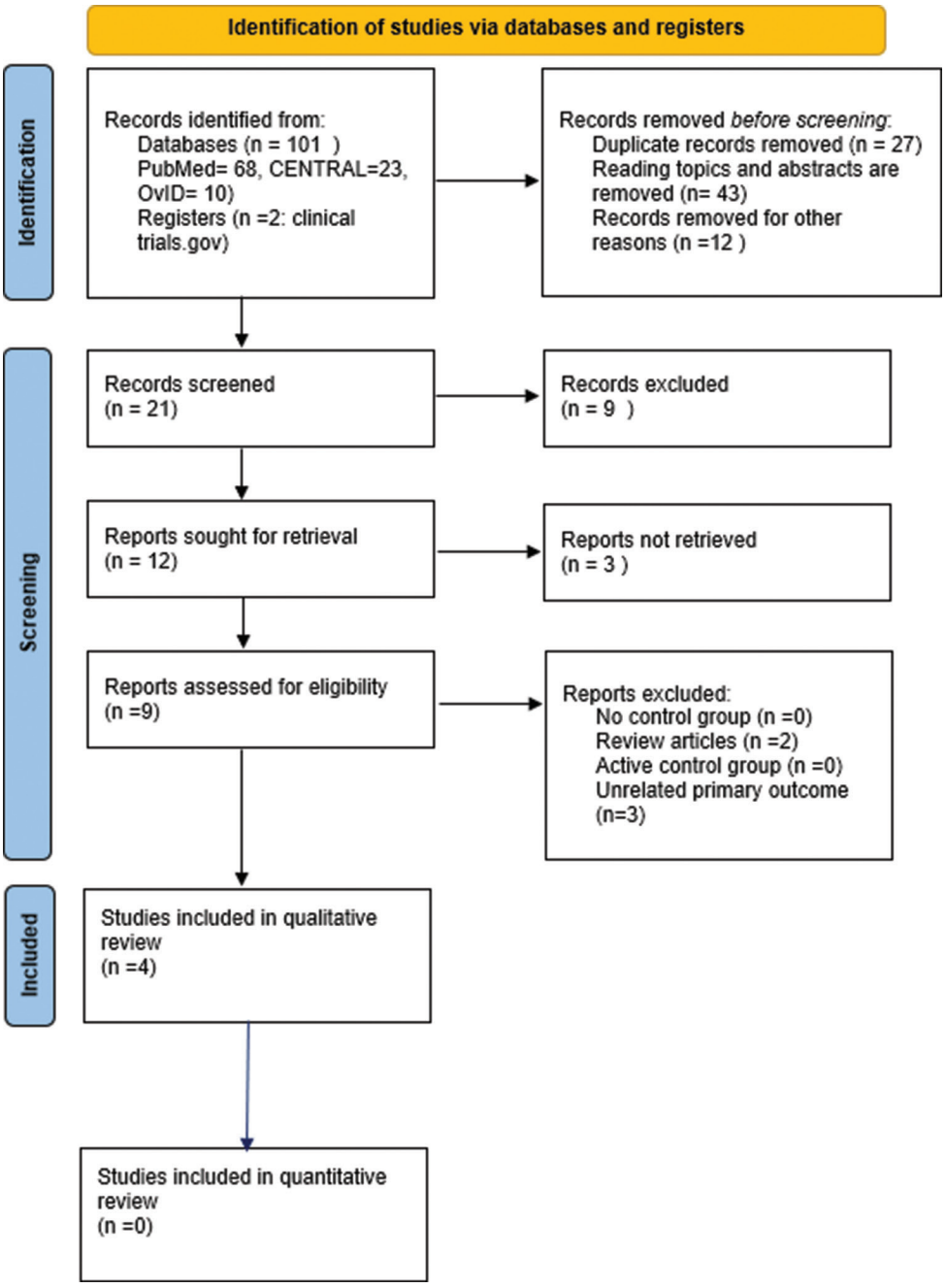

Figure 1: PRISMA flowchart

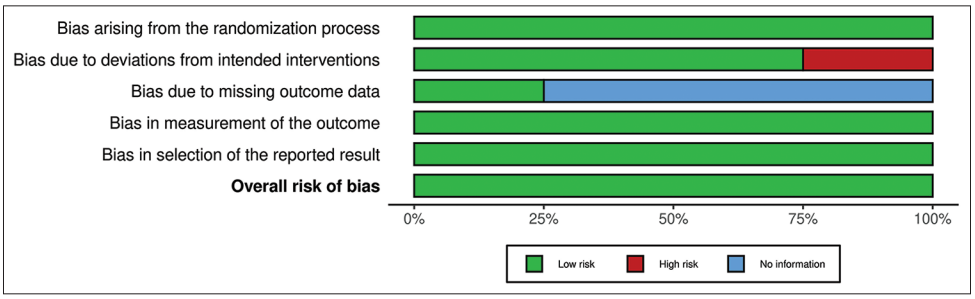

Figure 2: Traffic-light plot

hours postoperatively in the patients showed that VAS score intensity in patients receiving buprenorphine was significantly lower than that compared to those in the fentanyl group 6 hours after surgery ($P = 0.005$) and overall as well ($P = 0.002$).[13]

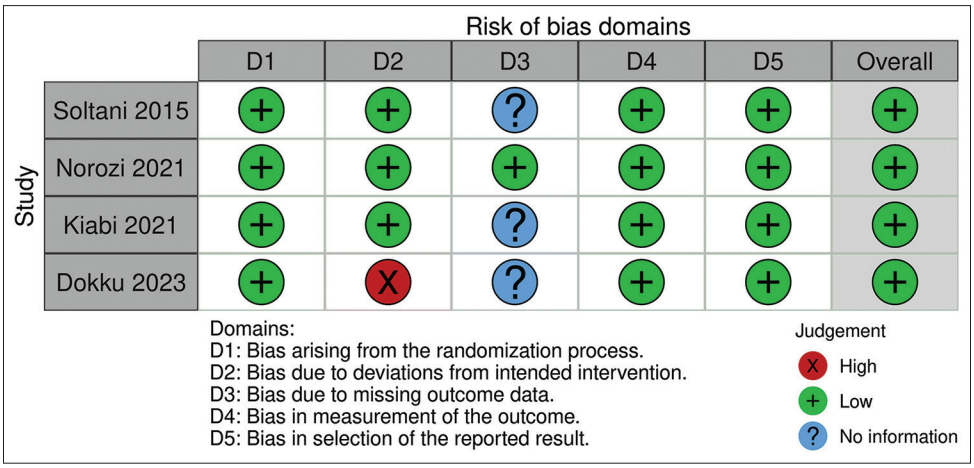

Figure 3: Summary plot

In the study by Kiabi *et al.*, pain scores were monitored at 1, 6, 12, and 24 hours.[14] At 1, 6, and 12 hours, the pain scores were statistically significant in the SL buprenorphine group compared to the placebo ($P < 0.001$, $P < 0.001$, and $P = 0.045$, respectively). However, at 24 hours, the pain scores were comparable ($P = 0.44$). Both groups experienced significant changes in pain intensity over time, according to the Friedman test, and buprenorphine considerably reduced early postoperative pain ($P < 0.001$). In the study by Dokku *et al.*, pain scores at different postoperative time points (0, 1, 3, 6, 12, 18, and 24 hours) were comparable between the two groups at rest and during movement, except for the 0- and 3-hour time points during movement where the patients in the tramadol group experienced less pain ($P = 0.029$ and 0.0133, respectively).[15] Overall, the use of SL buprenorphine provided either better or comparable postoperative analgesia.

Secondary outcomes

PONV:

Nausea and vomiting were reported in four studies (154 in the SL buprenorphine group and 152 in the control group).[12-15] Soltani *et al.* assessed nausea at 0, 0.5, 3, 6, and 12 hours after the patients reached the recovery room.[12] It was not significant at 0, 0.5, and 3 hours ($P = 0.5$) and not documented at 6 and 12 hours as no patients complained of nausea. Vomiting was assessed at 0, 0.5, 3, 6, and 12 hours after the patients reached the recovery room, and no patients in either group had this adverse event. Norozi *et al.* documented nausea and vomiting scores at 0, 2, 6, 12, 18, and 24 hours following surgery.[13] When compared to the fentanyl group, the buprenorphine group experienced less nausea and vomiting within the first 2–6 hours following surgery. However, the difference was not statistically significant ($P = 0.42$, 0.788, 0.766, 0.756, 0.558, and 0.314, respectively). In the study by Kiabi *et al.*, throughout the period of the study, 2.6% of patients receiving placebo and 18.3% of patients receiving buprenorphine did not experience any vomiting.[14] The overall frequency of vomiting was 1.92 ± 0.35 in the placebo group and 1.641 ± 0.778 in the buprenorphine group. There was no difference in the frequency of vomiting between the two groups ($P = 0.068$). In the study by Dokku *et al.*, patients experiencing PONV were comparable in both the SL buprenorphine group (12 out of 30 patients) and the tramadol group (8 out of 28 patients), with a P value of 0.36.[15] Overall, PONV was either lesser or comparable in patients who received SL buprenorphine when compared to the control group.

Pruritus:

Two studies analyzed pruritus in the postoperative period (84 in the SL buprenorphine group and 84 in the control group).[12,14] In the study by Soltani *et al.*, the rate of pruritus in the recovery room was significantly higher in the morphine group than in the SL buprenorphine group ($P = 0.01$).[12] Kiabi *et al.* compared itching between the SL buprenorphine group and placebo at 1, 6, 12, and 24 hours after surgery.[14] The itching intensity was comparable between both groups at 1, 6, 12, and 24 hours ($P = 0.621$, 0.672, 0.155, and 0.317, respectively). The overall difference in the intensity of itching at different time intervals was not different in the SL buprenorphine group, ($P = 0.801$); however, it was significantly different in the placebo group ($P = 0.029$).

Sedation and consciousness:

Two studies compared sedation scores between two groups (75 in the SL buprenorphine group and 73 in the control group).[12,15] Soltani *et al.* found that the level of sedation and consciousness documented at 3, 6, and 12 hours after entering the recovery room showed no significant difference between the two groups;[12] 48.9% of patients in the buprenorphine

group and 86.7% patients in the morphine group were conscious when received in the recovery area ($P = 0.001$). The level of sedation in the SL buprenorphine group was higher after 30 minutes. The authors reported that 84.4% of the buprenorphine group and 97.8% of the morphine group were conscious, which was statistically significant ($P = 0.02$). In the study by Dokku *et al.*, the authors documented Ramsay's sedation scores at 0, 1, 3, 6, 12, 18, and 24 hours after surgery.[15] On analysis, they reported that the sedation scores at the abovementioned time points were comparable ($P = 0.14$, 0.77, 0.34, 0.12, 0.61, 0.88, and 0.94, respectively). Overall, the sedation scores were either better with buprenorphine or comparable to the control group.

Other outcomes:

Urinary retention was reported by Soltani *et al.* at 3, 6, and 12 hours.[12] In the SL buprenorphine group, at 3 hours, 4.2% of patients had urinary retention and no retention at 6 and 12 hours. In the control group (morphine), 6.7% at 3 hours, 2.2% at 6 hours, and none of the patients at 12 hours had urinary retention. This outcome was not statistically significant ($P = 0.3$ at 3 hours and $P = 0.5$ at 6 hours). The rescue analgesic requirement was reported by Dokku *et al.*[15] In the SL buprenorphine group, four out of 30 patients required a rescue analgesic at some point. In the control group (tramadol), no patients out of 28 required a rescue analgesic ($P = 0.11$).

Data analysis:

There was a lot of heterogeneity across the studies in this systematic review in terms of the type of surgery performed, the comparison groups, doses of buprenorphine, and the outcomes that were assessed. A meta-analysis of effect estimates is either impossible or inappropriate in various situations. This happens when effect estimates are not reported entirely or when research variables (e.g., study designs, intervention types, or outcomes) are too diverse to produce a meaningful summary estimate of the effect.[17]

We used the Synthesis Without Meta-analysis (SWiM) reporting guidelines in addition to the PRISMA checklist as a quantitative meta-analysis was not possible with this qualitative systematic review.[18] Swim includes nine items to guide in reporting systematic review without meta-analysis: seven in methods and one each in results and discussion. The checklist is provided in Supplementary File 2.

Discussion

Summary of main results

This is the first systematic review to investigate the safety and efficacy of SL buprenorphine for providing pain relief in 306 adult patients undergoing various surgeries. All the studies that fulfilled inclusion criteria were RCTs with an overall low risk of bias. However, there were a lot of inconsistencies in the methodology and outcome assessment and reporting [Table 2]. The timing of administering SL medication was variable in different studies, along with the dose, which ranged from 0.2 mg to 1 mg. The control group was also inconsistent and comprised IV morphine, IV tramadol, IV fentanyl, and a placebo. In addition, the reporting of the primary outcome (pain scores) was at different time points. Furthermore, the surgeries performed were of varying nociception. The adverse events profile, although lesser with SL buprenorphine, could not be considered acceptable due to the small sample size, different doses, and frequency of administration.

Buprenorphine is used IV, intrathecal/epidural, as transdermal patches, and also SL with variable dosage and frequency of administration depending upon the route of administration.[19-21] In a recently published SRMA, Albaqami *et al.* concluded that both transdermal and SL buprenorphine provide better pain scores when used in the management of acute post-surgical pain.[22] However, the use of buprenorphine led to more adverse effects than NSAIDs and placebo, which could affect overall patient satisfaction scores. One of the major limitations of this systematic review was that it investigated both transdermal and SL buprenorphine. A transdermal patch needs to be placed 4–6 hours before surgery so that it can provide desirable analgesia, which raises ethical concerns.[23] In another systematic review and meta-analysis by White *et al.*, the authors investigated the efficacy of buprenorphine in acute pain, which included renal colic and chest pain due to myocardial infarction along with acute postoperative pain, thus leading to significant clinical heterogeneity.[24]

SL buprenorphine has been traditionally used for the management of chronic pain and opioid use disorder.[25,26] However, over the last decade, SL buprenorphine has also been found to be an effective alternative to traditional opioids for the management of acute pain, including postoperative pain.[5,6] Another study found that SL buprenorphine is effective in the management of acute pain in patients with sickle cell disease.[27] In the retrospective study by Heldreich *et al.*, the authors retrospectively reviewed the outcomes of 146 patients who underwent emergency and elective gastrointestinal and colorectal surgeries.[16] In these patients, they studied the complete transition to SL buprenorphine instead of oral oxycodone. On analysis, the authors concluded that there was a clinically significant decrease in the 24-hourly post-parenteral opioid transition of oral morphine equivalent daily dose (OMEDDs) and better pain scores without any difference in the length of hospital stay.

Table 2: Shows inconsistencies in the outcomes

	Soltani *et al.*[12]	Norozi *et al.*[13]	Kiabi *et al.*[14]	Dokku *et al.*[15]
Primary outcome	Pain scores at 0, 30 min and 3, 6, and 12 hours	Pain scores a 0, 2, 6, 12, 18, and 24 hours	Pain scores at 1, 6, 12, and 24 hours	Pain scores at rest and movement at 0, 1, 3, 6, 12, 18, and 24 hours
The primary outcome is expressed as	Mean±SD	Number and percentage	Frequency, Mean±SD	Mean±SD
Secondary outcomes and expressed as	Pruritus' nausea, vomiting, urinary retention, sedation Expressed as percentage	Nausea and vomiting Expressed as number and percentage	Nausea, vomiting pruritus Expressed as frequency/ percentage and mean±SD	Nausea, vomiting, and rescue analgesia requirement: expressed as a number Sedation score: expressed as mean±SD

SL buprenorphine has several advantages over traditional opioids in the management of acute pain. One of the most significant advantages is its superior safety profile. Traditional opioids are associated with a high risk of respiratory depression, which is a significant cause of opioid-related deaths.[28] In a postoperative setting, opioids are prescribed for a short duration; therefore, any risk of abuse or addiction is minimal.

The strengths of this systematic review are that it is the first review in which the study of the safety and efficacy of SL buprenorphine was limited to postoperative patients. Only RCTs with limited bias were included in this systematic review. There are several limitations in this systematic review. First, there was significant heterogeneity in the studies included in this review, such as closed reduction, open cholecystectomy, mastectomy, and lumbar discectomy with different levels of nociception. Second, the doses of SL buprenorphine used ranged from 0.2 mg to 1 mg. Third, the control groups were variable, such as fentanyl PCA, IV morphine, IV tramadol, and placebo. Fourth, there was a difference in measuring outcomes and time points used to monitor outcomes. Our analysis was descriptive because the heterogeneity made it difficult to compare the results of the research with one another. Therefore, performing a quantitative analysis was not justified. The number of studies that fulfilled the inclusion criteria was small.

Conclusions

Based on the results of this review, there is insufficient evidence to support or invalidate the hypothesis that SL buprenorphine is a safe and efficacious medication in relieving acute pain after various surgeries. Although the clinical trials attest to the efficacy and safety of SL buprenorphine, we suggest adequately powered studies with a robust methodology to investigate the safety and efficacy of SL buprenorphine to establish a place in the armamentarium of multimodal analgesia.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary File 1: Database search details

Database	Search details
PubMed	(“administration, sublingual”[MeSH Terms] OR (“administration”[All Fields] AND “sublingual”[All Fields]) OR “sublingual administration”[All Fields] OR “sublingual”[All Fields] OR “sublingually”[All Fields]) AND (“buprenorphine”[All Fields] OR “buprenorphine”[MeSH Terms] OR “buprenorphine”[All Fields] OR “buprenorphine s”[All Fields]) AND (“pain, postoperative”[MeSH Terms] OR (“pain”[All Fields] AND “postoperative”[All Fields]) OR “postoperative pain”[All Fields] OR (“postoperative”[All Fields] AND “pain”[All Fields]))
Ovid	(Buprenorphine and Sublingual and Acute pain and Postoperative pain).mp.[mp=tx, bt, ti, ab, ct, sh, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, an, ui, ds, on, sy, pt]

Supplementary File 2: Synthesis without meta-analysis checklist

SWiM reporting item	Page number
Methods:	
1. Grouping studies for synthesis	3, 4
2. Describe the standardized metric and transformation methods used	3, 4
3. Describe the synthesis methods	5
4. Mention criteria used to prioritize results by summary and synthesis	5
5. Investigation of heterogeneity in reported effects	Table 2
6. Certainty of evidence	Table 2
7. Data presentation methods	3
Results:	
8. Reporting of results	6–10
Discussion:	
9. Limitations of the synthesis	12, 13

SWiM: Synthesis without meta-analysis