**Liposomal Bupivacaine versus conventional anesthetic or Placebo for Hemorrhoidectomy: A systemic review**

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**Introduction:**

Liposome bupivacaine (LB) is a long-acting anesthetic to enhance postoperative analgesia. Studies evaluating the efficacy of the LB against an active comparator (bupivacaine or placebo) on acute postoperative pain control in hemorrhoidectomy procedures are few and heterogeneous. Therefore, we sought to perform a systematic review comparing LB's analgesic efficacy and side effects to conventional/placebo anesthetic in hemorrhoidectomy patients.

**Methods:**

This is a systematic review of articles published from the time of inception of the datasets to August 19, 2022. The electronic databases included English publications in Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, and Scopus.

**Results:**

338 patients who underwent a hemorrhoidectomy procedure enrolled in 3 randomized clinical trials were included. The overall mean age was 45.84 years (standard deviation [SD] ± 11.43), and there was a male predominance (53.55% male). 194 patients (52.2 %) received LB, and 144 (47.8 %) received either bupivacaine or placebo. Pain scores at 72 hours in the LB (199, 266, and 300 mg) were significantly lower than in the bupivacaine HCl group (p=0.002). Compared to the bupivacaine/placebo group, the time to first use of opioids in the LB group was significantly longer at LB 199mg (11h vs. 9h); at LB 266 mg (19h vs. 9h), and LB 300 mg (19h vs. 8h) (p-value <0.05). Moreover, compared to the bupivacaine/epinephrine group, it was significantly lower in LB 266 mg group (3.7 vs. 10.2 mg) and at LB 300 mg (13 vs. 33 mg) (p-value <0.05). Finally, regarding adverse effects, conventional anesthetic/placebo reported more pain in bowel movement than LB (OR 2.60, 95% CI 1.31- 5.16).

**Conclusion:**

Comparing LB to conventional anesthetic/placebo anesthetic for hemorrhoidectomy, we found a statistically significant reduction in pain through 72 hours, decreased opioid requirements, and delayed time to first opioid use. Moreover, there was no difference in adverse effects between LB and conventional anesthetic/placebo.

**Introduction**

Liposome bupivacaine (LB) is a long-acting anesthetic used for postoperative analgesia. Studies evaluating the efficacy of LB against an active comparator (bupivacaine or placebo) on acute postoperative pain control are few and heterogeneous1,2. We specifically sought to study its efficacy in analgesia following a historically known painful operation, hemorrhoidectomy. Thus, we systematically compared LB's analgesic efficacy and side effects to conventional anesthetics in hemorrhoidectomy patients.

**Methods**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The protocol for this study is registered at PROSPERO.

**Eligibility criteria**

We included randomized, double-blind, placebo-controlled clinical trials (RCT) in men and nonpregnant women aged 18 years or older scheduled to undergo excisional hemorrhoidectomy. Patients were excluded if they received less than 133 mg LB or took analgesics (non-steroidal anti-inflammatory drugs, acetaminophen, or opioids), antidepressants, or glucocorticoids within the three days before surgery. Studies with less than 20 participants were excluded.

The primary outcome of interest was a pain score at 72 hours. Secondary outcomes were time to first opioid, the dose of rescue medication over 72 hours, and adverse effects (AE).

**Data sources and searches**

A comprehensive search of several databases was conducted from inception until August 2022. The databases included were Ovid MEDLINE(R) and Epub Ahead of Print, CINAHL, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science - searched Science Citation Index (SCI), Conference Proceedings Citation Index (CPCI) and BIOSIS Citation Index (BCI). The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of Liposomal Bupivacaine for Hemorrhoidectomy (Supplementary XX).

**Study selection**

Search records were uploaded into Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. All stages of the review (title and abstract screen, full-text screen, and data extraction) were duplicated by three independent reviewers (P.S-P., K.O., K.L, L.F). Before beginning each stage, pilots were performed to understand and accurately understand the eligibility criteria. Disagreements at each stage of the review were resolved by the senior author (Y. N.). Full-text screening agreement was assessed using Cohen's kappa (k=0.63).

**Data collection**

The following data were extracted: 1) general characteristics (first author, publication date, country, study design, data collection period); 2) setting (single-center, multicenter); 3) preoperative characteristics (age, sex, BMI, ASA score, Charlson Comorbidity Score); 4) primary outcomes (pain relief) was assessed by the cumulative pain score as reflected in the pain intensity at rest measured using a validated 10-point numeric rating scale (NRS; 0= no pain and 10= worst possible pain) area under the curve through 72 hours after study drug administration (AUC0 –72)

Secondary outcomes were the total amount (milligrams) of opioid rescue medication consumed 72 hours after surgery, the time to first postsurgical use of opioid rescue medication, and adverse effects (AE). For total postsurgical consumption of opioid rescue medications, all opioid doses were converted to an equianalgesic parenteral morphine amount using standard conversion factors. Adverse effects were defined as any AE occurring after administration of the study drug. All AEs were classified by system organ class and summarized by treatment group.

**Risk of bias assessment**

Study quality was assessed by three independent reviewers (P.S-P., K.O., K.L). Disagreements were resolved through consensus by including two reviewers (Y.N., P.S-P.). To assess the risk of bias in RCT, we used the RoB2 Cochrane tool. The domains of this tool are 1) the randomization process;

2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; and

5) selection of the reported result. Each question had four possible responses: "yes", "probably yes", "probably no", "no", and “no information”. For a better understanding, "definitively yes" was interpreted as low risk of bias; "probably yes" and "probably no" as unclear, and "definitively no" as a high risk of bias.

The overall risk of bias was calculated based on the responses to each of the five domains. Studies with at least one domain considered as "high risk of bias" or with multiple domains considered as "some concerns" in a way that substantially lowers confidence in the result were judged to be at a high overall risk of bias; studies with at least one domain at "some concerns" were considered to be at the some concerns overall risk of bias. Those studies with all domains classified as "low risk of bias" without any "some concerns" or "high risk of bias" domains were considered to be at the low overall risk of bias. This approach has been used before.

**Certainty in the body of evidence**

The quality or certainty of the evidence was assessed with the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) approach4. This assessment reflects the confidence level that the effect sizes or estimates from this systematic review are correct.

Working individually, one reviewer (P.S-P) assessed the quality of evidence, and disagreements were resolved by consensus involving a second reviewer (Y.N). Overall, the quality of the evidence of each treatment-comparison-outcome triad can be graded as very low, low, moderate, and high. To assign these, we began by rating randomized trials as high-quality and observational studies as low-quality evidence. Then, based on different factors, we either downgraded (risk of bias, inconsistency, indirectness, imprecision, and publication bias) or upgraded (large magnitude of effect, plausible confounding, and dose-response gradient) the initial rating.

**Statistical Analyses**

We calculated each study's odd ratio (OR) and 95% confidence interval (CI) using an intention-to-treat analysis approach for dichotomous outcomes. For continuous variables, we calculated the overall mean difference (MD) and 95% CI by using a random-effects model with the REML method. We used the reported mean after the intervention period and at different follow-ups to calculate the MD.

To analyze the total postsurgical consumption of rescue opioid medication, all opioids were converted to an equianalgesic parenteral morphine amount using standard conversion factors. Fisher’s exact test was used to compare between-group differences.

We used RStudio, an integrated development environment for R5, to perform the analyses and generate forest plots. Heterogeneity across studies was assessed with a study variance estimate (tau squared). The proportion of variability in effect size estimates attributed to between-study heterogeneity was assessed with the *I2* statistic6. Medians were converted to means and ranges or interquartile ranges to standard deviations (SDs). The means and SDs of each variable were pooled using the weighted mean and weighted SD7

**Results**

**Search Results**

The initial literature search generated a total of 138 studies. After deduplication and screening, three randomized clinical trials (RCT) met our inclusion criteria (Figure 1).

**Study characteristics**

Three studies were randomized, double-blind, and placebo-controlled (Table 1). The studies were published from 2011 to 2012. The overall risk of bias was considered unclear in XX studies and high in XX studies (Supplementary XX). Two were multicenter studies (conducted in more than nine centers). All were conducted in the United States.

**Patient’s characteristics**

Patient demographics and preoperative variables are outlined in Table 1. In total, 338 patients were included; 194 received LB at four different doses (119 at LB-300 mg, 25 at LB-199 mg, 25 at LB 225 mg, 25 at LB-266 mg), and 144 received control medication (51 bupivacaine/epinephrine, and 93 normal saline). The overall mean age was 45.8 years (standard deviation [SD] ± 11.4), and there was a male predominance in the overall cohort (181 [53.5%] men vs. 82 [46.5%] women).

**Primary outcome**

*Pain Scores*

Two studies reported pain intensity, as reflected by the mean cumulative pain scores (AUC of NRS). Table 2 showed that pain scores at 72 hours in the LB 199 mg and 266 mg groups were significantly lower (AUC 180) than in the bupivacaine HCl group (AUC 340, p=0.002). Additionally, one study reported that pain was significantly less in LB 300 mg compared with placebo (0.9% sodium chloride) (AUC 141.8 vs. 202.5, p <0.0001).

**Secondary outcomes**

*Time to the first opioid*

Three studies reported the median time to the first use of opioid rescue medication after surgery. Compared to the bupivacaine/placebo group, the time to first use of opioids in the LB group was significantly longer at LB 199mg (11h vs. 9h), at LB 266 mg (19h vs. 9h), and LB 300 mg (19h vs. 8h) (p-value <0.05). Moreover, the time to opioid rescue in LB at 300mg was longer than normal saline (14 h 20 min vs. 1 hour 10 min, P < .0001).

*Dose of opioid rescue medication*

Three studies report this outcome. At 72 hours after the study drug administration, the mean total amount of opioid rescue medication (morphine equivalents) consumed was significantly lower in the LB 300 mg group (22.3 vs. 29.1 mg; p < .0006) compared to normal saline. Moreover, compared to the bupivacaine/epinephrine group, it was significantly lower in LB 266 mg group (3.7 vs. 10.2 mg) and at LB 300 mg (13 vs. 33 mg) (p-value <0.05).

*Adverse Effects (AE)*

Two studies reported on AE. Regarding vomiting, our meta-analysis revealed no difference in LB compared to conventional anesthetic/placebo (OR 2.72, 95% CI 0.00- 1973.83). However, conventional anesthetic/placebo reported more pain in bowel movement than LB (OR 2.60, 95% CI 1.31- 5.16).

**Discussion**

To our knowledge, this is the first systematic review evaluating the effects of LB on pain at 72 hours for patients undergoing hemorrhoidectomy. We found that LB was associated with decreased pain score at 72 hours, longer time to first opioid use, decreased opioid use postoperatively, and comparable adverse effects to control or placebo.

Although LB was approved by the FDA in 2011, its role in colorectal surgery is only relatively recently reported. In 2018 Raman et al8., in a meta-analysis including seven high-risk bias studies (n=1008) in patients undergoing laparoscopic or open colectomy, reported that pain scores were significantly lower in patients who received LB (local or transversus abdominis plane (TAP) administration) (SMD -0.56 95% CI -1.07, -0.06, p = .03) compared to conventional opioids. Moreover, LB was associated with decreased length of stay (SMD - 0.34, 95% CI - 0.56, -0.13, p= .001) and decreased IV opioid use in the first 48–72 h (SMD -0.49 95% CI -0.69, -0.28, p < .00001). Moreover, Byrnes et al.9, in a network meta-analysis that included twelve trials with a total of 2512 patients undergoing colorectal resections (open or minimally invasive), demonstrated that LB-based wound infiltration (either local infiltration or TAP administration) reduced morphine usage (mean difference 36.64 mg, 95% credibility interval 15.64-59.20) and length of stay (mean difference 1.79 days, 95% credibility interval 0.59-3.81) compared to standard analgesia (intravenous use of systemic opiates, including infiltration short-acting local anesthetic). However, after a meta-regression, the findings were only held for minimally invasive surgery. In contrast, other studies did not show a difference in outcomes between LB and short-acting local anesthetic. Recently the TINGLE clinical trial10 included 102 adults undergoing minimally invasive colorectal surgery with multimodal analgesia. They were randomly assigned to receive a laparoscopic transversus abdominis plane block with liposomal bupivacaine or bupivacaine with epinephrine and dexamethasone. It showed that LB block does not provide superior or extended analgesia in the standardized multimodal analgesia protocols era.

The role of enhanced recovery programs in hemorrhoidectomy is being explored. Chitty et al.11, in a pre-and post-implementation quality improvement study in patients undergoing hemorrhoidectomy, reported that patient-reported pain scores in the post-anesthesia care unit (PACU) were significantly higher in the bupivacaine compared to the liposomal bupivacaine group (median 3 [IQR 0–6] vs. 0 [IQR 0–4], p = 0. But they did not find a difference between opioid rescue and opioid refill requests. However, Schmidt et al12. conducted a review study on analgesia evaluation, emphasizing the need for a global assessment. He found that comparing LB to the placebo group, the LB group showed a significant reduction in pain intensity at 12 to 24 hours (mean NRS: LB=2.2, placebo=2.9, P=0.04) and consumed less opioid rescue medication over 72 hours (mean opioids: LB=10 mg, placebo=18 mg, P=0.0006).

Our study did not find a difference regarding adverse effects, like vomiting. However, conventional anesthetic/placebo reported more pain in bowel movement than LB (OR 2.60, 95% CI 1.31- 5.16). Knudson et al.13, in an RCT of 57 patients undergoing elective colon resection, also showed no differences in opiate side effects (anti-nausea medication, return to flatus, or urinary retention) between LB and bupivacaine.

Our present study has several strengths. This is the first systematic review comparing liposomal bupivacaine with other anesthetics in patients undergoing hemorrhoidectomies. Given the scarce data, this review provides more specific results regarding this type of surgery. The literature search included only double-blind clinical trials. Our search was comprehensive, following a systematic methodology, applying pre-specified and detailed data tabulation and extraction and standardized evaluation of evidence quality and publication bias. Multiple researchers rigorously performed all steps. This approach facilitated the identification of a “clean” dataset from comparative studies of different methods to allow better generalizability of the results.

We acknowledge several limitations in our study that are important to address. Firstly, we should have analyzed the cost-effectiveness of LB. Considering the current landscape, the cost-effectiveness of LB is a significant aspect that merits further examination and debate. One notable factor that warrants attention is the cost associated with LB. Our study found that a tenfold increase in cost accompanies the tenfold increase in the duration of a half-life with LB. Specifically, the cost of LB ranged from $204 to $315, whereas the cost of non-long-acting alternatives (NLB) was only $3. This substantial difference in cost between LB and NLB raises concerns about the potential barriers to adoption due to its affordability. Further limitation includes the relatively small number of patients in the only three studies included. Additionally, there was some variability in the dose of LB used and in the control group.

Conclusion

Overall, this systematic review provides valuable insights into the benefits of using liposomal bupivacaine in pain management for hemorrhoidectomy patients. The findings suggest that LB may be a valuable tool in reducing postoperative pain and opioid consumption in this specific surgical context compared to short-acting analgesics and placebo. However, further research and standardized studies are needed to fully ascertain its optimal use, cost-effectiveness, and potential barriers to widespread adoption in ERAS protocol following a hemorrhoidectomy.

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