

# Meta-analysis on the Efficacy of Liposomal Bupivacaine in Reducing Postoperative Pain Following Perianal Surgery

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**Abstract:** **Background:** Liposomal bupivacaine (LB), a novel long-acting local anaesthetic, possesses a multi-vesicular liposomal structure that delays drug release, theoretically providing up to 72 hours of postoperative analgesia. However, high-quality studies evaluating LB's analgesic efficacy in perianal surgery (including haemorrhoidectomy, anal fistula, and perianal abscess surgery) remain limited, with existing evidence exhibiting significant heterogeneity. Consequently, we conducted this meta-analysis to comprehensively evaluate the efficacy and safety of LB compared with conventional bupivacaine and placebo in post-operative analgesia for perianal surgery. **Methods:** Computerised searches were performed in English databases (Cochrane Library, Embase, PubMed) and Chinese databases (Wanfang Database, China National Knowledge Infrastructure, VIP Database, China Biomedical Literature Database). All randomised controlled trials (RCTs) published between 1983 and 2025 concerning LB for postoperative analgesia following perianal surgery were included. The methodological quality of included studies was assessed using the Cochrane risk of bias tool, and meta-analysis was performed using Stata 8.0 software. **Results:** Four randomised clinical trials involving 425 patients undergoing perianal surgery were included. A total of 219 patients (51.5%) received LB therapy, while 206 (48.5%) received bupivacaine or placebo. The LB group exhibited significantly reduced VAS scores at 24 hours postoperatively [SMD = -0.91, 95% CI (-1.25, -0.57)]. Pain scores at 72 hours were significantly lower in the LB groups (199, 266, and 300 mg) compared to the control group ( $p = 0.002$ ). The time to first opioid use was significantly delayed in the LB groups compared with the control group: LB 199 mg (11h vs 8h), LB 266 mg (19h vs 8h), LB 300 mg (14.2h vs 1.2h) ( $p < 0.0001$ ). Mean opioid doses administered within 72 hours were significantly reduced in the LB 266 mg group (3.7 vs 10.2 mg) and LB 300 mg group (22.3 vs 29.1 mg) compared with the control group. Patient satisfaction was significantly enhanced [RR=1.26, 95% CI (1.13, 1.40)]. No significant difference in adverse reaction incidence was observed between LB groups and the control group. **Conclusion:** LB demonstrated comparable clinical efficacy to the control group in post-operative analgesia following perianal surgery, including reduced VAS scores within 24 hours, significantly diminished pain within 72 hours, decreased opioid requirements, delayed first opioid administration, and enhanced patient satisfaction, while exhibiting favourable safety profiles.

**Keywords:** Liposomal bupivacaine, Perianal surgery, Postoperative pain, Meta-analysis.

## 1. Introduction

In recent years, alongside shifts in lifestyle and dietary patterns, the incidence of colorectal and anal diseases has risen significantly. Surgery, as a primary treatment modality for such conditions, presents particularly pronounced postoperative pain challenges [1]. Due to the dense neurovascular distribution and complex neural architecture of the anorectal region, pain symptoms often persist throughout the entire perioperative period [2]. Perioperative pain can adversely affect patients in multiple ways: from increasing oxygen consumption and inducing emotional and sleep disturbances (impeding postoperative recovery) to exacerbating the primary disease or even leading to chronic pain. Consequently, the rational selection of perioperative analgesic strategies holds significant clinical importance [3]. Among numerous analgesic approaches, local administration holds unique value in post-operative pain management for anorectal surgery due to its rapid onset, low hepatotoxicity and nephrotoxicity, and minimal gastrointestinal adverse effects [4].

Liposomal bupivacaine (LB), as a novel long-acting local anaesthetic, employs a multi-vesicular liposomal structure to prolong drug release. This not only extends the duration of local anaesthesia (up to 72 hours) but also reduces peak plasma concentrations [5]. Although existing randomised controlled trials support its analgesic efficacy, substantial

heterogeneity between studies compromises the reliability of conclusions [6–8]. Therefore, this study employs meta-analysis to systematically evaluate the clinical value of liposomal bupivacaine in perianal postoperative analgesia.

## 2. Data and Methods

### 2.1 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Randomised controlled trials (RCTs); (2) Participants aged  $\geq 18$  years scheduled for perianal surgery (haemorrhoidectomy, perianal abscess surgery, anal fistula surgery, anal fissure surgery), regardless of gender (excluding pregnant women). Exclusion Criteria: (1) LB dosage  $< 133$  mg (current evidence-based medicine lacks confirmation of efficacy at lower doses) [9,10]; (2) Patients taking analgesics (non-steroidal anti-inflammatory drugs, paracetamol, or opioids), antidepressants, or glucocorticoids within 3 days prior to surgery; (3) Concurrent haematological disorders (severe anaemia, haemostatic abnormalities), immunological diseases, major organ dysfunction (cardiac, cerebral, hepatic, renal, pulmonary, etc.), malignancies, or infectious diseases; (4) Psychiatric disorders or communication difficulties.

### 2.2 Scope of Search and Screening

Computerised searches were conducted across major databases including China National Knowledge Infrastructure

(CNKI), Wanfang Full-text Database, VIP Chinese Science and Technology Journal Database, China Biomedical Database (CBM), PubMed, Embase, and the Cochrane Library. Searches were conducted in both Chinese and English, covering the period from each database's inception to June 2025. Retrieval employed a combination of subject headings and free-text keywords. Chinese database search formula: (1) Subject term: 'Liposomal bupivacaine'; (2) Subject term: "Anorectal", with free terms including 'perianal disease, haemorrhoids, anal fistula, perianal abscess, anal fissure'; (3) Subject term: 'Postoperative analgesia', with free terms including 'analgesia, pain'. Each subject term and free term was linked with OR, yielding the final search formula: (1) AND (2) AND (3). English database search formula: (1) Subject term: 'Liposomal bupivacaine'; Free terms: 'LB, depobupivacaine'; (2) Using 'Anorectal Disease' as the subject term, with 'Rectal Disease, Rectal Disorders, Rectal Disorder, Anorectal Diseases, Anorectal Disease, Anorectal Disorders, Anorectal Disorder' as free-text terms; (3) Using "Hemorrhoidectomy" as the subject term, with 'Hemorrhoidectomies' as the free-text term; (4) Using 'Anal Fistula' as the subject term, with 'Fistula, Rectal, Anal Fistula' as free-text terms; (5) Using 'Fissure in Ano' as the subject term, with 'Anal Fissure, Fissure, Anal, Anal Ulcer, Anal Ulcers, Ulcer, Anal, Ulcers, Anal' as free-text terms; (6) Using "Abscess" as the subject term, with 'Abscesses' as the free-text term. Each subject term and free term was linked with OR, resulting in the final search formula: (1) AND (2) AND (3) AND (4) AND (5) AND (6).

### 2.3 Quality Assessment of Included Literature

The methodological quality of included studies was assessed using the Cochrane systematic review 'Risk of Bias tool'. Seven key domains were assessed: random sequence generation, allocation concealment, blinding of participants and/or intervention personnel, blinding of outcome assessors,

completeness of outcome data, selective reporting of results, and other potential sources of bias. Each assessment item employed a three-tier rating system: low risk, unclear risk, and high risk.

### 2.4 Outcome Measure Extraction and Statistical Methods

A data extraction form was developed, and two researchers independently extracted data from the literature. Disagreements were resolved through discussion or third-party arbitration. Statistical analysis was performed using Stata 18.0 software. Continuous variables: standardised mean difference (SMD) and 95% confidence interval (CI). Dichotomous variables: relative risk (RR) and 95% CI.

The  $I^2$  statistic assessed heterogeneity:  $I^2 \leq 50\%$  – fixed-effect model (Mantel-Haenszel method) for pooling;  $I^2 > 50\%$  – (1) explore sources of heterogeneity (via subgroup analysis or meta-regression); (2) if heterogeneity persists but studies show clinical homogeneity, use random-effects model (DerSimonian-Laird method). Statistical significance was defined as  $P < 0.05$ .

## 3. Results

### 3.1 Number of Retrieved Studies

Following the predefined search strategy, an initial search yielded 193 publications. After deduplication and sequential screening, four eligible randomised controlled trials (RCTs) were ultimately included. The detailed literature screening process and reasons for exclusion are presented in Figure 1. The baseline characteristics of the included studies are summarised in Table 1. The levobunolol (LB) dose ranged from 199 to 300 mg, with sample sizes between 20 and 94 participants.

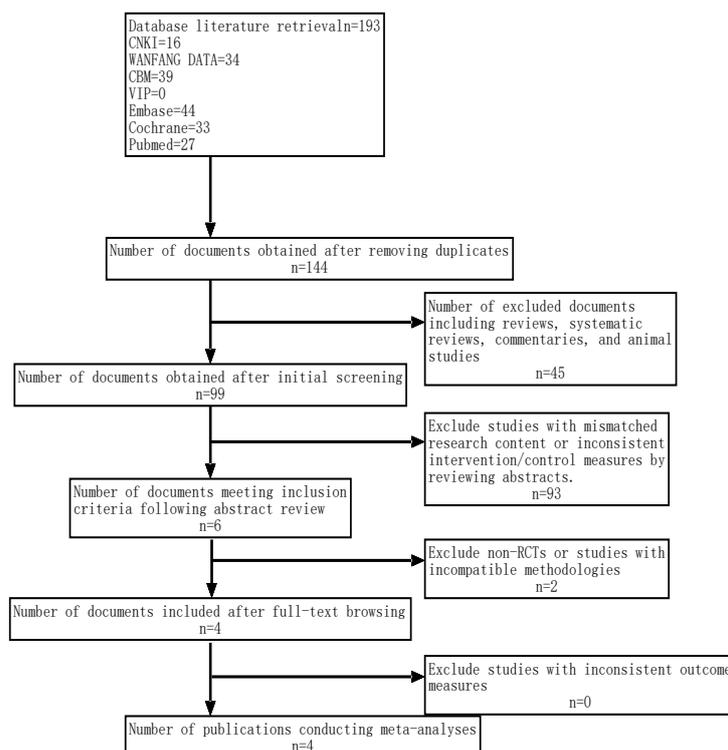


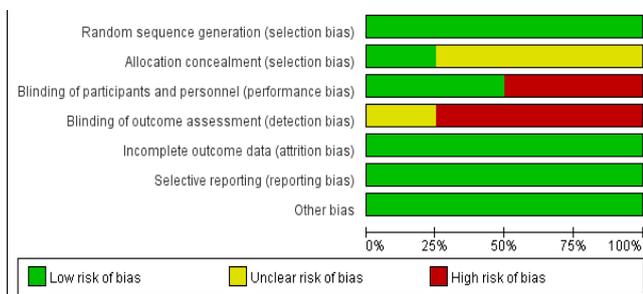
Figure 1: Literature Screening Process and Outcomes

**Table 1:** Basic Characteristics of Included Studies

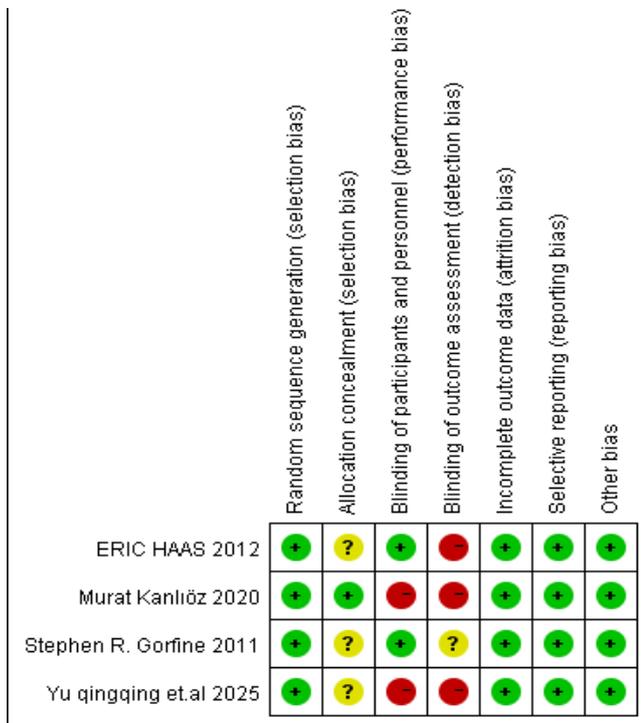
Author	Method	Intervening measure		Number of people	Age (years) Mean (Standard deviation)	Male (%)	Women (%)
HAAS et al.	Randomised controlled Double-blind	Experimental group	LB 199mg LB 266mg	25 25	42(11) 46(11)	16(64) 22(88)	9(36) 3(12)
		Control group	Bupivacaine HCl 75mg with epinephrine*	26	44(11)	15(75)	11(25)
Gorfine et al.	Randomised controlled Double-blind	Experimental group	LB 300mg	94	48(12.2)	62(66)	32(34)
		Control group	0.9%NaCl 30mL	93	48.7(11.9)	66(71)	27(29)
Kanlıože et al.	Randomised controlled Non-blind	Experimental group	LB 300mg LB 300mg +AVC** 1cm <sup>3</sup> AVC 1cm <sup>3</sup>	20 20 20	42.7(14.06) 33.5(11.43) 38.5(12.27)	13(65) 11(55) 16(80)	7(35) 9(45) 4(20)
		Control group	Placebo cream 1cm <sup>3</sup>	32	35.25(12.07)	20(62.5)	12(37.5)
		Experimental group	LB 266mg	35	49.0(5.5)	19(54.3)	16(45.7)
Yu Qingqing et al.	Randomised controlled Non-blind	Control group	0.5% Ropivacaine 10mL	35	49.1(5.5)	20(57.1)	15(42.9)

Note: \*Bupivacaine hydrochloride 75 mg with epinephrine 1:20,000.\*\*Aloe vera ointment

**3.2 Quality Assessment**



**Figure 2:** Proportion of Each Component in the Methodological Quality Assessment of Literature in This Study



**Figure 3:** Schematic Diagram of the Methodological Quality Assessment of Literature in This Study

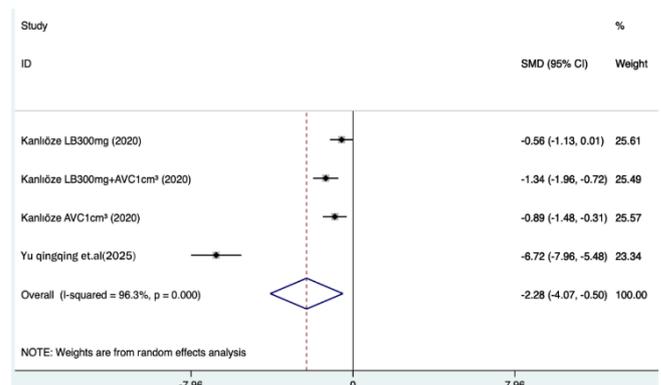
Figure 3 presents the quality assessment of included studies. In the methodological quality assessment of the included literature (Figure 3), four studies (100%) were classified as high quality (low risk of bias). Three of these studies achieved

a score of 5, whilst the remaining study was classified as having moderate risk of bias. The assessment utilised a three-tiered marking system: ‘+’ (low risk), ‘-’ (high risk), and ‘?’ (uncertain risk). Figure 2 presents a statistical distribution chart of the proportion of items across each category in the methodological assessment.

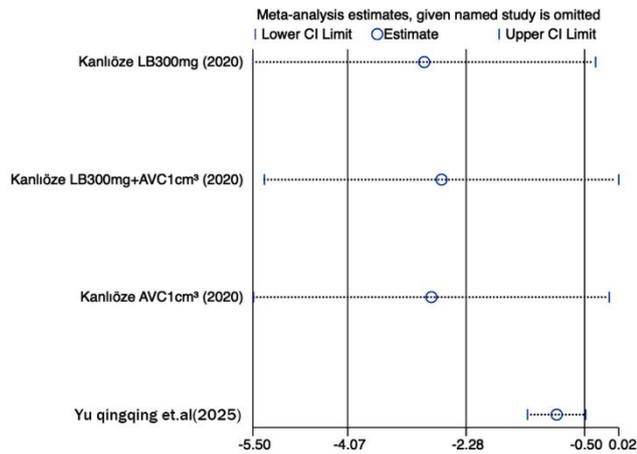
**3.3 Meta-analysis Results**

**3.3.1 Comparison of 24-hour VAS scores between groups**

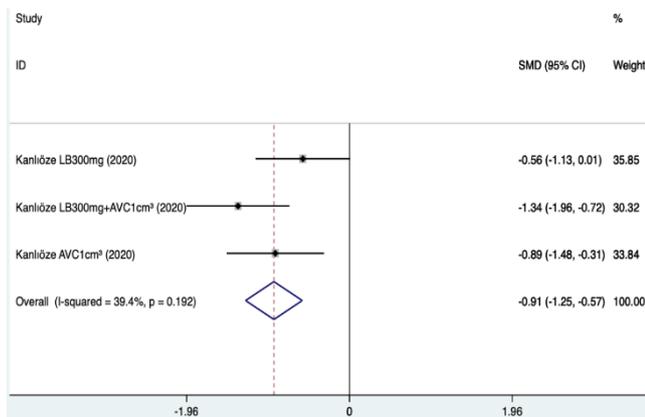
Significant heterogeneity was observed between groups ( $I^2=96.3\%$ ,  $P=0.000$ ). Analysis using a random-effects model (Figure 4) indicated a significant reduction in 24-hour VAS scores in the LB group [SMD=-2.28, 95% CI (-4.07, -0.50)], but the effect size was severely distorted, rendering the result unreliable. Due to substantial heterogeneity, sensitivity analysis was conducted by sequentially excluding studies. Results (Figure 5) indicated this outcome remained stable and unaffected by any single study. The study by Yu Qingqing et al. contributed to extremely high heterogeneity; its methodological consistency and data accuracy could not be verified. Upon exclusion of this study, no significant heterogeneity was observed between groups ( $I^2=39.4\%$ ,  $p=0.192$ ). Analysis using a fixed-effects model demonstrated that, compared with the control group, the LB-containing group exhibited a significant reduction in 24-hour postoperative VAS scores [SMD = -0.91, 95% CI (-1.25, -0.57], Figure 6].



**Figure 4:** Comparison of VAS scores at 24 hours post-surgery between the two groups



**Figure 5:** Sensitivity analysis of VAS scores at 24 hours post-surgery for the two groups



**Figure 6:** Exclusion of Yu Qingqing's study on the two groups' 24-hour postoperative VAS scores

3.3.2 Comparison of mean cumulative pain scores

Both studies employed the area under the curve (AUC) of the numerical rating scale (NRS) to assess cumulative pain intensity over 72 hours. Table 2 demonstrates that the 72-hour pain scores in the LB 199mg and 266mg groups were significantly lower than those in the bupivacaine hydrochloride group ( $p=0.002$ ) [11]. The high-dose LB 300mg group exhibited superior analgesic efficacy compared to the placebo group ( $p<0.0001$ ) [12].

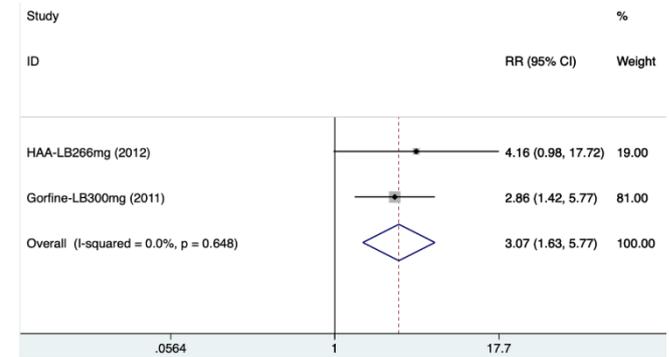
**Table 2:** Postoperative pain scores at 72 hours post-administration

Author	Intervening measure	Number of people	AUC Mean (SD)	Mean difference	P value
HASS et al.	Experimental group LB 199mg LB 266mg	25	180(NR)	160(154-166)	0.002
		25	180(NR)		
	Control group Bupivacaine HCl 75mg with epinephrine	26	340(NR)		
Gorfi ne et al.	Experimental group LB 300mg	94	141.8(10.7)	60.7(58-64)	<0.0001
		93	202.5(10.7)		
	Control group 0.9%NACI	93	202.5(10.7)		

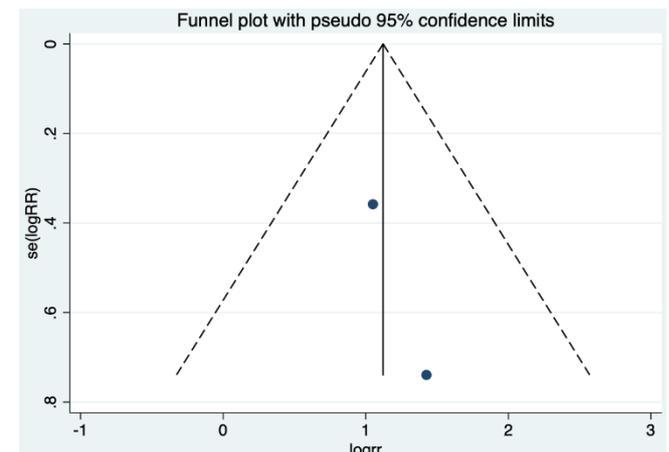
Note: A smaller area under the curve (AUC) value indicates lower overall pain intensity. All comparisons employed two-tailed t-tests. Consistent assessment timepoints (72 hours) and scoring criteria (Numerical Rating Scale, NRS) were maintained across studies.

3.3.3 Comparison of opioid-free status at 72 hours

No significant heterogeneity was observed between groups ( $I^2=0.0\%$ ,  $p=0.648$ ). Fixed-effect model analysis indicated that, compared with the control group, the liposomal bupivacaine group had more patients not requiring opioid use at 72 hours postoperatively. Thus, compared with the control group, the liposomal bupivacaine group effectively reduced opioid use at 72 hours [SMD=3.07, 95% CI (1.63, 5.77, Figure 7)]. Publication bias was assessed using Egger's test and a funnel plot. The funnel plot (Figure 8) exhibited symmetry with no evident publication bias, indicating high reliability of the results.



**Figure 7:** Comparison of the two groups not receiving opioid medication within 72 hours post-surgery



**Figure 8:** Comparison funnel plot of two groups not receiving opioid medication within 72 hours post-surgery

3.3.4 Comparison of First Postoperative Opioid Rescue Medication Use

**Table 3:** Time of First Opioid Use

Author	Intervening measure	Number of people	Time of first opioid use (hours) Median (range)	p value
HAAS et al.	Experimental group LB 199mg LB 266mg	25	11(0.2-96.0)	0.005
		25	19(0.1-96.0)	
	Control group Bupivacaine HCl 75 mg with epinephrine	26	8(0.3-96.0)	
Gorfi ne et al.	Experimental group LB 300 mg	94	14.3(none)	<0.0001
		93	1.2(none)	
	Control group 0.9%NACI	93	1.2(none)	

Two studies reported the median time to first postoperative opioid use. Table 3 demonstrates that all LB dose groups significantly prolonged the time to first opioid administration compared with the bupivacaine/placebo group. HASS et al.

indicated a trend towards prolonged analgesic duration with increasing LB doses (199→266mg) ( $p=0.0005$ ) [11]. Gorfine et al. demonstrated the most pronounced advantage of the 300 mg LB dose over the saline group (approximately 13-fold prolongation,  $p<0.0001$ ) [12].

### 3.3.5 Comparison of opioid doses within 72 hours

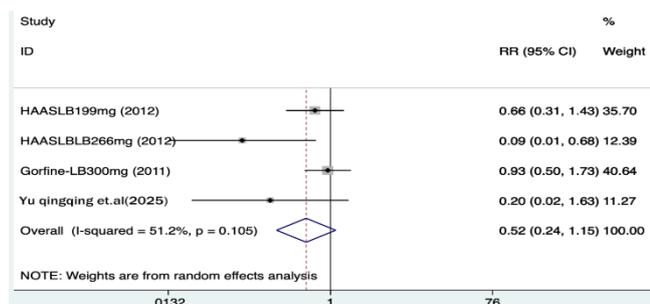
Two studies reported this outcome. In the LB group, 66 patients (70.2%) received opioid rescue therapy, whilst 28 patients (29.8%) did not. In the placebo group, 84 patients (90%) received opioid rescue medication, while 9 patients (10%) did not. Table 4 shows that at 72 hours post-study drug administration, the mean total opioid rescue medication consumption (morphine equivalents) in the LB 300mg group was significantly lower than in the saline group ( $p<0.0006$ ) [11,12]. Furthermore, compared with the bupivacaine / epinephrine group, both the LB 266 mg and LB 300 mg groups demonstrated significant reductions ( $p<0.05$ ).

**Table 4:** Doses of opioid rescue medication within 72 hours (mg)

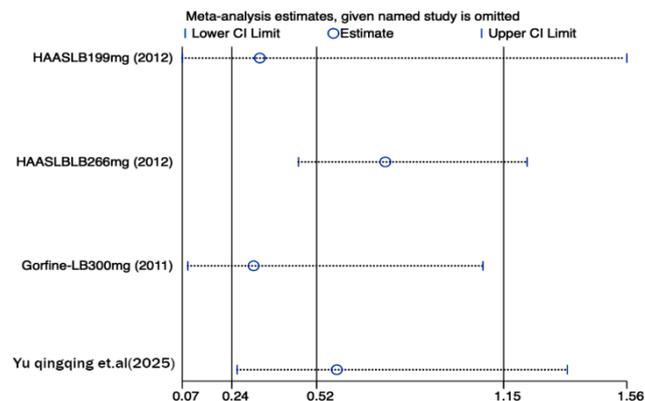
Author	Intervening measure		Number of people	Opioid dosage in milligrams within 72 hours (standard deviation)	P value
HAAS et al.	Experimental group	LB 199mg LB 266mg	25	3.7 (NR)	0.0019
	Control group	Bupivacaine HCl 75 mg with epinephrine	26		
Gorfine et al.	Experimental group	LB 300 mg	94	22.3(21)	<0.0006
	Control group	0.9%NACI	93	29.1(20.7)	

### 3.3.6 Comparison of all postoperative adverse reactions following administration

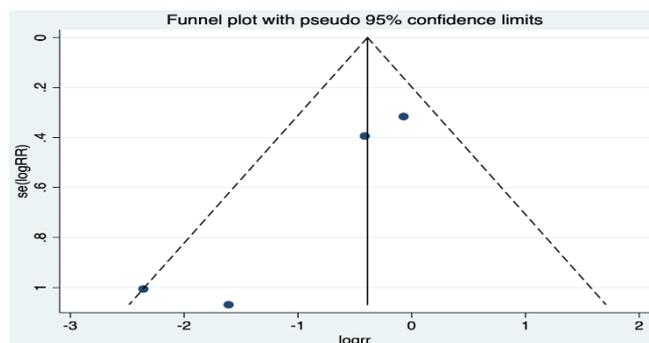
A total of three studies reported adverse reactions. Heterogeneity testing ( $I^2=51.2\%$ ,  $P=0.105$ ). Analysis using a random-effects model (Figure 9) indicated no statistically significant difference between groups regarding adverse reactions [ $RR=0.52$ , 95% CI (0.24, 1.15)]. Given substantial heterogeneity, sensitivity analysis was conducted by sequentially excluding studies. Results (Figure 10) indicate this outcome remains stable and unaffected by individual studies. Publication bias was assessed using Egger's test and a funnel plot. The funnel plot (Figure 11) exhibited asymmetry, and Egger's test ( $P=0.038$ ) indicated significant publication bias.



**Figure 9:** Comparison of adverse reactions between the two groups after administration



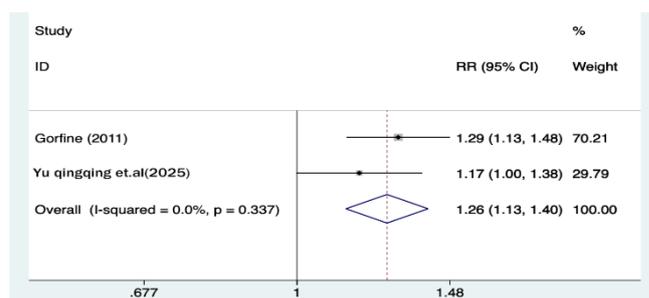
**Figure 10:** Sensitivity analysis of adverse reactions in both groups following administration



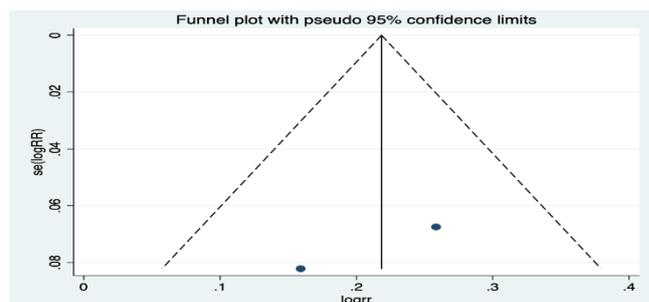
**Figure 11:** Adverse reaction funnel plots for both groups following administration

### 3.3.7 Comparison of satisfaction

No significant heterogeneity was observed between the two groups ( $I^2=0.0\%$ ,  $P=0.337$ ). Analysis using a fixed-effects model indicated that postoperative satisfaction was significantly higher in the bupivacaine liposome group compared with the control group [ $RR=1.26$ , 95% CI (1.13, 1.40)] (Figure 12). Publication bias was assessed using Egger's test and a funnel plot. The funnel plot (Figure 13) exhibited symmetry with no evident publication bias, indicating high reliability of the results.



**Figure 12:** Satisfaction Forest Plot



**Figure 13:** Satisfaction Funnel Diagram

#### 4. Discussion

The findings of this study indicate that LB offers multiple clinical benefits in anorectal surgery, primarily manifested in the following aspects: (1) significantly reducing the VAS score within 24 hours post-operatively; (2) effectively improving the cumulative pain score over 72 hours; (3) prolongation of the time to first opioid analgesic rescue; (4) reduction in total postoperative opioid consumption; and (5) enhanced patient satisfaction. Although LB received US FDA approval as early as 2011, its clinical utility in colorectal surgery has only recently undergone systematic evaluation. Current evidence-based medical data indicate: Raman et al. [13]'s 2018 meta-analysis (encompassing 7 studies, n=1008) demonstrated that LB (administered locally or at the transverse abdominis muscle plane) significantly reduced pain scores compared to conventional opioid analgesia in colon resection procedures (including both laparoscopic and open surgery) [SMD=-0.56, 95% CI (-1.07 to -0.06); p=0.03]. It also reduced intravenous opioid consumption within 48–72 hours [SMD=-0.49, 95% CI (-0.69 to -0.28); p<0.00001]. Byrnes et al.'s [14] network meta-analysis (12 trials, n=2512) further confirmed that during colorectal resection, LB wound infiltration (local or TAP block) reduced morphine consumption by 36.64mg [95% CI (15.64-59.20)] compared to standard analgesia protocols. However, some studies failed to demonstrate significant differences in clinical outcomes between LB and short-acting local anaesthetics, potentially attributable to factors such as study design, surgical procedure type, and administration method. This inconsistency suggests the need for more rigorous randomised controlled trials to further validate the precise value of LB across different surgical procedures.

Schmidt et al. [15] assessed analgesia in adults undergoing haemorrhoidectomy. They found that pain intensity at 12–24 hours was significantly lower in the LB group (NRS=2.2) compared to the control group (placebo=2.9, p=0.04), with reduced opioid consumption within 72 hours (mean opioids: LB=10 mg, placebo=18 mg, p=0.0006). Our study observed no significant difference in adverse reaction incidence between the LB group and the control group. Li Lei et al. [16] similarly demonstrated no difference in local anaesthetic-related adverse reactions between LB and conventional local anaesthetics in an RCT involving 96 patients undergoing elective laparoscopic colorectal cancer radical resection.

The strengths of this study lie in its pioneering systematic evaluation of LB's analgesic efficacy following perianal surgery via meta-analysis, thereby addressing a gap in existing evidence-based medical literature. Only randomised controlled trials were included, with rigorous inclusion/exclusion criteria formulated according to PICOS principles. A comprehensive systematic search protocol was employed, covering major Chinese and English databases without publication date or language restrictions. Data extraction was performed independently by two researchers using standardised forms, with cross-checking. Included studies spanned diverse surgical types (haemorrhoidectomy, anal fistula, perianal abscess surgery, etc.), featured multiple control interventions (placebo, conventional local anaesthetics, etc.), and assessed several clinically relevant

outcomes, yielding good external validity.

This study has the following limitations: 1) the number of included publications was limited, resulting in a small sample size; 2) considerable heterogeneity existed within both the control group and the LB dosage groups; 3) as P<0.05 indicates statistical significance but not necessarily clinical significance, small-sample studies may yield negative results due to insufficient statistical power, potentially leading to unstable final outcomes.

#### 5. Conclusions

Despite methodological limitations, this study provides preliminary scientific evidence supporting the clinical application of LB in perianal surgery. Results indicate that compared with conventional short-acting analgesics and placebo, LB demonstrates significant clinical value in reducing postoperative pain intensity, decreasing opioid consumption, prolonging time to first analgesic requirement, and improving patient satisfaction scores. Notably, LB provides high-quality analgesia without increasing adverse reaction rates, exhibiting favourable safety characteristics.

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