Research Square

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Modified Multimodal Local Infiltration versus Liposomal Bupivacaine for Early Pain Control and Recovery after Mixed Hemorrhoid Surgery: A Randomized Trial

Rui Zhang
West China Hospital of Sichuan University
Bowen Hu
West China Hospital of Sichuan University
Chengfu Deng
Huize County Traditional Chinese Medicine Hospital
Keqiang Yu
West China Hospital of Sichuan University
Huixiang Li
West China Hospital of Sichuan University
Jingjie Li
West China Hospital of Sichuan University
Hanlin Gong
West China Hospital of Sichuan University
Weiguo Wang
wwg-email@wchscu.edu.cn

West China Hospital of Sichuan University

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Abstract

Purpose

To compare a modified multimodal local infiltration cocktail with liposomal bupivacaine (LB) for pain control and recovery after mixed hemorrhoid surgery.

Methods

360 patients were assigned 1:1 to perianal infiltration with LB or a modified cocktail containing ropivacaine, dexamethasone, magnesium sulfate, and sodium bicarbonate. The primary outcome was the dynamic numeric rating scale (NRS) trajectory from 6 h to postoperative day 7. Secondary outcomes included analgesic use, recovery, and adverse events; hospital costs were explored separately.

Results

Dynamic NRS trajectories differed between groups (group-by-time interaction, $P < 0.001$). Adjusted scores were lower with the modified cocktail at 6 and 12 h (mean differences,−0.86 and−0.61; both $P < 0.001$), with no statistically significant differences thereafter. The modified cocktail also reduced first-defecation pain, the proportion requiring rescue analgesia within 24 h (38.3% vs 48.9%), and 24-h opioid consumption; it was also associated with earlier ambulation. No statistically significant differences were detected in resting pain, gastrointestinal recovery, QoR−15, length of stay, wound healing, defecation function, or 72-h opioid consumption. An exploratory analysis showed lower hospital costs, and no serious adverse events occurred.

Conclusion

Compared with LB, the modified cocktail modestly reduced early movement- and defecation-related pain and reduced rescue analgesic use and opioid consumption within 24 h; it was also associated with earlier ambulation. No statistically significant differences were detected in later pain or most other short-term outcomes. Further multicenter evaluation is warranted.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2600116630; registered 13 January 2026.

1. Introduction

Hemorrhoidal disease is one of the most common anorectal disorders worldwide, affecting approximately one-quarter of the global population [1] and imposing a substantial clinical burden in China. Epidemiological surveys in China have reported an overall prevalence of anorectal disorders of 59.1%, with hemorrhoids accounting for the majority of cases. Rather than representing simple varicosities, hemorrhoidal disease is now understood as symptomatic enlargement and distal displacement of the normal anal cushions, accompanied by degeneration of the supporting connective tissue and abnormal dilation or distortion of the vascular channels [2, 3]. Although most patients achieve

symptom relief with conservative management, surgery remains an important treatment option for advanced or clinically significant disease [4].

Postoperative pain remains a major barrier to recovery after hemorrhoid surgery. Pain is often aggravated by movement, wound stimulation, and defecation and may restrict early ambulation, disturb sleep, increase anxiety and fear of defecation, and impair patient-reported quality of recovery [5, 6]. Inadequate analgesia may also increase reliance on systemic opioids [7], which are associated with nausea, vomiting, constipation, urinary retention, and sedation [8, 9]. Effective local analgesic strategies that provide early pain control while limiting opioid exposure are therefore important for postoperative recovery.

Local infiltration analgesia is an important component of multimodal postoperative pain management because it delivers analgesic agents directly to the surgical field while limiting systemic exposure. Bupivacaine produces local analgesia by reversibly blocking voltage-gated sodium channels, thereby inhibiting the initiation and propagation of nociceptive impulses. Liposomal bupivacaine (LB) encapsulates bupivacaine within multivesicular liposomes, allowing gradual drug release after tissue infiltration. This prolonged local availability may extend analgesia for up to 72 h and reduce the need for repeated dosing or systemic rescue analgesics [10, 11]. Previous studies have shown that LB can reduce postoperative pain, delay rescue analgesia, and decrease opioid consumption after hemorrhoidectomy [12, 13].

Multimodal infiltration cocktails combining local anesthetics with adjuvants are widely used in orthopedic surgery. The same four agents used in the present study—ropivacaine, dexamethasone, magnesium sulfate, and sodium bicarbonate—have been evaluated in knee and hip arthroplasty, with randomized trials reporting improved analgesia and reduced opioid consumption without an apparent increase in postoperative complications [14, 15]. We retained this combination but adjusted the doses for anorectal infiltration. Ropivacaine provides local anesthetic blockade, whereas the adjuvants may enhance analgesic duration and modulate nociceptive and inflammatory responses. Whether this formulation is effective and safe after hemorrhoid surgery remains uncertain.

LB has demonstrated favorable analgesic efficacy after hemorrhoidectomy [12, 13], but its relatively high cost may limit wider clinical use. The modified multimodal cocktail consists of readily available agents, yet direct evidence comparing it with LB in hemorrhoid surgery remains limited [16]. We therefore conducted an active-controlled randomized trial to compare postoperative pain, rescue analgesic requirements, recovery, inflammatory responses, safety, and hospital costs between LB and the modified cocktail. We hypothesized that the modified cocktail would provide effective postoperative analgesia while reducing rescue analgesic requirements and overall treatment costs.

2. Methods

2.1 Clinical study

2.1.1 Study design and participants

This prospective, single-center, double-blind randomized controlled trial enrolled patients undergoing hemorrhoid surgery at West China Hospital, Sichuan University, from January 20 to July 15, 2026. Eligible patients were aged 15–75 years, had mixed hemorrhoids, an ASA physical status of I–III, and a BMI of 18–28 kg/m^2. Written informed consent was obtained from all patients or legal guardians for those younger than 18 years. Exclusion criteria were previous anorectal surgery; concurrent enrollment in another clinical trial; allergy to any study drug, local anesthetic, or opioid; severe cardiovascular disease, severe hepatic or renal dysfunction, or a coagulation disorder; analgesic use within 24 h before surgery; planned concomitant or multiple surgical procedures; and long-term opioid use or drug abuse. Concomitant anorectal conditions were recorded at baseline but were not treated during the index operation. Patients requiring an additional anorectal procedure were excluded.

2.1.2 Ethics statement

The study was approved by the Clinical Research Ethics Committee of West China Hospital, Sichuan University (approval No. 2025 Review [2546]) and registered in the Chinese Clinical Trial Registry (ChiCTR2600116630). Written informed consent was obtained from all participants.

2.1.3 Randomization and blinding

The allocation sequence was generated by an independent statistician and concealed in sequentially numbered, opaque, sealed envelopes until the assigned intervention was prepared. Patients were randomly assigned in a 1:1 ratio to either the liposomal bupivacaine group or the modified cocktail group. Patients, postoperative outcome assessors, data collectors, and statisticians were blinded to treatment allocation. To reduce interoperator variability, all surgical procedures and local infiltration analgesia were performed by experienced colorectal surgeons according to a predefined, standardized protocol.

2.1.4 Interventions

All patients underwent standardized surgery under neuraxial anesthesia. Before wound closure, local infiltration analgesia was administered using a six-point fan-shaped perianal technique (3 mL/site; total 18 mL), with repeated aspiration to avoid intravascular injection. The liposomal bupivacaine solution was Aihengping® (Jiangsu Hengrui Pharmaceuticals; 266 mg/20 mL), of which 18 mL was administered. In the modified cocktail group, the study solution was prepared immediately before use by mixing 10 mL of 1% ropivacaine injection (100 mg/10 mL), 0.4 mL of dexamethasone injection (2 mg; 5 mg/mL), 0.2 mL of magnesium sulfate injection (50 mg; 2.5 g/10 mL), and 6 mL of sodium bicarbonate injection (0.3 g; 0.5 g/10 mL), with normal saline added to a final volume of 20 mL; 18 mL was administered. The solution was prepared immediately before use and gently mixed to maintain a uniform suspension during infiltration. All patients received oral ibuprofen 400 mg every 8 h for 48 h as part of the standardized postoperative analgesic regimen. Intravenous tramadol was given as rescue analgesia when a blinded assessor confirmed a resting NRS score > 4 or dynamic NRS score > 6. Each rescue dose

consisted of intravenous tramadol 50 mg, repeatable at intervals of at least 4 h, with a maximum total dose of 400 mg within 24 h. Tramadol dose was converted to MME using a conversion factor of 0.2. Rescue analgesic timing and dose were recorded and converted to morphine equivalents.

2.1.5 Outcome measures

Follow-up continued through postoperative day 7. Postdischarge pain and recovery outcomes were assessed by telephone, whereas wound healing was evaluated during an in-person dressing-change visit on postoperative day 7 by a blinded assessor. The primary outcome was the postoperative trajectory of dynamic NRS scores across the prespecified assessment times of 6, 12, 24, 48, and 72 h and postoperative day 7. Secondary analgesic outcomes included resting NRS scores at the same time points, first-defecation NRS score, the proportion of patients requiring rescue analgesia, the number of rescue analgesic administrations, time to first rescue analgesia, and morphine milligram equivalent (MME) consumption. Other secondary outcomes included inflammatory biomarkers, time to first ambulation, flatus, and defecation, QoR-15 score, postoperative length of stay, wound healing, defecation function, and adverse events. Dynamic pain AUCs over 6–24 h and 24–72 h were examined post hoc. Total hospital cost was evaluated as an exploratory economic outcome aligned with the registered economic objective. Detailed definitions of pain assessment, randomization and blinding procedures, wound-healing and defecation-recovery grading, biomarker and recovery measurements, adverse-event criteria, AUC calculation, and hospital-cost assessment are provided in Online Resource 1.

2.1.6 Statistical analysis

Statistical analyses were performed using SPSS 32.0.0 and R 4.6.1. All efficacy analyses were performed according to the intention-to-treat principle, including all randomized participants in the groups to which they were originally assigned. No data were missing for the prespecified outcome analyses, and no imputation was performed. The sample size for the repeated-measures primary outcome was conservatively based on the 6-h dynamic NRS contrast, the only time point for which preliminary variance data were available. Assuming a between-group difference of 0.75 points and an SD of 2.0, 150 patients per group provided 90% power at a two-sided α of 0.05; the target was increased to 180 per group to allow for attrition. Continuous variables are presented as mean ± SD or median [IQR], and categorical variables as n (%). Baseline characteristics were summarized descriptively and assessed using absolute standardized mean differences (SMDs), with values > 0.10 indicating potential imbalance. Repeated NRS scores were analyzed using baseline-adjusted MMRMs with group, categorical time, and group-by-time interaction as fixed effects, an unstructured covariance matrix, and Kenward–Roger degrees of freedom. The dynamic and resting models adjusted for their corresponding preoperative NRS scores; Holm-adjusted time-specific contrasts followed the global interaction test. In post hoc analyses, dynamic pain AUCs over 6–24 h and 24–72 h were calculated using the trapezoidal rule and compared using Welch's t test. Other continuous outcomes were analyzed using independent-samples or Welch's t tests, Mann–Whitney U tests, or linear regression, as appropriate, and categorical outcomes using Pearson's χ^2 test. Time to first rescue analgesia was analyzed in the intention-to-treat population using Kaplan–Meier methods and the log-rank test, with patients who did not receive rescue analgesia censored at 72 h.

Hazard ratios and 95% confidence intervals were estimated using a Cox proportional-hazards model. In an exploratory economic analysis, total hospital costs were compared using bootstrap estimation. Postoperative inflammatory biomarkers were analyzed using ANCOVA adjusted for baseline values; CRP and IL-6 were log-transformed, and Holm correction was applied across biomarkers. Adverse events were summarized descriptively. All tests were two-sided, with $P < 0.05$ considered statistically significant.

3. Results

3.1 Participant flow and baseline characteristics

A total of 385 patients scheduled for surgery for mixed hemorrhoids were assessed for eligibility. Of these, 25 were excluded: 12 declined participation, 10 had a history of anorectal surgery, 2 had allergies to amide local anesthetics, and 1 was concurrently enrolled in another clinical trial. The remaining 360 patients were randomly assigned in a 1:1 ratio to the liposomal bupivacaine group or the modified cocktail group (n = 180 each). No participants withdrew after randomization, and all 360 randomized participants completed follow-up and were included in the analyses. Participant flow is shown in Fig. 1.

Baseline demographic and clinical characteristics were generally balanced between groups. Potential imbalances were observed in ASA physical status (absolute SMD = 0.112) and preoperative resting NRS score (absolute SMD = 0.192) (Table 1).

Table 1
Baseline demographic and clinical characteristics of the study population

Characteristic	Liposomal bupivacaine group (n = 180)	Modified cocktail group (n = 180)	Absolute SMD
Age, years	45.87 ± 12.39	45.61 ± 12.21	0.021
Sex, male/female	75/105	70/110	0.057
Body mass index, kg/m^2	23.31 ± 2.57	23.28 ± 2.13	0.013
ASA physical status (I/II/III)	29/138/13	34/137/9	0.112
Baseline dynamic NRS	2.03 ± 0.93	1.98 ± 0.89	0.061
Baseline resting NRS	1.44 ± 0.81	1.29 ± 0.76	0.192
Surgical technique			0.085
Milligan–Morgan hemorrhoidectomy	93	87	
Stapled hemorrhoidopexy	52	59	
Transanal hemorrhoidal dearterialization	35	34	
Concomitant anorectal conditions, n (%)			
Rectal mucosal prolapse	55 (30.6)	51 (28.3)	0.049
Anal fissure	45 (25.0)	53 (29.4)	0.100
Rectal polyp	57 (31.7)	65 (36.1)	0.094
Anorectitis	53 (29.4)	61 (33.9)	0.096
Relevant underlying diseases, n (%)			
Hypertension	23 (12.8)	29 (16.1)	0.095
Diabetes mellitus	8 (4.4)	7 (3.9)	0.028
Anemia	6 (3.3)	9 (5.0)	0.083

Note. Data are presented as mean ± SD, n, or n (%), as appropriate. ASA, American Society of Anesthesiologists; NRS, numeric rating scale; SMD, standardized mean difference. An absolute SMD > 0.10 was considered indicative of potential baseline imbalance. Participants could have more than one concomitant anorectal condition. Concomitant anorectal conditions were not treated during the index operation.

3.2 Postoperative analgesic efficacy and rescue analgesic requirements

Dynamic NRS trajectories differed between groups over time (group-by-time interaction, $F(5,354) = 10.31$, $P < 0.001$). Adjusted scores were lower in the modified cocktail group at 6 and 12 h. From 24 h onward, no statistically significant between-group differences in dynamic NRS scores were detected after Holm adjustment. In post hoc exploratory analyses, the 6–24 h dynamic NRS AUC was lower in the modified cocktail group, whereas no statistically significant difference was detected in the 24–72 h AUC (Fig. 2). The group-by-time interaction was not statistically significant for resting NRS scores ($F(5, 354) = 2.01$, $P = 0.077$), and no time-specific contrast remained significant after Holm adjustment (Table 2).

Table 2
Postoperative pain scores at prespecified time points and during first defecation

Outcome	Liposomal bupivacaine group (n = 180)	Modified cocktail group (n = 180)	Effect estimate (95% CI)	P value
Dynamic NRS[a]				
6 h	5.15 ± 1.30	4.27 ± 1.22	MD − 0.858 (− 1.117 to − 0.598)	< 0.001
12 h	4.49 ± 1.24	3.86 ± 1.38	MD − 0.613 (− 0.873 to − 0.354)	< 0.001
24 h	3.87 ± 1.45	3.54 ± 1.42	MD − 0.313 (− 0.573 to − 0.054)	0.072
48 h	3.04 ± 1.32	2.92 ± 1.28	MD − 0.102 (− 0.362 to 0.157)	1.000
72 h	2.49 ± 1.21	2.40 ± 1.34	MD − 0.069 (− 0.328 to 0.191)	1.000
POD 7	1.51 ± 1.26	1.49 ± 1.14	MD − 0.002 (− 0.262 to 0.257)	1.000
Resting NRS[a]				
6 h	3.24 ± 1.26	2.92 ± 1.19	MD − 0.259 (− 0.489 to − 0.029)	0.165
12 h	2.96 ± 1.27	2.93 ± 1.28	MD 0.035 (− 0.195 to 0.266)	1.000

Note. Data are presented as mean ± SD. Adjusted MDs were estimated using MMRMs controlling for the corresponding baseline NRS score. MD, mean difference; CI, confidence interval; NRS, numeric rating scale; POD, postoperative day. [a] P values for time-specific dynamic and resting NRS comparisons were Holm-adjusted; the corresponding 95% CIs were not multiplicity-adjusted. [b] NRS during first defecation was analyzed using linear regression without multiplicity adjustment.

Outcome	Liposomal bupivacaine group (n = 180)	Modified cocktail group (n = 180)	Effect estimate (95% CI)	P value
24 h	2.66 ± 1.24	2.58 ± 1.10	MD − 0.015 (− 0.245 to 0.216)	1.000
48 h	1.89 ± 1.20	1.98 ± 1.21	MD 0.147 (− 0.084 to 0.377)	1.000
72 h	1.68 ± 1.16	1.71 ± 1.09	MD 0.085 (− 0.145 to 0.316)	1.000
POD 7	1.04 ± 0.95	1.06 ± 0.90	MD 0.080 (− 0.151 to 0.310)	1.000
NRS during first defecation[b]	5.15 ± 1.96	4.61 ± 2.05	MD − 0.54 (− 0.95 to − 0.12)	0.011

Note. Data are presented as mean ± SD. Adjusted MDs were estimated using MMRMs controlling for the corresponding baseline NRS score. MD, mean difference; CI, confidence interval; NRS, numeric rating scale; POD, postoperative day. [a] P values for time-specific dynamic and resting NRS comparisons were Holm-adjusted; the corresponding 95% CIs were not multiplicity-adjusted. [b] NRS during first defecation was analyzed using linear regression without multiplicity adjustment.

Within 24 h, the modified cocktail group had a lower proportion of patients requiring rescue analgesia, fewer rescue analgesic administrations, and lower MME consumption than the LB group. No statistically significant between-group differences were detected in rescue analgesic administrations or MME consumption from 24 to 72 h, or in the cumulative 72-h proportion requiring rescue analgesia, total rescue administrations, or MME consumption (Table 3). In the intention-to-treat population, time to first rescue analgesia over 72 h favored the modified cocktail group (hazard ratio, 0.729; 95% CI, 0.539–0.985; log-rank P = 0.036; Fig. 3).

Table 3
Postoperative rescue analgesic requirements and morphine-equivalent rescue analgesic consumption between the two groups

Outcome	Liposomal bupivacaine group (n = 180)	Modified cocktail group (n = 180)	Effect estimate (95% CI)	P value
Patients requiring rescue analgesia, 0–72 h, n (%) [a]	94 (52.2)	77 (42.8)	RR 0.819 (0.658 to 1.020)	0.073
Patients requiring rescue analgesia, 0–24 h, n (%) [a]	88 (48.9)	69 (38.3)	RR 0.784 (0.618 to 0.995)	0.043
Total rescue analgesic administrations, 0–72 h [b]	1 [0–3]	0 [0–2]	—	0.102
Rescue analgesic administrations, 0–24 h [b]	0 [0–2]	0 [0–1]	—	0.015
Rescue analgesic administrations, 24–72 h [b]	0 [0–1]	0 [0–1]	—	0.653
Time to first rescue analgesia among rescued patients, h [c]	15.80 ± 7.73	18.05 ± 10.45	MD 2.25 (− 0.58 to 5.09)	0.118
Total MME, 0–72 h, mg [c]	14.83 ± 17.03	12.44 ± 17.06	MD − 2.39 (− 5.92 to 1.14)	0.185
MME, 0–24 h, mg [c]	9.28 ± 11.19	6.44 ± 9.55	MD − 2.83 (− 4.99 to − 0.68)	0.010
MME, 24–72 h, mg [c]	5.56 ± 10.42	6.00 ± 10.65	MD 0.44 (-1.74 to 2.63)	0.689

Note. Data are presented as mean ± SD, median [IQR], or n (%), as appropriate. RR, risk ratio; MD, mean difference; CI, confidence interval; MME, morphine milligram equivalents. [a] Pearson's χ^2 test. [b] Mann–Whitney U test. [c] Welch's t test.

3.3 Postoperative recovery and quality of recovery

Time to first ambulation was shorter in the modified cocktail group. In the exploratory economic analysis, total hospital cost was also lower than in the LB group. No significant between-group differences were observed in time to first flatus, time to first defecation, QoR-15 score on POD 2, or length of stay. Wound healing and defecation function on POD 7 were also comparable between groups (Table 4).

Table 4
Comparison of postoperative recovery outcomes between the two groups

Outcome	Liposomal bupivacaine group (n = 180)	Modified cocktail group (n = 180)	Effect estimate (95% CI)	P value
Time to first ambulation, h [a]	11.31 ± 5.17	10.12 ± 4.84	MD − 1.19 (− 2.22 to − 0.15)	0.025
Time to first flatus, h [a]	23.65 ± 5.76	23.02 ± 6.06	MD − 0.63 (− 1.86 to 0.59)	0.311
Time to first defecation, h [a]	37.90 ± 8.19	37.21 ± 8.33	MD − 0.69 (− 2.40 to 1.02)	0.430
QoR-15 score on POD 2 [a]	117.86 ± 11.77	117.06 ± 12.23	MD − 0.80 (− 3.29 to 1.68)	0.527
Length of stay, d [a]	3.02 ± 0.74	3.04 ± 0.70	MD 0.03 (− 0.12 to 0.17)	0.737
Wound healing at POD 7, n (%) [b]			—	0.623
Good	49 (27.2)	45 (25.0)		
Fair	101 (56.1)	98 (54.4)		
Poor	30 (16.7)	37 (20.6)		
Defecation function at POD 7, n (%) [b]			—	0.367
Good	128 (71.1)	135 (75.0)		
Fair	46 (25.6)	36 (20.0)		
Poor	6 (3.3)	9 (5.0)		
Hospital cost, CNY [c]	7915.51 ± 1024.62	7065.06 ± 1101.81	MD − 850.45 (− 1067.65 to − 631.18)	< 0.001

Note. Data are presented as mean ± SD or n (%), as appropriate. MD, mean difference; CI, confidence interval; POD, postoperative day; QoR-15, 15-item Quality of Recovery score; CNY, Chinese yuan. [a] Independent-samples t test. [b] Pearson's χ^2 test. [c] Bootstrap analysis for the mean difference and 95% CI.

3.4 Perioperative inflammatory response

As shown in Table 5, after adjustment for the corresponding preoperative values and Holm correction for multiple comparisons, postoperative IL-6 was significantly higher in the liposomal bupivacaine group than in the modified cocktail group. No significant between-group differences were observed in CRP, WBC count, or absolute neutrophil count.

Table 5
Adjusted between-group differences in postoperative inflammatory biomarkers

Biomarker	Effect estimate (95% CI)	P value	Holm-adjusted P value
CRP, mg/L	GMR 1.002 (0.904 to 1.110)	0.968	1.000
IL-6, pg/mL	GMR 0.818 (0.735 to 0.909)	< 0.001	< 0.001
WBC count, $\times 10^9$/L	MD -0.201 (-0.565 to 0.163)	0.278	0.834
Absolute neutrophil count, $\times 10^9$/L	MD 0.059 (-0.263 to 0.381)	0.718	1.000

Note. GMR, geometric mean ratio; MD, mean difference. Estimates are baseline-adjusted and presented as modified cocktail versus LB. CRP and IL-6 are reported as GMRs; WBC and absolute neutrophil counts as MDs. Holm adjustment was applied across the four biomarkers.

3.5 Adverse events and safety

Adverse events were infrequent in both groups, and no serious adverse events were observed. Ten patients (5.6%) in the liposomal bupivacaine group and 14 patients (7.8%) in the modified cocktail group experienced at least one adverse event. In the liposomal bupivacaine group, adverse events included dizziness (n = 2), nausea (n = 3), pruritus (n = 1), and headache (n = 4). In the modified cocktail group, adverse events included dizziness (n = 7), nausea (n = 3), insomnia (n = 3), and headache (n = 1).

4. Discussion

This randomized trial showed that the between-group differences were concentrated in the early postoperative period. Compared with LB, the modified cocktail was associated with modestly lower adjusted dynamic NRS scores at 6 and 12 h and less pain during the first defecation. Fewer patients required rescue analgesia within 24 h, early rescue analgesic use and MME consumption were lower, and ambulation occurred earlier. In the post hoc analysis, the 6–24 h dynamic NRS AUC was also lower, whereas no statistically significant difference was detected for the 24–72 h AUC. From 24 h onward, no statistically significant between-group differences were detected in dynamic NRS scores. Resting pain, 72-h cumulative MME consumption, gastrointestinal recovery, QoR-15, length of stay, wound healing, and defecation function also showed no statistically significant between-group differences.

The prolonged analgesic effect of LB after hemorrhoidectomy has been supported by previous clinical studies. Gorfine et al.[13] reported in a multicenter randomized trial that LB reduced cumulative pain intensity over 72 h, delayed the first use of opioids, and reduced 72-h opioid consumption. A subsequent systematic review and meta-analysis by Solis-Pazmino et al.[12] further confirmed the benefits of LB in postoperative pain control and opioid use. More recently, Huang et al.[16] directly compared perianal infiltration with LB and ropivacaine alone and found that LB provided lower resting and activity-related pain from 5 to 72 h, together with less rescue analgesic use. The present findings do not contradict the prolonged analgesic profile of LB but show a different temporal pattern. Adjusted dynamic NRS scores were modestly lower with the modified cocktail at 6 and 12 h, whereas pain levels were similar between groups after 24 h. When compared with an active long-acting analgesic such as LB, the absence of a clear late rebound in pain with the modified cocktail supports its potential clinical value as a locally infiltrated regimen composed of conventional agents.

This difference may be related to the composition of the modified cocktail. Unlike the ropivacaine-only regimen used by Huang et al.[16], the present formulation combined ropivacaine with dexamethasone, magnesium sulfate, and sodium bicarbonate. Ropivacaine provides local sensory blockade [17, 18]; sodium bicarbonate may alter the ionization of local anesthetics and facilitate onset [19]; dexamethasone may prolong local anesthetic effects; and magnesium may modulate nociception and sensitization through NMDA receptor-related mechanisms [20–23]. These agents act at different points in the pain pathway and may have contributed to the modest early reduction in dynamic NRS scores. However, because the study compared the complete cocktail with LB, the contribution of each individual adjuvant cannot be determined, nor can the current formulation and dosing be regarded as optimal. Although slight precipitation occurred after mixing, a previous orthopedic study using a similar modified local infiltration cocktail also observed immediate precipitation following the addition of sodium bicarbonate. In that study, no obvious injury to the injected nerve or surrounding tissues was identified in rats, and complication rates were comparable between the clinical groups [15, 24]. Consistent with these findings, no serious or apparent wound-related safety signals were observed in our trial. Nevertheless, the physicochemical compatibility and stability of the multicomponent solution require further formal evaluation.

The pattern of rescue analgesic use was consistent with the early pain findings. Within the first 24 h, fewer patients required rescue analgesia, and both rescue analgesic administrations and MME consumption were lower in the modified cocktail group. From 24 to 72 h, no statistically significant between-group differences were detected in rescue administrations or MME consumption; cumulative 72-h proportions, total administrations, and MME consumption also did not differ significantly, although the intention-to-treat time-to-event analysis favored the modified cocktail. Thus, the observed opioid-sparing benefit was confined to the early postoperative period without a detected increase in later rescue analgesic use.

Resting pain did not differ significantly between groups at any assessed time point, whereas the advantage of the modified cocktail was mainly observed in dynamic pain and pain during the first

defecation. These pain domains are particularly relevant after hemorrhoid surgery. Walking, changes in position, and defecation place direct mechanical stress on the perianal wound, and movement- and defecation-related pain may therefore have a greater effect on early postoperative activity and patient experience than resting pain. Yano et al.[6] specifically evaluated pain during the first defecation after hemorrhoidectomy and identified defecation as an important postoperative pain event. Mallmann et al.[5] also reported an association between greater early postoperative pain and persistent pain on postoperative day 7. In the present study, lower early dynamic pain and first-defecation pain were accompanied by less rescue analgesic use and earlier ambulation, providing a broader picture of improved early postoperative pain control.

Postoperative recovery outcomes further contextualized these findings. Patients in the modified cocktail group ambulated earlier, whereas time to first flatus, time to first defecation, POD 2 QoR-15 score, and length of stay were similar to those in the LB group. The early analgesic benefit therefore appeared first in functional mobilization and did not extend to all dimensions of recovery. For hemorrhoid surgery, the potential effect of local infiltration on wound and defecatory recovery is also clinically relevant. Wound status and defecation function on POD 7 were comparable between groups. Thus, the improvements in early pain and mobilization with the modified cocktail were not accompanied by unfavorable short-term wound or defecatory outcomes. This is consistent with contemporary enhanced recovery principles in colorectal surgery, which emphasize multimodal analgesia, opioid reduction, and early mobilization [25].

Hospital cost represented another clinically relevant difference between the two regimens. Total hospital costs were lower in the modified cocktail group, despite a similar length of stay. LB is relatively costly, whereas the modified cocktail consists of commonly available medications. With similar later pain control, wound healing, defecation function, and other short-term recovery outcomes, the lower cost may improve the practical feasibility of this regimen in routine hemorrhoid surgery. However, the present study assessed only total hospital costs and did not separately analyze medication, investigation, or other healthcare costs. No formal cost-effectiveness analysis was performed, and the economic implications therefore require more comprehensive evaluation.

With regard to inflammatory markers, only IL-6 was lower in the modified cocktail group after adjustment for baseline values and multiple comparisons, whereas CRP, white blood cell count, and absolute neutrophil count did not differ significantly between groups. Dexamethasone and magnesium sulfate may influence inflammatory and nociceptive pathways [20–23], but a change in a single circulating biomarker does not adequately characterize the local inflammatory response of the perianal wound. Local tissue or wound inflammation was not directly assessed in this study, and the clinical significance of the IL-6 difference therefore requires further investigation. Adverse events were infrequent in both groups, and no serious adverse events occurred.

This study has several limitations. First, it was a single-center randomized trial with follow-up limited to postoperative day 7, precluding assessment of longer-term wound recovery, anorectal function, and recurrence. Second, the modified cocktail was a multicomponent intervention, and the present design

did not allow the independent effects of each component to be determined or the optimal dose combination to be established. Third, three surgical techniques were included; although their distribution was balanced between groups, the trial was not powered to assess technique-specific treatment effects. In addition, inflammatory and cost outcomes were secondary or exploratory endpoints, and the economic analysis did not use formal health economic methods. These findings should therefore be further evaluated in larger multicenter studies.

Overall, the observed benefits of the modified cocktail were concentrated in the early postoperative period, including lower dynamic and first-defecation pain, less rescue analgesic use and MME consumption within 24 h, and earlier ambulation. Beyond 24 h, no statistically significant between-group differences were detected in pain or additional analgesic use, and most other short-term outcomes also did not differ significantly. Together with the lower hospital cost, these findings support further multicenter evaluation of the modified cocktail as a practical option for multimodal analgesia after mixed hemorrhoid surgery.

Declarations

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Competing interests
The authors have no relevant financial or non-financial interests to disclose.

Author contributions
Rui Zhang: Conceptualization, methodology, investigation, data curation, formal analysis, and writing—original draft. Bowen Hu: Investigation, data curation, and methodology. Chengfu Deng: Investigation, data curation, and methodology. Keqiang Yu: Investigation and data collection. Huixiang Li: Investigation and data collection. Jingjie Li: Investigation and data collection. Hanlin Gong: Conceptualization, supervision, resources, and writing—review and editing. Weiguo Wang: Conceptualization, supervision, funding acquisition, and writing—review and editing. All authors read and approved the final manuscript. All authors interpreted the results, critically revised the manuscript, and approved the final version.

Data availability

Individual participant data are not publicly available because of participant privacy and ethical restrictions. Aggregated data supporting the findings may be available from the corresponding author on reasonable request and subject to institutional approval.

Code availability
The analysis code is available from the corresponding author on reasonable request.

Ethics approval

This study was approved by the Clinical Research Ethics Committee of West China Hospital, Sichuan University (No. 2025 Review [2546]) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all participants or from the legal guardians of participants younger than 18 years.

Consent for publication

Not applicable.

Electronic supplementary material

Online Resource 1. Supplementary Methods for pain assessment, randomization and blinding, wound-healing and defecation-recovery grading, biomarker and recovery assessments, adverse-event definitions, NRS AUC calculation, and hospital-cost assessment.

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Figures

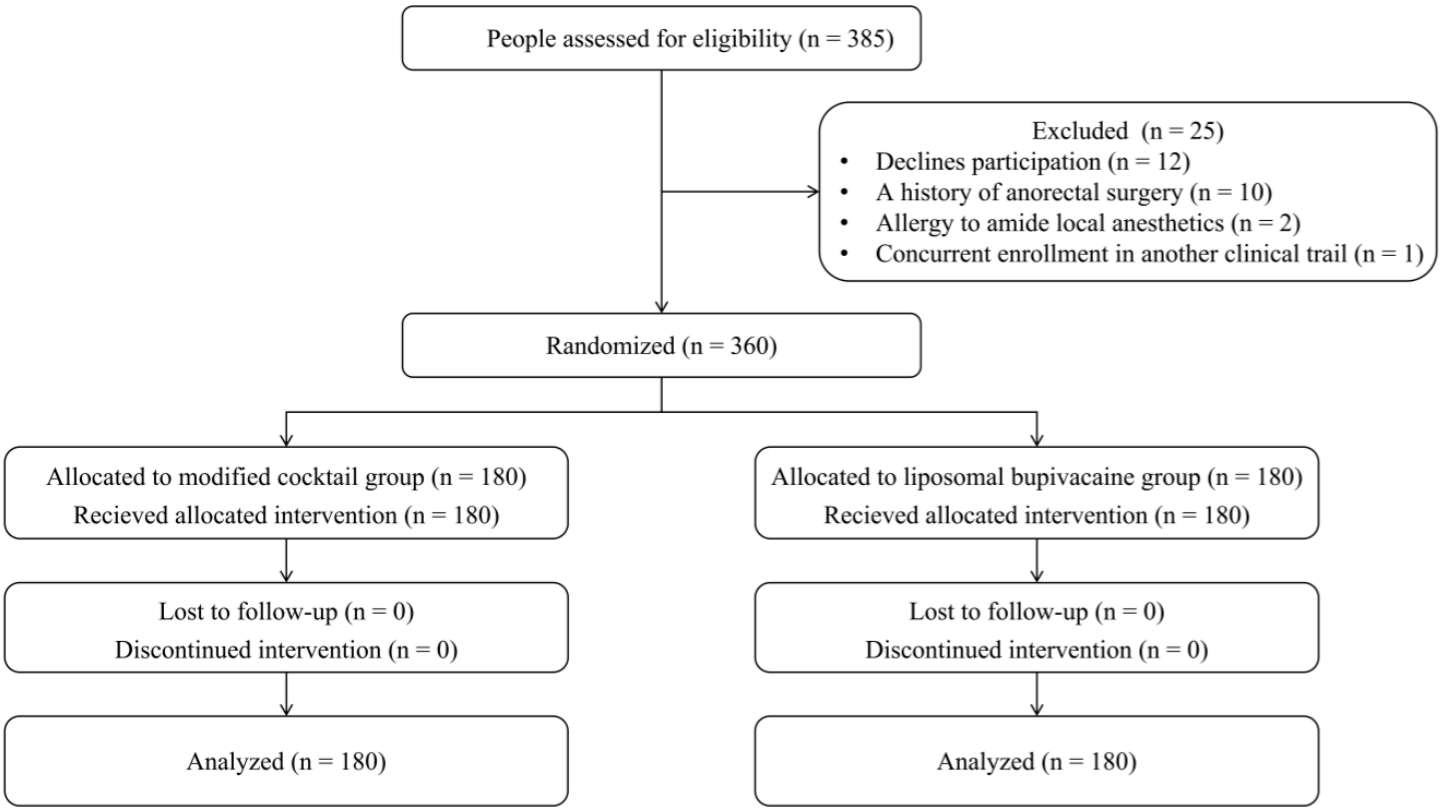


Figure 1

CONSORT flow diagram

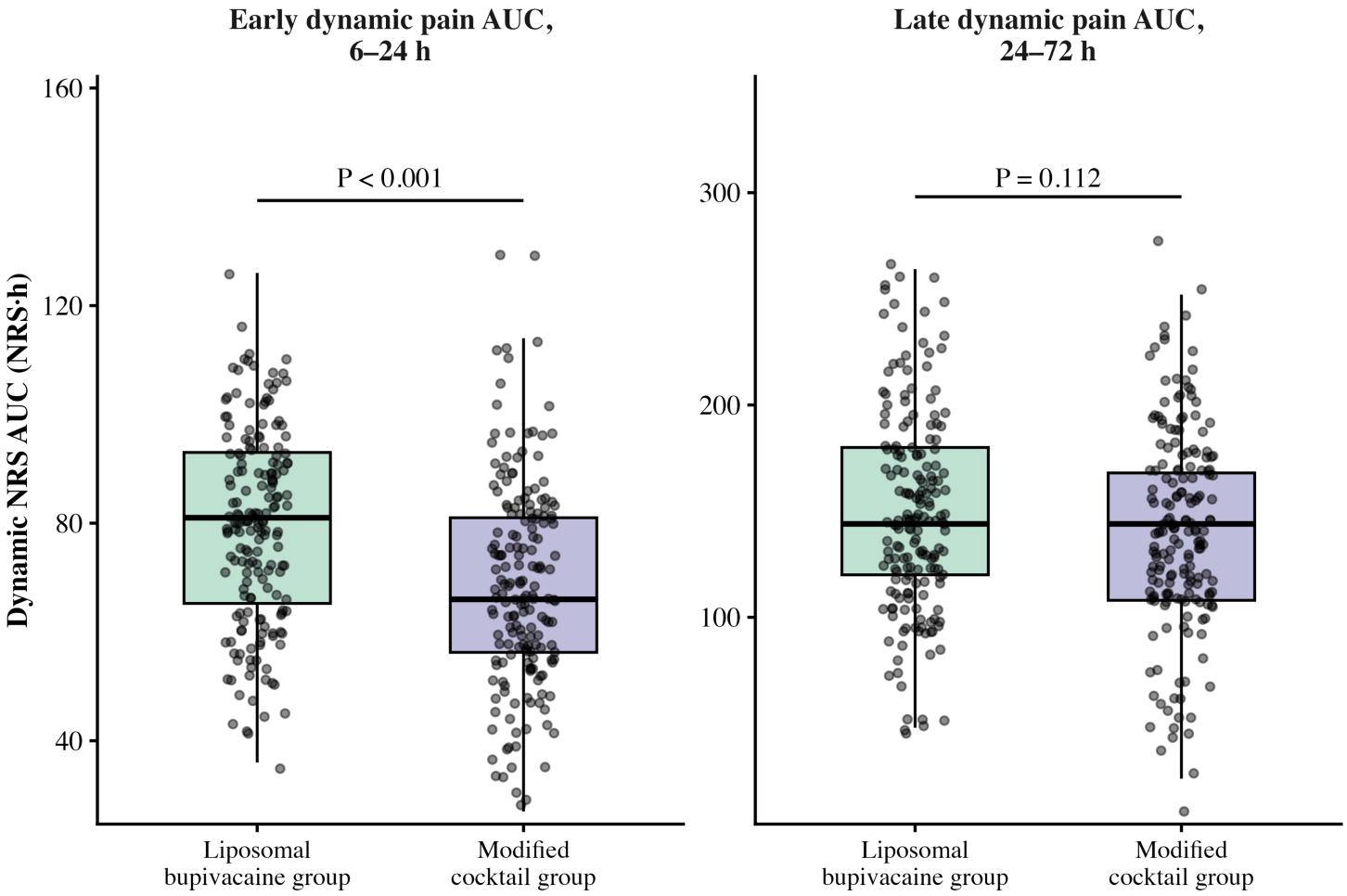


Figure 2

Post hoc comparison of dynamic NRS AUCs during the early (6–24 h) and late (24–72 h) postoperative periods

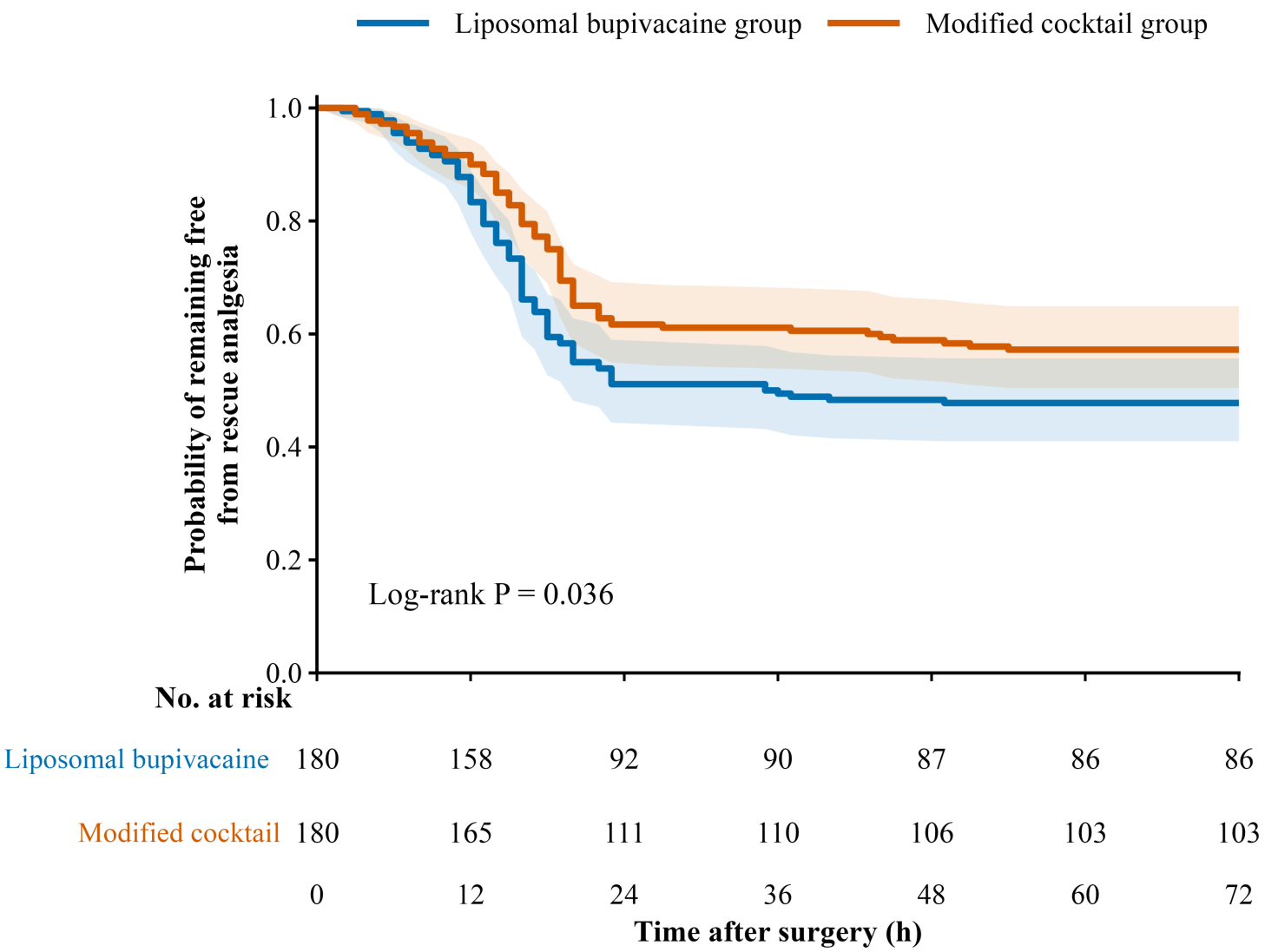


Figure 3

Kaplan-Meier curves for time to first rescue analgesia in the intention-to-treat population

Supplementary Files

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