Online Resource 1

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

International Journal of Colorectal Disease

Rui Zhang[a,1], **Bowen Hu**[a,1], **Chengfu Deng**[b,1], **Keqiang Yu**[a], **Huixiang Li**[a], **Jingjie Li**[c], **Hanlin Gong**[a,*], **Weiguo Wang**[a,*]

[a] *Department of Integrated Traditional Chinese and Western Medicine Surgery, West China Hospital of Sichuan University, No. 37, Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan, China*

[b] *Department of Anorectal Surgery, Huize County Traditional Chinese Medicine Hospital, No. 771 Tongbao Road, Huize County, Qujing City, Yunnan Province, China 654200*

[c] *Department of Integrated Chinese and Western Medicine, West China Hospital of Sichuan University, No. 37, Guoxue Lane, Wuhou District, Chengdu 610041, Sichuan, China*

[1] Rui Zhang, Bowen Hu and Chengfu Deng contributed equally to this work.

[*] Weiguo Wang and Hanlin Gong are co-corresponding authors.

Corresponding authors: (co-corresponding authors)

Weiguo Wang*: wwg-email@wchscu.edu.cn. West China Hospital of Sichuan University, Chengdu, Sichuan, 610041, China.

Hanlin Gong*: hanlin_gong@163.com. West China Hospital of Sichuan University, Chengdu, Sichuan, 610041, China.

Supplementary Methods

Pain assessment

Pain intensity was assessed using an 11-point numerical rating scale (NRS), where 0 indicated no pain and 10 indicated the worst imaginable pain. Resting NRS was recorded while the patient was

at rest, and dynamic NRS was recorded during standardized movement or activity, such as position change, sitting, standing, or ambulation. Pain scores were assessed preoperatively and at 6, 12, 24, 48, and 72 hours and 7 days after surgery. Pain scores were assessed within predefined time windows around each scheduled time point, and the actual assessment time was recorded. For the 12-hour assessment, a window of ±2 hours was allowed. If a valid score could not be obtained within the predefined window because the patient was asleep, transferred, refused assessment, or was unable to cooperate, the corresponding score was recorded as missing, with the reason documented. Missing NRS values were not imputed in the primary analysis.

Pain during first defecation was defined as the maximum NRS pain score reported during or within 30 minutes after the first spontaneous defecation. No prespecified outcome data were missing in this trial. If a score had been unavailable within the predefined assessment window, it would have been recorded as missing and not imputed.

Randomization, allocation concealment, and blinding

The random allocation sequence was generated by an independent statistician and concealed in sequentially numbered, opaque, sealed envelopes. After participant enrollment, an independent research nurse who was not involved in surgery, postoperative care, outcome assessment, data collection, or statistical analysis opened the next envelope and prepared the assigned study solution in a separate preparation area.

Each 18-mL study solution was divided into six identical opaque 3-mL syringes labeled only with the participant identification number. The syringes were delivered to the operating room in an opaque container, and the original drug packaging and any residual solution were removed before

administration. The operating surgeon was not present during allocation disclosure or solution preparation and received no information regarding treatment assignment.

Except for the designated preparation nurse, participants, operating surgeons, ward nurses, outcome assessors, data collectors, and statisticians remained blinded to treatment allocation. The treatment groups were coded as group A and group B for statistical analysis, and the allocation code was released only after completion of the prespecified analysis.

Wound-healing grading criteria

Wound healing was assessed during the dressing-change follow-up on postoperative day 7 and classified as good, fair, or poor according to a five-point wound-healing scale.

Grade	Definition
1	Sloughy or necrotic wound with obvious exudation or debris
2	No granulation tissue
3	Granulation tissue formation
4	Ongoing epithelialization
5	Complete epithelialization

Grades 4–5 were defined as good wound healing, grade 3 as fair wound healing, and grades 1–2 as poor wound healing. Wound infection, purulent discharge, secondary bleeding, or the need for additional wound-related treatment was classified as poor wound healing regardless of the original wound score.

Defecation recovery grading criteria

Defecation recovery within the first 7 postoperative days was assessed at the postoperative day 7 follow-up and classified as good, fair, or poor according to the timing of first spontaneous defecation, defecation difficulty, and need for additional defecation-related intervention. Spontaneous defecation was defined as defecation without mechanical assistance, such as glycerin enema, enema, suppository, or digital evacuation. Routine stool softeners or oral laxatives prescribed to all patients according to the standard postoperative protocol were not considered additional interventions.

Category	Definition
Good	First spontaneous defecation within 72 hours after surgery without obvious defecation difficulty
Fair	First spontaneous defecation >72 hours and ≤96 hours after surgery, or mild defecation difficulty, sensation of incomplete evacuation, or need for additional oral laxatives/stool softeners beyond the routine protocol
Poor	First spontaneous defecation >96 hours after surgery, no spontaneous defecation within 7 days, need for glycerin enema, enema, suppository, or digital assistance, or occurrence of fecal impaction, marked abdominal distension, or need for additional medical treatment

If a patient met criteria for more than one category, the most severe category was used for analysis.

Inflammatory biomarkers

C-reactive protein, interleukin-6, white blood cell count, and absolute neutrophil count were measured preoperatively and on postoperative day 1. Postoperative values were compared using

analysis of covariance adjusted for the corresponding preoperative value. C-reactive protein and interleukin-6 were log-transformed before analysis.

Postoperative recovery variables

Postoperative recovery outcomes included time to first ambulation, time to first flatus, time to first defecation, QoR-15 score on postoperative day 2, and hospital length of stay. Time to first ambulation was defined as the interval from the end of surgery to the first out-of-bed walking activity. Time to first flatus and first defecation were defined as the intervals from the end of surgery to the first passage of flatus and first bowel movement, respectively. Hospital length of stay was defined as the number of days from admission to discharge. The QoR-15 questionnaire was completed on postoperative day 2 under the guidance of a blinded assessor.

Adverse events

Adverse events were recorded throughout the postoperative observation period and during postoperative day 7 follow-up. Events of interest included dizziness, nausea, vomiting, pruritus, urinary retention, headache, insomnia, wound infection, delayed bleeding, allergic reaction, and symptoms suggestive of local anesthetic systemic toxicity. Serious adverse events were defined as events resulting in death, life-threatening complications, prolonged hospitalization, persistent disability, or the need for urgent intervention.

Area under the curve analysis of NRS scores

Dynamic NRS AUCs were calculated separately over 6–24 h and 24–72 h using the trapezoidal rule. The 6–24 h AUC was based on the 6-, 12-, and 24-h assessments, and the 24–72 h AUC on the

24-, 48-, and 72-h assessments. AUCs were expressed as NRS·h and compared using Welch's independent-samples t test. These analyses were post hoc and exploratory.

Hospital cost assessment

Hospital costs were assessed from the healthcare-provider perspective using itemized inpatient billing records and were expressed in Chinese yuan (CNY). Total hospital cost included all eligible direct medical costs incurred from admission to discharge, including the assigned study infiltration medication, surgery and anesthesia, ward and nursing care, laboratory and imaging examinations, postoperative medications, and medical consumables. Costs incurred after discharge, transportation expenses, productivity losses, and other indirect costs were not included.