

Liposomal bupivacaine alone or combined with tranexamic acid and flurbiprofen axetil for local infiltration analgesia in total hip arthroplasty for displaced femoral neck fractures: a randomized controlled trial

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Abstract

Background

The incremental analgesic value of adding tranexamic acid and flurbiprofen axetil to liposomal bupivacaine-based local infiltration analgesia (LIA) after total hip arthroplasty (THA) remains uncertain. We evaluated these regimens in patients undergoing THA for displaced femoral neck fractures.

Methods

In this prospective, randomized, controlled, observer-blinded study, 120 patients undergoing primary unilateral THA were assigned to a modified cocktail, liposomal bupivacaine (LB), or control group (n = 40 each). The cocktail group received LIA with LB, tranexamic acid, and flurbiprofen axetil; the LB group received LB alone; and the control group received no LIA. Primary outcomes were resting and movement visual analog scale (VAS) pain scores. Secondary outcomes included opioid consumption, hip range of motion, operative and follow-up outcomes, and complications. Continuous outcomes were analyzed using one-way analysis of variance with Bonferroni-adjusted comparisons; categorical outcomes were analyzed using chi-square or Fisher exact tests.

Results

At 6 h, resting VAS scores were 2.69 ± 0.93 , 2.90 ± 0.84 , and 3.50 ± 0.76 in the cocktail, LB, and control groups, respectively; movement VAS scores were 4.47 ± 0.87 , 4.68 ± 0.74 , and 5.53 ± 0.82 (both $P < 0.001$). On postoperative days 1 and 2, both LIA groups had lower resting and movement VAS scores than the control group (all $P < 0.05$), with no differences between the LIA groups. The 0–72 h morphine milligram equivalent consumption was 26.20 ± 16.50 , 26.85 ± 18.63 , and 37.10 ± 20.60 mg, respectively ($P = 0.0158$). On postoperative day 2, active hip flexion and abduction were greater in both LIA groups than in the control group (all $P < 0.05$). Later pain, discharge range of motion, operative, follow-up, and complication outcomes did not differ significantly.

Conclusions

Liposomal bupivacaine-based LIA reduced early postoperative pain scores and opioid consumption. Adding tranexamic acid and flurbiprofen axetil provided no statistically significant incremental analgesic benefit.

Trial registration:

Registration with a WHO/ICMJE-recognized clinical trial registry is currently under review. The registration number and date will be provided upon completion of the registration process.

Background

Hip fractures, including femoral neck fractures, are clinically consequential injuries in older adults, and their global burden continues to increase with population aging [1]. In older patients with displaced femoral neck fractures, arthroplasty generally reduces the risks of fixation failure, femoral head osteonecrosis, and reoperation compared with internal fixation. Total hip arthroplasty (THA) is an important treatment option for patients with good preinjury mobility, high anticipated functional demands, and sufficient physiological reserve [2]. Nevertheless, a substantial proportion of patients experience moderate-to-severe pain during the early postoperative period. Inadequate pain control may delay mobilization and rehabilitation, increase opioid requirements and related adverse events, reduce patient satisfaction, and prolong recovery [3–4].

Multimodal analgesia is an important component of enhanced recovery after joint arthroplasty [4–5]. Local infiltration analgesia (LIA) delivers local anesthetics and analgesic adjuvants directly into the surgical field, thereby suppressing peripheral nociceptive input and reducing systemic analgesic requirements. Because LIA is not intended primarily to block major motor nerves, it may have less impact on early postoperative muscle strength than some peripheral nerve block techniques [6–7]. LIA cocktails commonly combine long-acting local anesthetics with nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, epinephrine, or glucocorticoids [8]. However, the analgesic benefit of single-shot LIA appears to be concentrated mainly in the early postoperative period, and the optimal formulation, drug combination, and concentration remain uncertain [9–11].

Liposomal bupivacaine is a sustained-release local anesthetic designed to prolong local analgesic activity through gradual bupivacaine release. Although some studies have reported reductions in early postoperative pain scores and opioid consumption after THA [12], others have found inconsistent clinical benefits [13–16]. Because postoperative pain after THA is also influenced by inflammation, local bleeding, and soft-tissue swelling, prolonging local anesthetic activity alone may not fully address its multifactorial pathophysiology [17]. Combining liposomal bupivacaine with adjuvants targeting inflammation, nociceptive sensitization, bleeding, or swelling may therefore further optimize LIA.

Tranexamic acid reduces perioperative blood loss and transfusion requirements in THA [18–19], and a recent randomized study in total knee arthroplasty suggested that its addition to an LIA cocktail may reduce early resting pain [20]. Flurbiprofen axetil inhibits cyclooxygenase-mediated prostaglandin synthesis and may reduce postoperative pain when used as a cocktail adjuvant [21]. However, direct clinical evidence supporting the inclusion of either agent in THA LIA cocktails remains limited.

Accordingly, this prospective, randomized, controlled study evaluated the efficacy and safety of liposomal bupivacaine-based LIA and a modified cocktail containing liposomal bupivacaine, tranexamic acid, and flurbiprofen axetil in patients undergoing THA for displaced femoral neck fractures. We further

examined whether the modified cocktail provided additional analgesic benefit over liposomal bupivacaine alone.

Methods

Study design, setting, and participants

This prospective, randomized, controlled, observer-blinded, single-center study was conducted in the Department of Orthopaedics at Leshan People's Hospital, Leshan, China. The study aimed to evaluate the efficacy and safety of LB-based LIA and to determine whether adding tranexamic acid and flurbiprofen axetil provided an incremental analgesic benefit over LB alone.

This study was approved by the Ethics Committee of Leshan People's Hospital (approval No. LYLL[2025]KY101), and written informed consent was obtained from all patients or their legal representatives before enrollment. The study was filed in the Medical Research Registration and Filing Information System (registration No. MR-51-26-049832).

Between June 2025 and December 2025, consecutive patients scheduled to undergo primary unilateral THA for acute, closed, displaced femoral neck fractures were screened for eligibility.

The inclusion criteria were as follows: (i) age ≥ 65 years; (ii) a radiographically confirmed acute, closed, displaced femoral neck fracture classified as Garden type III or IV; (iii) American Society of Anesthesiologists (ASA) physical status I–III; (iv) planned primary unilateral THA followed by early weight-bearing and rehabilitation training; (v) ability to understand the visual analog scale (VAS) and complete perioperative and follow-up assessments; and (vi) provision of written informed consent by the patient or a legal representative.

The exclusion criteria were as follows: (i) known allergy to any study medication, including bupivacaine, flurbiprofen axetil, tranexamic acid, or other NSAIDs; (ii) previous surgery or infection involving the affected hip, or active local or systemic infection; (iii) a congenital or acquired coagulation disorder, active deep vein thrombosis, pulmonary embolism, or other active venous or arterial thromboembolic disease; (iv) severe renal insufficiency, active gastrointestinal bleeding, a history of severe peptic ulcer disease, or another contraindication to NSAIDs or tranexamic acid; (v) severe cognitive impairment, psychiatric disease, communication difficulty, or another condition preventing completion of VAS assessment or follow-up; and (vi) expected or actual completion of surgery after 16:00, to standardize postoperative pain assessment time points.

Randomization and Blinding

Enrolled patients were randomized in a 1:1:1 ratio to the LB, cocktail, or control group. The randomization sequence was computer-generated by an independent statistician who was not involved in patient

management, study implementation, or outcome assessment. Group assignments were placed in sequentially numbered, opaque, sealed envelopes. On the day of surgery, a research nurse who was not involved in postoperative care or outcome assessment opened the envelopes in sequence and prepared the corresponding study solution according to group allocation. Patients, anesthesiologists, outcome assessors, and data collectors were blinded to group allocation. Because the operating surgeon was required to administer or omit LIA according to allocation, surgeon blinding was not feasible; however, the surgeon did not participate in postoperative analgesic management, data collection, or outcome assessment.

Surgery and Perioperative Management

All patients received standardized perioperative management. Before surgery, patients were instructed in VAS assessment, and preoperative resting VAS scores were recorded. Lornoxicam was used for preoperative analgesia unless contraindicated. Patients with renal insufficiency, active gastrointestinal bleeding, or other contraindications to NSAIDs did not receive lornoxicam, and this was documented in accordance with the study protocol. Except for tranexamic acid included in the local infiltration solution in the cocktail group, routine intravenous tranexamic acid was not administered perioperatively in any group. The use of additional hemostatic agents, when clinically required, was recorded in detail. Continuous nerve blocks and epidural analgesia were not routinely used to avoid interference with early postoperative pain assessment. All patients received a standardized general anesthesia protocol, with induction, maintenance, and intraoperative analgesia administered by the same anesthesia team according to a uniform procedure. Prophylactic antibiotics were administered intravenously 30–60 min before skin incision. All procedures were performed by the same team of senior joint surgeons experienced in hip arthroplasty. Primary unilateral THA was performed under general anesthesia through a direct anterior approach using cementless prostheses, and surgical drains were not routinely placed. All patients received standardized thromboprophylaxis. Mechanical prophylaxis, including ankle-pump exercises, intermittent pneumatic compression of the lower limbs, and elastic stockings, was initiated immediately after surgery. In the absence of active bleeding or another contraindication to anticoagulation, low-molecular-weight heparin was initiated 6 h postoperatively. After discharge, oral rivaroxaban 10 mg once daily was continued for a duration determined according to each patient's thrombotic and bleeding risks and institutional practice. Rehabilitation was uniformly supervised by physiotherapists who were not involved in treatment allocation or outcome assessment and included bed-based hip exercises, ambulation with a walker, and training in activities of daily living.

Interventions and the Multimodal Analgesia Protocol

Patients received the intervention assigned by randomization. In the LB group, intraoperative LIA consisted of 20 mL (266 mg) of liposomal bupivacaine diluted with normal saline to a total volume of 50 mL. After acetabular reaming, 20 mL of the solution was infiltrated in a clockwise manner into the periacetabular tissues and joint capsule. After prosthesis implantation, 20 mL was infiltrated into the

vastus lateralis, tensor fasciae latae, and proximal iliotibial band, and the remaining 10 mL was infiltrated into the superficial fascia, subcutaneous tissues, and peri-incisional tissues. In the cocktail group, the modified LIA solution comprised 20 mL (266 mg) of liposomal bupivacaine, 5 mL (50 mg) of flurbiprofen axetil, and 5 mL (0.25 g) of tranexamic acid, diluted with normal saline to a total volume of 50 mL. The infiltration technique was identical to that used in the LB group. Patients in the control group received no LIA.

All patients received the same multimodal analgesic protocol. Celecoxib 200 mg was administered twice daily after surgery and continued for 2 weeks. Local cold therapy was applied for 6 h postoperatively. A data collector blinded to group allocation assessed VAS pain scores and analgesic use. For VAS scores of 4–6, oral oxycodone hydrochloride 10 mg was administered as rescue analgesia, with repeat dosing determined according to pain severity and physician orders. For VAS scores ≥ 7 , subcutaneous morphine 5 mg was administered immediately. All opioid doses were converted to oral morphine milligram equivalents (MME).

Outcome Measures

The primary outcomes included postoperative VAS pain scores. Secondary outcomes included opioid consumption, hip range of motion on POD 2 and at discharge, duration of surgery, intraoperative blood loss, complications, and follow-up outcomes. Preoperative HHS was assessed after the hip fracture and before surgery.

Visual Analog Scale

Hip pain was assessed using a self-reported VAS ranging from 0 to 10, with 0 indicating no pain, 1–3 mild pain, 4–6 moderate pain, and 7–10 severe pain. Resting and movement VAS pain scores were assessed at 6 h postoperatively, on POD 1, POD 2, POD 3, and at discharge. Movement VAS was defined as the pain score reported during active bedside hip flexion or ambulation with a walker.

Opioid Consumption

Opioid consumption was converted to oral MME using the following ratios: 10 mg of subcutaneous morphine was considered equivalent to 30 mg of oral morphine, and 10 mg of oral oxycodone hydrochloride was considered equivalent to 15 mg of oral morphine [22–23]. Opioid consumption was recorded over the first 0–72 h postoperatively and throughout hospitalization.

Range of Motion

Hip range of motion included active and passive flexion and abduction. Flexion and abduction were measured from the neutral position (0°) to the maximum achievable angle. Hip range of motion was

assessed on POD 2 and at discharge.

Complications

Safety outcomes included opioid-related adverse events and perioperative complications, including postoperative nausea and vomiting, superficial infection, deep infection, hematoma, deep vein thrombosis, pulmonary embolism, gastrointestinal bleeding, and wound necrosis.

Follow-up Outcomes

Follow-up assessments were performed at 3 and 6 months after surgery. Follow-up outcomes included resting and movement VAS pain scores, the 12-Item Short Form Health Survey (SF-12), Harris Hip Score (HHS), and Pittsburgh Sleep Quality Index (PSQI). SF-12 physical component summary (PCS) and mental component summary (MCS) scores were calculated using standardized scoring methods. Preinjury SF-12 scores were assessed retrospectively at enrollment by asking patients to recall their health status before the fracture.

Statistical Analysis and Sample Size

Statistical analyses were performed using R software (version 4.5.3). The normality of continuous variables was assessed using the Shapiro-Wilk test, and homogeneity of variance was assessed using Levene's test. Continuous variables are presented as the mean $\pm$ standard deviation (SD). Normally distributed continuous variables with homogeneous variances were compared among groups using one-way analysis of variance (ANOVA), followed by Bonferroni-adjusted post hoc pairwise comparisons. Non-normally distributed continuous variables were analyzed using the Kruskal-Wallis test, followed by the Nemenyi test for post hoc pairwise comparisons. Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher's exact test. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

The sample size was estimated from preliminary data obtained from 21 patients using G*Power version 3.1.9. A fixed-effects one-way ANOVA model was specified with $\alpha = 0.05$ and a power of 0.80. The calculation indicated that at least 32 patients were required per group. Allowing for a 20% loss to follow-up, the planned sample size was 40 patients per group, for a total of 120 patients.

Use of generative artificial intelligence

During the preparation and revision of this manuscript, the authors used ChatGPT (OpenAI) solely to assist with English-language editing, improve clarity and readability, and condense selected passages. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

Results

Participant flow

Figure 1 summarizes patient screening, randomization, and follow-up. Between June and December 2025, 152 patients scheduled to undergo THA for femoral neck fracture were screened; 32 were excluded because they did not meet the inclusion criteria (n = 21), declined participation (n = 8), or had surgery cancelled (n = 3). The remaining 120 patients were randomized in a 1:1:1 ratio to the cocktail, LB, and control groups. All patients completed perioperative observation and follow-up and were included in the final analysis.

Baseline Characteristics

Baseline demographic and preoperative clinical characteristics are summarized in Table 1.

Table 1
Baseline demographic and preoperative clinical characteristics

Variable	Cocktail (n = 40)	LB (n = 40)	Control (n = 40)	Statistic	P value
Age (years)	75.98 ± 8.02	75.40 ± 8.07	75.65 ± 8.00	F = 0.05	0.95
Sex, n (%)				$\chi^2 = 3.29$	0.193
Female	22 (55.0%)	14 (35.0%)	19 (47.5%)		
Male	18 (45.0%)	26 (65.0%)	21 (52.5%)		
Operative side, n (%)				$\chi^2 = 3.89$	0.143
Left	22 (55.0%)	14 (35.0%)	15 (37.5%)		
Right	18 (45.0%)	26 (65.0%)	25 (62.5%)		
Height (cm)	163.69 ± 9.57	163.03 ± 9.03	164.91 ± 10.30	F = 0.39	0.679
Weight (kg)	63.00 ± 11.50	60.80 ± 10.90	62.00 ± 10.40	F = 0.40	0.668
BMI (kg/m ²)	23.49 ± 3.72	22.87 ± 3.58	22.77 ± 3.17	F = 0.49	0.611
ASA, n (%)				$\chi^2 = 2.07$	0.723
I	4 (10.0%)	6 (15.0%)	5 (12.5%)		
II	29 (72.5%)	31 (77.5%)	30 (75.0%)		
III	7 (17.5%)	3 (7.5%)	5 (12.5%)		
Garden classification, n (%)				$\chi^2 = 0.80$	0.67
III	21 (52.5%)	19 (47.5%)	17 (42.5%)		
IV	19 (47.5%)	21 (52.5%)	23 (57.5%)		
Resting VAS	4.91 ± 0.67	4.68 ± 0.63	4.82 ± 0.56	F = 1.40	0.251
HHS	14.83 ± 6.30	13.68 ± 5.66	14.18 ± 5.44	F = 0.39	0.675
PSQI	9.60 ± 3.89	8.80 ± 3.52	9.20 ± 3.30	F = 0.50	0.608
Preinjury SF-12					
PCS	41.25 ± 8.18	39.98 ± 9.31	40.70 ± 8.72	F = 0.21	0.809
Note: Values are presented as mean ± SD or n (%).					

Variable	Cocktail (n = 40)	LB (n = 40)	Control (n = 40)	Statistic	P value
MCS	51.35 ± 9.75	49.95 ± 10.10	50.80 ± 9.40	F = 0.21	0.812
Note: Values are presented as mean ± SD or n (%).					

No significant differences were observed among the three groups in demographic or preoperative clinical characteristics. Age, sex, operative side, height, weight, BMI, ASA class, and Garden classification were comparable among groups. Preoperative resting VAS, HHS, PSQI, and preinjury SF-12 PCS and MCS scores also did not differ significantly among the three groups, indicating that the groups were comparable at baseline.

Postoperative VAS Scores and Opioid Consumption

Postoperative VAS pain scores and opioid consumption are summarized in Table 2.

Table 2
Postoperative VAS pain scores and opioid consumption expressed as morphine milligram equivalents during hospitalization

Variable	Cocktail (n = 40)	LB (n = 40)	Control (n = 40)	Statistic	P value
Resting VAS					
6 h	2.69 ± 0.93	2.90 ± 0.84	3.50 ± 0.76	F = 9.86	< 0.001***
POD 1	2.38 ± 0.85	2.40 ± 0.79	2.89 ± 0.73	F = 5.33	0.006**
POD 2	2.12 ± 0.84	2.35 ± 0.79	2.80 ± 0.69	F = 7.96	< 0.001***
POD 3	1.84 ± 0.98	2.04 ± 0.90	2.10 ± 0.72	F = 0.98	0.378
Discharge	1.30 ± 0.94	1.35 ± 0.68	1.60 ± 0.75	F = 1.62	0.202
Movement VAS					
6 h	4.47 ± 0.87	4.68 ± 0.74	5.53 ± 0.82	F = 19.13	< 0.001***
POD 1	4.31 ± 0.63	4.59 ± 0.70	5.45 ± 0.83	F = 26.99	< 0.001***
POD 2	4.07 ± 1.03	4.29 ± 0.87	4.86 ± 0.93	F = 7.44	< 0.001***
POD 3	3.17 ± 0.97	3.38 ± 0.71	3.59 ± 0.86	F = 2.42	0.093
Discharge	2.92 ± 0.62	3.09 ± 0.71	3.30 ± 0.79	F = 2.91	0.059
MME consumption (mg)					
0–72 h	26.20 ± 16.50	26.85 ± 18.63	37.10 ± 20.60	F = 4.30	0.0158*
In-hospital total	29.40 ± 18.70	30.60 ± 21.20	42.81 ± 25.40	F = 4.58	0.0122*
Note: Values are presented as mean ± SD. *P < 0.05; **P < 0.01; ***P < 0.001.					

Bonferroni-adjusted post hoc pairwise comparisons are presented in Table 3.

Table 3
Post hoc comparisons of postoperative VAS pain scores and opioid consumption

Variable	Cocktail (n = 40)	LB (n = 40)	Control (n = 40)	P value	P ₁	P ₂	P ₃
Resting VAS							
6 h	2.69 ± 0.93	2.90 ± 0.84	3.50 ± 0.76	< 0.001***	0.803	< 0.001***	0.006**
POD 1	2.38 ± 0.85	2.40 ± 0.79	2.89 ± 0.73	0.006**	1.000	0.014*	0.020*
POD 2	2.12 ± 0.84	2.35 ± 0.79	2.80 ± 0.69	< 0.001***	0.559	0.0004***	0.032*
Movement VAS							
6 h	4.47 ± 0.87	4.68 ± 0.74	5.53 ± 0.82	< 0.001***	0.750	< 0.001***	< 0.001***
POD 1	4.31 ± 0.63	4.59 ± 0.70	5.45 ± 0.83	< 0.001***	0.260	< 0.001***	< 0.001***
POD 2	4.07 ± 1.03	4.29 ± 0.87	4.86 ± 0.93	< 0.001***	0.900	0.0009***	0.024*
MME consumption (mg)							
0–72 h	26.20 ± 16.50	26.85 ± 18.63	37.10 ± 20.60	0.0158*	1.000	0.030*	0.046*
In-hospital total	29.40 ± 18.70	30.60 ± 21.20	42.81 ± 25.40	0.0122*	1.000	0.022*	0.043*
Note: Values are presented as mean ± SD. P ₁ , cocktail vs. LB; P ₂ , cocktail vs. control; P ₃ , LB vs. control. *P < 0.05; **P < 0.01; ***P < 0.001.							

Resting and movement VAS pain scores differed significantly among the three groups at 6 h postoperatively, on POD 1, and on POD 2 (resting VAS: $F = 9.86$, $P < 0.001$; $F = 5.33$, $P = 0.006$; and $F = 7.96$, $P < 0.001$, respectively; movement VAS: $F = 19.13$, $F = 26.99$, and $F = 7.44$, respectively; all $P < 0.001$). Bonferroni-adjusted pairwise comparisons showed that both resting and movement VAS pain scores were lower in the cocktail and LB groups than in the control group at all three time points, whereas no significant differences were observed between the two LIA groups. Resting and movement VAS pain scores did not differ significantly among the three groups on POD 3 or at discharge.

Postoperative MME consumption over 0–72 h was 26.20 ± 16.50 mg, 26.85 ± 18.63 mg, and 37.10 ± 20.60 mg in the cocktail, LB, and control groups, respectively ($F = 4.30$, $P = 0.0158$). Total in-hospital

MME consumption was 29.40 ± 18.70 mg, 30.60 ± 21.20 mg, and 42.81 ± 25.40 mg, respectively ($F = 4.58$, $P = 0.0122$). Both LIA groups had lower 0–72 h and total in-hospital MME consumption than the control group, with no significant differences between the cocktail and LB groups.

Range of Motion

Hip range-of-motion outcomes are summarized in Table 4.

Table 4
Hip range of motion

Variable	Cocktail (n = 40)	LB (n = 40)	Control (n = 40)	Statistic	P value	P ₁	P ₂	P ₃
POD 2 active flexion (°)	67.60 ± 8.50	66.41 ± 7.80	61.70 ± 7.20	F = 6.32	0.002**	1.000	0.003**	0.025*
POD 2 passive flexion (°)	77.40 ± 6.80	76.09 ± 7.49	74.81 ± 8.30	F = 1.18	0.313	-	-	-
POD 2 active abduction (°)	14.45 ± 3.28	14.10 ± 3.57	12.21 ± 3.38	F = 4.99	0.008**	1.000	0.012*	0.044*
POD 2 passive abduction (°)	18.70 ± 3.90	18.30 ± 3.29	17.80 ± 3.70	F = 0.61	0.545	-	-	-
Discharge active flexion (°)	80.30 ± 7.40	79.60 ± 8.10	78.90 ± 6.70	F = 0.36	0.699	-	-	-
Discharge passive flexion (°)	92.71 ± 6.65	92.20 ± 8.05	91.70 ± 7.30	F = 0.19	0.828	-	-	-
Discharge active abduction (°)	23.86 ± 3.31	23.26 ± 3.82	22.80 ± 4.40	F = 0.76	0.472	-	-	-
Discharge passive abduction (°)	27.54 ± 3.76	26.74 ± 3.66	25.67 ± 4.68	F = 2.14	0.122	-	-	-
Note: Values are presented as mean ± SD. P ₁ , cocktail vs. LB; P ₂ , cocktail vs. control; P ₃ , LB vs. control. *P < 0.05; **P < 0.01; ***P < 0.001.								

On POD 2, active hip flexion and abduction differed significantly among the three groups. Active flexion was $67.60 \pm 8.50^\circ$, $66.41 \pm 7.80^\circ$, and $61.70 \pm 7.20^\circ$ in the cocktail, LB, and control groups, respectively ($F = 6.32$, $P = 0.002$), while active abduction was $14.45 \pm 3.28^\circ$, $14.10 \pm 3.57^\circ$, and $12.21 \pm 3.38^\circ$, respectively ($F = 4.99$, $P = 0.008$). Both measures were greater in the two LIA groups than in the control group, with no significant differences between the two LIA groups. Passive hip flexion and abduction on POD 2, as well

as active and passive hip flexion and abduction at discharge, did not differ significantly among the three groups.

Operative Outcomes and Follow-up Outcomes

Operative and follow-up outcomes are summarized in Table 5.

Table 5
Operative and follow-up outcomes

Variable	Cocktail group (n = 40)	LB group (n = 40)	Control group (n = 40)	Statistic	P value
Duration of surgery (min)	61.83 ± 16.88	64.50 ± 14.43	67.00 ± 12.78	F = 1.23	0.298
Intraoperative blood loss (mL)	104.88 ± 49.66	103.10 ± 43.67	108.45 ± 55.34	F = 0.12	0.887
Follow-up					
PSQI					
3 months	5.85 ± 2.23	6.18 ± 2.48	6.78 ± 2.43	F = 1.55	0.216
6 months	4.80 ± 2.56	5.30 ± 2.49	5.90 ± 2.26	F = 2.03	0.136
Resting VAS					
3 months	0.59 ± 0.25	0.66 ± 0.28	0.72 ± 0.31	F = 2.12	0.125
6 months	0.37 ± 0.21	0.40 ± 0.20	0.43 ± 0.23	F = 0.86	0.424
Movement VAS					
3 months	0.84 ± 0.51	0.91 ± 0.55	0.96 ± 0.52	F = 0.58	0.563
6 months	0.74 ± 0.42	0.80 ± 0.45	0.86 ± 0.49	F = 0.70	0.501
HHS					
3 months	88.93 ± 2.21	88.75 ± 2.49	87.74 ± 2.35	F = 2.96	0.056
6 months	92.10 ± 3.12	91.76 ± 2.94	91.58 ± 2.75	F = 0.32	0.725
SF-12 at 3 months					
PCS	41.80 ± 6.90	42.50 ± 8.20	43.20 ± 7.60	F = 0.34	0.713
MCS	51.70 ± 6.55	52.10 ± 5.88	52.60 ± 5.69	F = 0.22	0.801
SF-12 at 6 months					
PCS	44.70 ± 7.05	45.40 ± 7.72	46.20 ± 7.35	F = 0.41	0.662
MCS	54.93 ± 6.55	54.36 ± 6.17	54.78 ± 6.82	F = 0.08	0.921
Note: Values are presented as mean ± SD.					

No significant between-group differences were observed in duration of surgery or intraoperative blood loss (P = 0.298 and P = 0.887, respectively). Similarly, no significant differences were found in PSQI, resting or movement VAS, HHS, or SF-12 scores at the 3- or 6-month follow-up assessments.

Complications

Postoperative complications are summarized in Table 6.

Table 6
Postoperative complications

Variable	Cocktail group (n = 40)	LB group (n = 40)	Control group (n = 40)	P value
PONV	2	3	4	0.911
Superficial infection	0	0	0	-
Deep infection	0	0	0	-
Wound-related complication	1	1	2	1.000
Hematoma	0	1	2	0.774
Deep vein thrombosis	0	0	0	-
Pulmonary embolism	0	0	0	-
Gastrointestinal bleeding	0	0	0	-
Note: Values are presented as n.				

Postoperative complication rates did not differ significantly among the three groups. Postoperative nausea and vomiting occurred in two, three, and four patients in the cocktail, LB, and control groups, respectively ($P = 0.911$). No cases of superficial or deep infection, deep vein thrombosis, pulmonary embolism, or gastrointestinal bleeding were observed. Wound-related complications and hematomas were uncommon, with no significant between-group differences.

Discussion

In this prospective, randomized, controlled, observer-blinded study, liposomal bupivacaine-based LIA improved resting and movement pain from 6 h postoperatively to POD 2 and reduced postoperative opioid consumption in patients undergoing THA for displaced femoral neck fractures. After tranexamic acid and flurbiprofen axetil were added to liposomal bupivacaine, several pain, opioid consumption, and early functional outcomes showed slight numerical advantages; however, the differences between the cocktail and LB groups did not reach statistical significance. These findings suggest that liposomal bupivacaine-based LIA may improve early postoperative pain control and reduce opioid requirements, whereas the addition of tranexamic acid and flurbiprofen axetil did not provide a detectable incremental analgesic benefit.

LIA is an important component of perioperative multimodal analgesia in joint arthroplasty. It acts mainly through infiltration of local anesthetics and analgesic adjuvants into the surgical field. Compared with peripheral nerve block techniques that may cause motor blockade, LIA is not primarily intended to block

major motor nerves and may therefore be more favorable for preserving early postoperative motor function [24]. Although LIA has been evaluated as a component of multimodal analgesic protocols for THA, the magnitude and consistency of its analgesic benefit have not been definitively established, given the heterogeneous findings reported in previous studies. Previous randomized studies have reported reductions in pain during the first postoperative hours and, in some cases, lower early opioid consumption after THA [9, 25–26]. By contrast, other studies have shown that LIA provided no additional overall analgesic benefit when incorporated into an established multimodal analgesic regimen for THA [10, 27]. In the present study, both liposomal bupivacaine–based LIA and the modified cocktail regimen were associated with lower early postoperative VAS pain scores and reduced opioid consumption, expressed as MME, compared with the control intervention. These findings are broadly consistent with previous studies reporting beneficial effects of LIA and suggest that its principal clinical value may lie in improving early pain control and reducing opioid requirements after THA. Notably, most previous studies have evaluated LIA in patients undergoing elective primary THA for nontraumatic hip disorders, whereas the present study specifically enrolled older patients undergoing THA for displaced femoral neck fractures. In this vulnerable population, effective early analgesia may be particularly important for promoting postoperative mobilization while minimizing opioid exposure.

Liposomal bupivacaine uses multivesicular liposome technology to provide sustained bupivacaine release, with a proposed analgesic duration of up to 48–72 h [28]. Nevertheless, evidence regarding the analgesic efficacy of liposomal bupivacaine (LB) as part of intraoperative LIA in THA remains inconclusive. Some studies have suggested that the analgesic effect of LB-based LIA may extend for up to 48 h after surgery [12]. By contrast, Perets et al. [13] reported that the addition of LB to conventional bupivacaine periarticular infiltration conferred no additional benefit in terms of postoperative pain, opioid consumption, or early functional recovery. These discrepant findings may reflect heterogeneity in patient populations, surgical indications and techniques, background multimodal analgesic protocols, comparator interventions, infiltration formulations, and outcome assessment time points. Accordingly, the analgesic efficacy of LB-based LIA warrants specific evaluation in patients undergoing THA for displaced femoral neck fractures. In the present study, the LB group exhibited lower VAS pain scores from 6 h postoperatively through POD 2 and lower opioid consumption than the control group, suggesting that LB-based LIA may provide an early analgesic and opioid-sparing benefit relative to no LIA in this clinical setting.

Postoperative pain after THA arises from multiple pathophysiological mechanisms. In addition to peripheral nociceptor activation, surgery-induced inflammation, local bleeding, soft-tissue edema, and increased tissue tension may contribute to the development and persistence of early postoperative pain [17]. From this mechanistic perspective, incorporating multiple adjuvants into an LIA cocktail may complement the effects of local anesthetics by targeting distinct components of the postoperative pain response. Commonly used LIA formulations have included local anesthetics in combination with NSAIDs, opioids, epinephrine, or glucocorticoids. Wang et al. [25] reported that an LIA cocktail containing ropivacaine, Diprospan, and morphine reduced early postoperative resting VAS pain scores after primary THA, with the analgesic benefit persisting until the morning of POD 2. Whether the addition of

antifibrinolytic and anti-inflammatory agents to LB-based LIA can further enhance postoperative analgesia therefore remains clinically relevant. Kuchalik et al. [29] noted that, although NSAID adjuvants have a plausible mechanistic basis for local anti-inflammatory activity, their effects have not been consistently translated into measurable clinical analgesic benefits. Flurbiprofen axetil is a lipid microsphere–based prodrug that inhibits cyclooxygenase-mediated prostaglandin synthesis, and preclinical evidence supports its potential as a locally administered anti-inflammatory analgesic adjuvant [30]. In a retrospective TKA study, Wang et al. [21] reported that an LIA cocktail containing flurbiprofen axetil was associated with lower postoperative pain scores and reduced rescue analgesic requirements. Meta-analytic evidence has likewise suggested that NSAID adjuvants may improve the analgesic efficacy of LIA [8]. Although tranexamic acid has no direct analgesic effect, it may indirectly attenuate early postoperative pain by reducing perioperative bleeding, tissue edema, and local tissue tension [31–32]. Accordingly, the modified cocktail evaluated in the present study was designed to provide mechanistically complementary effects. Nevertheless, the addition of tranexamic acid and flurbiprofen axetil did not confer a statistically significant incremental analgesic benefit over LB alone.

Several factors may account for the lack of a statistically significant incremental benefit. First, the sustained analgesia provided by liposomal bupivacaine may have limited the detectable incremental effects of tranexamic acid and flurbiprofen axetil. Second, the potential analgesic effect of tranexamic acid is likely indirect and mediated through reductions in perioperative bleeding, tissue edema, and local tissue tension. However, intraoperative blood loss was comparable among the three groups, suggesting that the contribution of this pathway may have been limited. Nevertheless, intraoperative blood loss alone may not fully reflect postoperative occult blood loss or local soft-tissue swelling. Third, the optimal dose, local tissue retention, and clinical efficacy of flurbiprofen axetil as an NSAID adjuvant for periarticular infiltration in THA remain uncertain. Moreover, because local inflammatory mediators, tissue and plasma drug concentrations, and pharmacokinetic parameters were not assessed, the proposed local anti-inflammatory and analgesic mechanisms could not be directly verified. Finally, under the standardized multimodal analgesic protocol used in this study, postoperative pain intensity was generally mild to moderate, raising the possibility of a floor effect that may have limited the ability to detect small additional differences between the two active-treatment groups [33].

No between-group differences were observed in pain, sleep quality, health-related quality of life, or hip function at 3 or 6 months, indicating that the early analgesic benefits of LIA did not translate into detectable intermediate-term improvements. This pattern is consistent with the pharmacological profile of single-shot LIA and with previous studies showing that its benefits after THA are largely confined to the early postoperative period [25–26].

Postoperative complication rates were comparable among the three groups, and no serious adverse events attributable to local anesthetic use were observed. No deep vein thrombosis or pulmonary embolism occurred after local tranexamic acid administration under standardized thromboprophylaxis. Nevertheless, the sample size was insufficient to draw definitive conclusions regarding uncommon or rare adverse events.

This study has several limitations. First, it was conducted at a single center with a relatively modest sample size, which may have limited its ability to detect small but potentially clinically meaningful differences between the cocktail and LB groups and to reliably assess uncommon adverse events. Second, because the operating surgeon was required to administer or withhold LIA according to group allocation, surgeon blinding was not feasible. In addition, the control group did not undergo saline placebo infiltration for ethical and practical reasons. Consequently, potential performance bias, procedural effects related to tissue infiltration, and placebo effects cannot be entirely excluded. Third, the absence of a conventional bupivacaine- or ropivacaine-based LIA comparator precluded assessment of whether liposomal bupivacaine provides superior analgesic efficacy or cost-effectiveness relative to standard local anesthetics. Fourth, postoperative inflammatory biomarkers, local tissue and plasma drug concentrations, and objective measures of postoperative bleeding and soft-tissue edema were not assessed. Therefore, the respective mechanistic contributions of tranexamic acid and flurbiprofen axetil could not be directly determined. Larger multicenter trials incorporating conventional local anesthetic comparators, mechanistic assessments, and cost-effectiveness analyses are warranted.

Conclusions

In patients undergoing THA for displaced femoral neck fractures, liposomal bupivacaine–based LIA reduced resting and movement VAS pain scores from 6 h postoperatively through POD 2 and decreased opioid consumption. Adding tranexamic acid and flurbiprofen axetil produced modest numerical advantages in several outcomes but no statistically significant incremental analgesic benefit. The modified cocktail should therefore be considered an exploratory LIA regimen pending further evaluation of its safety, cost-effectiveness, and optimal target population in larger multicenter studies.

Abbreviations

ANOVA

analysis of variance

ASA

American Society of Anesthesiologists

BMI

body mass index

HHS

Harris Hip Score

LB

liposomal bupivacaine

LIA

local infiltration analgesia

MCS

mental component summary

MME

morphine milligram equivalent
NSAID
nonsteroidal anti-inflammatory drug
PCS
physical component summary
POD
postoperative day
PONV
postoperative nausea and vomiting
PSQI
Pittsburgh Sleep Quality Index
SD
standard deviation
SF-12
12-Item Short Form Health Survey
THA
total hip arthroplasty
VAS
visual analog scale.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Leshan People's Hospital (approval No. LYLL[2025]KY101). Written informed consent was obtained from all participants or their legal representatives before enrollment. All procedures involving human participants were performed in accordance with the relevant institutional and national guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

XQ and YW conceived and designed the study. XQ coordinated the study, reviewed the literature, participated in data collection and analysis, and drafted the manuscript. QH and ZW contributed to patient recruitment, clinical implementation, and perioperative data collection. YL and JZ contributed to outcome assessment, follow-up, and data curation. YR and MJ contributed to statistical analysis, interpretation of the results, and critical revision of the manuscript. YW supervised the study, contributed to the interpretation of the findings, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Data Availability

The datasets generated and analyzed during the current study are not publicly available because the informed consent obtained from the participants did not include permission for public data sharing, and the datasets contain potentially identifiable clinical information. Access to de-identified data may be considered upon reasonable request to the corresponding author, subject to approval by the institutional ethics committee and applicable data-protection requirements.

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Figures

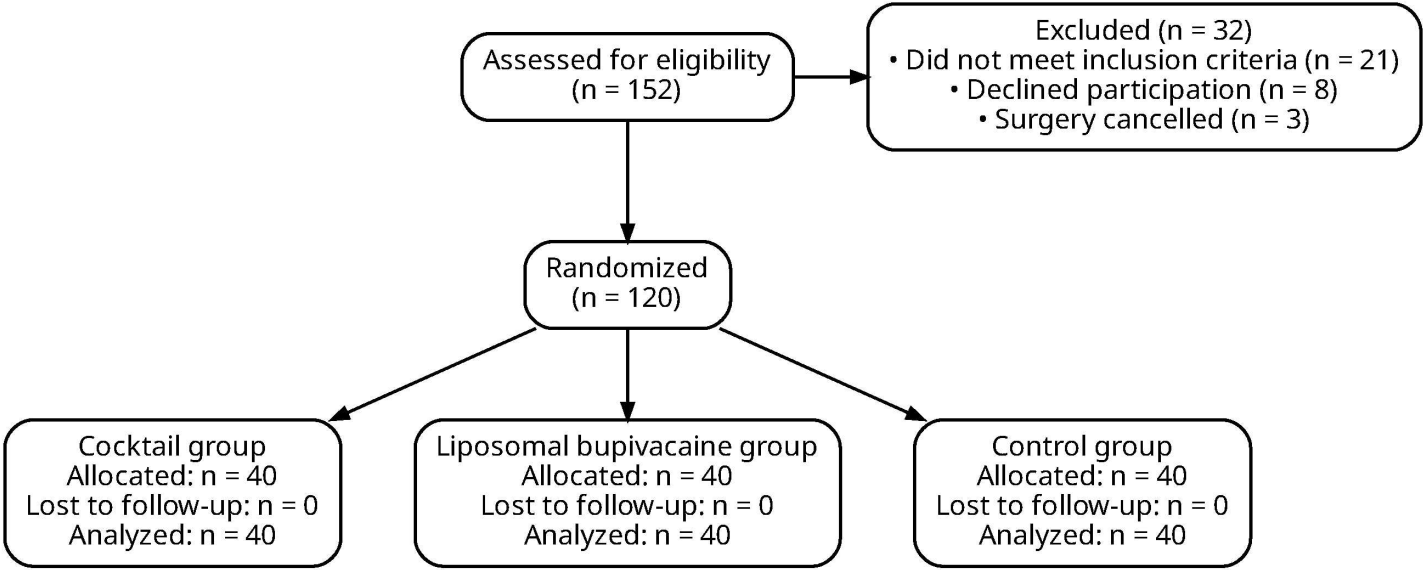


Figure 1

CONSORT flow diagram showing participant screening, randomization, follow-up, and analysis.