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CLINICAL TRIAL REPORT

Efficacy and Safety Comparison of Ulinastatin Versus Flurbiprofen Axetil for Preemptive Analgesia in Reducing Opioid Burden After Total Knee Arthroplasty: A Randomized Controlled Trial

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Background: Total knee arthroplasty (TKA) poses a significant challenge for acute pain. Opioid-based analgesia carries substantial risks, whereas non-steroidal anti-inflammatory drugs (NSAIDs) have adverse effects and ceiling effects. Ulinastatin may be a novel treatment option with improved efficacy and safety.

Purpose: To compare the efficacy and safety of single preoperative administration of ulinastatin (UTI), flurbiprofen axetil (FA), and control (saline) in reducing opioid consumption and adverse events in TKA.

Patients and Methods: In this prospective, double-blind, placebo-controlled trial, 150 TKA patients were randomized to receive intravenous UTI (30 IU), FA (100 mg), or saline 15 minutes before skin incision. Standardized postoperative analgesia utilizes patient-controlled intravenous analgesia (PCIA) to maintain visual analog scale (VAS) scores ≤30 mm. The primary outcome was cumulative morphine consumption within 72 h postoperatively, while the secondary outcomes included adverse reactions and inflammatory factor levels (IL-6 and IL-10).

Results: The final analysis included 149 patients. Median 72-hour morphine consumption was significantly lower with UTI (29.00 [22.50–33.50] mg) than with FA (40.00 [27.50–60.50] mg) and the control (54.40 [46.40–82.80] mg, $P < 0.001$). VAS scores showed no intergroup differences ($P > 0.05$). UTI reduced total adverse reactions (24.5%) versus FA (48.0%, $P = 0.015$) and control (52.0%, $P = 0.005$), specifically lowering vomiting (4.1 vs 20.0%), gastrointestinal discomfort (6.1 vs 26.0%), and delirium (4.1 vs 30.0%). UTI suppressed IL-6 and IL-10 elevation better than control (ΔIL-6:0.00 vs 1.63 pg/mL, $P = 0.003$; ΔIL-10:2.20 vs 19.92 pg/mL, $P < 0.001$).

Conclusion: Single preoperative UTI significantly reduced postoperative morphine consumption (~48%) and adverse reaction risks compared with FA and control by modulating the balance of proinflammatory and anti-inflammatory factors (IL-6 and IL-10). UTI provides an efficient and safe alternative, supporting its inclusion in enhanced recovery after surgery (ERAS) analgesia strategies.

Keywords: acute postoperative pain, preemptive analgesia, opioid-sparing, enhanced recovery after surgery

Introduction

Total knee arthroplasty (TKA) remains effective for end-stage knee osteoarthritis; however, its growing surgical volume and healthcare burden, driven by aging populations, pose significant challenges. Organization for Economic Co-operation and Development (OECD) data showed a 35% increase in knee arthroplasty rates from 2,009–2,019.[1] However, this growth has posed significant challenges, with postoperative acute pain a key barrier to rehabilitation: 72% of patients experience moderate to severe postoperative pain,[2] restricting functional exercise and prolonging hospital stays. This type

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of pain originates from systemic inflammation triggered by surgical trauma and prosthesis implantation, with the proinflammatory factor IL-6 significantly increasing within 24 h postoperatively to drive peripheral and central sensitization, thereby establishing persistence.[3]

Opioid-based patient-controlled intravenous analgesia (PCIA) remains a prevalent choice for postoperative analgesia but presents a dual dilemma: short-term adverse reactions (26% incidence of nausea/vomiting, 1.5% respiratory depression) extend hospital stays by 55%, increase nursing costs by 47%, and raise 30-day readmission rates by 36%;[4–7] long-term risks include 13% of patients developing opioid dependence within one year.[8] Consequently, current guidelines emphasize limiting opioid use while optimizing non-opioid adjuvant regimens.[9]

Non-steroidal anti-inflammatory drugs (NSAIDs) are common non-opioid drug options. Flurbiprofen axetil (FA) has a better analgesic effect than traditional NSAIDs due to its lipid microsphere carrier characteristics.[10] However, its clinical application is constrained by dose-related adverse reactions, commonly including gastric mucosal injury, nephrotoxicity, and cardiovascular event risks, particularly requiring caution in elderly patients.[11–15] Therefore, developing a novel prophylactic analgesic regimen that targets the inflammatory pain mechanism of TKA with high efficacy and low risk has become an urgent need to improve postoperative outcomes.

Ulinastatin (UTI), a broad-spectrum protease inhibitor, exhibits multitarget analgesic potential. Basic research shows that UTI inhibits neutrophil elastase and proinflammatory factors (TNF-α, IL-6) and alleviates neuroinflammation;[16–18] in nerve injury models, UTI downregulates calcineurin expression, promoting anti-inflammatory factor IL-10 production;[19] it also inhibits neuron and microglia activation to reduce hyperalgesia.[20] However, UTI's analgesic efficacy and safety in TKA lack validation from high-quality clinical randomized controlled trials (RCTs).

Therefore, this study hypothesized that the preoperative administration of UTI or FA can reduce morphine consumption after TKA (with an expected reduction of ≥30%) and related adverse reactions. Objectives include quantifying the differences in 72-hour morphine consumption between UTI, FA, and placebo controls, evaluating intergroup differences in postoperative adverse reactions, and analyzing UTI's potential anti-inflammatory analgesic mechanism by detecting inflammatory factors (IL-6) and anti-inflammatory factors (IL-10).

Methods

Study Design and Ethics

There was a single-center, double-blind, parallel, and placebo-controlled trial. This study strictly adhered to the ethical standards of the World Medical Association Declaration of Helsinki and relevant guidelines for human research, with all research procedures complying with ethical requirements. It was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (KYLL-2025-030) and was prospectively registered (ChiCTR2500096907). This report adhered to the SPIRIT and CONSORT guidelines.

Participants

This study was conducted at the First Hospital of Shanxi Medical University from February to May 2025. All the patients signed an informed consent form. Patients who met the eligibility criteria, aged 40 to 85 years, and planned for unilateral TKA were screened in accordance with the study's inclusion/exclusion criteria, as detailed in Supplement 1.

Randomization and Blinding

Independent statistician generated block randomization sequence (block size = 6; SAS 9.4) with a 1:1:1 allocation ratio. Group assignments were sealed in opaque envelopes. An independent pharmacy team, which was not involved in the clinical care, patient recruitment, or data analysis, prepared, packaged, and labeled all trial drugs. To robustly prevent differentiation based on the inherent color differences between UTI, FA, and placebo, all solutions were transferred into identical 20 mL syringes. Each syringe was then sealed and wrapped with opaque foil and labeled only with the patient ID and trial number to ensure that the appearance of each drug is consistent. This multi-layer blinding method ensured that anesthesiologists, patients, pain assessors, and data analysts were all successfully blinded to the group assignments throughout the trial.

Interventions and Standardized Protocols

Participants received one of three intravenous infusions via micro-pump 15 min before skin incision.

1. Ulinastatin (UTI) group: 30 IU ulinastatin injection (Tianpu Luoan, Techpool, Guangdong, China) was diluted to 20 mL with normal saline (NS).
2. Flurbiprofen axetil (FA) group: 100 mg flurbiprofen axetil (Kaifen®, TIDE, Beijing, China) diluted in 20 mL NS.
3. Control group: 20 mL NS.

To minimize confounders, no analgesics, high-dose steroids, or regional nerve blocks were administered to any participant before incision. All TKAs were performed via a standardized medial parapatellar approach. Implant selection and placement strictly adhered to institutional enhanced recovery after Surgery (ERAS) protocols and the manufacturer's technical specifications. Intraoperatively, all patients received periarticular cocktail injections containing 0.2% ropivacaine, 2.0 μg/mL adrenaline, and 0.1 mg/mL dexamethasone. Spinal anesthesia is the preferred anesthesia plan, with 0.5% ropivacaine at a dose of 10–15 mg. For patients with contraindications to spinal anesthesia, general anesthesia was permitted under a standardized regimen: propofol TCI (target BIS 40–60), sufentanil 30 μg for induction, and remifentanil at 0.1 μg/kg/min for maintenance. Additionally, no perioperative analgesics beyond this protocol were permitted. All patients received 4 mg of intravenous ondansetron postoperatively as antiemetic prophylaxis.

Postoperative Pain Management

All participants received a patient-controlled analgesia (PCIA) pump: morphine 120 mg diluted to 120 mL NS (concentration 1 mg/mL, background dose 0.2 mL/h, bolus dose 2.0 mL, and lockout 15 minutes). Patients were provided access to PCIA for up to 72 h postoperatively, with standardized use mandated for the initial 48 h to align with the nursing protocols. After 48 h, continued use was permitted based on individual analgesic requirements until the 72-hour endpoint. To optimize analgesia, patients received education on self-assessment of pain and PCIA utilization, targeting a resting visual analogue scale (VAS) score of ≤30 mm. For nausea/vomiting, intravenous ondansetron 1–2 mg or droperidol 1 mg was permitted. No other analgesics or glucocorticoids were allowed. Follow-ups were conducted at 24, 48, and 72 hours postoperatively.

Data Collection and Outcome Measures

- **Baseline Data**: Demographics, comorbidities, and surgical details were extracted from the medical records and operative reports.
- **Pain Assessment**: Resting VAS (0–100 mm) was evaluated at 24, 48, and 72 h postoperatively, and dynamic VAS (walking 5 m) at 72 h.
- **Morphine Consumption**: Cumulative usage at 24, 48, and 72 h was recorded. Missing data were imputed using the last observation carried forward.
- **Adverse Events**: Nausea, vomiting, fever, anorexia, gastrointestinal discomfort, and delirium were recorded within 0–72 h via patient reporting and medical observation.
- **Inflammatory Markers**: Venous blood samples (5 mL each) were collected at two time points: preoperatively (30 minutes before anesthesia induction) and immediately postoperatively (30 minutes after skin closure). All samples were centrifuged at 3000 rpm for 20 minutes, and the separated serum was stored at −80°C until subsequent analysis. IL-6 and IL-10 levels were detected by the Tianjin Marvelbio Medical Laboratory (using chemiluminescence immunoassay). The limits of detection (LOD) of IL-6 were 1.5 pg/mL, and IL-10 were 1.0 pg/mL. Difference values (ΔIL-6, ΔIL-10) were calculated as the postoperative minus the preoperative levels.

Statistical Analysis

Sample Size

Reference data showed placebo group consumption of 89.55 ± 42.09 mg morphine equivalents, FA group 71.54 ± 35.70 mg,[21] and an estimated 30% reduction with UTI based on a pilot study. Using PASS 2020, the sample size was calculated as 43 per group (with 20% dropout) at α=0.05 (two-sided) and β=0.20, leading to 50 participants per group (n=150).

Data Analyses

Data Were Analyzed Using IBM SPSS 26

1. **Continuous Data**: Normality was tested via the Shapiro–Wilk test. For normally distributed data with homogeneous variance, they were presented as mean ± standard deviation (SD) and analyzed using Analysis of Variance (ANOVA) for overall intergroup comparisons. For non-normally distributed data, they were presented as median [interquartile range (IQR)]; overall intergroup comparisons were performed using the Kruskal–Wallis test, while pairwise comparisons were conducted using the Mann–Whitney U-test. For all pairwise comparisons (whether for normally or non-normally distributed data), *Bonferroni* correction was applied to account for multiple comparisons, with the adjusted significance level set at $\alpha = 0.05/3 = 0.017$.
2. **Categorical Data**: Expressed as counts (frequency), intergroup comparisons were primarily performed using the chi-square test. The Fisher's exact test was applied instead of the chi-square test when the expected cell frequency of any group was <5. All P-values for pairwise comparisons were adjusted using the Bonferroni correction (α=0.05/3=0.017).
3. **Repeated Measures**: Repeated measurement data were derived from the morphine consumption in each independent time period (0–24 h, 24–48 h, 48–72 h). Normality tests using the Shapiro–Wilk procedure demonstrated that the data deviated from a normal distribution (all $P < 0.05$). Consequently, Generalized Estimating Equations (GEE) were employed instead of repeated-measures ANOVA to assess the main effects of group (Group) and time point (Time), as well as their interaction effect, on the dependent variable (morphine consumption). The Waldkar x^2 was adopted for the model effect test.
4. **Paired continuous variables**: The Wilcoxon signed-rank test was used to analyze the differences in the preoperative and postoperative levels of inflammatory factors.
5. **Missing Data**: Imputed via multiple imputations (< 5% missing) or case-wise deletions (≥ 5%). Data were double-entered and 10% of the samples were randomly verified for quality control.

Results

Participant Flow

After detailed eligibility screening, 150 participants were enrolled in the trial. One patient was excluded from the final analysis because they met the exclusion criteria identified after randomization, resulting in a primary analysis population of 149 patients: the UTI group (n = 49, 32.9%), FA group (n = 50, 33.6%), and control group (n = 50, 33.6%) (Figure 1). Follow-up rates were 99.3% (149/150) at 48 hours and 95.3% (143/150) at 72 hours, with three patients terminating early due to vomiting and three discharged early.

Baseline Characteristics

The baseline demographics, comorbidities, and surgical characteristics were comparable across the groups (all $P > 0.05$) (Table 1). Notably, the FA group had a higher proportion of stroke history than the control group (20.0 vs 2.0%, $P = 0.02$), which did not affect the primary outcome analysis.

Primary Outcome: Cumulative Postoperative Morphine Consumption

Under standardized pain management (resting VAS ≤ 30), no significant differences were observed in resting VAS at 24/48/72 hours or dynamic VAS at 72 h among the groups (all $P > 0.05$) (Table S1). Cumulative morphine consumption at 72 hours was significantly lower in the UTI group than in the FA and control groups ($P < 0.001$), with medians (IQR) of 29.00

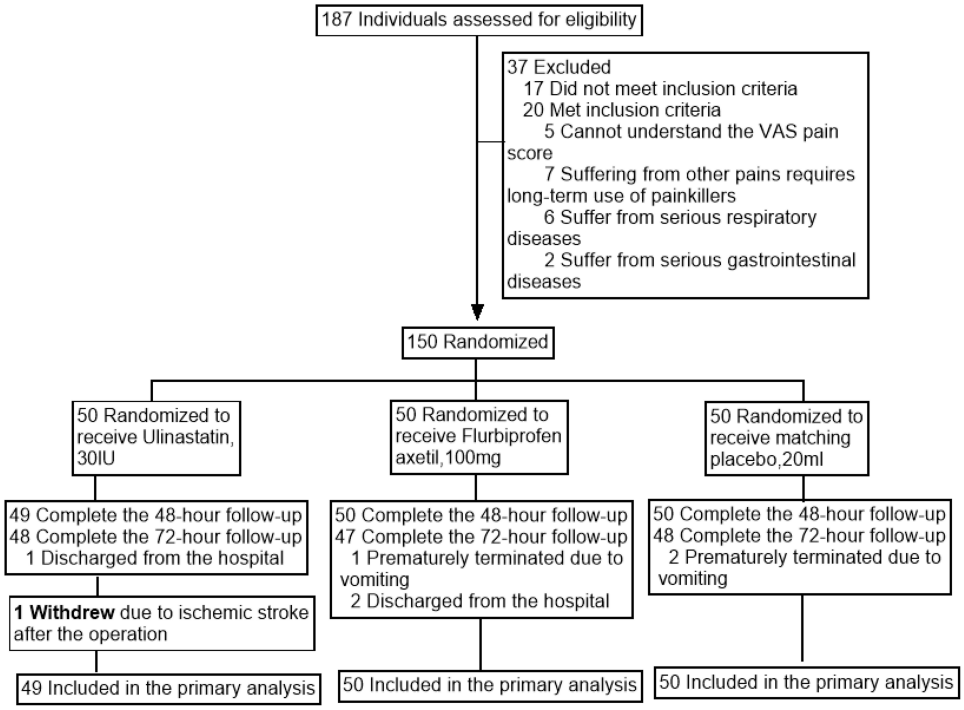

Figure 1 Patient flowchart.Flowchart showing the enrollment, exclusion, and grouping process of patients in this study.

(22.50–33.50) mg, 40.00 (27.50–60.50) mg, and 54.40 (46.40–82.80) mg, respectively. Pairwise comparisons showed lower consumption in the UTI group than in the FA and control groups at all time points (all $P < 0.01$): At 72 hours, UTI reduced consumption by 14.31 mg (95% CI: −21.86 ~ −6.77; $P = 0.001$) vs FA and 33.23 mg (95% CI: −41.30 ~ −25.16; $P < 0.001$) vs Control; FA reduced consumption by 18.92 mg (95% CI: −28.66 ~ −9.17; $P < 0.001$) vs control (Table 2 and Figure 2).

Table 1 Baseline Characteristics

	UTI Group	FA Group	Control Group	*P*-value
Demographics				
Case, n (%)	49 (32.9)	50 (33.6)	50 (33.6)	
Age, mean ± SD, years	70.08 ± 8.06	69.32 ± 8.27	67.40 ± 5.43	*0.178*
Sex, n (%)				
Male	18 (36.7)	22 (44.0)	15 (30.0)	*0.349*
Female	31 (63.3)	28 (56.0)	35 (70.0)	
ASA score, n (%)				
2	38 (77.6)	34 (68.0)	36 (72.0)	*0.565*
3	11 (22.4)	16 (32.0)	14 (28.0)	
Height, median (IQR), m	1.60 (1.56, 1.68)	1.62 (1.58, 1.71)	1.60 (1.55, 1.69)	*0.400*
Weight, mean ± SD, kg	67.37 ± 10.75	65.77 ± 9.72	66.67 ± 9.99	*0.738*
BMI, mean ± SD, kg/m^2	25.42 ± 2.82	24.67 ± 3.51	25.68 ± 2.78	*0.231*
Medical History				
Hypertension, n (%)	19 (38.8)	26 (52.0)	23 (46.0)	*0.417*
Diabetes, n (%)	7 (14.3)	11 (22.0)	9 (18.0)	*0.609*
Stroke, n (%)	6 (12.2)	10 (20.0)	1 (2.0)	*0.018*
Coronary artery disease, n (%)	7 (14.3)	7 (14.0)	2 (4.0)	*0.168*

(*Continued*)

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Table 1 (Continued).

	UTI Group	FA Group	Control Group	*P*-value
Surgery Characteristics				
Anesthesia method, n (%)				
Spinal anesthesia	24 (49.0)	24 (48.0)	32 (64.0)	*0.199*
General anesthesia	25 (51.0)	26 (52.0)	18 (36.0)	
Surgery duration, mean ± SD, min	99.14 ± 24.98	102.14 ± 31.82	90.32 ± 19.42	*0.064*
Blood loss, median (IQR), mL	50 (50, 100)	80 (50, 100)	87.5 (50, 100)	*0.066*
Preoperative resting pain, median (IQR), VAS (mm)	20 (10, 20)	20 (20, 30)	20 (20, 20)	*0.096*

Notes: Continuous data are presented as Mean ± SD for normally distributed variables or Median (IQR) for non-normally distributed variables, with normality determined by the *Shapiro–Wilk* test. Categorical data are presented as n (%). For intergroup comparisons, *one-way Analysis of Variance (ANOVA)* was used to analyze normally distributed continuous data with homogeneous variance; the *Kruskal–Wallis* test was applied to non-normally distributed continuous data; and categorical data were compared using the *chi-square* test for general use or *Fisher's* exact test when more than 20% of expected cell counts were less than 5.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index = Weight(kg)/Height(m)^2; SD, Standard Deviation; IQR, Interquartile Range; VAS, Visual Analogue Scale.

Generalized Estimating Equations (GEE) analysis indicated good model fit (QIC = 37,862.895, QICC = 37,862.958). Significant effects were found for Time, Group, and Time × Group interaction (Wald χ^2 = 107.25, 73.05, and 12.81, respectively; all P < 0.05), suggesting differing declining trends among groups. Intra-group comparisons revealed declining consumption in all groups postoperatively. The UTI group showed significantly lower consumption only at 48–72h compared to earlier periods (P < 0.001), whereas the FA and control groups showed significant reductions at all intervals (P < 0.05). Inter-group comparisons showed that at 0–24h and 48–72h, the UTI group had lower consumption than the FA and control groups, and the FA group was lower than the control (all P < 0.05). At 24–48h, the UTI group remained lower than the other two groups (P < 0.001), but no significant difference was found between the FA and control groups (P = 0.116) (Table 3).

Secondary Outcomes

Adverse Events

The overall incidence of adverse events within 72 h was significantly lower in the UTI group (24.5%) than in the FA (48.0%, *P* = 0.015) and control (52.0%, *P* = 0.005) groups (Table 4). Specifically, UTI reduced morphine-related adverse events vs control: vomiting (4.1 vs 20.0%, *P* = 0.015) and nausea (12.2 vs 28.0%, *P* = 0.051). FA showed no significant differences compared to the control (all *P* > 0.017) but numerically higher rates than UTI. Gastrointestinal symptoms: anorexia (UTI 8.2 vs control 26.0%, *P* = 0.031; FA 8.0 vs control 26.0%, *P* = 0.017), gastrointestinal discomfort (UTI 6.1 vs control 26.0%, *P* = 0.007). Delirium: UTI (4.1%) < FA (18.0%, *P* = 0.028) < control (30.0%, *P* = 0.001).

Inflammatory Factor Levels

IL-6: Preoperative and postoperative levels were similar between groups (*P* > 0.05). Postoperatively, only the control group showed increased IL-6 levels (*ΔIL-6* median 1.63 pg/mL, *P* = 0.033), whereas UTI and FA showed no significant changes (*P* > 0.05). Group differences in *ΔIL-6* were significant (*P* = 0.013), with UTI (0.00 [−3.35,0.83] pg/mL) being significantly lower than the control (1.63 [−0.51~7.44] pg/mL, *P* = 0.003) (Table 5 and Figure 3).

IL-10: Postoperative levels differed significantly (*P* < 0.001), with all groups showing increased IL-10 levels compared to baseline (*P* < 0.001). *ΔIL-10* was highest in the control group (19.92 [3.82,67.33] pg/mL), significantly higher than UTI (2.20 pg/mL, *P* < 0.001) and FA (3.07 pg/mL, *P* < 0.001). UTI inhibited IL-10 elevation better than the control but did not differ from FA (*P* = 0.722) (Table 6 and Figure 3).

Discussion

This prospective, double-blind, placebo-controlled trial provides the first head-to-head comparison of single pre-incisional ulinastatin (UTI, 30 IU) and flurbiprofen axetil (FA, 100 mg) for postoperative analgesia in patients undergoing

Table 2 Comparison of Postoperative Morphine Consumption

Time	UTI Group (n = 49) Median (IQR), mg	FA Group (n = 50) Median (IQR), mg	Control Group (n = 50) Median (IQR), mg	*Overall p*-value (Kruskal–Wallis test)	UTI vs FA Mean Diff (95% CI), *p*-value (Bonferroni-Adjusted)	UTI vs Control Mean Diff (95% CI), *p*-value (Bonferroni-Adjusted)	FA vs Control Mean Diff (95% CI), *p*-value (Bonferroni-adjusted)
72-h [a]	29.00 (22.50, 33.50)	40.00 (27.50, 60.50)	54.40 (46.40, 82.80)	*<0.001*	−14.31 (−21.86, −6.77), *0.001*	−33.23 (−41.30, −25.16), *<0.001*	−18.92 (−28.66, −9.17), *<0.001*
48-h	24.00 (20.00, 30.00)	31.00 (20.60, 50.00)	47.20 (33.60, 54.80)	*<0.001*	−10.27 (−15.61, −4.94), *0.003*	−22.71 (−28.46, −16.96), *<0.001*	−12.44 (−19.52, −5.35), *0.001*
24-h	12.00 (9.00, 17.00)	20.00 (12.00, 26.50)	25.60 (21.40, 31.20)	*<0.001*	−7.94 (−11.68, −4.20), *<0.001*	−13.79 (−17.01, −10.57), *<0.001*	−5.84 (−10.16, −1.52), *0.001*

Notes: a: 6 cases were lost to follow-up in the 72-hour data (3 cases due to vomiting and 3 cases due to early discharge), and the last observation carried forward (LOCF) method was used to impute missing values. The data shows a non-normal distribution and is represented by the Median (IQR). The *Kruskal–Wallis* test was used for overall comparison between groups, and the *Mann–Whitney U*-test was used for pairwise comparison. The mean difference and 95% CI between groups were reported. After *Bonferroni* correction (corrected α=0.05/3=0.017), P≤0.017 was considered statistically significant.

Abbreviations: IQR, interquartile range; CI: Confidence Interval.

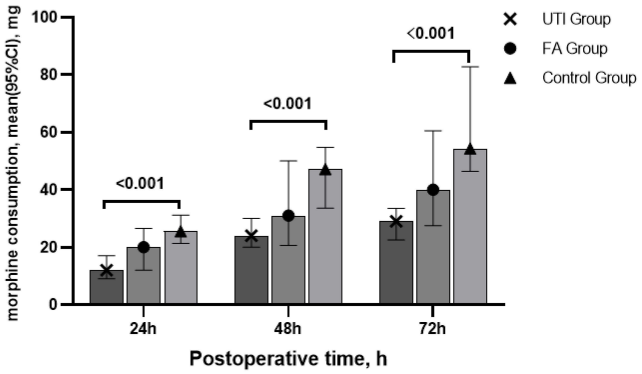


Figure 2 Postoperative morphine consumption in three groups. Values are expressed as medians (middle line in the box) with the 25th–75th percentiles (capped lines). The differences among the three groups in each period have been presented. The *P* values are on the horizontal line, and *P* <0.05 is statistically significant.

TKA. Key findings demonstrated that under standardized VAS-targeted PCIA, UTI significantly reduced 72-hour cumulative morphine consumption compared to FA and control (median 29.00 vs 40.00 vs 54.40 mg, $P < 0.001$), and the overall incidence of adverse reactions was the lowest (24.5 vs 48.0%, $P = 0.015$; vs control 52.0%, $P = 0.005$). Compared with the control group, the UTI group particularly excelled in reducing vomiting (4.1 vs 20.0%, $P = 0.015$), gastrointestinal discomfort (6.1 vs 26.0%, $P = 0.007$), and delirium (4.1 vs 30.0%, $P = 0.001$).

Table 3 Comparison of Morphine Consumption Among Three Groups at Different Postoperative Time Points by Generalized Estimating Equations (GEE) (Mg)

Group	Time	Mean ± SD	Mean Diff (95% CI), *p*-value	Mean Diff (95% CI), *p*-value
UTI	0-24h	13.76 ± 0.83	*Ref.*	–
	24-48h	11.81 ± 0.76	1.96 (−0.19, 4.10), *0.074*	*Ref.*
	48-72h	6.16 ± 1.08	7.60 (5.03, 10.17), *<0.001*	5.64 (3.54, 7.75), *<0.001*
FA	0-24h	21.71 ± 1.66	*Ref.*	–
	24-48h	14.14 ± 1.27	7.57 (4.14, 11.00), *<0.001*	*Ref.*
	48-72h	10.20 ± 1.45	11.50 (7.55, 15.46), *<0.001*	3.93 (1.54, 6.32), *0.001*
Control	0-24h	27.55 ± 1.37	*Ref.*	–
	24-48h	20.73 ± 1.46	6.82 (4.65, 8.98), *<0.001*	*Ref.*
	48-72h	16.68 ± 1.52	10.87 (7.71, 14.02), *<0.001*	4.05 (1.06, 7.04), *0.008*
UTI	0-24h	–	13.79 (10.65, 16.93), *<0.001*	7.94 (4.30, 11.58), *<0.001*
FA		–	5.84 (1.62, 10.06), *0.007*	*Ref.*
Control		–	*Ref.*	–
UTI	24-48h	–	8.92 (5.70, 12.15), *<0.001*	2.33 (−0.57, 5.23), *0.116*
FA		–	6.59 (2.80, 10.38), *0.001*	*Ref.*
Control		–	*Ref.*	–
UTI	48-72h	–	10.52 (6.86, 14.18), *<0.001*	4.04 (0.49, 7.59), *0.026*
FA		–	6.48 (2.36, 10.60), *0.002*	*Ref.*
Control		–	*Ref.*	–

(*Continued*)

Table 3 (Continued).

Group	Time	Mean ± SD	Mean Diff (95% CI), *p*-value	Mean Diff (95% CI), *p*-value
Effect				
Time	*Wald* x^2 = 107.25, *P <0.001*			
Group	*Wald* x^2 = 73.05, *P <0.001*			
Group×Time	*Wald* x^2 = 12.81, *P =0.012*			

Notes: The table presents the time effect, between-group effect, and interaction effect on morphine consumption, as well as the results of post-hoc pairwise comparisons across different time periods. Model goodness of fit: QIC = 37,862.895, QICC = 37,862.958. A smaller value indicates a good model fit. A *P*-value < 0.05 was considered statistically significant.
Abbreviations: SD, Standard Deviation; CI, Confidence Interval; Ref, Reference Value.

Table 4 Pairwise Comparison of Adverse Events After Surgery

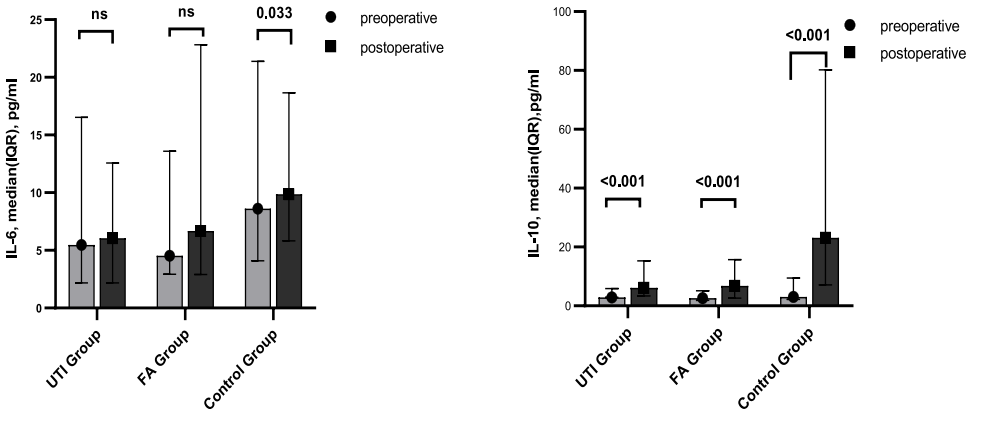
	UTI vs FA Group	UTI vs Control Group	FA vs Control Group
Adverse events,0–72 h postoperatively, n (%)	12 (24.5) vs 24 (48.0)	12 (24.5) vs 26 (52.0)	24 (48.0) vs 26 (52.0)
P-value	***0.015***	***0.005***	*0.689*
Nausea, n (%)	6 (12.2) vs 12 (24.0)	6 (12.2) vs 14 (28.0)	12 (24.0) vs 14 (28.0)
P-value	*0.129*	*0.051*	*0.648*
Vomiting, n (%)	2 (4.1) vs 5 (10.0)	2 (4.1) vs 10 (20.0)	5 (10.0) vs 10 (20.0)
P-value	*0.436* [a]	***0.015***	*0.161*
Fever, n (%)	3 (6.1) vs 5 (10.0)	3 (6.1) vs 6 (12.0)	5 (10.0) vs 6 (12.0)
P-value	*0.715* [a]	*0.487* [a]	*0.749*
Postoperative anorexia, n (%)	4 (8.2) vs 4 (8.0)	4 (8.2) vs 13 (26.0)	4 (8.0) vs 13 (26.0)
P-value	*1.00* [a]	*0.031*	*0.017*
Gastrointestinal discomfort, n (%)	3 (6.1) vs 4(8.0)	3 (6.1) vs 13 (26.0)	4 (8.0) vs 13 (26.0)
P-value	*1.00* [a]	***0.007***	*0.017*
Postoperative delirium, n (%)	2 (4.1) vs 9 (18.0)	2 (4.1) vs 15 (30.0)	9 (18.0) vs 15 (30.0)
P-value	*0.028*	***0.001***	*0.160*

Notes: a: *Fisher's* exact test was used (expected cell frequency < 5), and the *chi-square* test was used for the remaining indicators (eg, Vomiting in UTI vs FA group, n =2 vs 5).Data are presented as number of occurrences (percentage) [n (%)]; Inter-group comparisons were conducted using the *chi-square* test or *Fisher's* exact test (marked with item "a"), and were corrected by *Bonferroni* (corrected α=0.05/3=0.017). A P value ≤0.017 was considered statistically significant. In the table, the p value is highlighted in black to indicate its significance.

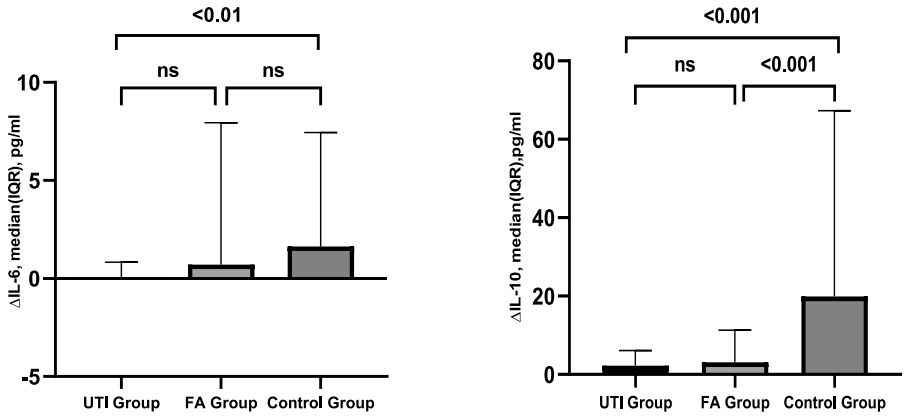
Table 5 Comparison of the Differences in IL-6

	UTI Group (n = 43)	FA Group (n = 42)	Control Group (n = 48)	*P*-value
IL-6 at preoperative, median (IQR), pg/mL[a]	5.47 (2.18, 16.54)	4.54 (2.92, 13.60)	8.62 (4.10, 21.39)	*0.395*
IL-6 at postoperative, median (IQR), pg/mL[a]	6.05 (2.90, 12.58)	6.67 (2.90, 22.82)	9.86 (5.82, 18.65)	*0.221*
Preoperative vs Postoperative, *P*-value[a]	*0.154*	*0.296*	*0.033*	
Δ**IL-6**, median (IQR), pg/mL[b]	0.00 (−3.35, 0.83)	0.70 (−1.42, 7.94)	1.63 (−0.51, 7.44)	*0.013*
Compared with FA group, mean (95% CI), pg/mL	−3.71 (−11.78, 4.37)	–	–	
P value[c]	*0.064*			
Compared with Control group, mean (95% CI), pg/mL	−15.56 (−29.20, −1.92)	−11.86 (−26.88, 3.17)	–	
P value[c]	*0.003*	*0.393*		

Notes: UTI group (n = 43, 4 samples excluded due to hemolysis, 2 samples excluded due to the values <1.00); FA group (n = 42, 3 samples excluded due to hemolysis, 5 samples excluded due to the values <1.00); Control group (n = 48, 2 samples excluded due to hemolysis). The samples excluded due to technical issues are non-systematic and random, and the *chi-square* test shows no significant difference in their distribution across all three groups (χ^2 = 3.929, *p* = 0.140). a. The *Wilcoxon signed-rank* test was used to analyze the differences in the preoperative and postoperative levels of IL-6. b. ΔIL-6 = Postoperative IL-6 level - Preoperative IL-6 level (pg/mL). c. *The Mann–Whitney U*-test was used for intergroup comparisons of ΔIL-6;*Bonferroni* correction was applied (adjusted α = 0.05/3 = 0.017 for multiple tests).



(a) IL-6 in different groups. (b) IL-10 in different groups.



(c) ΔIL-6 in different groups. (d) ΔIL-10 in different groups.

Figure 3 Comparison of IL-6 and IL-10 levels among the three groups.(**a**) Bar chart: Comparison of IL-6 levels before and after surgery in the UTI Group, FA Group, and Control Group; (**b**) Bar chart: Comparison of IL-10 levels before and after surgery in the three groups; (**c**) Bar chart: Comparison of ΔIL-6 levels (Postoperative – Preoperative) among the three groups; (**d**) Bar chart: Comparison of ΔIL-10 levels (Postoperative – Preoperative) among the three groups.

Notes: Subfigures are arranged in a 2×2 layout: (**a**) top-left, (**b**) top-right, (**c**) bottom-left, (**d**) bottom-right.In (**a**) and (**b**), data are presented as median + 25%–75% percentiles (interquartile range, IQR). The P-values labeled above each group (eg, 0.033, <0.001) represent the statistical differences in IL-6/IL-10 levels between preoperative and postoperative time points within the same group, with results of pre- vs post-operation comparisons labeled above the corresponding group.In (**c**) and (**d**), data are presented as median + IQR, and the bar chart of each group corresponds to "the difference in inflammatory factor levels (ΔIL-6/ΔIL-10) between preoperative and postoperative periods within that group". The P-values labeled above each group (eg, <0.01, <0.001) indicate the statistical significance of differences in ΔIL-6 or ΔIL-10 levels among patients during pairwise comparisons between different groups (UTI Group vs FA Group, UTI Group vs Control Group, FA Group vs Control Group). Explanation of statistical symbols: "ns" indicates no statistical difference ($P \geq 0.05$); P-values directly labeled in the subfigures (eg, <0.01, <0.001) indicate statistical differences, with $P < 0.05$ considered statistically significant.

Comparative Analysis with Current Standardized Protocols

The key challenge in postoperative analgesia for TKA is balancing efficacy with drug-related adverse events. Although nerve block combined with multimodal analgesia represents the recommended standard, it has limitations: Femoral nerve (FNB) or adductor canal blocks (ACB) impair neuromuscular function, significantly hampering rehabilitation, and often require supplemental techniques like periarticular infiltration or continuous catheter blocks to enhance efficacy, thereby increasing procedural complexity and complication risks.[22–24] Although NSAIDs, such as FA, reduce opioid needs (~26% reduction vs control observed), they exhibit a ceiling effect and inherent risks.[25] In contrast, the UTI group demonstrated a 48% reduction in morphine consumption, providing continuous pain control covering the critical first 72 h postoperatively. Furthermore, the UTI group's overall adverse reaction rate was 24%, which was significantly lower than that of the FA (48.0%) and control (52.0%) groups. The incidence of delirium was only 4.1%, supporting prior research indicating UTI's potential to improve postoperative cognitive function.[26–28] Although no direct comparative studies have evaluated UTI against nerve blocks or other multimodal protocols, its demonstrated profile—sustained opioid-sparing effect while maintaining a minimal adverse event rate—suggests that UTI could serve as a complementary

Table 6 Comparison of Differences in IL-10

	UTI Group (n = 44)	FA Group (n = 41)	Control Group (n = 48)	*P*-value
IL-10 at preoperative, median (IQR), pg/mL	2.86 (1.92, 5.84)	2.60 (1.91, 5.16)	3.01 (2.19, 9.45)	*0.204*
IL-10 at postoperative, median (IQR), pg/mL	6.10 (3.35, 15.31)	6.77 (2.62, 15.74)	23.09 (7.15, 80.23)	*<0.001*
Preoperative vs Postoperative, *P*-value[a]	*<0.001*	*<0.001*	*<0.001*	
ΔIL-10, median (IQR), pg/mL[b]	2.20 (0.49, 6.12)	3.07 (−0.02, 11.28)	19.92 (3.82, 67.33)	*<0.001*
Compared with FA group, mean (95% CI), pg/mL	−2.80 (−10.43, 4.84)	–	–	
P value[c]	*0.722*			
Compared with Control group, mean (95% CI), pg/mL	−32.40 (−46.10, −18.69)	−29.60 (−44.33, −14.86)	–	
P value[c]	*<0.001*	*<0.001*		

Notes: The table presents the time effect, between-group effect, and interaction effect on morphine consumption, as well as the results of post-hoc pairwise comparisons across different time periods. Model goodness of fit: QIC = 37,862.895, QICC = 37,862.958. A smaller value indicates a good model fit. A *P*-value < 0.05 was considered statistically significant.UTI group (n = 44, 4 samples excluded due to hemolysis, 1 sample excluded due to the values <1.00); FA group (n = 41, 3 samples excluded due to hemolysis, 6 samples excluded due to the values <1.00); FA group (n = 48, 2 samples excluded due to hemolysis). The samples excluded due to technical issues are non-systematic and random, and the chi-square test shows no significant difference in their distribution across all three groups ($\chi^2 = 5.134$, $p = 0.077$). a. The *Wilcoxon signed-rank* test was used to analyze the differences in the preoperative and postoperative levels of IL-10. b. ΔIL-10: the difference in inflammatory factors between postoperative and preoperative periods (Postoperative - Preoperative). c. The *Mann–Whitney U*-test was used for intergroup comparisons of ΔIL-10; Bonferroni correction was applied (adjusted $\alpha = 0.05/3 = 0.017$ for multiple tests).

approach in multimodal analgesia, particularly in cases where nerve blocks are not feasible or as an adjunct to enhance overall efficacy. This positions UTI as a potentially valuable clinical option for postoperative analgesia, though further comparative studies are warranted.

UTI's Mechanisms Underlying Efficacy

The preemptive analgesic use of UTI suppresses postoperative inflammatory outbreaks through multiple synergistic mechanisms, promoting a dynamic balance between pro-inflammatory and anti-inflammatory factors, thereby reducing pain. Previous studies have shown that UTI: (I) potently inhibits proinflammatory responses: directly suppresses the release of TNF-α, IL-6, etc., and downregulates the kinin system pathway to alleviate tissue inflammation;[29,30] (II) regulates neurogenic inflammation: inhibits neutrophil elastase to block the PAR2 pathway, reducing the release of pain-causing neuropeptides such as substance P (SP);[31–33] (III) intervenes in central sensitization: suppresses the activation of microglia and astrocytes, reducing central neuroinflammation.[34] The results of this study validate the mechanistic advantages of UTI: UTI significantly inhibited the postoperative increase in the proinflammatory factor IL-6 (median ΔIL-6 0.00 vs control 1.63 pg/mL, $P = 0.003$) and achieved more balanced regulation of the anti-inflammatory factor IL-10 (median ΔIL-10 2.20 vs control 19.92 pg/mL, $P < 0.001$), avoiding excessive compensatory anti-inflammatory response syndrome (CARS), indicating that it effectively restores inflammatory homeostasis.

This multitarget regulation directly alleviates the pain cascade: comprehensive inhibition of inflammatory outbreaks reduces peripheral and central pain sensitization, thereby decreasing postoperative opioid requirements (consistent with the 48% reduction in morphine consumption at 72 h in this study) and significantly reducing the risk of adverse reactions. In contrast, FA is primarily known for its COX inhibition mechanism, which plays a dominant role in its analgesic and anti-inflammatory effects. This study confirmed that its regulatory effect on IL-6 was limited (ΔIL-6 showed a downward trend but without a statistical difference, $P = 0.39$), making it difficult to block the inflammatory cascade comprehensively. Therefore, although it can save opioids, its ability to control adverse reactions is not significant, highlighting the clinical superiority of UTI.

While UTI's short plasma half-life (~40 min) might suggest transient activity,[35] its sustained suppression of IL-6 and modulation of IL-10 demonstrate prolonged bioactivity beyond pharmacokinetic persistence.[36–39] This apparent discrepancy can be attributed to UTI's irreversible inhibition of key proteases in the inflammatory cascade. Additionally, pre-incision administration allows UTI to establish its anti-inflammatory presence before surgical injury, potentially "pre-arming" the immune system and mitigating the peak inflammatory response. These findings support the clinical relevance of single-dose administration within the study design.

Study Design Strengths and Limitations

The placebo-controlled design isolated confounding effects to directly quantify the morphine-sparing effects and changes in inflammatory factors in the FA and UTI groups. All patients received standardized training enabling self-pain assessment and effective PCIA administration, achieving comparable analgesic outcomes (median resting VAS <30 mm, P >0.05). Under this pain management framework, intergroup differences in morphine consumption, attributable solely to interventions, reflect comparable analgesic needs among the patient groups. The UTI group achieved comparable pain control, with significantly lower morphine use, confirming its efficacy. The inclusion of the FA group as a modern multimodal analgesia reference further indirectly substantiates UTI's clinical value.

Limitations Must Be Acknowledged

First, the single-center design and moderate sample size limited the extrapolation of the results and affected the statistical power of subgroup analysis and adverse event assessment. Second, even after randomization, an accidental imbalance in anesthesia methods (64% spinal anesthesia in the control group vs 49% in the UTI group vs 48% in the FA group, P=0.199) and the prevalence of previous strokes was still observed. Although differences in anesthesia methods may theoretically introduce variations by influencing surgical stress responses and drug metabolism pathways, the following evidence indicates that their impact is limited: The comparable level of postoperative pain control across groups (VAS score P>0.05) mitigated concerns that differential pain perception might have confounded the intergroup differences in morphine consumption. Furthermore, the standardized anesthetic protocol and PCIA management minimized variability in perioperative analgesia practices, reducing potential procedural confounding. Additionally, the primary pharmacological mechanisms of the interventions—UTI's multi-target anti-inflammatory action and FA's COX inhibition—operate independently of the transient effects of regional versus general anesthesia on early surgical stress responses. Importantly, the absence of significant between-group differences in IL-6 levels (all P>0.05) further confirms that the observed anti-inflammatory effects reflect the efficacy of the study drugs rather than anesthesia-related bias. Even so, we must acknowledge this uneven distribution of anesthesia methods as a potential limitation. Future studies could further verify the robustness of our conclusions through designs such as "stratified randomization by anesthesia type" or by expanding the sample size. In addition, the absence of long-term outcome assessment—particularly for chronic pain and functional recovery—hampers the evaluation of UTI's sustained clinical benefits. This study only assessed short-term outcomes—without assessing long-term endpoints such as chronic postsurgical pain, functional recovery (eg, knee range of motion, daily living activities), or long-term cognitive function. The lack of long-term data hinders a comprehensive assessment of UTI's prolonged efficacy and potential late adverse effects, which is critical for defining its role in the long-term perioperative management of total knee arthroplasty.

Other limitations include: despite randomization, an imbalance in the prevalence of prior stroke was observed between groups. While this imbalance did not act as a confounding factor in the primary outcome analysis, it underscores the role of chance in patient allocation; lack of comparison against nerve blocks or other advanced modalities necessitates further trials to define UTI's role within current multimodal analgesia protocols; limited sample size affecting the test efficiency of secondary outcomes; the need to optimize the single-dose regimen due to the short half-life of UTI (approximately 40 min); absence of serial inflammatory biomarker monitoring; and lack of evaluation of long-term outcomes such as chronic pain.

Conclusion

This study confirms that single preoperative UTI (30 IU) significantly reduces opioid requirements and key adverse reactions (especially delirium) compared to FA and placebo control in TKA. Its advantages derive from multi-mechanistic synergistic regulation of the inflammatory balance and inhibition of pain sensitization. UTI provides a safe and efficient non-opioid option for high-risk patients, supporting its inclusion in ERAS pathways to optimize analgesic strategies.

Data Sharing Statement

1. Individual deidentified participant data: The authors do not intend to share individual deidentified participant data.
2. Specific data to be shared: No specific clinical trial data (including but not limited to raw participant-level data, processed data subsets related to morphine consumption, or data dictionaries) will be made available.
3. Other study documents available: The study protocol (which outlines the design, inclusion/exclusion criteria, intervention details, and outcome measurement methods of the clinical trial) will be made available.
4. Accessibility of Data and Documents: For access to the study protocol, interested parties may contact the corresponding author via Email at drliyan@163.com with a formal request. The corresponding author will respond to valid requests and provide the study protocol promptly.
5. Timing and duration of availability: The study protocol will be made available immediately following the publication of this manuscript, with no predefined end date for availability.

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Disclosure

The authors declare that there is no conflict of interest in this work. We do not have any possible conflicts of interest.

References

1. Kendir C, de Bienassis K, Slawomirski L, et al. International assessment of the use and results of patient-reported outcome measures for Hip and knee replacement surgery: findings of the OECD Patient-Reported Indicator Surveys (Paris) Working Group on hip and knee replacement surgery. 2022. doi:10.1787/6da7f06b-en
2. Gleicher Y, Siddiqui N, Mazda Y, et al. reducing acute hospitalization length of stay after total knee arthroplasty: a quality improvement study. *J Arthroplasty*. 2021;36(3):837–844. doi:10.1016/j.arth.2020.09.054
3. Bastian D, Tamburstuen MV, Lyngstadaas SP, et al. Systemic and local cytokine kinetics after total Hip replacement surgery. *Eur Surg Res*. 2008;41(4):334–340. doi:10.1159/000157176
4. Kessler ER, Shah M, Gruschkus SK, et al. Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes. *Pharmacotherapy*. 2013;33(4):383–391. doi:10.1002/phar.1223
5. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology*. 2010;112(1):226–238. doi:10.1097/ALN.0b013e3181c38c25
6. Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. *Clin Pharmacol Ther*. 2003;74(2):102–112. doi:10.1016/S0009-9236(03)00152-8
7. Paul AK, Smith CM, Rahmatullah M, et al. Opioid analgesia and opioid-induced adverse effects: a review. *Pharmaceuticals*. 2021;14(11):1091. doi:10.3390/ph14111091
8. Cook DJ, Kaskovich SW, Pirkle SC, et al. Benchmarks of duration and magnitude of opioid consumption after total hip and knee arthroplasty: a database analysis of 69,368 patients. *J Arthroplasty*. 2019;34(4):638–644e631. doi:10.1016/j.arth.2018.12.023
9. Dowell D, Ragan KR, Jones CM, et al. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1–95. doi:10.15585/mmwr.rr7103a1
10. Ohmukai O. Lipo-NSAID preparation. *Adv. Drug Delivery Rev*. 1996;20(2):203–207. doi:10.1016/0169-409X(95)00123-O
11. Wongrakpanich S, Wongrakpanich A, Melhado K, et al. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. *Aging Dis*. 2018;9(1):143–150. doi:10.14336/AD.2017.0306
12. Holzer P, Jocic M, Cabré F, et al. Estimation of acute flurbiprofen and ketoprofen toxicity in rat gastric mucosa at therapy-relevant doses. *Inflamm Res*. 2001;50(12):602–608. doi:10.1007/PL00000241
13. Wang Y, Zhou M, Wang J, et al. Developmental cardiotoxicity and hepatotoxicity of flurbiprofen axetil to zebrafish embryo. *Assay Drug Dev Technol*. 2022;20(3):125–135. doi:10.1089/adt.2021.127
14. Ziesenitz VC, Welzel T, van Dyk M, et al. Efficacy and Safety of NSAIDs in infants: a comprehensive review of the literature of the past 20 years. *Paediatr Drugs*. 2022;24(6):603–655. doi:10.1007/s40272-022-00514-1
15. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574–584. doi:10.1038/s41569-020-0366-z

16. Park KH, Lee KH, Kim H, et al. The anti-inflammatory effects of ulinastatin in trauma patients with hemorrhagic shock. *J Korean Med Sci*. 2010;25(1):128–134. doi:10.3346/jkms.2010.25.1.128
17. Jung KT, Lee HY, Yoon MH, et al. The effect of urinary trypsin inhibitor against neuropathic pain in rat models. *Korean J Pain*. 2013;26(4):356–360. doi:10.3344/kjp.2013.26.4.356
18. Oh SH, So HJ, Lee HY, et al. Urinary trypsin inhibitor attenuates the development of neuropathic pain following spinal nerve ligation. *Neurosci Lett*. 2015;590:150–155. doi:10.1016/j.neulet.2015.01.070
19. Ouyang H, Nie B, Wang P, et al. Ulinastatin attenuates neuropathic pain induced by L5-VRT via the calcineurin/IL-10 pathway. *Mol Pain*. 2016;12. doi:10.1177/1744806916646785
20. Shi Y, Qin W, Nie F, et al. Ulinastatin attenuates neuropathic pain via the ATP/P2Y2 receptor pathway in rat models. *Gene*. 2017;627:263–270. doi:10.1016/j.gene.2017.06.045
21. Wang L, Wu LX, Han Z, et al. Effect of flurbiprofen axetil combined with "Cocktail" therapy on opioid dosage in patients after total knee arthroplasty. *Pak J Med Sci*. 2022;38(3Part–I):724–729. doi:10.12669/pjms.38.3.4735
22. Zhao C, Liao Q, Yang D, et al. Advances in perioperative pain management for total knee arthroplasty: a review of multimodal analgesic approaches. *J Orthop Surg Res*. 2024;19(1):843. doi:10.1186/s13018-024-05324-4
23. Lavand'homme PM, Kehlet H, Rawal N, et al. Pain management after total knee arthroplasty: pROcedure SPEcific postoperative pain managemenT recommendations. *Eur J Anaesthesiol*. 2022;39(9):743–757. doi:10.1097/EJA.0000000000001691
24. Fillingham YA, Hannon CP, Kopp SL, et al. The efficacy and safety of regional nerve blocks in total knee arthroplasty: systematic review and direct meta-analysis. *J Arthroplasty*. 2022;37(10):1906–1921.e1902. doi:10.1016/j.arth.2022.03.078
25. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and Hip osteoarthritis: network meta-analysis. *BMJ*. 2021;375:n2321. doi:10.1136/bmj.n2321
26. Cho EH, Seo EH, Hong SW, et al. The preventive effect of ulinastatin on blood-brain barrier dysfunction in rats with postoperative cognitive dysfunction after general anaesthesia with isoflurane. *Int J Mol Sci*. 2024;25(23):12505. doi:10.3390/ijms252312505
27. Duan M, Liu F, Fu H, et al. Effect of ulinastatin on early postoperative cognitive dysfunction in elderly patients undergoing surgery: a systemic review and meta-analysis. *Front Neurosci*. 2021;15:618589. doi:10.3389/fnins.2021.618589
28. Xia X, Li J, Zhang M, et al. Ulinastatin modulates TRPM4 expression and apoptosis to mitigate cognitive dysfunction in aged perioperative neurocognitive disorder rats. *Sci Rep*. 2025;15(1):17774. doi:10.1038/s41598-025-01394-4
29. Zhang Q, Ruan H, Wang X, et al. Ulinastatin attenuated cardiac ischaemia/reperfusion injury by suppressing activation of the tissue kallikrein-kinin system. *Br J Pharmacol*. 2024;181(24):4988–5008. doi:10.1111/bph.16477
30. Dray A, Perkins M. Bradykinin and inflammatory pain. *Trends Neurosci*. 1993;16(3):99–104. doi:10.1016/0166-2236(93)90133-7
31. Zhang W, Gao J, Zhao T, et al. Proteinase-activated receptor 2 mediates thermal hyperalgesia and is upregulated in a rat model of chronic pancreatitis. *Pancreas*. 2011;40(2):300–307. doi:10.1097/MPA.0b013e318201cbc1
32. Vergnolle N, Bunnett NW, Sharkey KA, et al. Proteinase-activated receptor-2 and hyperalgesia: a novel pain pathway. *Nat Med*. 2001;7(7):821–826. doi:10.1038/89945
33. Vergnolle N. Proteinase-activated receptor-2-activating peptides induce leukocyte rolling, adhesion, and extravasation in vivo. *J Immunol*. 1999;163(9):5064–5069. doi:10.4049/jimmunol.163.9.5064
34. Zhan MX, Tang L, Lu YF, et al. Ulinastatin exhibits antinociception in rat models of acute somatic and visceral pain through inhibiting the local and central inflammation. *J Pain Res*. 2021;14:1201–1214. doi:10.2147/JPR.S303595
35. Wei X, Zhu X, Jiang L, et al. Recent research progress on the role of ulinastatin in chronic kidney disease. *Nephrology*. 2021;26(9):708–714. doi:10.1111/nep.13906
36. Liu H, Qian SC, Zhu K, et al. Protective effect of ulinastatin against negative inflammatory response and organ dysfunction in acute aortic dissection surgery: the PANDA trial. *Cell Rep Med*. 2025;6(1):101888. doi:10.1016/j.xcrm.2024.101888
37. Pang XY, Fang CC, Chen YY, et al. Effects of ulinastatin on perioperative inflammatory response and pulmonary function in cardiopulmonary bypass patients. *Am J Ther*. 2016;23(6):e1680–e1689. doi:10.1097/MJT.0000000000000243
38. Shu H, Liu K, He Q, et al. Ulinastatin, a protease inhibitor, may inhibit allogeneic blood transfusion-associated pro-inflammatory cytokines and systemic inflammatory response syndrome and improve postoperative recovery. *Blood Transfus*. 2014;12(Suppl 1):s109–118. doi:10.2450/2013.0224-12
39. Hu Q, Teng Y, Yuan Y, et al. Effects of ulinastatin on inflammation response and lung tissue injury in deep hypothermic circulatory arrest. *Interdiscip Cardiovasc Thorac Surg*. 2025;40(9). doi:10.1093/icvts/ivaf177