

An Applied Study of Ulinastatin in Pain Management After Hip Replacement: Impact on Opioid Use

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Background: Due to the global prevalence of opioid drugs, postsurgical prescriptions can lead to substantial opioid consumption, highlighting the increasing need for alternative medications. Alternative medicines can markedly lessen the usage of opioids after surgery, but the variety and notable side effects of these alternatives require meticulous experimental support.

Objective: This study explored the efficacy and safety of ulinastatin for alleviating postsurgical pain, for reducing the need for opioids, and for inclusion in conventional treatment methods.

Methods: A total of 108 patients undergoing elective hip replacement were randomly allocated into either the experimental group (56 cases, standard pain relief treatment plus 60 IU ulinastatin) or the control group (40 cases, standard pain relief treatment). The main outcomes measured were the total consumption of opioids at 24, 48, and 72 h postoperatively. Secondary outcomes comprised patient-reported pain indices and levels of satisfaction with pain control. The frequency of adverse events evaluated medication safety.

Results: There were no statistically significant differences in age, sex, or underlying diseases between the two groups. Over 24 hours, opioid consumption was higher in the standard treatment group (66.6 mg; mean difference [MD]: 4.43 mg; 95% CI: 57.6–75.5) than in the intervention group (54.5 mg; MD: 1.91 mg; 95% CI: 50.7–58.3). The standard treatment group exhibited a notably higher incidence of adverse reactions. However, there was no disparity in post-discharge satisfaction between the groups, with an odds ratio of 1.058 (95% CI: 0.62–1.82; $P > 0.05$). Additionally, significant differences in C-reactive protein levels were observed immediately and 6 h after surgery between the two groups.

Conclusion: Within 72 h post-surgery, ulinastatin was effective in substantially reducing the use of opioids while maintaining adequate pain control. Ulinastatin may be beneficial for postoperative pain management and for reducing the risks associated with opioid use.

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Keywords: ulinastatin, postoperative pain, pain management, opioid

Introduction

Total Hip Arthroplasty (THA), commonly referred to as hip replacement surgery, is heralded as one of the most significant advancements in orthopedic surgery over the past century.¹ Known for its ability to restore mobility and alleviate pain, THA has become increasingly prevalent as the population ages. In the United States alone, approximately 450,000 procedures are performed annually, reflecting its critical role in addressing the debilitating effects of hip joint diseases such as osteoarthritis, rheumatoid arthritis, and osteonecrosis.² In the United States alone, the number of these surgeries is expected to reach 572,000 annually by 2030.² The incidence of femoral neck fractures is also increasing yearly, accompanied by a rise in the number of artificial femoral head replacements, also known as hemiarthroplasties. The choice of THA over hemiarthroplasty is often dictated by the need for complete joint restoration. Although THA can

have a higher dislocation rate compared to HA, it is often offset by its lower rate of other complications like acetabular erosion, which is more common in HA.³ The comprehensive replacement in THA helps in mitigating issues that arise from partial replacements used in HA. This distinction is crucial as THA typically offers better long-term outcomes, including lower revision rates and improved functionality, particularly in younger and more active patients. These advantages underscore the importance of THA in achieving superior pain relief and functional recovery, justifying its predominance over hemiarthroplasty in many clinical scenarios.⁴

The widespread misuse of opioids worldwide is significantly impacted by the abundant use of opioids in postoperative prescriptions.⁵ Opioids are well known for their strong pain-relieving properties and are thus frequently used in surgeries such as hip replacements, which are known to cause moderate to severe postoperative pain.⁶ In addition to acute pain caused by surgical trauma, secondary inflammatory pain further intensifies the patient's perception of pain postoperatively. The release of inflammatory factors and nociceptive substances such as prostaglandins, kinins, and substance P from neutrophils intensifies patient pain, reduces their pain threshold, and heightens their perception of pain.⁷ Current analgesic treatments and methods are not fully effective. Excessive use of opioids not only increases the risk of adverse reactions but also the potential for long-term postoperative hyperalgesia.⁸ Meanwhile, nonsteroidal anti-inflammatory drugs (NSAIDs), although reducing opioid use, are limited in clinical application due to gastrointestinal side effects and cardiovascular suppression.^{9–12}

Originally derived from adult male urine, ulinastatin is an anti-inflammatory drug that has demonstrated potential as an adjuvant to opioids in empirical studies. Numerous studies have confirmed the effectiveness and safety of ulinastatin in treating patients with acute pancreatitis and systemic inflammatory response syndrome.^{13–15} Clinical findings indicate that ulinastatin can reduce the release of elastase from neutrophils, diminish the secretion of kinins, mitigate inflammation, and alleviate inflammatory pain.^{16,17} Additionally, ulinastatin can enhance the efficacy of the opioid drug sufentanil when used in combination. However, current research on ulinastatin is limited by factors such as small sample sizes and a narrow range of patient demographics.^{18,19} In light of the extensive practice of hip replacement surgeries and the prevailing issue of opioid misuse, investigating effective, practical, and secure multimodal approaches for postoperative pain management is essential. The objective of this study was to explore whether the addition of ulinastatin to perioperative pain management plans can alleviate patient pain, decrease the need for opioids, and assess its safety for inclusion in analgesic protocols, thus contributing further evidence for its integration into pain management.^{20–22}

Methods

Study Design

This study was a randomized controlled trial initiated by researchers. Before the study commenced, the research protocol received approval from the Ethics Committee of the Tianjin Jizhou People's Hospital, and all participants provided written informed consent (IRB2023-15) prior to inclusion.

Calculation of Sample Size

Based on the results of a pilot study, we chose 72-hour morphine consumption as the primary outcome. The experimental group was expected to have an average morphine consumption of 50 mg, while the control group was expected to use 70 mg. A two-sided α of 0.05 was used, accounting for a 30% loss to follow-up and potential crossover between groups. To achieve a power of 80% ($\beta = 0.20$), the minimum sample size for each group was 45 participants (total of 90), determined using G*Power 3.1.9.2 (Universitat Kiel, Germany). In our study, there were 52 subjects in the control group and 56 in the intervention group. Therefore, our study sample size was appropriate.

Randomization Methodology

The randomization of participants in this study was executed using a computer-generated method. Herein, we detail the specific processes and tools employed during the randomization process:

The randomization sequence was generated using a stratified randomization algorithm. This method was chosen to control for potential confounding variables such as age and disease severity, ensuring that these factors were evenly

distributed across the treatment groups. The random sequence was created using the R statistical software package (version 3.6.1). R's `sample()` function was utilized.

The allocation ratio was set at 1:1, assigning participants equally to either the control group or the treatment group. To prevent allocation bias and protect the integrity of the study, the randomization sequence was concealed using a centralized, automated system that assigns participants to their groups only after the full registration and baseline assessment have been completed. This method of concealment ensures that neither the participants nor the research staff could predict or influence group assignments. Experimenters were unaware of the patient group assignments before inclusion.

Blinding

Patients were assigned to their respective groups through randomization and were given the same educational material. No significant differences existed in orthopaedic medications between the experimental and control groups; the orthopaedic doctors involved in the study were also unaware of the patient group assignments. Outcome assessors and data analysts were blinded to the group allocations; all data analysis was completed using blinded data, and the blinding was only lifted after these analyses were performed.

Patient Allocation

Before recruiting the first participant, the trial was registered on ClinicalTrials.gov (ChiCTR2300072126) and adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. This study recruited elective hip replacement surgery patients from June to September 2023 at the Jizhou People's Hospital in Tianjin. The surgeries were performed by two teams; each team consisted of three orthopaedic surgeons and two nurses. To ensure the feasibility of the study, the choice of administering local and/or general anaesthesia was made by anaesthesiologists. Prior to initiating the study, the research team reviewed standardized literature and clinical guidelines and consulted with expert surgeons, anaesthesiologists, perioperative nurses, and pharmacists. To reduce bias, both the control group and the experimental group used identical electronic drug infusion pumps and adhered to the same drug administration protocols.

Both groups of patients refrained from using nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen as part of the study protocol and were instructed not to use such over-the-counter medications.

Patients in the experimental group were included in the perioperative analgesia plan with 60 IU of ulinastatin (10 IU infused during surgery and 50 IU placed in the postoperative analgesia pump, with the same pump ratio as the control group).

The control group patients were subjected to a standard analgesia protocol: they received postoperative analgesia through an open electronic drug infusion pump (manufactured by Jiangsu Aipeng Medical Technology Co., Ltd) with a morphine concentration of 0.8 mg/mL. The background dosage was set at 0.5 mL, the single dosage was set at 1.5 mL, and the lockout period was fixed between 8 and 10 min.

Inclusion Criteria

Patients scheduled for elective hip joint replacement surgery; aged between 40 and 80; with ASA classification from I to III; provided informed consent prior to the commencement of the study; and signed a consent form.

Exclusion Criteria

1. Patients with neuropathic pain, for example, pain induced by tumour compression of neural structures (nerve roots, nerve plexuses, or spinal cord).
2. Patients who were currently using or needed to use anticholinergic medication, antidepressants, or any pain medication other than the ones used in the study, including NSAIDs.
3. Patients with unstable comorbid conditions or evident organ functional impairments.
4. Patients who may change concomitant medications during the study, excluding changes related to the treatment of adverse reactions to opioid medications.
5. Patients showing poor adherence or who were unable to comply with the intervention.
6. Patients who were terminated from the study due to severe adverse events.

Evaluation of the Postoperative Analgesic Effect

At the 24 h, 48 h, and 72 h postoperative time points, a visual analogue scale was used for pain assessment, as follows: A 10 cm line was drawn on paper; one end of the line was labelled “0”, representing no pain, and the other end was labelled “10”, representing extreme pain; the middle portion represented varying degrees of pain. After discharge, the Global Pain Scale (GPS), which is a self-assessment scale developed by the American scholar Gentile, was used. The GPS uses a simple numerical score to assess the subjective and objective multidimensional pain perceptions of individuals with pain. The scale is divided into four dimensions: pain, emotional perception, clinical presentation, and daily behaviour, with a total of 20 items. A 0–10 grading system is used, where 0 means “no pain” or “strongly disagree” and 10 means “most painful” or “strongly agree”. A higher total score indicates a more severe subjective and objective impact of pain.

Postoperative Adverse Reaction Assessment

Adverse drug reactions experienced by patients were meticulously documented in the research logs collected within 72 h after surgery. The determination of adverse events was made by an independent, blinded adjudication committee composed of three clinicians: a physician from the anaesthesiology department, a nurse, and a surgeon.

Education and Follow-Up for Patients

All patients in the two groups received postoperative education regarding pharmacological and nonpharmacological pain management, including the monitoring of oxygen saturation by relatives at the bedside, precautions for physical pain treatment, and awareness of the risks of opioid abuse. Accessible contact details were given to patients for emergency pain relief if the analgesic effect was inadequate and for immediate treatment in case of other adverse events. All patients were monitored and contacted via phone at the postoperative time points of 24 h, 48 h, 72 h, 2 weeks, and 1–4 months.

Safety Measures

Before the study, all patients underwent tests including ECG, complete blood counts, urinalysis, blood chemistry analysis, and liver and kidney function evaluations, followed by blood chemistry and liver and kidney function evaluations after the study. Immediate action was taken and recorded for any adverse reactions during the patient’s hospital stay, as well as reasons for readmission within 30 days post discharge. The anaesthesia and pain management team at Tianjin Jizhou People’s Hospital was on standby at all times in case of emergency situations, such as severe uncontrolled pain, signs of serious drug adverse reactions, or other urgent health issues. The team was equipped to respond quickly, provide expert care, and take necessary measures to protect the health and well-being of patients participating in this study. The study was structured with several layers of patient safety and support mechanisms, and the research team pledged to focus on the health and comfort of all participants during the entire postsurgical timeframe.

Measurement of Data and Outcomes

During the initial clinical assessments, comprehensive patient data, including age, sex, body mass index (BMI), smoking and drinking histories, disease course, initial medical conditions, and hip pain scores, were collected. Prior pain medications and durations were also recorded. The outcome metrics for analysis included surgical details (such as the type and duration of surgery, anaesthesia time, type of anaesthesia, total and postsurgical hospital stay durations, intraoperative blood loss and transfusions); postoperative data covering 24 h, 48 h, and 72 h rest and activity pain scores (with a VAS minimal significant difference set at 1); total morphine consumption at different time intervals (rescue tramadol doses were also considered in the total consumption); and rates of adverse reactions (such as nausea, vomiting, headaches, respiratory depression, and urinary retention).

Statistical Analysis

Data recording and analysis were conducted using the WINDOWS IBM SPSS version 25.0. Normally distributed continuous data with homogeneity of variance were compared using independent sample *t*-tests and are presented herein

as the mean \pm standard deviation ($x \pm s$). For skewed data, Mann–Whitney U -tests were used for comparison and are presented as the median [interquartile range (IQR)]. Categorical and count data are presented as frequencies (rates) and were compared using chi-squared or Fisher's tests. Repeated measures analysis of variance was used to compare indicators at 24 h, 48 h, and 72 h. The Shapiro–Wilk test was used to test the normality of the data. Bonferroni corrections were applied for multiple comparisons within groups. A P value < 0.05 (two-tailed) was considered statistically significant.

Subgroup analyses were conducted based on sex (male/female), age categories (40–64, 65–70, 71–80 years), type of anaesthesia (general/epidural), primary disease type (aseptic necrosis/fracture), and surgical method (total hip replacement/artificial femoral head replacement). The results of the subgroup analyses are provided in [Figures 5–7](#).

Results

Participant Flow and Recruitment

Out of 103 patients screened for eligibility, 96 were randomized: 56 to the experimental group and 40 to the control group, the latter of which received the standard treatment ([Figure 1](#)). Following randomization, 7 patients were excluded from further analysis—one for unspecified reasons and six due to postoperative tonic pain. Regarding the primary outcome, the follow-up rate was 100% (96 out of 96) at 48 h and 96.8% (94 out of 96) at 72 h. The recruitment process commenced in May 2023, and the final follow-up concluded in September 2023.

Baseline Characteristics

The average age of the enrolled patients was 68.13 years, with a standard deviation (SD) of 6.037. Both groups had a nearly equal sex distribution, with males representing 37.5% (36 out of 96). The mean body mass index (BMI) was 23.38, calculated as body weight (in kg) divided by the square of height (in m). The predominant type of injury was a femoral neck fracture, affecting 77.1% (74 out of 96) of the patients, and this distribution was consistent across both groups. In terms of surgical procedures, 56 patients (58.3%) underwent an artificial total hip replacement, making it the most common procedure. Meanwhile, 40 patients (41.7%) received an artificial femoral head replacement. The anaesthesia methods differed; four patients (4.2%) were administered general anaesthesia, while 92 (95.8%) received lumbar anaesthesia. The average duration of the operations was 76.8 min (SD, 15.97), with comparable times observed in both groups ([Table 1](#)).

Primary Outcomes: Morphine Consumption

Seventy-two hours post-surgery, the mean morphine consumption for the control group was 66.6 mg (MD, 4.43 mg; 95% CI: 57.6–75.5), whereas it was 54.5 mg for the experimental group (MD, 1.91 mg; 95% CI: 50.7–58.3). The distribution of morphine consumption deviated from a normal pattern, a trend that persisted even after the log transformation. Consequently, based on the prespecified SAP, the Mann–Whitney U -test was utilized. In the primary analysis of the main outcome, patients in the experimental group consumed significantly fewer opioids (median, 50.0 mg; IQR, 18.0) than those in the control group (median, 60.0 mg; IQR, 37.5; $z = -2.6$; $P < 0.001$). [Figure 2](#) provides a histogram illustrating the total opioid consumption for each group.

Secondary Outcomes: Pain Scores and Adverse Events

Seventy-two hours post-surgery, the average pain score for the control group stood at 1.6 (95% CI, 1.28–1.92), whereas the experimental group registered a score of 1.84 (95% CI, 1.61–2.07; $P = 0.211$). This difference in pain scores did not surpass the preestablished minimum clinically significant difference of one point. [Figure 3](#) presents the VAS scores for mean resting pain across both groups over a span of 72 h. Upon discharge, most patients from both the standard treatment and ulinastatin groups expressed satisfaction with their pain management, with no noteworthy differences between the groups. The odds ratio for dissatisfaction in the standard treatment group was 1.058 (95% CI, 0.62–1.82; $P > 0.05$). During the 72-hour observation period, six adverse events were documented: four occurred in the standard treatment group (10%) and two in the ulinastatin group (3.6%). In the standard treatment cohort, four serious adverse events were reported, including joint dislocation and a high fever not related to postoperative pain management. The investigative commission attributed two

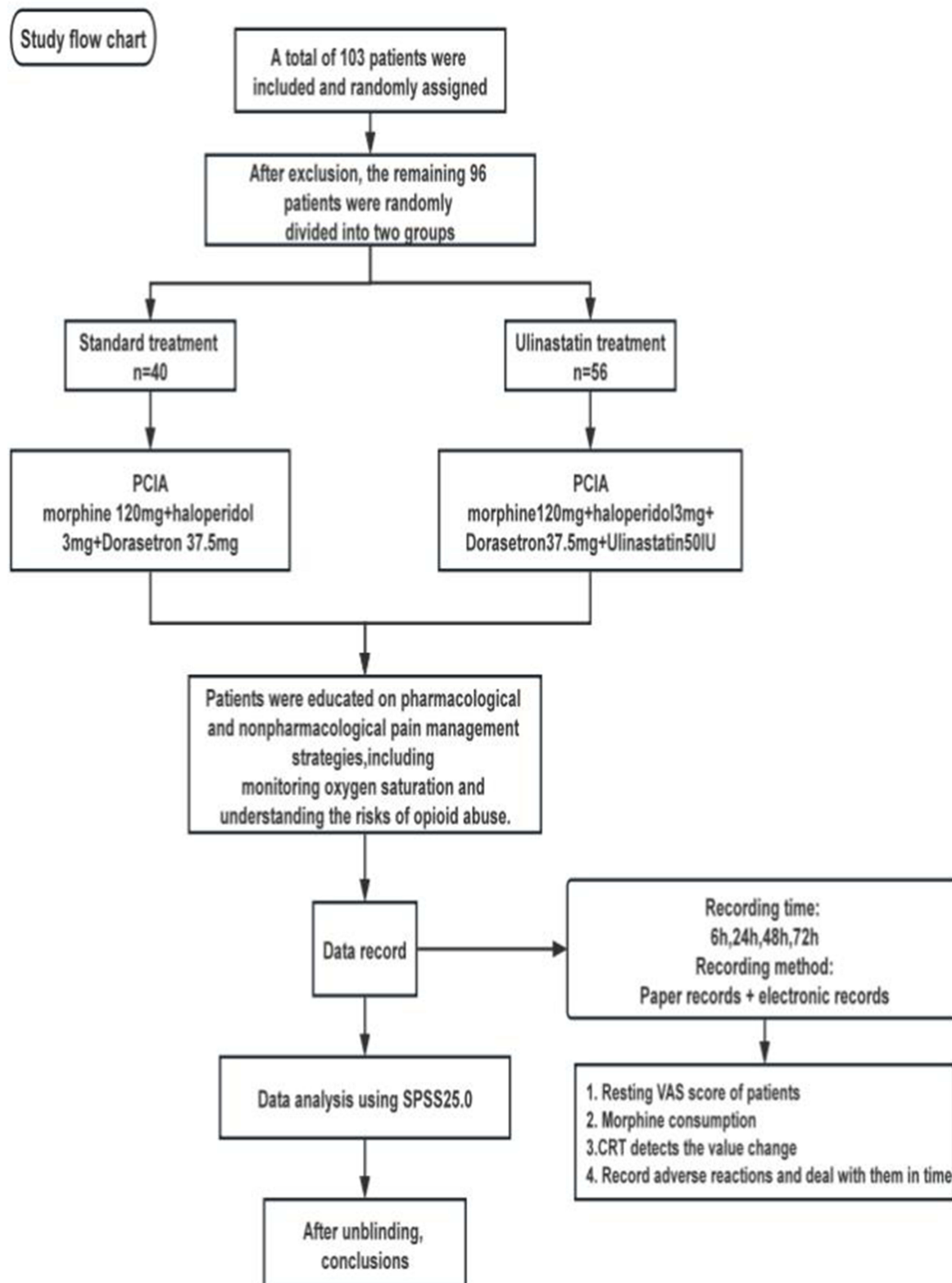


Figure 1 Study flow chart.

of these serious events (joint dislocations) directly to the surgical procedures rather than to the medications administered during the trial. In contrast, the two adverse events noted in the ulinastatin group involved calf swelling, which the committee identified as tension pain. This condition exacerbated the patients' pain and led to an increase in the use of pain relievers.

Table 1 Baseline Characteristics

Characteristics	No. (%) of Patients Standard Group (n=40)	Ulinastatin Group (n=56)
Ages		
≤64	10 (25)	16 (28.6)
65 to 70	8 (20)	16 (28.6)
≥71	22 (55)	24 (42.8)
Sex		
Men	12 (30)	24 (43)
Women	28 (70)	32 (57)
BMI		
Underweight <18.5	6 (15)	0 (0)
Normal weight 18.5 to <25	26 (65)	44 (78.6)
Overweight 25 to <30	6 (15)	8 (14.3)
Obese 30 to <40	2 (5)	4 (7.1)
Anaesthetic strategy, No./total (%)		
General	2 (5)	2 (3.5)
Spinal	38 (95)	54 (96.5)
Side		
Left	18 (45)	24 (42.9)
Right	22 (55)	32 (57.1)
Comorbidities		
Diabetes	14 (35)	16 (28.6)
Previous surgical	18 (45)	12 (21.4)
Asthma	20 (50)	26 (46.4)
Primary disease		
Fracture	34 (85)	40 (71.4)
Aseptic necrosis of the femoral head	6 (15)	16 (28.6)
Procedures performed		
Total hip arthroplasty	20 (50)	36 (64.3)
Artificial femoral head replacement	20 (50)	20 (35.7)
Use of tobacco product		
None	34 (85)	54 (96.4)
Previous smoker	6 (15)	2 (3.6)
Operating time		
<90 min	32 (80)	43 (76.8)
≥90 min	8 (20)	13 (23.2)

Within the standard treatment group, the most commonly reported adverse reactions included drowsiness in 15 patients (37.5%), gastrointestinal discomfort in 13 (32.5%), and dizziness in 4 (10%). In contrast, the ulinastatin group reported gastrointestinal discomfort in 5 patients (8.9%), drowsiness in 2 patients (3.6%), and dizziness in 1 patient (1.9%).

Additional Prespecified Outcomes: C Response Protein

In the control group, the patients' median protein C response protein (T1-T0) value was 3.5 with a quartile range of 12.5, whereas the median value in the ulinastatin group was -8.7 with an interquartile range of 14.0 ($z=-3.572$, $P<0.01$). Six hours post-surgery, the standard treatment group showed a median of 9.00 and a quartile range of 23.10, in contrast to the ulinastatin group, which had a median of -1.25 and an interquartile range of 4.50. Twenty-four hours post-surgery, the respective values for the standard treatment and ulinastatin groups were a median of 41.150 with a quartile range of 58.48 and a median of 31.05 with a quartile range of 31.1. By 48 h, the figures for the standard treatment were a median of 67.90 and a quartile range of 60.45, while the ulinastatin group had a median of 50.15 and an interquartile range of 160.1. Seventy-two hours post-surgery, the standard

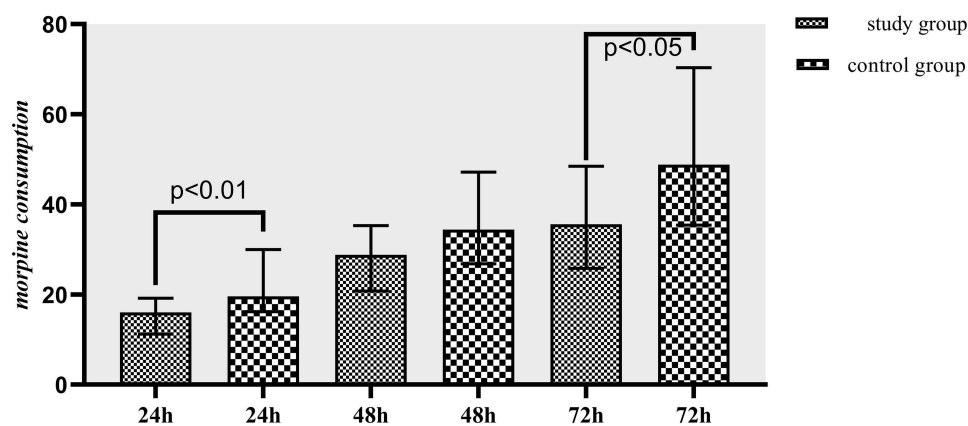


Figure 2 Morphine consumption when patients under post Hip replacement.

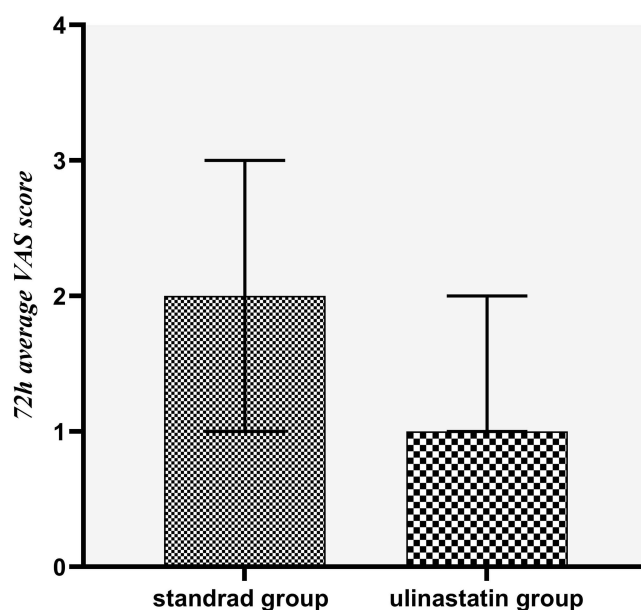


Figure 3 Average pain scores when patients under post Hip replacement.

treatment group showed a median of 64.20 and a quartile range of 46.73 versus the ulinastatin group's median of 39.35 and interquartile range of 180.1. Statistically significant changes were observed in C-reactive protein levels in the standard treatment group specifically at 6 h after surgery, with z values of -3.810 and -3.967 , both significant at $P < 0.01$. See [Figure 4](#) and [Table 2](#).

Subgroup Analyses

We conducted prespecified subgroup analyses as outlined earlier. Across all subgroups, which encompassed sex, anaesthesia type, age groups, primary disease type, and procedure selection, significant differences were observed at 24 h, 48 h, and 72 h for individuals under 65 years ($P < 0.05$), see [Figure 5](#). Notably, in the context of total hip replacement, significant differences persisted at 24 h, 48 h, and 72 h ($P < 0.05$), as illustrated in [Figures 6](#). And in primary disease type “fracture”, significant differences persisted at 24 h, 48 h, and 72 h ($P < 0.05$), as illustrated in [Figures 7](#).

Post Hoc Analyses

Incorporation of these variables as random effects into the mixed-effects model revealed no significant interaction effect between the site or surgery type on the primary outcome. Postsurgically, during days 0–3, the average VAS pain score showed no significant difference between the 1.93 rated for the standard treatment group and the 1.63 rated for the

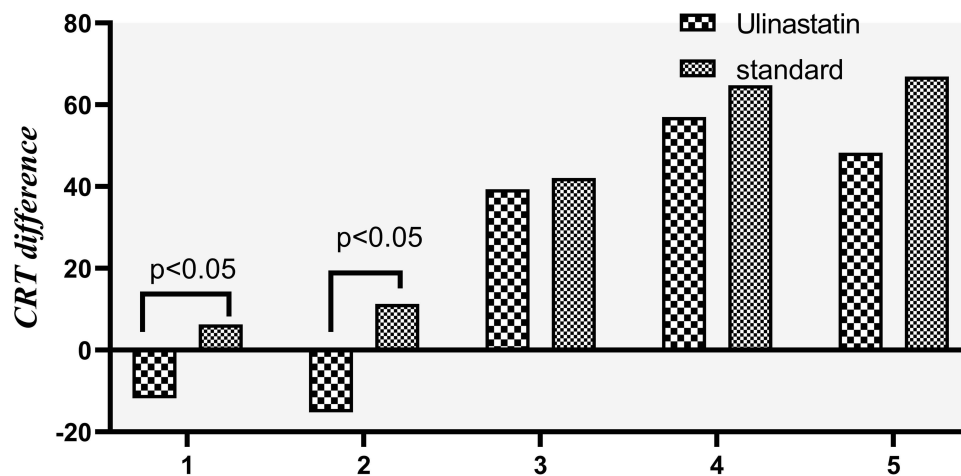


Figure 4 Postoperative changes of C-reactive protein in patients (T1 Immediately after the operation, T2 6 h after surgery, T3 24 h after surgery, T4 48 h after surgery, T5 72 h after surgery).

intervention group ($P = 0.110$). In the same postoperative timeframe, the total opioid consumption was notably higher in the standard treatment group than in the intervention group (average: 66.6 mg vs 54.5 mg; median: 60.0 mg vs 50.0 mg $z = -1.935$; $P < 0.001$). When patient satisfaction was evaluated, no significant difference was observed between the two groups.

Discussion

In this randomized controlled trial (RCT), we assessed the efficacy of ulinastatin as a component of postoperative pain management. Our study results indicate that the use of opioid medications significantly decreased within 72 h postsurgically when ulinastatin was incorporated into the pain management regimen compared to the standard analgesic protocol. Notably, despite the promising initial outcomes, there were no significant differences in reported pain, use of rescue analgesics, or patient satisfaction scores within 72 h postoperatively between the two groups. Our findings contribute to the growing body of evidence supporting the effectiveness of multimodal analgesic regimens across various surgical fields. In these regimens, the concurrent use of multiple analgesics is thought to produce a synergistic effect, potentially reducing opioid consumption while optimizing pain control.^{23,24} Within this framework, ulinastatin emerged as a promising adjunctive drug in our study, as evidenced by its role in reducing total opioid consumption and patient-reported adverse reactions to medications.

Comparison of Adverse Events Between Treatment Groups

Our analysis revealed a notable difference in the incidence and severity of adverse events between the ulinastatin and standard treatment groups. The ulinastatin group exhibited a lower rate of adverse events (3.6%) compared to the standard treatment group (10%). This suggests that ulinastatin may have a safer profile with respect to the incidence of adverse effects. The adverse events observed in the ulinastatin group, specifically calf swelling leading to tension pain,

Table 2 C Reaction Protein Difference in Two Group

	Ulinastatin	Standard	P
T1-T0	-11.77±14.78	6.30±11.49	<0.01
T2-T0	-15.24±43.48	11.30±15.78	<0.01
T3-T0	39.34±40.48	42.08±37.88	0.91
T4-T0	56.98±92.68	64.77±56.60	0.26
T5-T0	48.31±94.72	66.89±64.43	0.04

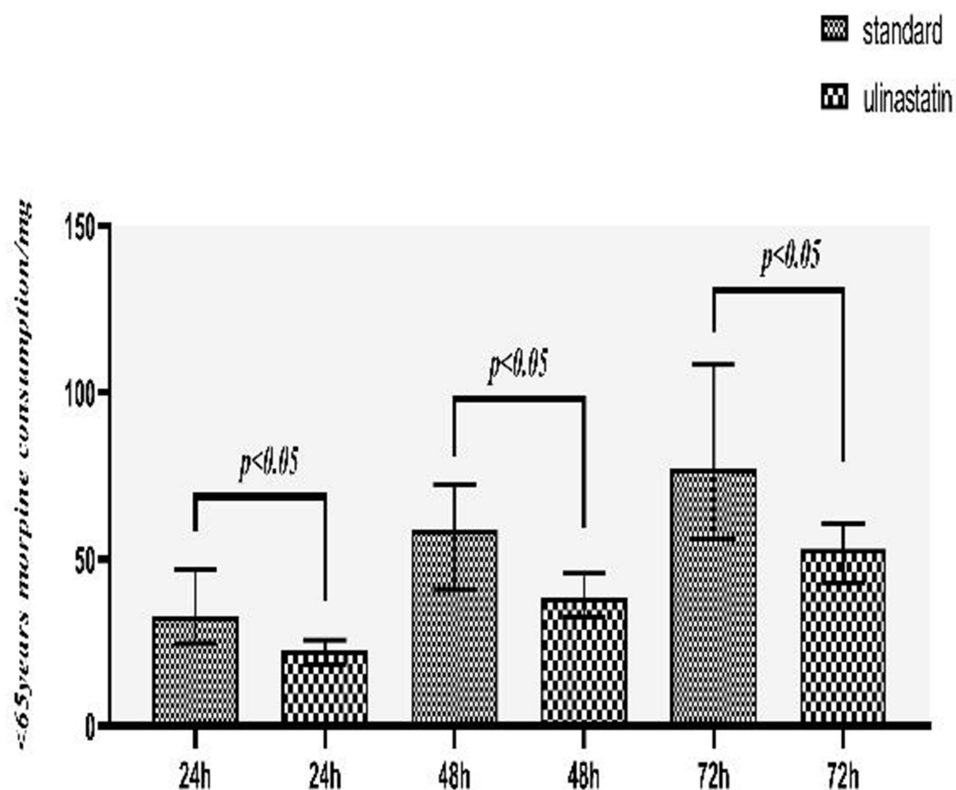


Figure 5 Morphine consumption in subgroup below 65 years.

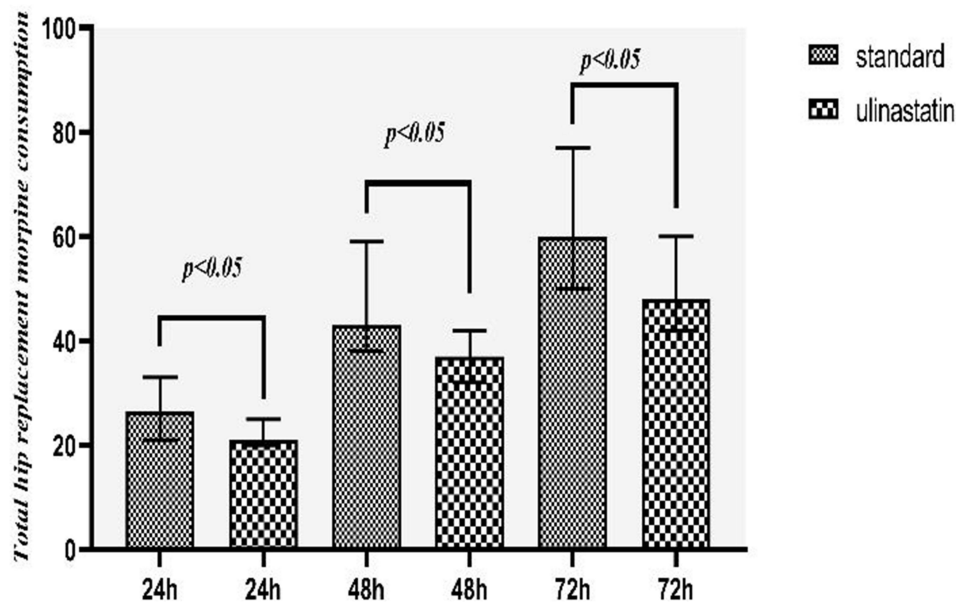


Figure 6 Morphine consumption in total Hip replacement subgroup.

were significantly less severe compared to those in the standard treatment group, which included serious adverse events like joint dislocation and high fever unrelated to postoperative analgesia. These findings highlight a potential advantage of ulinastatin in minimizing the risk of severe complications associated with surgical interventions.

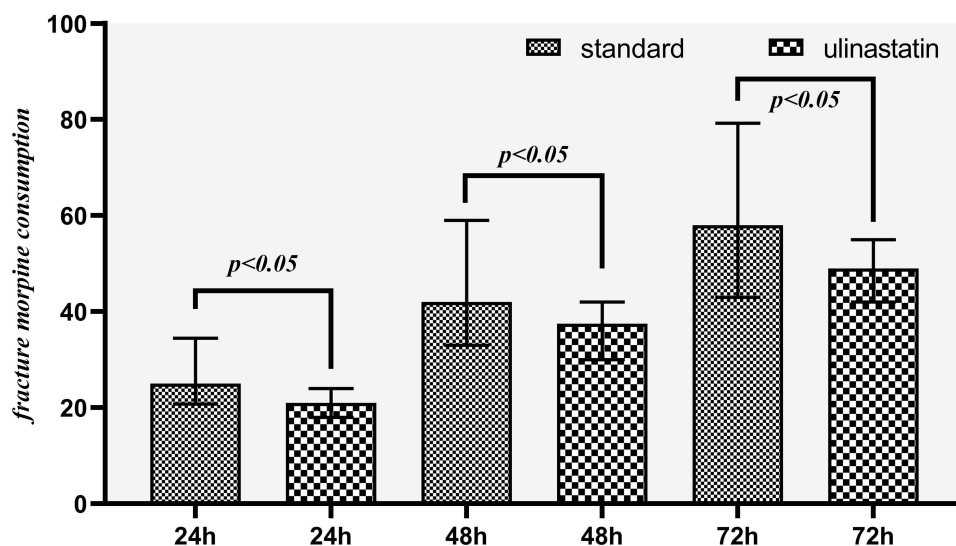


Figure 7 Morphine consumption in fracture subgroup.

The nature of the adverse events associated with ulinastatin, particularly the calf swelling resulting in increased pain and subsequent higher analgesic consumption, raises questions about whether these effects are dose-dependent or if they might be mitigated through other therapeutic strategies. The calf swelling described as tension pain suggests a possible mechanical or procedural origin rather than a pharmacological response, indicating that dosage adjustment may not necessarily prevent such outcomes.²⁵ However, a lower or adjusted dose could potentially reduce the severity or frequency of these symptoms if they are indeed dose-responsive.

To better manage and possibly prevent the escalation of such adverse effects, additional interventions may be required. This could include more stringent monitoring for early signs of calf swelling and proactive management of pain post-surgery. Implementing routine checks and early intervention protocols may help in managing these symptoms more effectively and preventing the increased consumption of analgesics.²⁶

Given these observations, future clinical trials should aim to establish a comprehensive understanding of the dose-response relationship and evaluate the effectiveness of additional preventive measures. Such studies could significantly enhance the therapeutic application of ulinastatin, ensuring both efficacy in surgical settings and minimization of adverse effects.

Rationale for Dosage Selection

In this study, we administered 60 IU of ulinastatin to the experimental group, a dosage determined based on preliminary data and consultations with clinical experts.²⁷ While comprehensive dose-ranging studies specific to ulinastatin are not currently available in the literature,²⁸ the dose chosen reflects a conservative approach based on analogous clinical scenarios and expert consensus.

We acknowledge a significant gap in the existing literature regarding specific dosage recommendations for ulinastatin. Current studies provide limited guidance on the optimal doses for achieving desired therapeutic outcomes without adverse effects. This gap underscores the need for our study and highlights its potential contribution to the field. By documenting our findings associated with the 60 IU dosage, we aim to provide a preliminary foundation for dose-related efficacy and safety that can be further explored in subsequent research.

Given the preliminary nature of the dosage used in this study, we are committed to further investigating ulinastatin's dosing requirements. Planned future studies include dose-gradient tests designed to methodically vary the amount of ulinastatin administered to determine the most effective and safest therapeutic dose. These studies will not only help in optimizing the dosage but also in establishing a more robust pharmacodynamic profile of ulinastatin.

In existing clinical guidelines, nonsteroidal anti-inflammatory drugs (NSAIDs) are a key component of multimodal plans and are well tolerated by patients.²⁹ Given the recognized risks of NSAIDs, they should be selectively chosen as first-line analgesics and used with care, particularly for patients without contraindications. Our research provides a foundation for subsequent exploration into the coadministration of NSAIDs and ulinastatin, to further clarify their potential to reduce postsurgical opioid usage. Our results hold significant implications against the backdrop of the ongoing opioid crisis.

Our study also introduces the potential of patient education as an effective strategy to reduce postoperative opioid use. Educating patients preoperatively about pain expectations, management approaches, and opioid-related risks may contribute to reduced postoperative opioid usage in the short and long term and enhance patient satisfaction.³⁰

This randomized controlled trial had multiple strengths, such as blinding of both outcome assessors and data analysts to mitigate possible biases. This study's broad eligibility criteria and inclusion of common orthopaedic surgeries suggest that our findings may be applicable to a wide patient population.

Limitations

First, due to the feasibility limitations of the trial, the anaesthetists were not blinded to the intervention during the surgery.

Second, the secondary outcomes of the trial were dependent on patient-reported symptoms.

Third, no significant differences were observed in morphine consumption 48 h postoperatively in this study.

Fourth, the interpretation of the subgroup analysis in this study carries risk.

Fifth, this study primarily involved patients receiving a particular type of surgical procedure.

Sixth, this study did not exclude patients who were long-term users of opioids. However, given regional variations, in China, the prevalence of long-term opioid use is lower. Hence, these findings should be cautiously interpreted when considering their applicability to this particular patient group, as the responses to pain management strategies could vary significantly between long-term opioid users and the patients enrolled in this study.

Conclusion

In patients undergoing hip replacement surgery, the administration of ulinastatin was associated with a significant reduction in opioid consumption within the first 72 h after surgery. Specifically, patients who received ulinastatin as a part of their postoperative pain management strategy needed significantly lower doses of opioids to manage pain during this period than those who were managed with the standard analgesic regimen alone. This reduction in opioid use did not result in increased pain scores, indicating that ulinastatin effectively contributed to pain control.

Data Sharing Statement

1. Will individual participant data be available (including data dictionaries)?

No.

1. What data in particular will be shared?

Not available.

1. What other documents will be available?

Study Protocol.

1. When will data be available (start and end dates)?

Immediately following publication. No end date.

1. With whom?

Not applicable.

1. For what types of analyses?

Not applicable.

1. By what mechanism will data be made available?

Not applicable.

Ethics Approval and Consent to Participate

The study was performed in compliance with the guidelines for human studies and conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was given by the participants and the study was approved by the the Ethics Committee of Tianjin Jizhou People's Hospital. (IRB2023-15, approval date: May 26, 2023).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Chunliu Hou and Ying Liu are co-first authors for this study. The authors declare that they have no competing interests in this work.

References

1. Koehler RM, Okoroafor UC, Cannada LK. A systematic review of opioid use after extremity trauma in orthopedic surgery. *Injury*. 2018;49(6):1003–1007. doi:10.1016/j.injury.2018.04.003
2. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK. Future projections of total hip and knee arthroplasty in the UK: results from the UK clinical practice research datalink. *Osteoarthritis Cartilage*. 2015;23(4):594–600. doi:10.1016/j.joca.2014.12.022
3. Tang X, Wang D, Liu Y, et al. The comparison between total hip arthroplasty and hemiarthroplasty in patients with femoral neck fractures: a systematic review and meta-analysis based on 25 randomized controlled trials. *J Orthopaedic Surg Res*. 2020;15(1):596. doi:10.1186/s13018-020-02122-6
4. Liu Y, Chen X, Zhang P, Jiang B. Comparing total hip arthroplasty and hemiarthroplasty for the treatment of displaced femoral neck fracture in the active elderly over 75 years old: a systematic review and meta-analysis of randomized control trials. *J Orthopaedic Surg Res*. 2020;15(1):215. doi:10.1186/s13018-020-01725-3
5. Dahl V, Raeder JC. Non-opioid postoperative analgesia. *Acta Anaesthesiol Scand*. 2000;44(10):1191–1203. doi:10.1034/j.1399-6576.2000.441003.x
6. Kehlet H, Rung GW, Callesen T. Postoperative opioid analgesia: time for a reconsideration? *J Clin Anesth*. 1996;8(6):441–445. doi:10.1016/0952-8180(96)00131-6
7. Gazendam A, Ekhtiari S, Horner NS, Nucci N, Dookie J, Ayeni OR. Perioperative nonopioid analgesia reduces postoperative opioid consumption in knee arthroscopy: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2021;29(6):1887–1903. doi:10.1007/s00167-020-06256-2
8. Sullivan MD, Edlund MJ, Zhang L, Ünützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166(19):2087–2093. doi:10.1001/archinte.166.19.2087

9. Guo ZB, Tang L, Wang LP, et al. The analgesic effects of ulinastatin either as a single agent or in combination with sufentanil: a novel therapeutic potential for postoperative pain. *Eur J Pharmacol.* 2021;907:174267. doi:10.1016/j.ejphar.2021.174267
10. Andelman SM, Bu D, Debellis N, et al. Preoperative patient education may decrease postoperative opioid use after meniscectomy. *Arthrosc Sports Med Rehabil.* 2020;2(1):e33–e38. doi:10.1016/j.asmr.2019.10.006
11. Probst P, Zschke S, Heger P, et al. Evidence-based recommendations for blinding in surgical trials. *Langenbecks Arch Surg.* 2019;404(3):273–284. doi:10.1007/s00423-019-01761-6
12. Rucinski K, Cook JL. Effects of preoperative opioid education on postoperative opioid use and pain management in orthopaedics: a systematic review. *J Orthop.* 2020;20:154–159. doi:10.1016/j.jor.2020.01.020
13. Atal SS, Atal S. Ulinastatin - a newer potential therapeutic option for multiple organ dysfunction syndrome. *J Basic Clin Physiol Pharmacol.* 2016;27(2):91–99. doi:10.1515/jbcpp-2015-0003
14. Lee B, Lee SY, Kim NY, et al. Effect of ulinastatin on postoperative renal function in patients undergoing robot-assisted laparoscopic partial nephrectomy: a randomized trial. *Surg Endosc.* 2017;31(9):3728–3736. doi:10.1007/s00464-017-5608-8
15. Wang N, Liu X, Zheng X, et al. Ulinastatin is a novel candidate drug for sepsis and secondary acute lung injury, evidence from an optimized CLP rat model. *Int Immunopharmacol.* 2013;17(3):799–807. doi:10.1016/j.intimp.2013.09.004
16. He QL, Zhong F, Ye F, et al. Does intraoperative ulinastatin improve postoperative clinical outcomes in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Biomed Res Int* 2014;2014:630835. doi:10.1155/2014/630835
17. Nakahama H, Obata K, Sugita M. Ulinastatin ameliorates acute ischemic renal injury in rats. *Renal Failure.* 1996;18(6):893–898. doi:10.3109/08860229609047715
18. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int.* 2012;32(6):1491–1502. doi:10.1007/s00296-011-2263-6
19. Nuutinen LS, Laitinen JO, Salomäki TE. A risk-benefit appraisal of injectable NSAIDs in the management of postoperative pain. *Drug Safety.* 1993;9(5):380–393. doi:10.2165/00002018-199309050-00006
20. Howard R, Fry B, Gunaseelan V, et al. Association of opioid prescribing with opioid consumption after surgery in Michigan. *JAMA Surgery.* 2019;154(1):e184234. doi:10.1001/jamasurg.2018.4234
21. Payne R. Limitations of NSAIDs for pain management: toxicity or lack of efficacy? *J Pain.* 2000;1(3 Suppl):14–18. doi:10.1054/jpai.2000.16611
22. Shanahan CW, Reding O, Holmdahl I, et al. Opioid analgesic use after ambulatory surgery: a descriptive prospective cohort study of factors associated with quantities prescribed and consumed. *BMJ open.* 2021;11(8):e047928. doi:10.1136/bmjopen-2020-047928
23. Helander EM, Menard BL, Harmon CM, et al. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep.* 2017;21(1):3. doi:10.1007/s11916-017-0607-y
24. Kandarian BS, Elkassabany NM, Tamboli M, Mariano ER. Updates on multimodal analgesia and regional anesthesia for total knee arthroplasty patients. *Best Pract Res Clin Anaesth.* 2019;33(1):111–123. doi:10.1016/j.bpa.2019.02.004
25. Leow KS, Chew KM, Chawla A, Lim TC. Sonographic assessment of musculoskeletal causes of calf pain and swelling. *Emerg Radiol.* 2019;26(3):349–359. doi:10.1007/s10140-019-01680-5
26. Wang Q, Jin Q, Cai L, et al. Efficacy of diosmin in reducing lower-extremity swelling and pain after total knee arthroplasty: a randomized, controlled multicenter trial. *J Bone Joint Surg Am Vol.* 2024;106(6):492–500. doi:10.2106/JBJS.23.00854
27. Jiang W, Yu X, Sun T, et al. ADJunctive ulinastatin in sepsis treatment in China (ADJUST study): study protocol for a randomized controlled trial. *Trials.* 2018;19(1):133. doi:10.1186/s13063-018-2513-y
28. Guo M, Zhou B. Clinical efficacy of ulinastatin in the treatment of unliquefied pyogenic liver abscess complicated by septic shock: a randomized controlled trial. *Immun Inflamm Dis.* 2023;11(4):e822. doi:10.1002/iid3.822
29. Belcaid I, Eipe N. Perioperative pain management in morbid obesity. *Drugs.* 2019;79(11):1163–1175. doi:10.1007/s40265-019-01156-3
30. Darville-Beneby R, Lomanowska AM, Yu HC, et al. The impact of preoperative patient education on postoperative pain, opioid use, and psychological outcomes: a narrative review. *Can J Pain.* 2023;7(2):2266751.

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