Journal of Pain Research

Dovepress
Taylor & Francis Group

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LETTER

Comment on "Efficacy and Safety Comparison of Ulinastatin versus Flurbiprofen Axetil for Preemptive Analgesia in Reducing Opioid Burden After Total Knee Arthroplasty: A Randomized Controlled Trial" [Letter]

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Dear editor

We read with great interest the article entitled "Efficacy and Safety Comparison of Ulinastatin Versus Flurbiprofen Axetil for Preemptive Analgesia in Reducing Opioid Burden After Total Knee Arthroplasty: A Randomized Controlled Trial" by wang et al.[1] This well-designed, double-blind, randomized, placebo-controlled trial provides the first head-to-head comparison of a single pre-incisional dose of ulinastatin (UTI) versus flurbiprofen axetil (FA) for preemptive analgesia in patients undergoing Total Knee Arthroplasty (TKA). The study convincingly demonstrates the superiority of UTI in significantly reducing cumulative 72-hour morphine consumption and lowering the incidence of adverse reactions, particularly delirium. The preliminary exploration of its mechanism, involving the modulation of the balance between pro-inflammatory (IL-6) and anti-inflammatory (IL-10) factors, is commendable. These findings position UTI as a promising non-opioid option for multimodal analgesia in the perioperative period of TKA. However, we would like to highlight several limitations that warrant further discussion and which also point toward valuable directions for future research.

Firstly, the article selected a single preoperative dose of UTI (30 IU) and FA (100 mg) but did not elaborate on the rationale for these specific dosage choices. For instance, UTI is often administered at higher or divided doses in other studies.[2,3] It is recommended to cite prior dose-finding studies or present pharmacodynamic data to justify the current dose selection. Alternatively, incorporating multiple dose groups in the study design would have been valuable to explore the optimal dosing regimen. Furthermore, we have identified a critical discrepancy in the reported dosage of UTI. The authors state a dose of "30 IU", which is equivalent to 30 International Units. However, UTI is commercially available in vials containing 50,000 IU or 100,000 IU per vial. A 30 IU dose is pharmacologically implausible and represents a reduction of three orders of magnitude from the lowest available unit. We strongly suspect a spelling error where "300,000 IU" was intended but mistakenly written as "30 IU". This requires immediate clarification and correction, as it fundamentally impacts the interpretation and reproducibility of the study.

Secondly, despite randomization, a significant imbalance in stroke history was observed between the FA group (20%) and the control group (2%). Although the authors stated that this did not affect the primary outcome, the disparity may confound the incidence of postoperative delirium or other neurological adverse events, which are key secondary endpoints. It is recommended to implement stratification by stroke history during randomization or explicitly exclude patients with recent or symptomatic stroke in the exclusion criteria.

Thirdly, the authors concluded that "the analgesic effect of the ulinastatin group is not inferior to the control group" based on "no difference in VAS" and "a difference in morphine consumption." However, this overlooks the potential

Received: 20 November 2025
Accepted: 10 December 2025
Published: 16 December 2025

ceiling effect of the pain score,[4,5] which may fail to reflect the true difference in pain levels. We recommended to supplement the analysis with data on the number of "breakthrough pain" episodes or PCIA compressions to evaluate the analgesic effect more comprehensively.

In conclusion, the study makes a meaningful contribution to TKA analgesia research. Addressing the above points in future studies would strengthen the evidence base for UTI and better inform clinical decision-making. We appreciate the authors' efforts in advancing non-opioid analgesic strategies and look forward to more comprehensive investigations in this field.

Disclosure

The authors declare that there is no conflict of interest in this communication.

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https://doi.org/10.2147/JPR.S583232