



Intraoperative Ketamine and Postoperative Outcomes After Total Knee Arthroplasty: Association with Revision Surgery and Analgesic Use

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Abstract

Background: Ketamine is widely used as an anesthetic adjunct in total knee arthroplasty (TKA), yet its association with surgical revision and postoperative analgesic exposure remains unclear.

Objectives: To evaluate the association between intraoperative ketamine and one-year revision surgery as well as early postoperative analgesic exposure following primary TKA.

Methods: We conducted a retrospective, propensity-matched cohort study on the TriNetX Global Collaborative Network. Adults undergoing primary TKA with documented intraoperative ketamine were compared to those without ketamine exposure. Matching used demographic, diagnostic, and perioperative factors. Outcomes included one-year arthroplastic revision, 90-day exposure to any analgesic and specific classes (opioids, NSAIDs, acetaminophen), and prescription counts.

Results: After 1:1 matching, 31,575 ketamine-exposed patients were compared with 31,575 controls. Ketamine exposure was associated with higher one-year revision risk (1.7% vs 1.2%; HR 1.38, $p < 0.001$) and increased 90-day exposure to any analgesic (87.3% vs 84.1%; RR 1.04; HR 1.09, $p < 0.001$) and opioids (83.1% vs 79.8%; RR 1.04; HR 1.09, $p < 0.001$), while NSAID exposure was slightly lower (5.3% vs 5.9%; RR 0.90; HR 0.91, $p < 0.001$). The mean number of prescriptions among exposed patients was modestly lower in the ketamine group.

Conclusion: In this large multicenter cohort, intraoperative ketamine was associated with greater risks of revision surgery and early postoperative opioid and analgesic exposure. While confounding by indication is possible, these findings raise concerns about ketamine's long-term impact in TKA. Prospective randomized studies are warranted.

Keywords: Total Knee Arthroplasty; Ketamine; Revision Surgery; Postoperative Analgesia; Opioid Exposure

Introduction

Total knee arthroplasty (TKA) is one of the most frequently performed orthopedic procedures worldwide, with over 1.2 million cases projected to be performed in the United States by 2030 [1]. However, despite its overall success in decreasing pain and reviving function, TKA still maintains numerous challenges related to postoperative pain control and risk of revision surgery [2, 3]. A multimodal approach is therefore essential to optimize recovery while minimizing opioid-related complications [4].

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has gained popularity as an anesthetic adjunct in orthopedic surgery [5]. Some reasons for its common use include its ability to prevent opioid induced hyperalgesia, reduction in acute postoperative pain, and thus overall decrease opioid consumption [6-8]. These effects have led to its inclusion in some enhanced recovery protocols for TKA [9]. However, even with all these short term benefits, little is known about the long term impact that intraoperative ketamine use has on extended analgesic requirements.

Although randomized trials suggest ketamine can reduce opioid consumption in the short term [7, 10], these studies were underpowered to assess long-term outcomes. Recent large-scale



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EHR analyses have suggested an association between intraoperative ketamine and higher one-year revision risk after TKA. Additionally, ketamine was associated with higher levels of short-term exposure to analgesics, especially opioids, postoperatively. These results show that despite its predetermined pain relief effects, ketamine in the setting of TKA could lead to higher rates of adverse long term postoperative outcomes.

The implications are clinically significant; as TKA revision is associated with increased morbidity, higher cost, and resource utilization compared to the initial procedure [11, 12]. Similar complications were shown in other studies where long term analgesic exposure post TKA proved to be a predictor of delayed recovery and long-term opioid dependence [13]. Clarifying the association between ketamine exposure and these outcomes is therefore critical.

Our goal with this study was to use the TriNetX Global Collaborative Network to conduct a retrospective analysis to determine whether intraoperative ketamine use with primary TKA is linked to revision surgery and early postoperative analgesic exposure. Our hypothesis was that ketamine is associated with decreased postoperative pain medication use but initial evidence showed higher rates of complications so considering the possibility of harm is necessary.

Methods

A retrospective cohort analysis using de-identified EHR data from the TriNetX Global Collaborative Network Adults was conducted. Adults undergoing primary TKA between January 1, 2020 and January 1, 2025 were identified with CPT 27447 and ICD-10-PCS knee-replacement families 0SRC–0SRW. Additionally, a supporting SNOMED CT concept for TKA (e.g., 609588000 or 52734007) was permitted per cohort configuration.

The primary surgical outcome was any knee revision or removal within one year, identified by ICD-10-PCS 0SWC–0SWD (revision, right/left) and 0SPC–0SPD (removal, right/left). Medication outcomes were EHR medication-order-based exposure within one year to any analgesic, opioids, NSAIDs, and acetaminophen, plus the number of order-instances among exposed patients.

Exposure was defined as documented ketamine (RxNorm 6130) given on the day of surgery or on the preceding or following calendar day (–1 to +1 day relative to the index TKA). We excluded patients with opioid-related disorders or chronic pain syndromes recorded before index using ICD-10-CM F11.*, G89.2, G89.3, and G89.4. Follow-up for surgical outcomes was one year after index TKA. Medication outcomes were evaluated over the first 90 days; in sensitivity analyses we repeated medication outcomes over one year with similar conclusions.

Each cohort received 1:1 nearest-neighbor propensity score matching without replacement using a standard deviation caliper on the propensity score. Covariates included age, sex, BMI, prevalent comorbidities, and regional/neuraxial anesthesia procedures (64447, 64448, 64449, 64450, 64451, 62320–62327), resulting in balanced cohorts.

Statistical analysis included estimated risks, risk differences, risk ratios, and odds ratios, each with 95% confidence intervals. Time-to-event analyses using Kaplan–Meier estimates with log-rank tests, and hazard ratios. For medication “number-of-instances,” means among exposed patients using two-sample t-tests were compared.

Additionally, zero-exposure patients were excluded from these instance counts.

Results

After propensity score matching, 31,575 patients who received intraoperative ketamine during TKA were compared with 31,575 matched controls. Baseline demographics, comorbidities, and anesthesia characteristics were balanced between groups.

At one year, revision surgery occurred in 1.7% of ketamine patients versus 1.2% of controls (HR 1.38, 95% CI 1.21–1.57; $p < 0.001$).

In the first 90 days postoperatively, ketamine exposure was associated with higher rates of analgesic use overall (87.3% vs 84.1%) and specifically opioid use (83.1% vs 79.8%), both with hazard ratios of approximately 1.09 ($p < 0.001$). NSAID use was slightly lower in the ketamine group (5.3% vs 5.9%; HR 0.91; $p = 0.009$). Additionally, acetaminophen use was more frequent in the ketamine cohort (75.1% vs 71.9%; HR 1.09; $p < 0.001$).

Among patients who received medications, the mean number of prescription instances was modestly lower in the ketamine group for analgesics overall (2.73 vs 2.97), opioids (2.58 vs 2.72), and acetaminophen (1.99 vs 2.16), while NSAID counts were similar between groups.

Overall, intraoperative ketamine use during TKA was associated with greater risk of revision surgery and higher early postoperative analgesic exposure, despite slightly fewer prescriptions per exposed patient.

Discussion

In this study, we found that patients who received intraoperative ketamine during TKA were associated with a higher one-year revision rate and increased short-term postoperative exposure to opioids and acetaminophen. These findings contrast with prior randomized trials and meta-analyses that demonstrated reduced acute pain and opioid consumption within the postoperative period [6–8]. More recent studies with S-ketamine have suggested improvements in early recovery quality and reduced rebound pain [15], yet our results highlight that these benefits may not translate to longer-term outcomes.

Several factors may explain this discrepancy, with the patient population itself being a major factor. Ketamine is often reserved for more complex or higher-risk cases, patients with significant baseline pain, opioid tolerance, or other comorbidities that already predispose them to worse outcomes. Despite rigorous matching and analysis, residual confounding variables likely reside. Another factor to consider may be practice variability across facilities. Unlike controlled clinical trials where dosing and timing are standardized, the real-world use of ketamine differs greatly across institutions, which may blunt its effectiveness or introduce additional risks. Furthermore, ketamine’s ability to block NMDA receptors can help reduce acute pain, but there is little evidence to suggest it has any meaningful effect on healing, implant survival, or long-term function [16].

Our observation that opioid use remained higher in the ketamine group despite slightly lower NSAID exposure reflects the nuance that short-term relief may not translate into durable benefit. Revision arthroplasty carries significant morbidity, economic burden, and diminished quality of life [17], while persistent opioid use after joint replacement has become a serious public health concern [18].

These findings emphasize the need to evaluate perioperative analgesic strategies not only for immediate pain relief but also for their impact on long-term outcomes.

Some limitations include reliance on retrospective electronic health record data, which means that we could not assess patient-reported pain scores, functional recovery, or the specific reasons why revisions were performed. Dose, route, and duration of ketamine were also unavailable, yet these are key details that likely influence outcomes.

Future studies should focus on clarifying these associations prospectively. Trials that standardize ketamine dosing, monitor patient-reported outcomes, and explore biological mechanisms underlying revision risk would help determine whether the association we observed represents true harm or is mainly the result of confounding. Until then, ketamine should be used thoughtfully and selectively in TKA, with recognition that its greatest strength may remain in short-term analgesia rather than long-term protection.

Limitations

This study is retrospective and observational, which limits causal inference. Despite propensity matching, residual confounding is likely, including case complexity, preoperative pain severity, opioid tolerance, implant type, surgical time, tourniquet use, tranexamic acid, block technique details, periarticular infiltration, rehabilitation protocols, and discharge disposition. Exposure was defined by medication orders within a narrow perioperative window, so dose, route, infusion versus bolus, and duration were unavailable, and true ingestion or administration could not be confirmed. Outcomes relied on coding and medication orders, not patient reported pain, function, or reasons for revision such as infection, instability, or stiffness. Site level practice variation may bias associations. Follow up for revision was one year, which may miss later failures. Generalizability is limited to health systems represented in the TriNetX network.

Clinical Implications

Use ketamine selectively rather than by default. Reserve it for clear indications such as documented opioid tolerance or high risk of hyperalgesia, and record dose, route, timing, and duration. Prioritize regional anesthesia and periarticular infiltration, and optimize scheduled acetaminophen and NSAIDs when not contraindicated. Implement preoperative opioid exposure screening, set realistic expectations, use limited discharge quantities with taper plans, and monitor for new persistent opioid use at 90 to 180 days. Build perioperative pathways that avoid auto selecting ketamine, and audit its use alongside revision drivers and infection rates. Consider alternative adjuncts when appropriate, such as dexmedetomidine, magnesium, or lidocaine infusions, within a multimodal regimen tailored to patient risk.

AI Declaration

Artificial intelligence tools, including ChatGPT (OpenAI), were used in the preparation of this manuscript for tasks such as language refinement, organization of author-drafted content, and formatting assistance. All data analysis, interpretation, and critical content were conducted and reviewed by the authors. The final manuscript was thoroughly edited and approved by all authors to ensure accuracy, originality, and compliance with ethical standards. No AI tool was used for data generation, statistical analysis, or drawing scientific conclusions.

Conclusion

In this large multicenter propensity matched cohort, intraoperative ketamine use during primary total knee arthroplasty was associated with a higher one year revision rate and greater early postoperative exposure to opioids and any analgesic, with slightly lower NSAID exposure. Although unmeasured confounding cannot be excluded, the pattern of associations suggests that routine ketamine use may not yield longer term benefits after total knee arthroplasty. Until prospective randomized studies clarify causality, teams should apply ketamine judiciously for defined indications within multimodal, regional heavy pathways, pair its use with structured opioid stewardship, and track long term outcomes rather than focusing only on immediate analgesia.

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