Randomized Controlled Study of Ketamine Administration for Postoperative Pain Management in Patients Undergoing Knee Arthroplasty

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1. Background and Rationale

Ketamine is a widely used NMDA receptor antagonist with strong analgesic properties. International studies demonstrate its efficacy and safety for perioperative and postoperative pain management, particularly as part of multimodal analgesia after major surgery. Subanesthetic doses (0.06–0.3 mg/kg/h) are associated with significant opioid-sparing effects and lower rates of postoperative nausea, vomiting, and neuropsychiatric complications. In Russia, ketamine is not currently labeled for postoperative analgesia, highlighting the need for high-quality evidence in this context.

2. Objectives

Primary Objective:

- ✓ To evaluate whether intravenous ketamine infusion reduces opioid consumption within the first 24 hours after knee arthroplasty compared to standard analgesia.

Secondary Objectives:

- ✓ To compare pain intensity at multiple time points within 24 hours postoperatively.
- ✓ To assess the incidence and severity of neuropsychiatric adverse events and postoperative nausea/vomiting.
- ✓ To determine the total number of ketamine boluses and cumulative dose administered in the ketamine group.

3. Study Design

Type: Prospective, randomized, controlled, single-center study.

Study Period: July 2025 – January 2026.

Setting: N.I. Pirogov National Medical and Surgical Center.

This study was preceded by a pilot phase (n=42, conducted separately) to inform sample size calculations and protocol refinement.

4. Study Population

Inclusion Criteria:

- ✓ Age >18 and <90 years.
- ✓ Undergoing knee arthroplasty.

Exclusion Criteria:

- ✓ Age <18 or >90 years.
- ✓ Spinal anesthesia intraoperatively.
- ✓ Epidural analgesia postoperatively.
- ✓ Sciatic nerve, genicular nerve, or lumbar plexus block perioperatively.
- ✓ Known allergy to ketamine or NSAIDs.
- ✓ Contraindications to ketamine as specified in the product instructions.
- ✓ More than 24 hours elapsed since the end of surgery.
- ✓ Ineffectiveness of analgesia provided by the study protocol.

5. Interventions

Intervention Group (Ketamine + Standard Analgesia):

- ✓ Ketoprofen 100 mg twice daily (dose adjustments allowed).
- ✓ Paracetamol 1000 mg every 8 hours (adjustments allowed).
- ✓ Continuous ketamine infusion via PCA: 0.15 mg/kg/h, 1 mg bolus, 5 min lockout, max 500 mg/24 h, administered via a dedicated peripheral line.
- ✓ Morphine 10 mg IM as needed for breakthrough pain.

Control Group (Standard Analgesia Only):

- ✓ Ketoprofen 100 mg twice daily (dose adjustments allowed).
- ✓ Paracetamol 1000 mg every 8 hours (adjustments allowed).
- ✓ Morphine 10 mg IM as needed for breakthrough pain.

Regional Anesthesia:

Repeat femoral nerve block under ultrasound guidance (ropivacaine 0.5% up to 10 ml)

in cases of severe femoral nerve pain postoperatively. Patients requiring repeated block will be analyzed separately.

6. Outcomes

Primary Outcome:

1. Total opioid analgesic consumption (converted to morphine equivalents, mg) within the first 24 hours after surgery.

Secondary Outcomes:

1. Pain intensity by NRS at 0, 2, 4, 6, 10, 14, 18, and 24 hours after surgery.
2. Incidence and severity of neuropsychiatric adverse events (graded by CTCAE).
3. Incidence of postoperative nausea and vomiting.
4. Total number of ketamine boluses and cumulative ketamine dose (intervention group).

7. Sample Size Calculation

A preliminary pilot study involving 42 patients was conducted separately to assess the variability of key parameters, including pain intensity measured by the Numeric Rating Scale (NRS) and opioid analgesic consumption. This pilot phase was completed prior to the initiation of the main study and served to inform protocol refinement and sample size estimation. Based on the pilot data, the standard deviation of the primary endpoint (total morphine equivalents consumed in the first 24 hours postoperatively) and the minimal clinically important difference between groups were calculated. Using these pilot-derived parameters, a formal sample size calculation was performed with a statistical power of 80% and a significance level of $p < 0.05$. An additional 10% margin was added to account for potential dropouts and study withdrawals, yielding an initial target of 68 patients (34 per group). However, the sample size was subsequently increased to 100 patients (50 per group) to further strengthen statistical validity and enable subgroup analyses, particularly for patients requiring repeated femoral nerve blocks. Patients undergoing knee arthroplasty who met the eligibility criteria were enrolled in the main study between July 2025 and January 2026. The pilot phase cohort (n=42) was conducted as a separate preliminary

investigation and is not included in the main study enrollment of 100 participants reported herein.

8. Statistical Analysis

A pilot study with 42 patients was initially conducted to assess the variability of key parameters such as NRS pain scores and opioid analgesic consumption. The collected data allowed for the calculation of standard deviations and the minimal clinically significant difference between groups, which were then used to determine the required sample size (power 80%, alpha 0.05). An additional 10% was added for potential loss to follow-up, resulting in a sample size of 68 patients (34 per group).

Data Analysis:

Categorical variables will be compared using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables will be tested for normality using the Shapiro–Wilk test. For normally distributed variables, independent samples t-tests will be used; for non-normally distributed variables, the Mann–Whitney U test will be applied. Correlation analyses will use Pearson or Spearman correlation coefficients, depending on data distribution. Statistical significance will be set at $p < 0.05$.

Multivariable Analysis:

A multivariate binary logistic regression will be performed with the occurrence of at least one neuropsychiatric adverse event (yes/no) as the dependent variable. Independent variables included in the model will be:

- ✓ Ketamine dose at the onset of adverse event (mg)
- ✓ Total ketamine dose over 24 hours (mg)
- ✓ NRS pain scores at three time intervals (0–2 hours, 3–10 hours, 11–24 hours)
- ✓ Sex (male/female)
- ✓ Age (years)
- ✓ Body weight (kg)
- ✓ Height (cm)
- ✓ Analgesia effectiveness (0 = effective, 1 = ineffective)

All continuous variables will be included without prior categorization. Categorical variables will be binary coded. The model will be assessed by β coefficients, odds ratios (OR) with 95% confidence intervals, and p-values. Model quality will be evaluated using the Hosmer–Lemeshow test. Results will be considered statistically significant at $p < 0.05$.

All analyses will be performed using IBM SPSS Statistics version 27.0.

9. Ethics

The study protocol was approved by the Local Ethics Committee of the N.I. Pirogov National Medical and Surgical Center (approval number: [Protocol №4, 21-May-2025]). Informed consent will be obtained from all participants prior to enrollment.

10. References

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