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Comparison of Ketamine-Paracetamol and Fentanyl-Paracetamol Combinations versus Paracetamol Monotherapy for Postoperative Pain Control via Patient-Controlled Analgesia in Femoral Fracture Surgery: A Randomized Controlled Trial

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Comparison of Ketamine-Paracetamol and Fentanyl-Paracetamol Combinations versus Paracetamol Monotherapy for Postoperative Pain Control via Patient-Controlled Analgesia in Femoral Fracture Surgery: A Randomized Controlled Trial

Running Title: Ketamine vs. Fentanyl for Postoperative Pain

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ABSTRACT

Background: Acute pain after femoral fracture surgery is a major clinical challenge. Although patient-controlled analgesia (PCA) with opioids is standard, adverse effects limit its use. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist without respiratory depression, may be a valuable adjunct. This randomized trial compared the efficacy of ketamine-paracetamol and fentanyl-paracetamol combinations versus paracetamol monotherapy.

Methods: In this double-blind randomized controlled trial, 60 patients undergoing femoral fracture fixation were randomized to paracetamol alone (control), fentanyl (1 μg/kg) + paracetamol, or ketamine (0.3 mg/kg) + paracetamol via PCA. Pain was assessed using the Visual Analog Scale (VAS), and sedation using the Ramsay Sedation Scale at 0, 2, 6, 12, 18, and 24 hours postoperatively. Data were analyzed using repeated-measures ANCOVA and generalized estimating equations (GEE).

Results: Both combinations significantly reduced pain versus control ($P < 0.001$), with no difference between combinations ($P = 1.000$). Adjusted mean pain scores were 4.80 ± 0.24 (control), 3.60 ± 0.20 (ketamine), and 3.35 ± 0.23 (fentanyl). Both combinations improved alertness (lower Ramsay scores) versus control ($P < 0.001$).

Conclusions: Ketamine-paracetamol and fentanyl-paracetamol were equally effective and superior to paracetamol alone. Ketamine-paracetamol offers a safe, opioid-sparing alternative for postoperative pain management after femoral fracture surgery.

Trial Registration: Iranian Registry of Clinical Trials (IRCT) IRCT20250121064471N2; registered on 17 May 2026 (prospectively registered).

.**Keywords:** Patient-Controlled Analgesia, Ketamine, Fentanyl, Paracetamol, Femoral Fracture, Postoperative Pain

Introduction

Acute pain following major orthopedic surgeries, particularly femoral fracture fixation, represents a significant clinical challenge. Femoral fractures are among the most severe musculoskeletal injuries, predominantly requiring urgent surgical intervention [1]. The postoperative period is associated with severe pain that, if inadequately controlled, can lead to tachycardia, myocardial ischemia, ileus, hyperglycemia, delayed healing, and chronic pain. Proper pain management reduces these complications, shortens hospital stay, and decreases healthcare costs [2].

Patient-controlled analgesia (PCA) is a standard and effective approach for managing acute postoperative pain, allowing patients to self-administer predetermined doses of analgesics by pressing a button [3]. Currently, opioids, particularly fentanyl, are the primary drugs used in this method [4]. Fentanyl produces potent analgesic effects by binding to μ-opioid receptors in the central nervous system. However, its use is associated with numerous adverse effects including nausea, vomiting, pruritus, constipation, urinary retention, and most importantly, respiratory depression, which can compromise patient safety [5].

In recent years, considerable efforts have been made to find alternative compounds and reduce dependence on opioids [6]. Among these alternatives is ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that produces analgesic and anesthetic effects by inhibiting pain transmission in the central nervous system [7]. At low doses, ketamine provides effective analgesia without causing respiratory depression [6]. Paracetamol (acetaminophen), with its different

mechanism of action, is effective in controlling mild to moderate pain and can be used in multimodal analgesia approaches [8].

Despite the potential benefits of ketamine, sufficient evidence for direct comparison of the ketamine-paracetamol regimen with the standard fentanyl-paracetamol regimen in Iran is lacking. Several domestic and international studies have investigated the individual or combined effects of these drugs, but each has had limitations. For instance, the study by Hashemi et al. lacked a control group [9], and the study by Nosoohi et al. required a standard morphine control group [10]. Furthermore, in international studies, lack of blinding or heterogeneity in anesthesia methods were among the weaknesses [11,12].

This randomized double-blind controlled trial directly compared the efficacy and safety of ketamine-paracetamol and fentanyl-paracetamol combinations versus paracetamol monotherapy for postoperative pain control via PCA in femoral fracture surgery.

Methods

Study Design and Setting

This double-blind, parallel-group, randomized controlled trial was conducted at Modares Hospital, Iran. The study protocol was approved by the Ethics Committee of Saveh University of Medical Sciences (approval code: IR.SAVEHUMS.REC.1404.073). The trial was registered in the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20250121064471N2 on 17 May 2026 (Trial ID: 89222). All participants provided written informed consent prior to enrollment. The trial was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) guidelines. No changes were made to the trial design after initiation. This trial was designed as a superiority trial. Patient recruitment was conducted between 19 May 2026 and 20 July 2026. Follow-up was completed on 21 July 2026.

Participants

Patients aged 20 to 60 years with American Society of Anesthesiologists (ASA) physical status I or II, who were candidates for femoral fracture fixation surgery under general anesthesia, were screened for eligibility. Patients were recruited from the orthopedic department of Modares Hospital through consecutive sampling.

Exclusion criteria comprised a history of substance abuse, known allergy to any study medications, pregnancy or lactation, hepatic dysfunction, a history of seizure disorder or psychiatric illness, chronic pain or daily analgesic use for more than one week, and receipt of any regional nerve blocks during the perioperative period.

All surgeries were performed by the same surgical team, and all outcome assessments were conducted by trained nurses who were blinded to group allocation.

Sample Size

Sample size was calculated using the ANOVA formula for clinical trials with three independent groups[13]:

$$n = \frac{2 \times (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times \sigma^2}{d^2} \times f$$

σ = 0.7 f = 1.08 d = 1.0 $Z_{1-\beta}$=0.84 $Z_{1-\alpha/2} = 1.96$

The calculated sample size was 16 patients per group. Accounting for a 20% dropout rate, the final sample size was determined as 20 patients per group (total N = 60). No interim analyses were planned or conducted, and the trial was not stopped early.

Randomization and Allocation Concealment

Eligible participants were randomly assigned to one of three groups in a 1:1:1 ratio using block randomization with variable block sizes. Stratification was performed according to sex (male/female) and age (≥50 years vs. <50 years) to ensure balance across groups. The randomization sequence was generated using the Blockrand package in R software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. An independent investigator, who was not involved in patient enrollment, intervention delivery, or outcome assessment, performed the randomization and envelope preparation.

Blinding

This was a double-blind trial. Patients, attending physicians, and outcome assessor nurses were blinded to group allocation. All patient-controlled analgesia (PCA) pumps were identical in appearance and labeled only with coded letters (A, B, or C). The code key was accessible only to the independent pharmacist who prepared the study solutions and to the data monitor, neither of whom had any contact with patients or outcome assessors. The blinding integrity was maintained throughout the 24-hour study period.

Interventions

All patients received standardized general anesthesia. After intravenous administration of remifentanil (1 μg/kg) and midazolam (20 μg/kg) for premedication, thiopental (5 mg/kg) and atracurium (0.5 mg/kg) were used for induction. Anesthesia was maintained with isoflurane 1.2% in oxygen and repeated doses of atracurium (0.2 mg/kg) every 30 minutes. The anesthetic protocol intentionally minimized intraoperative opioid use as part of an opioid-sparing strategy consistent with enhanced recovery principles. At the end of surgery, neuromuscular blockade was reversed with neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg), and patients were extubated after regaining consciousness (13, 14). No other concomitant pain medications were administered during the 24-hour study period.

PCA Setup: Postoperative PCA pumps were prepared with the following contents:

Group	PCA Content	Dose
Control (C)	Paracetamol	10 mg/kg
Fentanyl (A)	Fentanyl + Paracetamol	1 μg/kg + 10 mg/kg
Ketamine (B)	Ketamine + Paracetamol	0.3 mg/kg + 10 mg/kg

All pumps were filled to a total volume of 100 mL with normal saline and set to deliver a bolus of 2 mL, infusion rate of 5 mL/h, and lockout interval of 60 minutes. Paracetamol was administered via the PCA pump in all groups to maintain blinding and ensure identical drug delivery methods across study arms. While paracetamol is typically administered as scheduled intravenous or oral doses in clinical practice, this methodological approach was chosen to standardize the study protocol[13-15].

Rescue Analgesia: If VAS score exceeded 3, 2 mg of morphine was administered intravenously, and the amount was recorded. Rescue morphine administration was recorded for clinical safety purposes but was not defined as a prespecified outcome in this study; therefore, systematic quantitative analysis of morphine consumption was not performed.

Primary Outcome

Postoperative Pain Intensity

Pain intensity was assessed using the Visual Analog Scale (VAS) – a 10-cm (100-mm) horizontal line ranging from 0 (no pain) to 10 (worst imaginable pain) [16]. Patients were asked to mark a point on the line corresponding to their perceived pain level. The distance from the zero point was measured in millimeters and recorded as the pain score.

Assessment Time Points: Immediately after surgery, and at 2, 6, 12, 18, and 24 hours postoperatively.

Clinical Interpretation: A reduction of ≥30% in VAS score compared to baseline was considered a clinically meaningful change [17].

Validity and Reliability: The VAS is a well-validated and reliable tool for pain measurement, with established psychometric properties. Williamson and Hoggart (2005) demonstrated that this scale has appropriate validity and reliability for clinical use [17].

Secondary Outcomes

1. Sedation Level

Sedation level was evaluated by a trained nurse using the Ramsay Sedation Scale (RSS) , which ranges from 1 (anxious and agitated) to 6 (unresponsive to painful stimuli) [18]. Assessment Time Points: Immediately after surgery, and at 2, 6, 12, 18, and 24 hours postoperatively.

Validity and Reliability: The validity and reliability of this scale have been confirmed for the Persian population by Motahhedian Tabrizi et al. (2010) [18]. No changes were made to the outcomes after trial initiation.

Statistical Analysis

Data were analyzed using SPSS version 26.0 and R software version 4.2.1. For the primary outcome (VAS pain scores), a repeated-measures analysis of covariance (ANCOVA) was performed, adjusting for baseline pain scores as a covariate, with Bonferroni correction for multiple comparisons. For the secondary outcome (Ramsay Sedation Scale scores), a generalized estimating equation (GEE) model with cumulative logit link was used to account for the ordinal nature of the data and within-subject correlation across time points. Analysis was performed on an intention-to-treat basis. There were no missing data for the primary and secondary outcomes. No subgroup or sensitivity analyses were performed. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 60 patients were enrolled in this study and randomly allocated to three groups (n = 20 per group). The flow of participants through the trial is shown in **Figure 1** (CONSORT flow diagram).

The overall mean age of participants was 36.88 ± 11.47 years, with 41 patients (68.33%) being male and 19 (31.67%) being female.

Recruitment took place from 19 May 2026 to 20 July 2026, and follow-up was completed on 21 July 2026. The trial was not stopped early.

Baseline demographic and clinical characteristics were well balanced across the three groups. There were no significant differences in sex distribution, ASA physical status, age, weight, duration of surgery, or preoperative fasting time among the groups ($P > 0.05$ for all comparisons). However, the mean baseline VAS pain score before intervention differed significantly between groups, with the control group reporting higher pain levels (8.25 ± 1.41) compared to the fentanyl group (5.00 ± 1.45) and the ketamine group (6.20 ± 1.64) ($P < 0.001$). These baseline differences were controlled for in subsequent analyses using appropriate statistical methods **(Table 1)**.

No adverse events were reported during the study period. No additional analyses were performed.

Pain Intensity Outcomes

Repeated-measures ANCOVA, adjusting for baseline pain, revealed a significant main effect of time on pain scores ($F (2.83, 158.62) = 6.11$, $P < 0.001$, partial $\eta^2 = 0.098$), indicating a progressive decline in pain over the 24-hour period across all groups. The time × group interaction was not

significant (F (5.66, 158.62) = 1.39, P = 0.223, partial η^2 = 0.047), suggesting similar pain reduction patterns among the three groups.

Between-group analysis showed a significant effect of intervention type on overall pain scores (F (2, 56) = 8.39, P < 0.001, partial η^2 = 0.231). Both ketamine-paracetamol (M = 3.60, SE = 0.20) and fentanyl-paracetamol (M = 3.35, SE = 0.23) groups had significantly lower pain scores than the control group (M = 4.80, SE = 0.24) (P < 0.001 for both). The mean difference was 1.45 (95% CI: 0.75 to 2.15) for fentanyl-paracetamol versus control, and 1.20 (95% CI: 0.50 to 1.90) for ketamine-paracetamol versus control. No significant difference was observed between the two combination groups (P = 1.000) **(Table 2, Figure 2).**

Ramsay Sedation Scale Results

After adjusting for baseline scores using a GEE model with cumulative logit link, both treatment group (Wald $\chi^2(2)$ = 19.91, P < 0.001) and time (Wald $\chi^2(4)$ = 20.15, P < 0.001) had significant effects on sedation levels, while baseline score was not a significant predictor (Wald $\chi^2(1)$ = 1.45, P = 0.228) **(Table 3)**.

Parameter estimates **(Table 4)** revealed that both ketamine (B = 1.78, SE = 0.44, P < 0.001) and fentanyl (B = 2.55, SE = 0.59, P < 0.001) significantly increased the likelihood of higher consciousness levels (lower Ramsay scores) compared to the control group. Peak sedation occurred at 2 hours (B = -3.07, SE = 0.72, P < 0.001) and 6 hours (B = -1.86, SE = 0.54, P = 0.001) post-intervention. From 12 hours onward, sedation levels stabilized with no significant differences compared to the 24-hour mark (P > 0.05).

Discussion

This double-blind randomized controlled trial compared the efficacy of ketamine-paracetamol and fentanyl-paracetamol combination regimens versus paracetamol monotherapy for acute postoperative pain management in patients undergoing femoral fracture fixation. Our findings demonstrate that both combination regimens were significantly more effective than paracetamol alone in reducing pain scores over the 24-hour postoperative period, with comparable efficacy between the two combination groups.

The significant reduction in pain scores observed with both combination regimens compared to paracetamol monotherapy aligns with the principles of multimodal analgesia, which advocates for the use of multiple analgesics with different mechanisms of action to achieve superior pain control while minimizing opioid-related adverse effects [19]. Paracetamol, while effective for mild to moderate pain, appears insufficient as monotherapy for the severe pain associated with major orthopedic surgeries such as femoral fracture fixation [8].

A notable finding was the significant difference in baseline pain scores between groups, with the control group reporting higher preoperative pain levels (8.25 ± 1.41) compared to the fentanyl (5.00 ± 1.45) and ketamine (6.20 ± 1.64) groups ($P < 0.001$). This baseline imbalance, although statistically adjusted using ANCOVA, may have influenced the observed outcomes. However, the consistency of the results across different statistical models and the robustness of the findings suggest that the observed treatment effects are genuine and not solely attributable to baseline differences. Furthermore, the fact that both combination regimens demonstrated superior efficacy compared to the control group, despite the control group having higher baseline pain (and thus potentially more room for improvement), strengthens the validity of our conclusions. The mean difference of 1.20–1.45 points on the VAS (95% CI: 0.50–2.15) represents a clinically meaningful reduction, as a ≥30% decrease from baseline is considered clinically significant.

Our finding that ketamine-paracetamol was as effective as fentanyl-paracetamol is clinically significant. Fentanyl, a potent μ-opioid receptor agonist, is widely used in PCA protocols but carries substantial risks including respiratory depression, nausea, vomiting, and constipation [20]. Ketamine, a non-competitive NMDA receptor antagonist, provides analgesia through a different mechanism without causing respiratory depression [7]. The comparable efficacy between these two regimens suggests that ketamine-paracetamol could serve as a safe alternative to fentanyl-based protocols, potentially reducing the burden of opioid-related adverse events.

These results are consistent with previous studies. Akhavanakbari et al. demonstrated that adding ketamine to morphine in PCA after orthopedic surgery significantly reduced morphine consumption [13]. Similarly, Ratanasuwan et al. found that ketamine-morphine combination reduced morphine consumption by 31.2% in the first 48 hours after upper abdominal surgery, without compromising analgesic efficacy [11]. Our study extends these findings by directly comparing ketamine with fentanyl, providing evidence that ketamine can effectively replace fentanyl in combination with paracetamol.

Regarding sedation levels, both intervention groups demonstrated significantly higher alertness (lower Ramsay scores) compared to the control group. This finding is noteworthy because excessive sedation is a concern with opioid-based analgesia [20]. The higher alertness in the ketamine group may be attributed to ketamine's sympathomimetic effects and its lack of respiratory depression [7]. The most pronounced sedation occurred at 2 and 6 hours postoperatively in all groups, likely reflecting the residual effects of general anesthesia and the initial bolus doses of analgesics. The stabilization of sedation levels after 6 hours is clinically reassuring.

The comparable efficacy and better sedation profile of ketamine-paracetamol compared to fentanyl-paracetamol support its potential role as a first-line option in multimodal analgesia

protocols for femoral fracture surgeries. By reducing reliance on opioids, this regimen may decrease the incidence of opioid-related adverse events, shorten hospital stays, and improve patient satisfaction[21].

Limitations

This study has several limitations. First, the administration of paracetamol via PCA, while methodologically necessary to maintain blinding, does not reflect standard clinical practice where paracetamol is typically given as scheduled intravenous or oral doses. Second, the control group demonstrated significantly higher baseline pain scores (8.25 ± 1.41 vs. 5.00–6.20 in the combination groups), which was statistically adjusted using ANCOVA but remains a potential confounder. Third, the relatively high early postoperative pain scores in the control group (VAS 7.90 at 2 hours) suggest that paracetamol monotherapy may be inadequate for this patient population. Fourth, rescue morphine consumption was not defined as a prespecified outcome; although recorded for safety, systematic quantitative analysis was not performed. Fifth, this was a single-center study with a modest sample size (n=20 per group). Finally, the 24-hour follow-up period does not capture long-term outcomes or chronic pain development. Future multicenter studies with larger sample sizes, scheduled paracetamol dosing, and extended follow-up are recommended to confirm these findings.

Conclusion

This double-blind randomized controlled trial demonstrated that both ketamine-paracetamol and fentanyl-paracetamol combination regimens were significantly more effective than paracetamol monotherapy in managing acute postoperative pain following femoral fracture fixation surgery ($P < 0.001$). Importantly, no significant difference in efficacy was observed between the two

combination groups (P = 1.000), suggesting that ketamine-paracetamol is as effective as the opioid-based fentanyl-paracetamol regimen.

Furthermore, both combination regimens were associated with better sedation profiles, with significantly higher levels of alertness (lower Ramsay scores) compared to the control group (P < 0.001). The most pronounced sedation occurred at 2 and 6 hours postoperatively, stabilizing thereafter.

These findings suggest that ketamine-paracetamol can serve as a safe and effective alternative to opioid-based regimens, potentially reducing opioid-related adverse effects while maintaining adequate analgesic efficacy. Clinicians should consider adopting this combination in multimodal analgesia protocols for patients undergoing major orthopedic surgeries. However, further multicenter studies with larger sample sizes are recommended to confirm these findings and evaluate long-term safety and efficacy.

Abbreviations

ANCOVA: Analysis of Covariance; ASA: American Society of Anesthesiologists; CONSORT: Consolidated Standards of Reporting Trials; GEE: Generalized Estimating Equations; IRCT: Iranian Registry of Clinical Trials; NMDA: N-methyl-D-aspartate; PCA: Patient-Controlled Analgesia; RCT: Randomized Controlled Trial; RSS: Ramsay Sedation Scale; SD: Standard Deviation; SE: Standard Error; VAS: Visual Analog Scale.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Saveh University of Medical Sciences (approval code: IR.SAVEHUMS.REC.1404.073). The trial was registered in the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20250121064471N2 on 17 May

2026 (Trial ID: 89222). All participants provided written informed consent prior to enrollment. The trial was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Consent for Publication

Not applicable.

Availability of Data and Materials

The trial protocol and statistical analysis plan are available from the corresponding author upon reasonable request. The de-identified individual participant data that support the findings of this study are also available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

M.S.S. and M.H. contributed to the conception and design of the study. M.S.S. performed the anesthetic procedures and data collection. M.H. contributed to data collection, statistical analysis, and interpretation. M.H. drafted the manuscript. Both authors read and approved the final manuscript.

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REFERENCES

1. Roberts KC, Brox WT, Jevsevar DS, Sevarino K. Management of hip fractures in the elderly. *J Am Acad Orthop Surg*. Feb 2015;23(2):131-7. doi:10.5435/jaaos-d-14-00432
2. Fiore JF, Jr., El-Kefraoui C, Chay MA, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet*. Jun 18 2022;399(10343):2280-2293. doi:10.1016/s0140-6736(22)00582-7
3. Pastino A, Lakra A. Patient-Controlled Analgesia. *StatPearls*. StatPearls Publishing

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4. Jun MR, Kim JM, Kim JY, Lee JH, Kim CE, Lee MO. Evaluation of basal rate infusion in intravenous patient-controlled analgesia for post-cesarean section pain management: A randomized pilot study. *Medicine (Baltimore)*. Feb 23 2024;103(8):e37122. doi:10.1097/md.0000000000037122
5. Jung H, Lee KH, Jeong Y, et al. Effect of Fentanyl-Based Intravenous Patient-Controlled Analgesia with and without Basal Infusion on Postoperative Opioid Consumption and Opioid-Related Side Effects: A Retrospective Cohort Study. *J Pain Res*. 2020;13:3095-3106. doi:10.2147/jpr.S281041
6. Shetabi H, Farsani D, Razani M. Effects of Ketamine, Fentanyl and Paracetamol on Pain Intensity and Hemodynamic Parameters after Deep Vitrectomy. *Journal of Ardabil University of Medical Sciences*. 03/01 2021;21:90-101. doi:10.52547/jarums.21.1.90
7. Ma X, Yan J, Jiang H. Application of Ketamine in Pain Management and the Underlying Mechanism. *Pain Res Manag*. 2023;2023:1928969. doi:10.1155/2023/1928969
8. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis*. Mar 2016;75(3):552-9. doi:10.1136/annrheumdis-2014-206914
9. Hashemi SM, Kiyabi F, Nikooseresht M, et al. PCA and Postoperative Pain Management After Orthopedic Surgeries. *Alborz University Medical Journal*. 08/01 2016;5:157-162. doi:10.18869/acadpub.aums.5.3.157
10. Nosoohi G, Tavakkol K, Basiri P, Khayambashi A, Izadi-Zamanabadi M. Comparison of Ketamine and Paracetamol in Addition to Morphine on Post-operative Pain Intensity after Laminectomy. *Journal of Isfahan Medical School*. 2022;40(676):443-450. doi:10.48305/jims.v40.i676.0443
11. Nonphiaraj S, Chanthawong S. Efficacy of a Combination of Ketamine and Morphine for Intravenous Patient Controlled-Analgesia in Upper Abdominal Surgery: A Prospective, Double-blind, Randomized Controlled Trial. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. 09/15 2021;104:1528-34. doi:10.35755/jmedassocthai.2021.09.12996

12. Sakai Y, Imai N, Miyasaka D, et al. Comparison of Intravenous Acetaminophen and Intravenous Patient-Controlled Analgesia Fentanyl after Total Hip Arthroplasty: A Multicenter Randomized Controlled Trial. *J Clin Med*. Nov 30 2023;12(23)doi:10.3390/jcm12237445
13. Akhavanakbari G, Mohamadian A, Entezariasl M. Evaluation the effects of adding ketamine to morphine in intravenous patient-controlled analgesia after orthopedic surgery. *Perspect Clin Res*. Apr 2014;5(2):85-7. doi:10.4103/2229-3485.128028
14. Eddie EA, Zahedi A, Jamaluddin SFB, Noor JM. Low-dose short infusion ketamine as adjunct to morphine for acute long bone fracture in the emergency department: a randomized controlled trial. *BMC Emerg Med*. May 9 2024;24(1):80. doi:10.1186/s12873-024-00997-w
15. Yılmaz M, Kudu E, Sanri E, Karacabey S, Akoglu H, Denizbasi A. Comparison of the Analgesic Effects of Low-Dose Ketamine Versus Fentanyl in Patients With Long Bone Fractures in the Emergency Department: A Prospective Observational Study. *Cureus*. Oct 2023;15(10):e46344. doi:10.7759/cureus.46344
16. Norozi V, Ghazi A, Amani F, Bakhshpoori P. Effectiveness of Sublingual Buprenorphine and Fentanyl Pump in Controlling Pain After Open Cholecystectomy. *Anesth Pain Med*. Jun 2021;11(3):e113909. doi:10.5812/aapm.113909
17. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. Aug 2005;14(7):798-804. doi:10.1111/j.1365-2702.2005.01121.x
18. Mottahedian Tabrizi E, Tadrisi S, Mohammadyari A, Ebadi A, Mirhashemi S. Validity and reliability of Ramsy sedation scale in adult patients hospitalized in critical care units. *IJCCN*. 2010;3(1):15-16.
19. Wick EC, Grant MC, Wu CL. Postoperative Multimodal Analgesia Pain Management With Nonopioid Analgesics and Techniques: A Review. *JAMA Surg*. Jul 1 2017;152(7):691-697. doi:10.1001/jamasurg.2017.0898
20. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain*. Jun 2002;3(3):159-80. doi:10.1054/jpai.2002.123652
21. Morrison SR, Magaziner J, McLaughlin MA, et al. The impact of post-operative pain on outcomes following hip fracture. *Pain*. Jun 2003;103(3):303-311. doi:10.1016/s0304-3959(02)00458-x

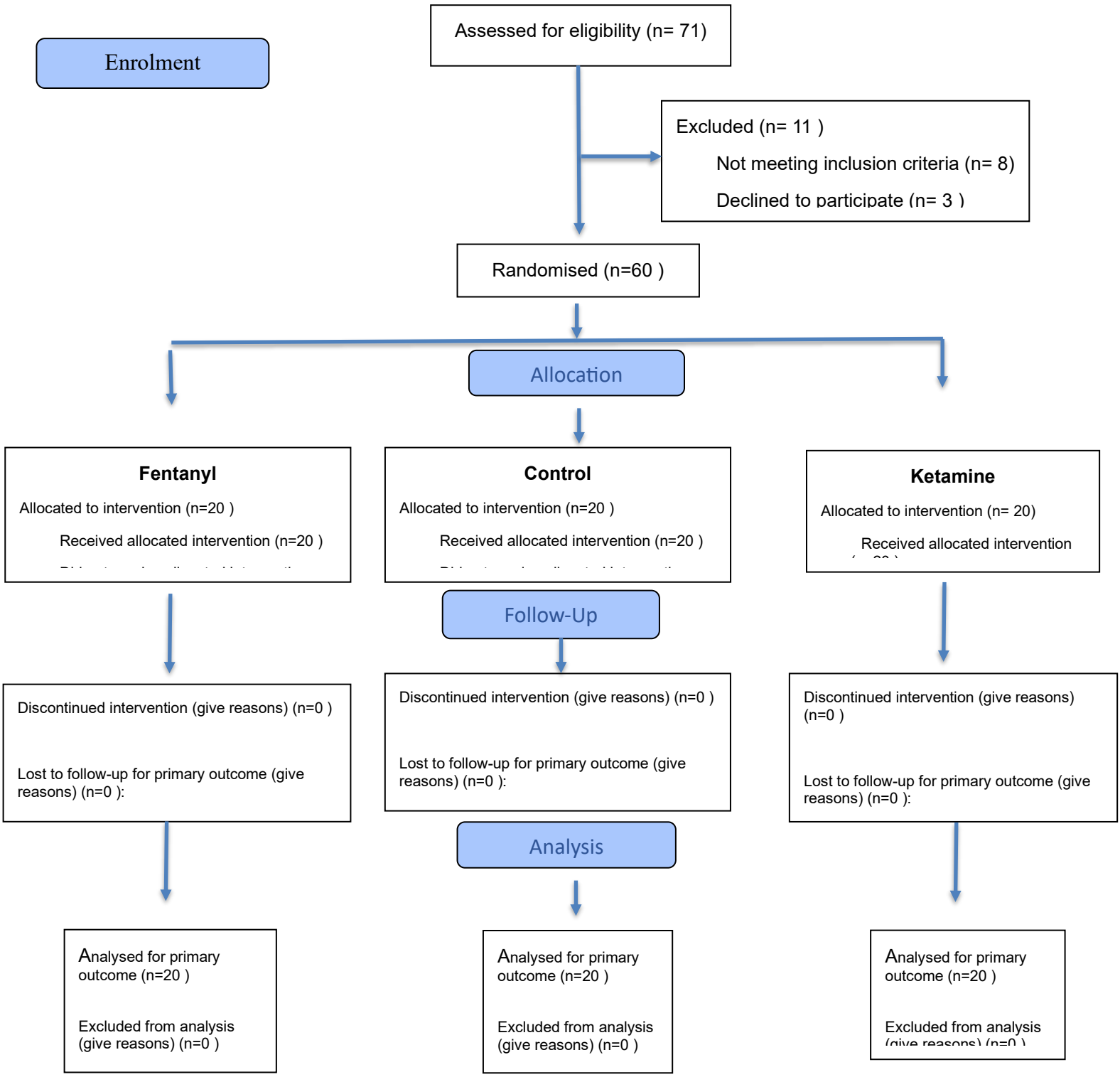


Figure 1: CONSORT 2025 Flow Diagram

Flow diagram of the progress through the phases of a randomised trial of three groups groups (that is, enrolment, intervention allocation, follow-up, and data analysis)

Table 1. Comparison of Demographic and Clinical Characteristics of Study Participants

Variable		Ketamine (n=20)	Fentanyl (n=20)	Control (n=20)	P-Value
Sex	Male	13 (65%)	15 (75%)	13 (65%)	0.735*
	Female	7 (35%)	5 (25%)	7 (35%)	
ASA	I	15 (75%)	18 (90%)	16 (80%)	0.589**
	II	5 (25%)	2 (10%)	4 (20%)	
Age, mean ± SD		35.90 ± 12.40	36.35 ± 11.40	36.88 ± 11.00	0.769***
Weight, mean ± SD		75.85 ± 16.00	77.80 ± 16.97	77.95 ± 16.24	0.903***
Surgery duration, mean ± SD		113.03 ± 21.72	115.25 ± 18.03	108.75 ± 29.01	0.668***
Fasting time, mean ± SD		8.20 ± 2.82	7.00 ± 1.84	7.95 ± 2.80	0.293***
Baseline VAS (pre-intervention), mean ± SD		6.20 ± 1.64	5.00 ± 1.45	8.25 ± 1.41	<0.001***

*Chi-square test; **Fisher's exact test; ***ANOVA

Table 2. Pain Scores (VAS) Across Time Points by Group

Time	Ketamine	Fentanyl	Control
VAS2	5.60 ± 1.05	4.80 ± 1.06	7.90 ± 1.45
VAS6	4.70 ± 1.22	3.85 ± 1.27	6.90 ± 1.74
VAS12	3.35 ± 1.14	2.70 ± 1.08	5.00 ± 1.69
VAS18	2.35 ± 0.93	1.85 ± 0.67	3.80 ± 1.47
VAS24	1.65 ± 0.75	1.55 ± 0.69	2.85 ± 1.18

Data are mean ± SD

Table 3. Main Effects of the GEE Model for Ramsay Sedation Score

Source	Wald Chi-Square	df	P-Value
Group	19.91	2	<0.001
Time	20.15	4	<0.001
Baseline (RAM0)	1.45	1	0.228

Table 4. Parameter Estimates from the GEE Model

Variable	B	SE	P-Value
Group (vs. Control)			
Ketamine	1.780	0.443	<0.001
Fentanyl	2.550	0.594	<0.001
Time (vs. 24h)			
2 hours	-3.072	0.725	<0.001
6 hours	-1.866	0.538	0.001
12 hours	-0.406	0.375	0.279
18 hours	0.170	0.158	0.283
Baseline (RAM0)	0.269	0.223	0.228

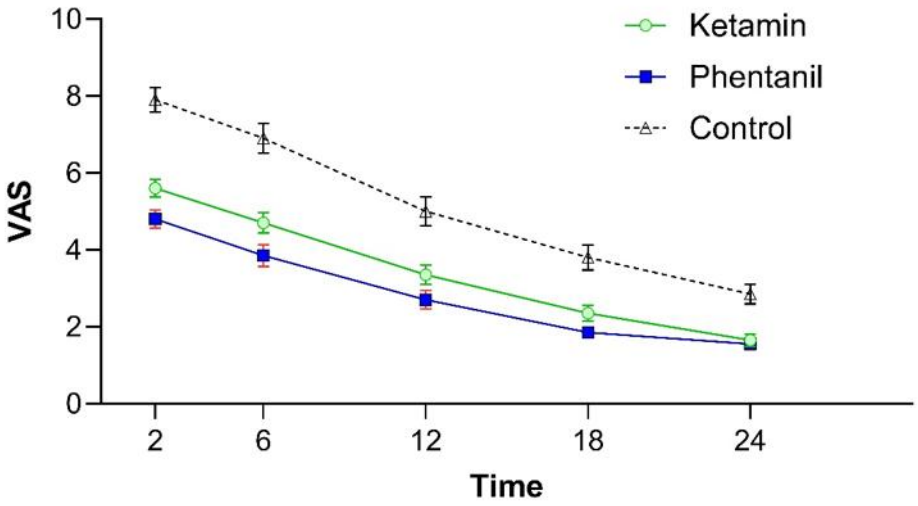


Figure 2. Mean Pain Scores (VAS) in the Three Groups Over the Study Period

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2025flowdiagram.docx
- CONSORT2025editablechecklist.docx