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# ANALGESIC EFFICACY OF NALBUPHINE WITH KETAMINE VERSUS NALBUPHINE WITH PLACEBO IN PATIENTS OF SCIATICA IN THE EMERGENCY DEPARTMENT

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**Abstract**

***Objective:*** *To compare*

***Study Design:*** *Quasi-experimental study*

***Place and Duration of Study:*** *Department of Emergency Medicine, Combined Military Hospital, Rawalpindi from January 2025- June 2025*

***Methodology:*** *A total of 192 patients were analyzed, divided into Group-A (n = 96) receiving IV nalbuphine with ketamine and Group-B (n = 96) receiving IV nalbuphine with placebo. Primary variables studied were the change in pain intensity, measured as the difference in Numerical Rating Scale (NRS) scores.*

***Results:*** *The median pre-treatment NRS score was 8.55 (1.2) in Group-A and 8.30 (1.1) in Group-B (p = 0.037). Pain scores at 60 minutes were 2.65 (2.2) versus 3.50 (2.1) (p < 0.001), and at 120 minutes 2.20 (1.6) versus 3.05 (1.8) (p < 0.001), respectively. The mean change in NRS from baseline at 30 minutes was significantly higher in Group-A being 4.65 (1.5) compared with Group-B 3.65 (1.5), (p<0.001). Group-A also demonstrated a markedly shorter mean time to effective pain relief 14.38 ± 5.53 minutes compared with Group-B of 22.17 ± 8.77 minutes (p < 0.001). The requirement for rescue analgesia was lower in Group-A with 0.89 ± 1.40 mg compared with Group-B of 3.91 ± 3.00 mg, (p < 0.001).*

***Conclusion:*** *The study concluded that combination of IV Nalbuphine with IV Ketamine provided superior analgesia, less rescue analgesia dose, comparative safety profile and less stay in the emergency department*

## INTRODUCTION

Sciatica, characterized by radiating pain along the sciatic nerve path, is a common neurological condition frequently encountered in emergency departments (ED). It often results from nerve root compression due to lumbar disc herniation, causing acute, debilitating pain that necessitates rapid and effective analgesia.[1] Opioids have traditionally served as the cornerstone of acute

pain management, yet concerns about side effects and dependency have stimulated interest in opioid-sparing strategies.[2] Among alternatives, nalbuphine, a mixed kappa agonist and mu antagonist, provides effective analgesia with a favorable safety profile, especially in terms of respiratory depression and abuse potential.[3] Similarly, ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a valuable analgesic adjunct due to its opioid-sparing effect and efficacy in neuropathic pain.[4]

Despite increasing adoption of these agents individually or in procedural sedation, there remains limited clinical evidence evaluating their synergistic use specifically in sciatica management within the ED setting which requires rapid patient assessment and treatment due to higher patient turnover.[5] Recent studies have explored ketamine's utility in nerve blocks and as an adjuvant in multimodal pain regimens, but these often lack direct comparison with commonly used analgesics like nalbuphine in this acute context.[6] Moreover, while nalbuphine has demonstrated analgesic parity with morphine in trauma and prehospital settings, its role when combined with sub-anesthetic ketamine doses for radicular pain has not been systematically investigated.[3] A combined approach reducing opioid associated side effects while providing adequate analgesia would serve to be conducive in the ED setting.

This study aims to address this gap by comparing the analgesic efficacy of nalbuphine combined with ketamine versus nalbuphine with placebo in patients presenting with sciatica in the ED. The findings may contribute to optimizing pain management strategies for acute neuropathic conditions while minimizing opioid exposure in high patient turnover settings.

## METHODOLOGY:

This quasi-experimental study was carried out at the Orthodontics department of Armed Forced Institute of Dentistry (AFID), Rawalpindi from January 2025-July 2025 after approval from the ethical review board (vide letter no. 918/Trg/May/2024). Sample size was calculated using the WHO sample size calculator for comparing two means, keeping the confidence interval at 95%, power at 90%, and margin of error based on the anticipated difference in pain reduction between treatment arms with addition of low-dose ketamine to opioid therapy produced a greater reduction in pain scores than opioids alone with placebo, with a mean difference of approximately 2.4 NRS points and a pooled standard deviation of 3.0.[7] Using these estimates, the expected detectable difference for the present study was conservatively set at 1.5 NRS points. The minimum sample size calculated using the WHO calculator was 84 patients per group. Allowing for a 10% rate of dropouts and incomplete data, the final sample size was raised to 96 patients per group, resulting in a total of 192 participants included in the final analysis according to the predetermined inclusion criteria.

**Inclusion criteria** consisted of patients between 18 and 65 years of age and presented with acute radicular leg pain radiating below the knee in a dermatomal pattern that was clinically consistent with nerve root irritation, baseline pain score of 5 or more on the Numerical Rating Scale (NRS), patients with symptom onset within seven days or those experiencing an acute exacerbation of known sciatica requiring parenteral analgesia, hemodynamically stable patients who could understand the study information and provide informed consent

**Exclusion criteria**

comprised patients exhibiting any red-flag findings suggesting serious spinal pathology, including suspected cauda equina syndrome, progressive neurological deficit, recent significant trauma, malignancy, or spinal infection, individuals with hypersensitivity to nalbuphine or ketamine, pregnant or breastfeeding women, or patients with significant cardiovascular instability, patients receiving chronic opioid therapy or those who had received opioids within six hours prior to presentation, patients lost to follow-up or non-consented to be included in the study.

Ethical approval had been obtained from the Institutional Review Board before commencement of the study, and all procedures adhered to the principles of the Declaration of

Helsinki. Written informed consent was obtained from each patient following adequate explanation of study objectives, risks, and benefits. Participation was entirely voluntary, and patients were informed that declining participation or withdrawing at any time would not affect the standard of care they were entitled to receive. Serious adverse events, if any occurred, were handled according to institutional guidelines, with provisions for emergency unblinding only when necessary for patient safety.

The study method included all patients as per the inclusion criteria furnished. The patients were divided into Group A (n=96) to receive IV Nalbuphine with IV Ketamine and Group B (n=96) to receive IV Nalbuphine with placebo. Once the eligibility assessment had been completed and written informed consent had been obtained, participants were allocated designated groups. Allocation concealment was maintained through sequentially numbered, sealed envelopes and coded infusion sets. All study medications were prepared in identical syringes and infusion bags to preserve blinding. Treating physicians, nursing staff, patients, and data collectors remained unaware of group assignments throughout the study period. Patients in Group-A (n = 96) received IV nalbuphine at a dose of 0.2 mg/kg administered slowly over 2–3 minutes, followed by IV ketamine at a sub-dissociative dose of 0.3 mg/kg diluted in 50 mL normal saline and infused over 10–15 minutes. Patients in Group-B (n = 96) received the same IV nalbuphine dose of 0.2 mg/kg administered in an identical manner, followed by an infusion of 50 mL normal saline over 10–15 minutes as placebo. All infusions were prepared in identical syringes and bags to ensure maintenance of blinding, and no additional ketamine or nalbuphine was administered outside the protocol except as documented rescue analgesia when required.

Data collection was carried out by the resident on duty in the Emergency Department. Pain scores were recorded before drug administration and at 15, 30, 60, and 120 minutes after infusion using the Numerical Rating Scale. Vital signs were monitored at the same intervals. Rescue analgesia was provided if pain remained uncontrolled, following a standardized protocol when NRS scores remained above 6 despite treatment for 30 minutes. Rescue analgesia given was in the form of IV Nalbuphine at a dose of 0.1 mg/kg. Adverse events, including hemodynamic changes, nausea, vomiting, dizziness, hallucinations, or respiratory depression, were recorded systematically. All data were entered into a secure electronic database with coded identifiers to ensure confidentiality.

Primary variables studied were the change in pain intensity, measured as the difference in Numerical Rating Scale (NRS) scores between baseline and 30 minutes after completion of the study drug infusion and the total rescue analgesia required in 120 minutes. Secondary variables included pain scores at 15, 60, and 120 minutes, the proportion of patients achieving ≥50% pain reduction at 30 minutes; time to onset of meaningful analgesia (≥3-point NRS reduction), hemodynamic parameters recorded at predefined intervals, incidence of adverse events including nausea, vomiting, dizziness, hallucinations, and hemodynamic instability, and emergency department length of stay.

Statistical data for age was checked for normality and was normally distributed. Variables including age, rescue analgesia used, time to initial pain relief, emergency room stay vital signs including systolic, diastolic blood pressure, heart rate, respiratory rate before and after treatment intervals were expressed as mean±SD and compared using the independent samples t-test. Pain scores assessed at specified interval using the NRS system were expressed as median with inter-quartile ranges and compared using the Mann-Whitney U test. Adverse effects including nausea, vomiting, dizziness, hallucinations and hemodynamic instability were expressed as frequency and percentage and compared using the Chi-square and Fisher exact test as appropriate. A p value of ≤0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 31.00.

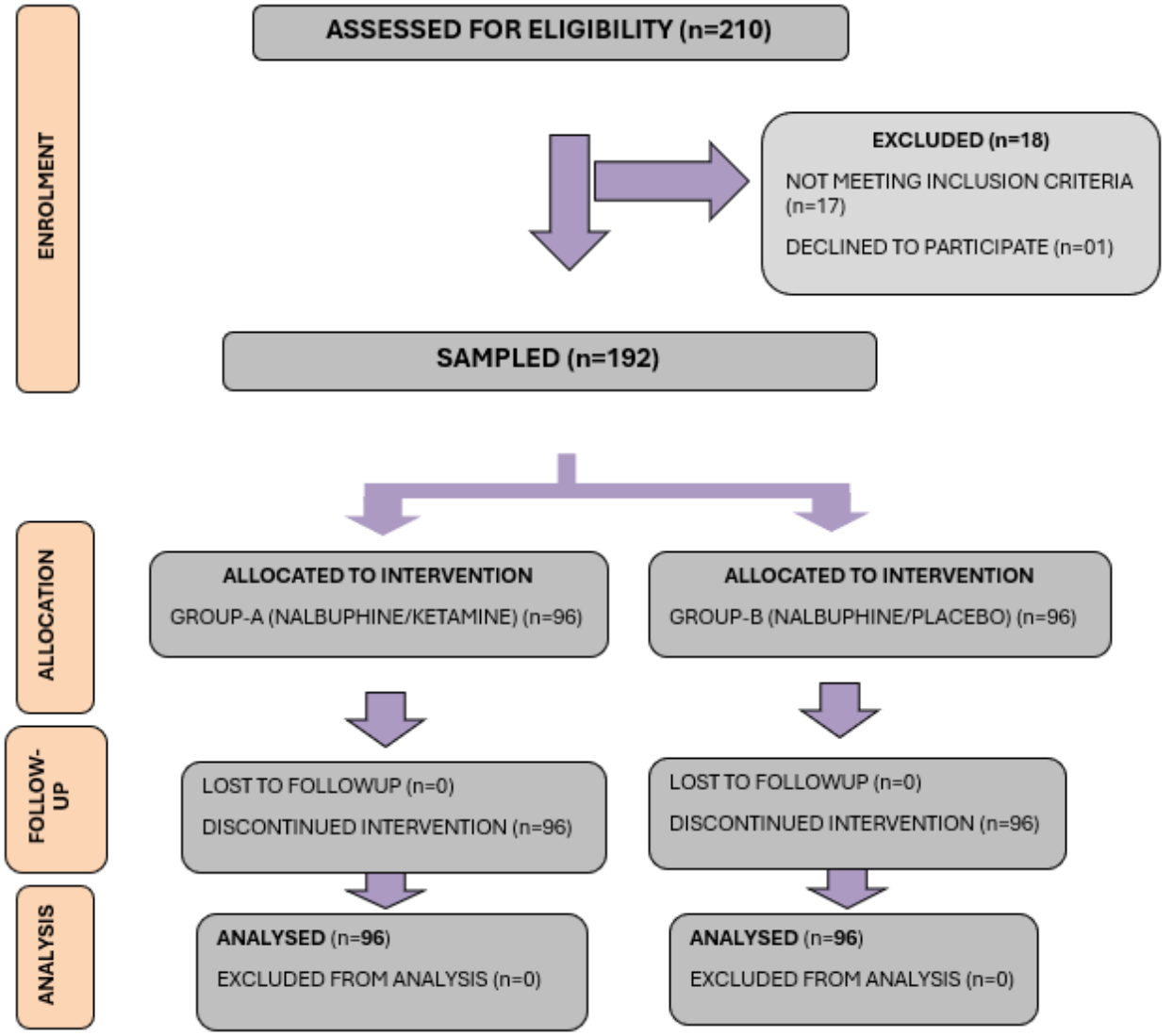


**FIGURE I: PATIENT FLOW DIAGRAM**

**RESULTS:**

A total of 192 patients were analyzed, divided into Group-A (n = 96) receiving IV nalbuphine with ketamine and Group-B (n = 96) receiving IV nalbuphine with placebo. The mean age in Group-A was 42.88 ± 9.24 years, while Group-B demonstrated a mean age of 45.31 ± 9.91 years (p = 0.081). Male patients constituted 53 (55.2%) in Group-A and 49 (51.0%) in Group-B, whereas female representation was 43 (44.8%) and 47 (49.0%), respectively (p = 0.563). Baseline vitals before treatment showed mean systolic blood pressure recorded as 129.09 ± 12.91 mmHg in Group-A versus 130.11 ± 10.26 mmHg in Group-B (p = 0.545), mean diastolic pressure as 79.08 ± 8.31 mmHg versus 79.06 ± 8.05 mmHg (p = 0.986), heart rate as 92.23 ± 9.71 beats/min versus 92.27 ± 9.96 beats/min (p = 0.977), and respiratory rate as 17.69 ± 2.93 breaths/min versus 18.34 ± 2.81 breaths/min (p = 0.116) (Table-I).

Assessment of analgesic response demonstrated that Group-A consistently achieved superior pain reduction compared with Group-B. The median

pre-treatment NRS score was 8.55 (1.2) in Group-A and 8.30 (1.1) in Group-B (p = 0.037). Pain scores at 15 minutes were 6.10 (1.9) versus 6.50 (1.8) (p = 0.019), at 30 minutes 3.80 (1.9) versus 4.80 (1.8) (p < 0.001), at 60 minutes 2.65 (2.2) versus 3.50 (2.1) (p < 0.001), and at 120 minutes 2.20 (1.6) versus 3.05 (1.8) (p < 0.001), respectively. The mean change in NRS from baseline at 30 minutes was significantly higher in Group-A being 4.65 (1.5) compared with Group-B 3.65 (1.5), (p<0.001). Group-A also demonstrated a markedly shorter mean time to effective pain relief 14.38 ± 5.53 minutes compared with Group-B of 22.17 ± 8.77 minutes (p < 0.001). The requirement for rescue analgesia within the first 120 minutes was significantly lower in Group-A with 0.89 ± 1.40 mg compared with Group-B of 3.91 ± 3.00 mg, (p < 0.001). Additionally, the mean emergency department stay was shorter among patients receiving nalbuphine with ketamine being 187.81 ± 39.14 minutes compared with the placebo group 211.84 ± 46.47 minutes, (p < 0.001). Vitals recorded 30 minutes post-intervention remained similar between groups, including systolic and diastolic pressures, heart rate, respiratory rate, and oxygen saturation, with no significant differences observed (Table-II).

Evaluation of adverse effects revealed that nausea occurred in 17 (17.7%) patients in Group-A and 16 (16.7%) in Group-B (p = 0.848), while vomiting occurred in 8 (8.3%) and 11 (11.5%) patients, respectively (p = 0.468). Dizziness was more frequent in Group-A with 26 (27.1%) cases compared with 16 (16.7%) in Group-B (p = 0.081). Hallucinations were observed in 9 (9.4%) patients in Group-A compared with 2 (2.1%) in Group-B (p = 0.058). Hemodynamic instability was uncommon overall, occurring in 5 (5.2%) patients receiving ketamine versus 1 (1.0%) patient in the placebo group (p = 0.211) (Table-III).

**TABLES**

**TABLE-I DEMOGRAPHIC CHARACTERISITICS (n=192)**

| VARIABLE | GROUP-A (n=96) | GROUP-B (n=96) | p VALUE |
|---|---|---|---|
| MEAN AGE (YEARS) | 42.88±9.24 | 45.31±9.91 | 0.081 |
| GENDER | | | |
| • MALE | 53 (55.2%) | 49 (51.0%) | 0.563 |
| • FEMALE | 43 (44.8%) | 47 (49.0%) | |
| VITALS BEFORE TREAMTENT | | | |
| • SYSTOLIC BLOOD PRESSURE (MM HG) | 129.09±12.91 | 130.11±10.26 | 0.545 |
| • DIASTOLIC BLOOD PRESSURE (MM HG) | 79.08±8.31 | 79.06±8.05 | 0.986 |
| • HEART RATE (BEATS/MIN) | 92.23±9.71 | 92.27±9.96 | 0.977 |
| • RESPIRATORY RATE (BREATHS/MIN) | 17.69±2.93 | 18.34±2.81 | 0.116 |

TABLE-II COMPARISON OF PAIN SCORES AND CLINICAL OUTCOMES (n=192)

| VARIABLE | GROUP-A (n=96) | GROUP-B (n=96) | p VALUE |
|---|---|---|---|
| MEDIAN POST-OPERATIVE PAIN SCORES ON NRS | | | |
| • PRE-TREATMENT | 8.55 (1.2) | 8.30 (1.1) | 0.037 |
| • AT 15 MIN | 6.10 (1.9) | 6.50 (1.8) | 0.019 |
| • AT 30 MIN | 3.80 (1.9) | 4.80 (1.8) | <0.001 |
| • AT 60 MIN | 2.65 (2.2) | 3.50 (2.1) | <0.001 |
| • AT 120 MIN | 2.20 (1.6) | 3.05 (1.8) | <0.001 |
| • CHANGE IN NRS SCORE FROM INITIAL | 4.65 (1.5) | 3.65 (1.5) | <0.001 |
| MEAN TIME TO INITIAL PAIN RELIEF (MIN) | 14.38±5.53 | 22.17±8.77 | <0.001 |
| RESCUE ANALGESIA REQUIRED IN 120 MIN (MG) | 0.89±1.40 | 3.91±3.00 | <0.001 |
| MEAN LENGTH OF EMERGENCY ROOM STAY (MIN) | 187.81±39.14 | 211.84±46.47 | <0.001 |
| VITALS 30 MIN AFTER TREATMENT | | | |
| • SYSTOLIC BLOOD PRESSURE (MM HG) | 125.19±10.13 | 124.55±11.75 | 0.689 |
| • DIASTOLIC BLOOD PRESSURE (MM HG) | 78.05±7.83 | 77.98±7.96 | 0.949 |
| • HEART RATE (BEATS/MIN) | 88.75±10.14 | 88.57±10.49 | 0.905 |
| • RESPIRATORY RATE (BREATHS/MIN) | 17.86±3.14 | 17.94±3.29 | 0.876 |

TABLE-III ADVERSE EFFECTS PROFILE BETWEEN BOTH GROUPS (n=192)

| VARIABLE | GROUP-A (n=96) | GROUP-B (n=96) | p VALUE |
|---|---|---|---|
| NAUSEA | 17 (17.7%) | 16 (16.7%) | 0.848 |
| VOMITING | 08 (8.3%) | 11 (11.5%) | 0.468 |
| DIZZINESS | 26 (27.1%) | 16 (16.7%) | 0.081 |
| HALLUCINATIONS | 09 (9.4%) | 02 (2.1%) | 0.058 |
| HEMODYNAMIC INSTABILITY | 05 (5.2%) | 01 (1.0%) | 0.211 |

## DISCUSSION:

Our study concluded that combining IV nalbuphine with sub-dissociative dose ketamine produced significantly greater analgesia than nalbuphine alone. At 30 minutes post-infusion, the mean NRS pain reduction was substantially larger in Group A than Group B. The time to meaningful analgesia (≥3-point NRS drop) was significantly shorter in the ketamine group. Rescue analgesia over 120 minutes was markedly less in Group A. Hemodynamic stability was maintained in both groups. Adverse events such as nausea and vomiting were similar across groups, though neuro-perceptual effects (dizziness, hallucinations) were more frequent in the ketamine group, yet generally mild and self-limited.

Galili *et al.* (2024) reported that low-dose ketamine (0.1 mg/kg) as an adjunct to morphine in ED patients produced significantly greater pain reduction at 30 minutes compared to placebo, with reduced need for additional opioids and acceptable safety profile.[8] Their results mirror ours, reinforcing that sub-dissociative ketamine added to a primary opioid (or opioid analog) provides superior early analgesia compared to opioid (or analog) monotherapy. This concordance supports the external validity of our findings, though we used nalbuphine rather than morphine, suggesting

broader applicability to mixed agonist/antagonist opioids.

Fuller *et al.* (2024), in their narrative review of low-dose ketamine for acute pain, concluded that ketamine is a safe and effective analgesic, whether used alone or as adjunct, and is associated with opioid-sparing effects and lower risk of respiratory depression compared to traditional opioids.[9] Our results align with these conclusions, the lower rescue analgesia requirement in Group A supports a genuine opioid (or opioid-analog) sparing benefit, which is especially relevant in high-turnover ED settings.

In a randomized perioperative analgesia study, Seman *et al.* (2021) used a ketamine bolus of 0.3 mg/kg followed by a low-rate ketamine infusion postoperatively, finding reduced opioid consumption and improved pain scores in the ketamine group.[10] Though in a perioperative context, the similarity in dosing and analgesic benefit reinforces that sub-dissociative ketamine regimens can safely reduce additional opioid requirements supporting our rationale for combining nalbuphine with ketamine.

Viderman *et al.* (2024) described that IV ketamine reduces pain intensity and postoperative opioid use, while lowering the risk of nausea and vomiting compared to opioids alone.[11] This is consistent with our observation of comparable nausea/vomiting rates in both groups, and lower requirement for rescue opioids in the ketamine arm, suggesting ketamine adjunct therapy may maintain analgesia while minimizing opioid side-effects.

Schwarz *et al.* (2024) evaluated low-dose ketamine in ED adult patients with acute pain and concluded it safely reduces pain, producing more rapid but less sustained pain relief than morphine, with a side-effect profile dominated by mild neuropsychiatric symptoms rather than serious cardiorespiratory events.[12] This temporal pattern (rapid onset, less sustained duration) is compatible with our data, early significant NRS drop and shorter time to meaningful analgesia in Group A, albeit with the potential for rebound/slower further drop over time highlighting the need for rescue analgesia protocols, which we incorporated.

Ma *et al.* (2023) reviewed ketamine's application for chronic and acute pain and noted ketamine's ability to modulate central sensitization and reduce pain memory and hyperalgesia, making it attractive especially in neuropathic or radicular pain syndromes.[13] This mechanistic rationale underpins our study's use in sciatica, a radicular (neuropathic) pain condition. Our favorable results suggest ketamine's NMDA-antagonist effect may augment nalbuphine's opioid receptor-based analgesia, targeting both nociceptive and neuropathic pain pathways.

Azari *et al.* (2024) investigated ketamine's role in chronic neuropathic pain and found limited long-term effectiveness; however, acute pain episodes responded better.[14] This aligns with our focus on acute radicular pain in sciatica rather than chronic management, supporting the appropriateness of ketamine use in ED for early pain control but perhaps not for long-term pain management.

In a recent pre-hospital randomized trial, Le Cornec *et al.* (2024) compared IV sub-dissociative-dose ketamine with morphine for traumatic pain and found noninferiority for pain reduction at 30 minutes, advocating ketamine as a viable opioid-sparing alternative in emergency and pre-hospital care.[15] Although their population was trauma patients and our study focused on sciatica, the principle of ketamine's early analgesic effect and opioid-sparing effect remains consistent.

Moradi *et al.* (2025) compared ketamine–dexmedetomidine combination vs morphine in ED acute limb trauma. The ketamine-based group had significantly lower pain scores, reduced need for rescue analgesia, and faster onset of analgesia compared to morphine group, with only mild agitation as a side effect.[16] Their findings further support that ketamine-based multimodal analgesia gives faster relief and limits opioid use in emergency pain contexts, paralleling our nalbuphine-ketamine regimen for radicular pain.

The pharmacologic rationale for combining NMDA receptor antagonism with opioid receptor agonism is well described. As summarized by Orhurhu *et al.* (2023), ketamine's analgesic effects come via NMDA receptor blockade, reducing central sensitization, wind-up, and pain memory; when combined with opioid agonists (or agonist-antagonists), synergistic or additive analgesia may be achieved with lower opioid-equivalent doses and reduced side-effect risk.[17] Our study's results fit this pharmacologic model: significant analgesia, opioid sparing (rescue doses reduced), and acceptable safety.

Nevertheless, some caveats arise. As described in the 2024 meta-analysis by Guo *et al.*, while ketamine had better early analgesic effects than morphine, morphine maintained more durable effect over longer durations.[18] This suggests that ketamine-based regimens may need scheduled re-dosing or additional analgesia to maintain pain control beyond the first 1–2 hours. In our cohort, although the ketamine group required less rescue analgesia overall, we did not follow pain beyond 120 minutes; the possibility of pain recurrence or rebound after ketamine wearing off remains, a limitation that must temper wide generalization.

While adverse events in our study were generally mild and comparable to literature, neuropsychiatric effects such as dizziness and hallucinations occurred more frequently in the ketamine group. This is consistent with known ketamine side effects profiles described in both narrative and clinical studies. Although we did not record any serious events (hemodynamic collapse, respiratory depression), the higher rates of neuro-perceptual effects may limit acceptability in some settings, especially in patients with psychiatric comorbidities, requiring cautious patient selection, monitoring, and possibly pre-emptive measures (e.g., low-dose benzodiazepine, slower infusion).

In the context of sciatica and radicular pain, which has a neuropathic component, our data provide preliminary but promising evidence supporting a multimodal analgesia approach using nalbuphine plus ketamine. To our knowledge, there are very few published studies specifically addressing radicular pain in ED using this combination; most ketamine studies target musculoskeletal, traumatic, or nonspecific acute pain. The mechanistic plausibility via NMDA receptor antagonism for neuropathic pain adds biological plausibility to our clinical findings. This could represent an important shift from traditional opioid-heavy protocols to safer, opioid-sparing multimodal analgesia for radicular pain in busy ED settings, particularly in resource-limited or high-volume settings where rapid discharge and minimization of opioid use is desirable.

## CONCLUSION:

Low-dose ketamine combined with opioid or opioid-analog analgesia provides rapid, effective, and opioid-sparing pain control with significant reduction in NRS scores in acute pain settings. For sciatica and radicular pain presenting to the ED, this regimen appears promising; with further research, it may shift standard analgesic paradigms toward safer, multimodal pain management.

## LIMITATIONS:

This study had several limitations. First, it was conducted at a single tertiary-care emergency department, which may limit the generalizability of the findings to other settings with different patient populations or resource constraints. Second, the follow-up period was restricted to 120 minutes, preventing assessment of longer-term analgesic durability, rebound pain, or delayed adverse effects. Third, pain assessment relied on patient-reported NRS scores, which are subjective and may be influenced by anxiety, prior analgesic exposure, or individual pain thresholds. Fourth, although randomization minimized major confounders, we did not stratify patients based on chronicity of radicular symptoms, degree of nerve root compression, or imaging-confirmed diagnosis, which may affect treatment response. Lastly, rescue analgesia use was standardized but clinician discretion may still introduce variability. These limitations should be considered when interpreting the findings and

designing future multicenter trials with extended monitoring and broader clinical endpoints.

**CONFLICT OF INTEREST:**
None.

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