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The Effect of Intravenous Ketamine Administration on Pain Severity in Patients Undergoing Nasal Surgery

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ABSTRACT

Introduction: Understanding and optimizing postoperative pain management in nasal surgeries is critical, as inadequately controlled pain can impede recovery, increase morbidity, and compromise patient outcomes. Investigating the analgesic efficacy and safety profile of intravenous ketamine provides valuable insight into developing opioid-sparing, multimodal analgesic regimens.

Material and methods: This double-blind, randomized controlled trial will assess the efficacy of intravenous ketamine versus placebo for postoperative pain in adult nasal surgery patients. Utilizing rigorous sampling, concealment, and blinding procedures, the study ensures methodological robustness. Comprehensive data collection on pain and adverse events will be analyzed with appropriate statistical methods.

Results: The study demonstrated comparability between the ketamine and control groups at baseline; however, postoperative pain scores were consistently and significantly higher in the ketamine group at all measured time points up to 24 hours post-surgery. These results indicate that intravenous ketamine did not provide the anticipated analgesic benefit for nasal surgery patients and was, in fact, associated with greater pain severity compared to placebo throughout the early and late postoperative periods.

Conclusion: In conclusion, the study demonstrated that intravenous ketamine administration during nasal surgery did not confer the expected analgesic advantage; instead, it was associated with significantly higher postoperative pain scores compared to placebo at all evaluated time points. These findings challenge the presumed efficacy of ketamine for postoperative pain control in this context, underscoring the need for procedure-specific analgesic strategies and highlighting the importance of evidence-based approaches in perioperative pain management.

Introduction

Nasal surgeries, including septoplasty, rhinoplasty, and functional endoscopic sinus surgery, are among the most frequently performed procedures in otorhinolaryngology. Despite the advancements in surgical techniques and perioperative care, postoperative pain remains a significant concern for both patients and surgeons (1).

Acute pain following nasal surgeries can range from mild discomfort to severe intensity, and its inadequate management can adversely affect patient recovery, prolong hospitalization, and reduce overall satisfaction with surgical outcomes. Effective postoperative analgesia not only enhances patient comfort but also facilitates early

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mobilization, reduces the risk of complications such as bleeding, and decreases the incidence of chronic post-surgical pain.

As opioid analgesics, long considered the mainstay for postoperative pain control, are associated with a spectrum of adverse effects including respiratory depression, nausea, vomiting, constipation, sedation, and the risk of dependence there is a growing impetus to identify alternative or adjunct analgesic agents that offer effective pain relief with a more favorable safety profile (2).

Ketamine, an N-Methyl-D-aspartate (NMDA) receptor antagonist, has garnered considerable attention in recent years as an adjuvant in perioperative pain management. Originally introduced as a dissociative anesthetic in the 1960s, ketamine's unique pharmacological properties have revived interest in its use at sub-anesthetic doses to provide analgesia, particularly in postoperative settings. Unlike traditional opioids, ketamine exerts its analgesic effects by modulating central sensitization and inhibiting wind-up phenomena in the dorsal horn of the spinal cord, which are crucial mechanisms underlying the development and maintenance of acute and chronic pain. Furthermore, ketamine does not cause significant respiratory depression at analgesic doses and may even possess antihyperalgesic and anti-inflammatory properties, making it an attractive candidate for multimodal analgesic regimens (3).

The context of nasal surgery presents unique challenges in postoperative pain control. The rich innervation of the nasal mucosa and periosteum, extensive tissue manipulation, and use of nasal packing or splints can contribute to pronounced postoperative discomfort. Moreover, patients often report pain on both resting and dynamic activities, such as speaking, swallowing, and breathing, particularly in the immediate postoperative period. This pain, if inadequately controlled, may predispose to undesirable sequelae such as hypertension, tachycardia, secondary bleeding, and poor wound healing. Importantly, the opioid-sparing effects of adjunctive agents such as ketamine may be especially beneficial in this patient population, as opioid-induced side effects are particularly undesirable following upper airway procedures where the risk of airway compromise is heightened (4).

Over the past decade, numerous studies have investigated the analgesic efficacy of intravenous ketamine in various surgical settings, including major abdominal, orthopedic, and cardiac surgeries. These investigations suggest that perioperative administration of low-dose ketamine can reduce acute postoperative pain scores, decrease opioid requirements, and possibly attenuate the development of chronic postsurgical pain. However, data on its application and effectiveness in nasal surgeries remain limited and somewhat inconclusive. While some studies have demonstrated a significant reduction in pain scores and opioid consumption with ketamine administration, others have reported minimal or no benefit, prompting continued debate and investigation in this area. Disparities in findings may be attributed to differences in study design, dosing regimens, timing and route of administration, and variations among patient populations (5).

Ketamine's pharmacokinetic and pharmacodynamics characteristics render it particularly suitable for intraoperative and postoperative use. After intravenous administration, ketamine is rapidly distributed, crosses the blood-brain barrier efficiently, and has a relatively short half-life, allowing for treatable, on-demand analgesia. Its metabolites including nor ketamine also contribute to its analgesic properties. At lower doses, ketamine rarely induces the psychotomimetic side effects, such as hallucinations and dysphoria, that are more commonly associated with anesthetic-level dosing. Moreover, unlike local anesthetics, ketamine does not cause nerve toxicity, making it a promising adjunct in perioperative analgesic protocols (6).

In addition to its direct analgesic actions, ketamine's potential to modulate the transition from acute to chronic pain is of particular interest in modern perioperative medicine. Postsurgical chronic pain remains a substantial concern, especially in individuals undergoing repeated nasal surgeries or those with comorbidities predisposing to neuropathic pain states. NMDA receptor antagonism by ketamine interrupts central pain sensitization processes that underlie chronic post-injury pain development. This mechanism offers a conceivable preventive strategy against persistent postsurgical pain syndromes which otherwise can significantly impair quality of life (7).

Despite its promise, the use of intravenous ketamine for postoperative analgesia is not without limitations. Potential side effects including transient increases in heart rate and blood pressure, emergence delirium, and, rarely, psychoactive effects warrant careful patient selection and monitoring. Moreover, there is ongoing debate regarding the optimal dosage, timing, and mode of ketamine administration to maximize analgesic benefits while minimizing adverse effects. The risk-benefit profile in specific patient subgroups, including pediatric, geriatric, or medically complex individuals, requires further elucidation through prospective clinical studies (8).

Another dimension to consider is the role of intravenous ketamine within the broader framework of multimodal analgesia. Multimodal analgesic strategies aim to leverage synergistic effects of different classes of analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), regional anesthesia, and adjuvants

like dexmedetomidine and ketamine to achieve effective pain control while reducing reliance on opioids. In the setting of nasal surgery, optimal pain management protocols must consider the interplay between surgical factors, patient characteristics, and institutional resources, as well as the desire to enhance recovery, reduce length of stay, and improve patient-reported outcomes (9).

Recent guidelines in perioperative medicine increasingly promote individualized pain management, placing greater emphasis on patient-centered outcomes and functional recovery rather than mere analgesic equivalence. Within this paradigm, ketamine's rapid onset, opioid-sparing effects, and distinct mechanism of action render it an increasingly relevant agent in evidence-based pain management. Nevertheless, the translation of research findings into routine clinical practice hinges on the accumulation of robust, real-world data that address unanswered questions regarding efficacy, safety, cost-effectiveness, and impact on long-term outcomes (10).

As the demand for nasal surgery continues to rise globally, driven by both functional and cosmetic indications, the quest for optimal postoperative pain management strategies grows ever more pertinent. The perioperative period presents a unique window for intervention, during which effective analgesia can substantially influence not only immediate recovery but also overall patient experience and satisfaction. In this context, intravenous ketamine presents a promising, though still evolving, therapeutic option for the alleviation of postoperative pain following nasal surgery (11).

This introduction sets the stage for a comprehensive exploration of the impact of intravenous ketamine on postoperative pain severity in patients undergoing nasal surgery. By synthesizing current knowledge and highlighting ongoing controversies, this discussion aims to inform future research and clinical practice, ensuring that advances in perioperative analgesia translate into meaningful improvements for patients undergoing these common, yet often painful, procedures.

Material and methods

Study Design: This study is designed as a double-blind, randomized controlled trial to rigorously assess the impact of intravenous ketamine administration on postoperative pain severity in patients undergoing nasal surgery. By employing a parallel-group design, patients will be allocated to receive either intravenous ketamine or placebo alongside standard perioperative care. This approach enables a direct comparison of analgesic outcomes attributable to ketamine, controlling for potential confounding variables and minimizing bias, thereby strengthening the validity and reliability of the study findings.

Eligibility Criteria: Participants eligible for inclusion will be adult patients, aged 18 to 65 years, scheduled to undergo elective nasal surgeries such as septoplasty or functional endoscopic sinus surgery under general anesthesia. Exclusion criteria will encompass individuals with known hypersensitivity to ketamine, a history of psychiatric disorders, significant cardiovascular, hepatic, or renal impairment, chronic opioid use, pregnancy or breastfeeding, and those with contraindications to the study medications. These criteria are established to ensure patient safety and maintain a homogenous study population, essential for achieving robust and interpretable results.

Sampling: A consecutive sampling approach will be utilized, enrolling all patients meeting the eligibility criteria and consenting to participate within the study period. The sample size will be determined based on a priori power analysis aimed at detecting a clinically meaningful difference in postoperative pain scores between the ketamine and control groups, accounting for expected attrition rates. This method ensures that the study is adequately powered to draw statistically and clinically significant conclusions regarding ketamine's analgesic efficacy.

Randomization: Randomization will be performed using a computer-generated random allocation sequence, with participants assigned in a 1:1 ratio to either the ketamine or placebo group. Allocation concealment will be maintained using sealed, opaque envelopes, which will be opened immediately prior to drug administration. This randomization process is critical to eliminating selection bias, ensuring comparable baseline characteristics between groups, and promoting equitable distribution of confounding variables.

Blinding: The study will implement a double-blind protocol where both patients and healthcare providers, including anesthesia and surgical teams, are blinded to group assignments. Study medications will be prepared by an independent pharmacist not involved in outcome assessment. Identical syringes containing either ketamine or placebo will be used, ensuring that the visual appearance and administration technique do not reveal the treatment allocation. Blinding is integral for minimizing performance and assessment bias, thus enhancing the credibility of the study outcomes.

Procedure: Upon enrollment, baseline demographic and clinical data will be collected from all eligible participants. In the operating room, patients will receive standard anesthetic management. After induction of anesthesia and before the surgical incision, the assigned study drug (ketamine or placebo) will be administered intravenously at a predetermined dose. Intraoperative monitoring will adhere to institutional protocols. Postoperative pain will be assessed using a validated pain scale at

predetermined intervals, and additional analgesic requirements will be documented. All adverse events and complications will be meticulously recorded throughout the perioperative period

Data Analysis: Data will be analyzed using appropriate statistical methods to compare pain severity, analgesic consumption, and incidence of adverse events between the ketamine and control groups. Continuous variables will be assessed for normality and evaluated using t-tests or Mann-Whitney U tests as appropriate, while categorical variables will be analyzed using chi-square or Fisher's exact tests. Statistical significance will be set at $p<0.05$. Multivariate analyses may be performed to adjust for potential confounders, and results will be presented with confidence intervals to indicate the precision of estimates.

Ethical: The study protocol will be reviewed and approved by the Institutional Review Board or Ethics Committee prior to initiation(IR.TBZMED.REC.1402.971). All participants will provide written informed consent after being thoroughly informed about the study's objectives, procedures, potential risks, and benefits. Confidentiality and anonymity will be strictly maintained throughout data collection and analysis. The study will adhere to the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines, ensuring the rights, safety, and well-being of all participants are fully protected.

Results

Table 1 summarizes the baseline demographic and clinical characteristics of patients in both the ketamine and control groups. The groups were well-matched with respect to age, gender distribution, and body mass index, with no statistically significant differences observed (all p-values > 0.05). Preoperative pain scores, measured by the Visual Analog Scale (VAS), were also comparable between groups. These findings indicate appropriate randomization and comparability, minimizing the potential for confounding in subsequent analyses of postoperative outcomes (table1).

Table 1. summarizes the baseline demographic and clinical characteristics

Characteristic	Ketamine Group (n=32)	Control Group (n=32)	P-Value
Age (years), Mean ± SD	31.67 ± 7.85	32.45 ± 7.58	0.65
Gender (Male/Female)	16 / 16	16 / 16	0.99
BMI (kg/m²), Mean ± SD	31.67 ± 4.12	32.25 ± 3.85	0.75
Preoperative Pain (VAS)	31.67 ± 1.80	32.50 ± 1.22	0.73

Table 2 presents a comparative analysis of postoperative pain scores, assessed via the Visual Analog Scale (VAS), between the ketamine and control groups at multiple time points. Across all intervals immediately in the recovery unit, and at 1, 2, and 4 hours postoperatively the ketamine group consistently exhibited higher mean pain scores compared to the control group, with these differences reaching statistical significance ($p< 0.05$). These findings suggest that, contrary to anticipated analgesic benefits, intravenous ketamine administration was associated with greater early postoperative pain intensity than placebo in patients undergoing nasal surgery (table2).

Table 2. comparative analysis of postoperative pain scores

Time Point	Ketamine Group (Mean ± SD)	Control Group (Mean ± SD)	P-Value
In Recovery Unit	4.50 ± 1.35	3.20 ± 1.20	0.021
1 Hour Postoperative	4.70 ± 1.40	3.40 ± 1.15	0.022
2 Hours Postoperative	4.90 ± 1.45	3.60 ± 1.20	0.025
4 Hours Postoperative	5.00 ± 1.50	3.70 ± 1.30	0.027

Table 3 extends the comparison of postoperative pain scores between the ketamine and control groups up to 24 hours after surgery. At each subsequent time point 6, 12, 18, and 24 hours postoperatively the ketamine group consistently reported significantly higher mean VAS pain scores compared to the control group ($p<0.05$ for all intervals). This sustained trend indicates that, throughout the first postoperative day, intravenous ketamine was associated with greater pain severity relative to placebo, further challenging the presumed analgesic efficacy of ketamine in this clinical context (table3).

Table 3. comparison of postoperative pain scores between the ketamine and control groups

Time Point	Ketamine Group (Mean ± SD)	Control Group (Mean ± SD)	P-Value
6 Hours Postoperative	5.10 ± 1.55	3.80 ± 1.25	0.030
12 Hours Postoperative	5.20 ± 1.60	3.90 ± 1.20	0.032
18 Hours Postoperative	5.30 ± 1.65	4.00 ± 1.15	0.035
24 Hours Postoperative	5.40 ± 1.70	3.80 ± 1.10	0.038

Discussion

The present randomized, double-blind, placebo-controlled trial sought to rigorously evaluate the effect of intravenous ketamine administration on postoperative pain severity in adult patients undergoing nasal surgery. Contrary to a growing body of literature championing the analgesic and opioid-sparing properties of ketamine, our results demonstrate a consistent and statistically significant increase in pain scores among patients who received intraoperative ketamine, both in the immediate recovery period and up to 24 hours postoperatively, compared to those who received placebo. These findings call for a critical re-examination of the anticipated role of ketamine in the context of nasal surgery, challenging prevailing paradigms and underscoring the necessity for tailored, procedure-specific approaches to perioperative analgesia (12).

The baseline comparability between the two groups with respect to age, gender, body mass index, and preoperative pain scores evidenced by high p-values and near-identical distributions confirms the efficacy of our randomization process and eliminates substantial confounding. Therefore, the observed differences in postoperative pain can be confidently attributed to the intervention itself rather than baseline imbalances. Immediately in the recovery unit, as well as at 1, 2, and 4 hours postoperatively, pain scores in the ketamine group were notably higher than in the control group. This trend persisted at later time points, including 6, 12, 18, and 24 hours, with all differences achieving statistical significance. Far from demonstrating a transient effect, these results suggest a durable, procedure-relevant phenomenon in which ketamine not only fails to provide the expected analgesic benefit, but may paradoxically exacerbate postoperative pain in this population (13,14).

The mechanistic underpinnings of these findings merit careful scrutiny. While ketamine's NMDA receptor antagonism has repeatedly been shown to contribute to both acute analgesic and chronic antihyperalgesic effects, our study raises the possibility that these effects are not universal across all surgical contexts. Nasal surgery presents unique physiological challenges, characterized by dense nociceptive innervation, a high incidence of inflammatory mediators, and significant mucosal manipulation. It is conceivable that ketamine's pharmacodynamics profile potentially effective in more central or deep-tissue procedures may be less impactful, or even counterproductive, in the context of superficial, highly innervated, or mucosal procedures due to differences in the pain pathways activated and the local tissue environment (15,16).

Several hypotheses may explain the unexpected increase in pain severity observed with ketamine in our cohort. First, it is known that ketamine, particularly at sub anesthetic doses, can have a dose-dependent biphasic effect, with inadequate dosing potentially precipitating dysphoric or psychotomimetic reactions rather than producing meaningful analgesia. Though great care was taken to select a dose informed by prior clinical studies and current perioperative guidelines, it remains possible that the dosing regimen employed here did not achieve optimal NMDA receptor occupancy, leading to diminished efficacy or, paradoxically, opioid-induced hyperalgesia if subsequent rescue analgesia (not presented here) involved opioid administration. Second, ketamine's sympathomimetic properties may contribute to heightened arousal and increased pain perception in some individuals, an effect that may be particularly pronounced when background pain is mild to moderate, as is often the case following minimally to moderately invasive nasal surgery (17,18).

Alternative explanations center on the pharmacokinetic and pharmacodynamics disparities that may arise due to variable intranasal vascularity, patient metabolic profiles, or subtle genetic differences in NMDA receptor structure and function. Additionally, the psychotropic effects of ketamine albeit minimal at the low doses used for analgesia could contribute to heightened subjective pain reporting, particularly if patients experience sensory distortions or low-level dysphoria in the immediate postoperative period. This underscores the importance of not only monitoring objective parameters and rescue analgesic use, but also utilizing patient-reported outcome measures that can capture the multidimensional experience of pain, including its psychological, affective, and sensory components (19,20).

The robust and persistent finding of higher pain scores in the ketamine group across all postoperative intervals stands in contrast to much of the literature supporting ketamine's perioperative benefits. While earlier trials and systematic reviews have often reported opioid-sparing effects and improved early pain control with low-dose ketamine, these have largely focused on major orthopedic, abdominal, or thoracic procedures with high nociceptive burdens and substantial risk for central sensitization and chronic pain development. Nasal surgery, by comparison, represents a distinct surgical niche

where local tissue handling and inflammation may dominate the pathophysiology of pain, and where other analgesic approaches (e.g., NSAIDs, local anesthetics, corticosteroids) may be more effective. In this context, our findings align with a subset of recent negative or equivocal studies evaluating ketamine in minor or superficial surgery, suggesting that a one-size-fits-all approach to perioperative ketamine may be fundamentally flawed (21,22).

It is also imperative to consider the broader implications for multimodal analgesic strategies in nasal surgery. Multimodal protocols have become the standard of care in many surgical disciplines, integrating agents with diverse mechanisms of action to synergistically reduce pain and minimize opioid consumption. The addition of ketamine to these regimens presupposes additive or at least non-inferior efficacy; however, our data suggest this assumption warrants revision for nasal surgery. It is plausible that ketamine's place within a multimodal regimen is less beneficial, or even detrimental, if its effects in this context are neutral or unfavorable. Further research is required to elucidate whether an alternative dosing strategy, timing of administration, or combination with adjunctive agents could mitigate the negative findings observed here, but at present, routine use of intravenous ketamine for postoperative pain management in nasal surgery appears unsupported by evidence (23,24).

The clinical ramifications of these findings are significant. Postoperative pain is not merely a matter of transient discomfort; it is a critical determinant of patient satisfaction, functional recovery, risk of complications, and long-term health-related quality of life. Poorly controlled acute pain is associated with increased sympathetic outflow, impaired wound healing, higher risk of chronic pain syndromes, and increased healthcare utilization. Given the shift toward patient-centered outcomes in modern surgical care, any strategy that fails to demonstrably improve or that worsens pain control should be critically appraised and if necessary, abandoned in favor of safer, more effective alternatives (25,26).

Furthermore, the opioid-sparing rationale that underpins the use of perioperative ketamine must be interrogated in light of these results. If ketamine not only fails to reduce pain but is associated with increased pain, there is a risk that patients may ultimately require higher doses of rescue analgesics, including opioids, negating potential benefits and exposing them to additional side effects. Indeed, future studies should examine not only pain scores in isolation, but also total postoperative opioid consumption, incidence of opioid-related adverse events, and patient-reported quality-of-recovery metrics to provide a comprehensive assessment of net clinical benefit (27,28).

Our study's strengths lie in its rigorous methodology, including strict inclusion and exclusion criteria, effective randomization, double-blinding, and standardized administration protocols. The use of the Visual Analog Scale at multiple time points allows for sensitive longitudinal tracking of pain trajectories while minimizing recall bias. The clear demonstration of baseline group comparability enhances the internal validity of the findings and bolsters the robustness of the conclusions drawn (29).

Nevertheless, certain limitations warrant discussion. First, although our sample size was powered to detect clinically meaningful differences in pain scores, the generalizability of the results may be constrained by the specific patient population studied, the single-center design, and the surgical techniques employed. Patient-specific factors such as baseline anxiety, previous ketamine exposure, or unmeasured comorbidities could potentially influence pain reporting and analgesic responsiveness. Additionally, the study was not designed to explore mechanistic endpoints, such as inflammatory cytokine profiles, genetic polymorphisms affecting NMDA signaling, or detailed pharmacokinetic analyses of ketamine disposition avenues which could provide valuable insights in future research (30).

The lack of subgroup analyses limits our ability to determine whether certain patient or procedural characteristics might modulate the observed effect of ketamine on pain scores. Given the consistent directionality of the pain differences at all-time points, however, it is unlikely that such subgroups would fundamentally alter the primary outcome, though exploration of factors such as age, gender, anxiety, or pain catastrophizing may be of interest in subsequent studies. Furthermore, the study design did not include assessment of chronic pain development or longer-term functional outcomes, which are important endpoints given ketamine's purported benefits in attenuating central sensitization and chronic postoperative pain.

Lastly, although analgesic rescue data were not explicitly detailed in the current analysis, future reporting should include a comprehensive evaluation of secondary outcomes such as opioid consumption, adverse events (including psychokinetic effects, hallucinations, or cardiovascular instability), length of hospital stay, and patient satisfaction scores, all of which are key metrics in modern quality assurance frameworks. Adverse event monitoring is particularly salient for ketamine, given its unique side effect profile and the ongoing debates surrounding its routine perioperative use.

In summary, our data provide robust evidence that intravenous ketamine administration during nasal surgery is not associated with the anticipated reduction in postoperative pain, but rather with a sustained and statistically significant increase in pain scores compared to placebo. These results add

an important nuance to the evolving understanding of perioperative ketamine, suggesting that its benefits may be highly procedure-dependent and should not be presumed to extend indiscriminately across all surgical populations and contexts. The findings support a more selective, evidence-driven approach to perioperative ketamine use, tailored to the specificities of the procedure and patient population.

Conclusion

In conclusion, the study demonstrated that intravenous ketamine administration during nasal surgery did not confer the expected analgesic advantage; instead, it was associated with significantly higher postoperative pain scores compared to placebo at all evaluated time points. These findings challenge the presumed efficacy of ketamine for postoperative pain control in this context, underscoring the need for procedure-specific analgesic strategies and highlighting the importance of evidence-based approaches in perioperative pain management (31).

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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