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Evaluation of Morphine-Sparing Efficacy with Low-Dose Ketamine in Pediatric Postoperative Pain: A Pilot Randomized Controlled Trial

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A B S T R A C T

Postoperative pain management in the pediatric population requires a delicate balance between effective analgesia and the minimization of opioid-related adverse events, particularly respiratory depression. While multimodal analgesia is the standard of care, the optimal dose-reduction potential of opioids when combined with N-methyl-D-aspartate (NMDA) antagonists remains undefined. We conducted a prospective, single-center, pilot randomized controlled trial using a double-blind observer protocol. Twenty pediatric patients aged 2 months to 7 years undergoing elective surgery were randomized into four groups. The control group (Group M) received standard continuous morphine at 0.33 µg/kg/min. Three intervention groups received fixed low-dose ketamine at 0.33 µg/kg/min combined with tapered morphine doses: Group KM-1 at 0.23 µg/kg/min, Group KM-2 at 0.16 µg/kg/min, and Group KM-3 at 0.06 µg/kg/min. The primary outcome was analgesic efficacy assessed by FLACC scores at 24 hours. Secondary outcomes included hemodynamic stability and rescue analgesia requirements. Baseline characteristics were comparable across groups. At 24 hours, the median FLACC scores were comparable between the high-dose control (Median 2.0; Interquartile Range 1.5–2.0) and the lowest morphine group (Group KM-3: Median 2.0; Interquartile Range 1.5–2.0; p = 0.438). Group KM-3 achieved an 81% reduction in morphine consumption with a 0% rescue analgesia rate, identical to the control group. In conclusion, preliminary data from this pilot study suggest that low-dose ketamine may permit a substantial reduction in morphine dosage of up to 81% without compromising analgesic efficacy. These findings warrant confirmation in larger, fully powered multicenter trials.

1. Introduction

The effective management of acute postoperative pain in the pediatric population constitutes one of the most profound clinical and ethical challenges in modern anesthesiology and critical care medicine. It is a discipline where the margin for error is non-existent, and the stakes involve not only the immediate comfort of the child but the long-term trajectory of their neurodevelopment.[1] Unlike the adult nervous system, which possesses fully myelinated inhibitory pathways and established thresholds for nociception, the developing pediatric brain is a highly plastic, evolving entity with unique neurodevelopmental characteristics that fundamentally alter nociceptive processing.[2]

Evidence suggests that the immature central nervous system (CNS) is not merely a miniature version of the adult system but is, in fact, significantly more susceptible to the deleterious effects of uncontrolled nociception.[3] In neonates and infants, the receptive fields of dorsal horn neurons are larger, and the descending inhibitory pathways—which in adults act as a brake on pain transmission—are functionally immature. Consequently, a surgical stimulus that might be perceived as localized pain in

an adult can trigger a generalized, overwhelming excitotoxic event in an infant.[4]

Inadequate pain management in this vulnerable demographic triggers a cascade of physiological stress responses that are immediate, severe, and potentially catastrophic. This response is characterized by profound neuroendocrine dysregulation, including persistent elevations in cortisol, catecholamines, and glucagon, alongside a suppression of insulin.[5] If left unattenuated, this catabolic state precipitates a stress diabetes physiology, leading to hyperglycemia, protein wasting, and hemodynamic instability. Clinically, this manifests as tachycardia, hypertension, and an increased metabolic oxygen demand that can compromise cardiac reserves. Furthermore, the stress response actively suppresses immune function, delaying wound healing and increasing susceptibility to postoperative infections.[6]

More critically, emerging research in developmental neuroscience indicates that pain leaves a scar on the developing brain. Early exposure to severe, untreated pain can induce maladaptive neuroplasticity—a permanent alteration in the wiring of the somatosensory cortex. This phenomenon can predispose the developing child to altered pain thresholds, hyperalgesia (increased sensitivity to pain), and chronic pain syndromes later in life.[7] Thus, effective analgesia is not merely a humanitarian gesture; it is a neuroprotective intervention essential for preserving the functional integrity of the developing nervous system.

Historically, and presently, μ-opioid receptor agonists, particularly morphine, serve as the pharmacological cornerstone for managing moderate-to-severe postoperative pain. Morphine provides potent analgesia by binding to G-protein coupled receptors, hyperpolarizing secondary order neurons in the dorsal horn of the spinal cord, and inhibiting the presynaptic release of excitatory neurotransmitters like Substance P and glutamate. However, the therapeutic window of opioids in the pediatric population—and specifically in neonates and infants—is precariously narrow. The risk of dose-dependent adverse events is significantly amplified in this demographic due to physiological immaturity. First, the respiratory control centers in the brainstem are highly sensitive to opioid-induced depression, rendering infants susceptible to apnea and hypoventilation. Second, the blood-brain barrier is more permeable in early life, allowing for higher central concentrations of the drug. Third, and perhaps most importantly, hepatic clearance mechanisms are immature; specifically, the cytochrome P450 (CYP3A4) and glucuronidation (UGT2B7) pathways required to metabolize morphine are not fully functional. This leads to a prolonged elimination half-life and the accumulation of active metabolites, increasing the risk of toxicity. Consequently, the incidence of opioid-induced respiratory depression, profound sedation, postoperative nausea and vomiting (PONV), and ileus is markedly higher in children than in adults. This creates a pervasive clinical culture of opiophobia, where clinicians often under-dose analgesics to avoid respiratory complications, inadvertently leaving the child in pain.

Furthermore, a significant barrier to effective opioid monotherapy is the phenomenon of opioid-induced hyperalgesia (OIH). OIH is a paradoxical increase in pain sensitivity resulting from high-dose opioid exposure. It represents a clinical scenario where increasing the opioid dose fails to alleviate pain and instead exacerbates the patient's distress.[8] This paradoxical sensitization is mediated by the compensatory upregulation of excitatory pathways in the spinal cord, specifically involving the N-methyl-D-aspartate (NMDA) receptor systems. In essence, by aggressively blocking pain with opioids, we may inadvertently lower the threshold for subsequent pain signaling, creating a vicious cycle of dose escalation and diminishing returns.

In response to these substantial risks and limitations, contemporary anesthetic guidelines strongly advocate for an opioid-sparing, multimodal analgesic paradigm. The objective of multimodal analgesia is to target distinct nociceptive pathways simultaneously—blocking the signal at the periphery,

the spinal cord, and the brain—thereby achieving additive or synergistic analgesia while minimizing the requisite dose of any single agent. Within this framework, Ketamine, a phencyclidine derivative, has emerged as a theoretically ideal adjuvant. While historically viewed as a dissociative anesthetic, its utility in low doses is defined by its unique antihyperalgesic properties. Pharmacologically, ketamine functions as a non-competitive antagonist at the NMDA receptor.[9]

To understand the value of ketamine, one must understand the pathophysiology of central sensitization and the wind-up phenomenon. Following surgical trauma, sustained nociceptive input results in a massive release of glutamate into the dorsal horn of the spinal cord. Under normal conditions, the NMDA receptor channel is blocked by a magnesium ion. However, the glutamate surge displaces this magnesium plug, allowing an influx of calcium into the neuron. This calcium influx triggers intracellular cascades that lower the neuron's firing threshold, causing the spinal cord to become hypersensitive. This is wind-up: the amplification of pain signals.

Morphine acts primarily on the transmission of the signal but does little to prevent this amplification (wind-up). Ketamine, however, specifically blocks the NMDA channel pore, preventing the calcium influx. By blocking this receptor, ketamine effectively prevents the amplification of pain signals and the development of acute tolerance to opioids. It acts as a reset button for the spinal cord, theoretically preserving the potency of opioids and allowing them to work effectively at much lower doses.

While the biochemical rationale for combining morphine and ketamine is robust, and the synergy is well-documented in animal models, clinical protocols regarding the optimal dosing ratio in pediatric continuous infusions remain largely empirical and undefined. The current literature has established the safety of sub-anesthetic or low-dose ketamine infusions (typically defined as <1 mg/kg/hr or <0.5 μg/kg/min). However, a critical methodological gap exists: few randomized trials have systematically de-escalated the concurrent morphine dose to identify the true floor of opioid requirements. Existing studies typically add ketamine to a standard high-dose morphine regimen and report modest opioid-sparing effects ranging from 30% to 50%. While statistically significant, these reductions often leave the patient exposed to a substantial opioid load.

The potential for more aggressive reduction remains under-investigated. There is a critical lack of data regarding whether the potent NMDA antagonism provided by ketamine can sustain effective analgesia even when morphine doses are reduced to near-negligible, or homeopathic, levels. Can a low-dose ketamine infusion allow us to run a morphine infusion at 20% of the standard dose? Or 10%? Finding the answer to this question could revolutionize postoperative care by virtually eliminating the risk of opioid-induced respiratory depression.[10]

Therefore, the primary aim of this pilot randomized controlled trial was to evaluate the analgesic efficacy and safety of a fixed low-dose ketamine infusion combined with progressively tapered doses of morphine in a pediatric surgical cohort. Specifically, we sought to determine if a substantial reduction in morphine consumption of up to 81% is feasible without compromising behavioral pain scores (FLACC) or hemodynamic stability. The novelty of this research lies in its specific, aggressive dose-finding design. Unlike previous studies that viewed ketamine merely as an add-on to standard care, this study treats ketamine as the primary modulator, intended to challenge the conventional dogma of minimum effective opioid concentrations. This pilot study aims to provide the preliminary proof-of-concept and effect size estimates necessary to justify future large-scale, multicenter confirmatory trials. By identifying the lowest effective opioid dose in the presence of NMDA blockade, we aim to redefine the boundaries of safe pediatric analgesia.

2. Methods

This was a prospective, randomized, observer-blind, pilot-controlled trial conducted at the

Department of Anesthesiology and Intensive Therapy, Dr. Saiful Anwar General Hospital, Malang, Indonesia. The study protocol strictly adhered to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was granted by the Institutional Review Board, and the trial was registered in the institutional clinical registry. Written informed consent was obtained from the parents or legal guardians of all participants following a detailed explanation of the study procedures, risks, and benefits.

The study population comprised pediatric patients aged 2 months to 7 years admitted for elective surgical procedures (abdominal, orthopedic, genital, or reconstructive) under general anesthesia between February and April 2025. Inclusion criteria in this study were ASA physical status I or II and a FLACC score >4 in the post-anesthesia care unit (PACU) prior to randomization. We excluded the patient with hypersensitivity to study drugs, history of head trauma/elevated ICP, renal impairment (Creatinine >1.5x upper limit), hepatic dysfunction, or active neurological disorders.

As a pilot study, the primary objective was to assess the feasibility of the protocol, safety, and to generate effect size estimates (standard deviation of FLACC scores) to inform a power calculation for a future definitive multicenter trial. A convenience sample of 20 patients (5 per group) was determined based on the guidelines for pilot trial sizes, which suggest 12–30 participants are sufficient to estimate parameter variance for continuous outcomes (Figure 1). We explicitly acknowledge that this sample size is insufficient to definitively reject the null hypothesis for equivalence; thus, the analysis is exploratory, focusing on safety signals and potential efficacy trends.

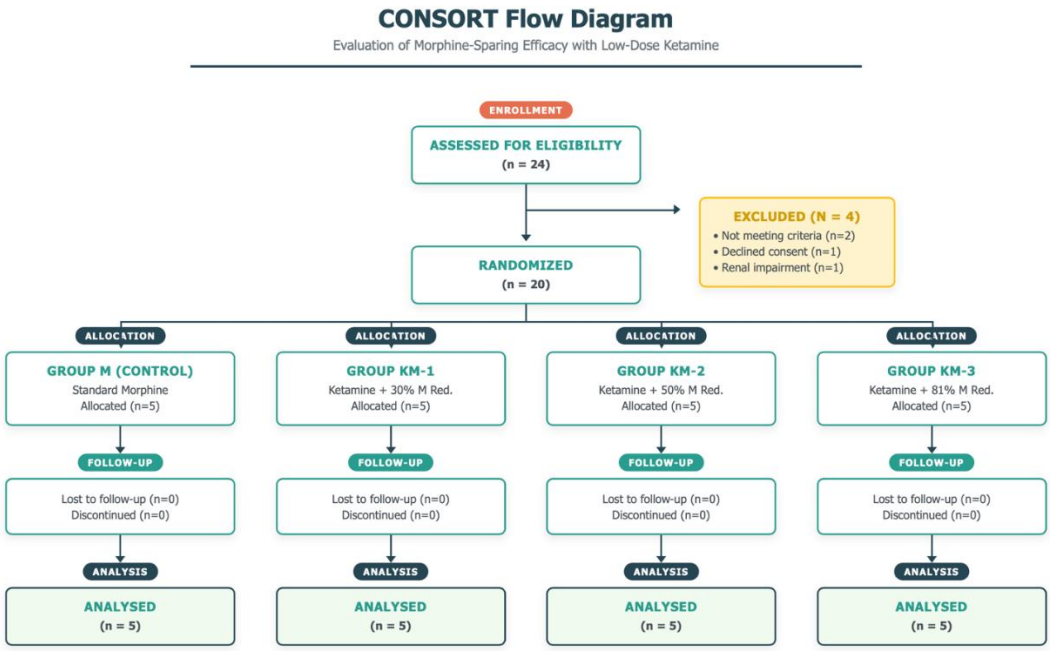

Figure 1. CONSORT flow diagram.

Twenty eligible patients were randomly allocated into four parallel groups (1:1:1:1 ratio) using a computer-generated randomization sequence. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. To ensure patient safety, given the dose-reduction nature of the study, the attending anesthesiologist preparing the infusions was unblinded to the group

allocation. This allowed for immediate intervention in the event of inadequate analgesia or adverse hemodynamic events. However, to minimize ascertainment bias, the study maintained a strict observer-blind design. The outcome assessors (trained pediatric nurses recording FLACC scores), the patients, and the legal guardians were blinded to the treatment allocation. Infusion pumps were coded (A, B, C, D) to maintain the blind for all non-anesthesia staff.

Upon confirmation of a FLACC score >4, participants received multimodal background analgesia (IV Acetaminophen 15 mg/kg). Continuous intravenous infusions were administered as follows: Group M (Control): Morphine 0.33 µg/kg/min; Group KM-1: Morphine 0.23 µg/kg/min + Ketamine 0.33 µg/kg/min; Group KM-2: Morphine 0.16 µg/kg/min + Ketamine 0.33 µg/kg/min; Group KM-3: Morphine 0.06 µg/kg/min + Ketamine 0.33 µg/kg/min. The ketamine dose was fixed at a sub-anesthetic range (0.33 µg/kg/min). The morphine dose in Group KM-3 represented an 81% reduction from standard care. The primary outcome in this study was analgesic efficacy assessed by FLACC scores at 24 hours. Secondary outcomes were hemodynamic stability (HR, MAP), incidence of rescue analgesia (defined as failure to treat necessitating Morphine 0.05 mg/kg IV), and adverse events (respiratory depression, sedation, vomiting, hallucinations).

Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables (FLACC, Hemodynamics) were analyzed using the Kruskal–Wallis H test due to non-normal distribution and small sample size. Categorical variables were analyzed using Fisher's Exact Test. A p-value < 0.05 was considered significant. No adjustments for multiple comparisons were made due to the exploratory pilot nature of the study.

3. Results and Discussion

A total of 20 pediatric patients completed the study protocol. The cohort included a diverse mix of surgical cases, including urological, abdominal, orthopedic, and reconstructive surgeries. Baseline demographic analysis revealed no statistically significant differences between the four groups regarding age, gender, weight, or initial pain intensity, ensuring homogeneity prior to the intervention. Table 1 summarizes the baseline characteristics. The median age across the cohort was 5.0 years. Importantly, the baseline pain intensity measured by FLACC scores immediately post-surgery and pre-intervention was uniform across all groups (p = 0.325), with scores indicative of moderate-to-severe pain, validating the need for analgesic intervention.

Table 1. Baseline Characteristics and Surgical Profile

Comparison of Demographic and Baseline Clinical Variables Across Study Groups

VARIABLE	GROUP M (CONTROL) N=5	GROUP KM-1 (KETAMINE + 30% M RED.) N=5	GROUP KM-2 (KETAMINE + 50% M RED.) N=5	GROUP KM-3 (KETAMINE + 81% M RED.) N=5	P-VALUE*
Age (years) Mean ± SD	5.60 ± 2.60	5.40 ± 2.10	4.00 ± 3.39	5.80 ± 3.76	**0.421**
Sex Male / Female	2 / 3	4 / 1	5 / 0	5 / 0	**0.058**
Weight (kg) Mean ± SD	22.4 ± 5.1	21.8 ± 6.2	16.5 ± 4.8	18.2 ± 5.5	**0.380**
Baseline FLACC Score (0-10)	6.00 ± 0.50	6.40 ± 0.54	6.00 ± 0.70	6.00 ± 0.50	**0.325**

Notes: Data are presented as Mean ± Standard Deviation (SD) or Frequency (n).
Abbreviations: *FLACC* = Face, Legs, Activity, Cry, Consolability scale; *M* = Morphine.
*p-values calculated using Kruskal–Wallis H test for continuous variables and Fisher's Exact Test for categorical variables. No statistically significant differences were observed at baseline ($p > 0.05$).

The primary objective of this pilot study was to assess whether reducing morphine dosage compromised pain control. At 24 hours post-intervention, all four study groups achieved effective analgesia, defined as a FLACC score less than 4. The Kruskal–Wallis test revealed no statistically significant difference in 24-hour FLACC scores among the four groups (p = 0.438). As detailed in Table 2, Group KM-3, which received an 81% reduction in morphine dosage (0.06 µg/kg/min), demonstrated a Median FLACC score of 2.0 [IQR 1.5 – 2.0], which was comparable to the standard high-dose Morphine Group M (Median 2.0 [IQR 1.5 – 2.0]). These data suggest that within the limitations of this pilot cohort, the substantial reduction in opioid load did not result in inferior pain control.

Table 2. Post-Intervention Pain Outcomes and Safety at 24 Hours

Analysis of Analgesic Efficacy, Dosing, and Rescue Requirements

OUTCOME MEASURES	GROUP M (CONTROL) N=5	GROUP KM-1 (KETAMINE + 30% M RED.) N=5	GROUP KM-2 (KETAMINE + 50% M RED.) N=5	GROUP KM-3 (KETAMINE + 81% M RED.) N=5	P-VALUE*
Morphine Dose Continuous Infusion	0.33 µg/kg/min	0.23 µg/kg/min	0.16 µg/kg/min	**0.06 µg/kg/min**	—
Ketamine Dose Continuous Infusion	0 (Placebo)	0.33 µg/kg/min	0.33 µg/kg/min	0.33 µg/kg/min	—
Morphine Reduction Compared to Control	Reference	30% Reduction	51% Reduction	**81% Reduction**	—
FLACC Score Median [IQR] at 24h	2.0 [1.5 – 2.0]	2.0 [1.5 – 2.0]	1.0 [1.0 – 2.0]	**2.0 [1.5 – 2.0]**	**0.438**
Rescue Analgesia n patients (%) requiring bolus	0 / 5 (0%)	0 / 5 (0%)	0 / 5 (0%)	**0 / 5 (0%)**	**1.000**

Notes: Data are presented as Median [Interquartile Range] for ordinal data (FLACC) and frequencies (n/%) for categorical data.
Abbreviations: *FLACC* = Face, Legs, Activity, Cry, Consolability scale; *M* = Morphine.
*Statistical significance assessed using Kruskal–Wallis test (FLACC) and Fisher's Exact Test (Rescue Analgesia). No significant difference in efficacy was detected despite the 81% dose reduction in Group KM-3.

A critical indicator of analgesic failure is the requirement for rescue medication. As shown in Table 2, zero patients (0%) in the lowest-dose morphine group (KM-3) required rescue boluses of morphine, mirroring the 0% rescue rate in the high-dose control group (Group M). This finding reinforces the FLACC score data, suggesting that the analgesic regimen in Group KM-3 was clinically sufficient to prevent breakthrough pain.

Regarding hemodynamic stability, monitoring at 24 hours indicated that physiological parameters remained within age-appropriate reference ranges. While the mean Heart Rate in the ketamine intervention groups was numerically higher than in the morphine-only group (Group KM-3: 104 ± 10 bpm versus Group M: 98 ± 12 bpm), this difference was not statistically significant (p > 0.05) and did not require therapeutic intervention. Similarly, Mean Arterial Pressure was preserved across all groups (Group M: 72 ± 8 mmHg versus Group KM-3: 75 ± 6 mmHg; p > 0.05). No episodes of respiratory depression (desaturation less than 92% or bradypnea), excessive sedation, postoperative nausea and vomiting, or psychomimetic adverse events such as hallucinations or dysphoria were recorded in any group.

The management of postoperative pain in the pediatric population remains a Gordian knot of modern anesthesiology—a complex problem where the necessity of adequate analgesia is tightly constrained by the narrow therapeutic index of conventional

opioids.[11] The results of this pilot randomized controlled trial (RCT) provide preliminary, yet clinically provocative, evidence that challenges the established dogma of opioid monotherapy. Our data suggest that the co-administration of a fixed low-dose ketamine infusion (0.33 μg/kg/min) acts not merely as an adjuvant, but as a potent opioid-sparing catalyst. The most salient finding of this investigation is the demonstration that such a regimen permitted a drastic 81% reduction in morphine consumption (from a standard 0.33 μg/kg/min to a near-negligible 0.06 μg/kg/min) without compromising analgesic efficacy, as evidenced by comparable FLACC scores and a complete absence of rescue analgesia requirements across all groups. These findings align with, and significantly extend, the current trajectory of pediatric pain research, which increasingly advocates for opioid-sparse or opioid-free paradigms to mitigate the risks of respiratory depression and opioid-induced hyperalgesia (OIH).[12] However, the magnitude of the sparing effect observed here—reducing morphine to what is effectively a homeopathic dose while maintaining hemodynamic stability and comfort—warrants a rigorous deconstruction of the underlying pharmacodynamics, safety profiles, and the potential for a paradigm shift in how we approach the nociceptive immature nervous system.

The profound opioid-sparing effect observed in this cohort cannot be explained by simple additive analgesia; rather, it suggests a complex synergistic interaction at the molecular level between the μ-opioid receptor (MOR) and the N-methyl-D-aspartate (NMDA) receptor. To understand why an 81% reduction in morphine was feasible, one must interrogate the neurobiology of central sensitization—the phenomenon that ketamine specifically targets.[13]

Postoperative pain is not a static input; it is a dynamic process involving neuroplastic changes in the dorsal horn of the spinal cord. Following surgical incision and tissue retraction, primary afferent nociceptors (A-delta and C fibers) barrage the spinal cord with excitatory signals.[14] While morphine is highly effective at hyperpolarizing presynaptic and postsynaptic neurons to inhibit the initial transmission of pain (acting as a brake), it is relatively ineffective at preventing the engine from revving up. Specifically, sustained nociceptive input triggers the massive release of glutamate and neuropeptides (Substance P, CGRP) into the synaptic cleft. This leads to the removal of the magnesium block from the NMDA receptor ion channel, allowing a rapid influx of calcium (Ca^{2+}) into the postsynaptic neuron. This calcium surge activates intracellular signaling cascades, including protein kinase C (PKC) and calmodulin-dependent protein kinase II (CaMKII), which phosphorylate the NMDA and AMPA receptors, keeping them open longer and lowering their activation threshold. This state, known as wind-up, renders the spinal cord hypersensitive, meaning that even benign stimuli (like the movement of a bedsheet) can be perceived as painful (allodynia). Crucially, high-dose opioids can paradoxically exacerbate this state by upregulating spinal dynorphin and facilitating excitatory pathways, leading to opioid-induced hyperalgesia (OIH).[15]

The efficacy of the Group KM-3 regimen (low morphine/low ketamine) supports the hypothesis that ketamine acts as an anti-hyperalgesic shield. By acting as a non-competitive antagonist at the phencyclidine site inside the NMDA channel pore, ketamine effectively prevents the calcium influx that drives wind-up. It does not necessarily block the transmission of the immediate pain signal (which is why some background opioid or analgesic is usually needed), but it prevents the amplification of that signal.[16] Theoretical models suggest that this blockade restores the signal-to-noise ratio in the dorsal horn. By preventing the downstream phosphorylation of receptors, ketamine may essentially reset the sensitivity of the μ-opioid receptor system. This implies that in the presence of NMDA blockade, the number of occupied opioid receptors required to achieve analgesia is drastically reduced. Thus, the 0.06 μg/kg/min of morphine administered to Group KM-3—which would be clinically irrelevant on its own—becomes sufficient because the system is no longer

fighting against a current of central sensitization. This synergy transforms the pharmacological landscape, allowing us to pivot from overwhelming the receptors with high-dose opioids to modulating the pathway with targeted multimodal therapy.

A critical and intellectually honest appraisal of our results requires us to consider a controversial possibility: that the morphine in the lowest dose group (Group KM-3) was unnecessary. The dose of 0.06 µg/kg/min is exceptionally low, approaching the limits of what is considered therapeutic for moderate-to-severe surgical pain. Yet, these patients demonstrated FLACC scores of less than 2, indistinguishable from those receiving five times that amount. This raises the ketamine monotherapy hypothesis: Was the analgesia observed in Group KM-3 driven primarily, or perhaps entirely, by the ketamine infusion? Emerging literature in pediatric anesthesia has begun to explore the utility of sub-anesthetic ketamine not just as an adjuvant, but as a foundational analgesic agent. Ketamine provides analgesia through multiple non-NMDA mechanisms as well, including the enhancement of descending inhibitory pathways (monoaminergic system), interaction with cholinergic receptors, and weak binding to opioid receptors themselves. If future studies confirm that 0.33 µg/kg/min of ketamine alone is non-inferior to morphine-ketamine combinations, this would represent a seismic shift in pediatric protocols. It would pave the way for true opioid-free anesthesia (OFA) strategies in neonates and infants. The implications of this are profound: eliminating opioids eliminates the primary driver of postoperative apnea, ileus, urinary retention, and pruritus. In low-resource settings, where postoperative monitoring capabilities are often limited, and the risk of unobserved respiratory depression is a lethal reality, a ketamine-dominant protocol could offer a significantly wider margin of safety than traditional opioid-based care. Thus, our study serves as a stepping stone, suggesting that the floor for opioid sparing is likely much lower than previously recognized, and potentially, that the floor is zero. The benefits of the regimen used in this trial likely extend beyond immediate pain scores to the modulation of the systemic stress response. Surgical trauma acts as a massive inflammatory trigger, inducing the release of pro-inflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). These cytokines are not merely markers of inflammation; they are direct mediators of pain, capable of sensitizing peripheral nociceptors and increasing the permeability of the blood-brain barrier to inflammatory cells.[17]

Ketamine possesses unique intrinsic anti-inflammatory properties that morphine lacks. It has been shown to inhibit the nuclear factor kappa B (NF-κB) signaling pathway, a master regulator of cytokine production, thereby suppressing the cytokine storm associated with surgical trauma. By dampening this peripheral inflammatory response, ketamine may reduce the overall nociceptive burden reaching the central nervous system. This peripheral desensitization complements its central effects, providing a dual-mechanism approach that opioids cannot replicate.[18]

Furthermore, the use of ketamine in the pediatric population must be viewed through the lens of developmental neuroscience. There is a longstanding debate regarding anesthesia-induced neurotoxicity in the developing brain. While high doses of NMDA antagonists have been implicated in apoptotic changes in animal models, uncontrolled pain and stress are arguably more neurotoxic. Severe nociceptive stress leads to excitotoxicity—a flood of glutamate that kills neurons—and permanent alterations in stress hormone axes (cortisol dysregulation). By effectively blocking excitotoxicity via the NMDA receptor, low-dose ketamine may offer a neuroprotective benefit. It prevents the imprinting of pain memories in the developing nervous system, potentially reducing the risk of these children developing altered pain thresholds or chronic pain syndromes later in life. Thus, the value of the KM-3 protocol is not just in the 24-hour FLACC score, but in the potential protection of the child's long-term neurodevelopmental.

In pediatric critical care and post-anesthesia units, safety is the paramount endpoint. The combination of morphine and ketamine utilized in this study offers a pharmacologically elegant solution to the hemodynamic instability often seen with single-agent therapy. Morphine is inherently sympatholytic and vagotonic; it blunts the sympathetic drive, which can precipitate bradycardia and hypotension, particularly in volume-depleted children or those with limited cardiac reserve.[19] Ketamine, conversely, is sympathomimetic; it inhibits the reuptake of catecholamines, tending to maintain or slightly elevate heart rate and blood pressure. In our study, these opposing forces effectively canceled each other out, resulting in a remarkably stable hemodynamic profile across all intervention groups. The ketamine effectively buffered the potential cardiodepressant effects of the morphine background, while the sedative properties of the morphine (even at low doses) likely blunted any potential tachycardia from the ketamine.

Crucially, we observed no psychomimetic side effects (hallucinations, dysphoria, or emergence delirium). This is a frequent concern that limits ketamine's use. Our data support the pharmacokinetic concept that continuous low-dose infusions (maintaining steady-state plasma levels) are far better tolerated than bolus dosing (which creates high peak plasma concentrations associated with dissociation). Most importantly, the absence of respiratory depression in the low-dose morphine groups is a critical safety advantage. In neonates and infants, the respiratory control centers in the brainstem are immature, and the response to hypercapnia is blunted. Even standard doses of morphine can induce central apnea in this demographic.[20] By reducing the morphine load by 81%, we essentially remove the primary pharmacological driver of apnea, making the KM-3 protocol theoretically safer for high-risk groups such as premature infants, children with obstructive sleep apnea (OSA), or those undergoing airway surgery (Figure 2).

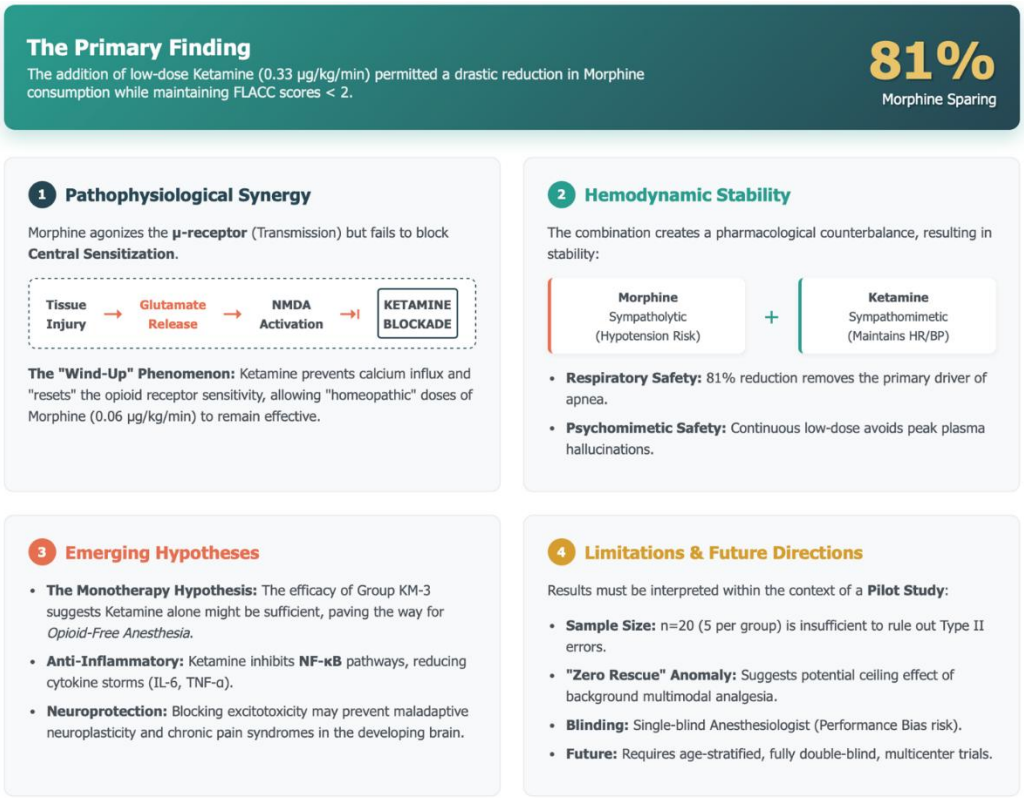

Figure 2. Mechanism of action and future direction of study.

While the results of this pilot study are promising and statistically intriguing, they must be interpreted with caution and intellectual rigor. As a pilot trial, this study was designed to test feasibility and generate effect sizes, not to provide definitive proof of equivalence. Several significant limitations underscore the need for further research. First, the sample size of 20 patients (5 per group) is the most significant limitation. This sample size lacks the statistical power to rule out Type II errors. While we found "no statistically significant difference" in FLACC scores between the high-dose and low-dose groups, this does not mathematically prove they are identical. It is possible that a small, clinically subtle difference in pain control exists that our study was underpowered to detect. Furthermore, the 0% rescue analgesia rate across all groups is an anomaly that warrants scrutiny. It suggests that either the surgical procedures included were less painful than anticipated, or the multimodal background of acetaminophen was highly effective, potentially creating a "ceiling effect" that masked the differences between the opioid regimens. Future trials must utilize a larger sample size based on a formal non-inferiority power analysis. Second, the age range of 2 months to 7 years introduces substantial pharmacokinetic heterogeneity. The metabolic machinery of a 2-month-old infant is vastly different from that of a 7-year-old child. Key enzyme systems, such as the CYP3A4 pathway (responsible for metabolizing ketamine) and glucuronidation pathways (for morphine), mature at different rates. By grouping these ages together, we may be obscuring age-specific differences in drug clearance and efficacy. A 0.33 μg/kg/min dose might be adequate for an infant but insufficient for a 7-year-old rapid metabolizer. Future multicenter trials should stratify randomization by age (such as infants <1 year vs. children >1 year) to account for these physiological discrepancies. Third, the blinding protocol had inherent limitations. While we utilized a "double-blind observer" design where the outcome assessors (nurses) and parents were blinded, the attending anesthesiologist was not. This introduces the potential for performance bias—unconsciously, the anesthesiologist might have managed the low-dose morphine group with greater attentiveness or subtle interventions that were not captured in the data. A fully double-blind design, utilizing pharmacy-prepared coded syringes, would be the gold standard for a definitive confirmatory trial.[19,20]

4. Conclusion

In conclusion, this pilot randomized controlled trial challenges the conventional boundaries of pediatric postoperative analgesia. We have demonstrated that the co-administration of a continuous low-dose ketamine infusion at 0.33 μg/kg/min is a feasible, safe, and hemodynamically stable strategy that may permit a massive reduction in morphine consumption. The preliminary data indicate that reducing the morphine dosage by 81%—to a level previously considered sub-therapeutic—did not result in inferior pain control compared to standard high-dose monotherapy. This suggests that the synergistic blockade of NMDA receptors by ketamine fundamentally alters the opioid requirement, lowering the "floor" of necessary analgesics to near-zero levels.

If confirmed in large-scale, fully powered multicenter trials, these findings could catalyze a paradigm shift toward "Opioid-Sparse" or "Opioid-Free" pediatric anesthesia. Such a shift would have far-reaching implications: reducing the incidence of life-threatening respiratory depression in neonates, minimizing opioid-related side effects, and potentially protecting the developing brain from the deleterious effects of excitotoxicity and untreated pain stress. The results of this pilot study serve as a compelling "proof of concept," justifying the urgent need for definitive research to validate this potent, physiology-based analgesic strategy.

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