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Original Research Article

KETAMINE PREMEDICATION – EFFECT ON POSTOPERATIVE PAIN SCORES IN INFANTS AND CHILDREN

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ABSTRACT

Background: Managing postoperative discomfort in infants and young children is difficult because they cannot describe their pain clearly. This study examined whether a specific premedication regimen—ketamine, midazolam, and glycopyrrolate—improves postoperative comfort and reduces early pain scores, assessed using the FLACC scale.

Materials and Methods: In this prospective, randomized, double-blind trial, 304 infants and children (≤8 years) scheduled for major elective surgery at a tertiary centre were enrolled. They were assigned to either the standard premedication group (Group S) or the intervention group (Group I), which received ketamine 0.5 mg/kg, midazolam 0.03–0.04 mg/kg, and glycopyrrolate 0.005-0.01mg/kg intravenously. Anaesthetic and analgesic techniques were standardized. Postoperative pain and physiological variables were recorded at baseline and at 15, 30, 45, 60, 90 and 120 minutes using the FLACC scale. Adverse events were documented. Statistical comparison included independent t-tests and repeated-measures ANOVA.

Results: Baseline characteristics were comparable between groups. In Group I, 94% of children maintained FLACC scores below 3 throughout the observation period, indicating good comfort. Group S exhibited significantly higher pain scores at 45 and 60 minutes ($p < 0.05$), often requiring rescue analgesia. Cardiovascular and respiratory parameters remained stable in both groups. Transient respiratory slowing occurred in 2–3% of patients and resolved without intervention. Brief oversedation occurred in one patient from each group.

Conclusion: A premedication regimen combining ketamine, midazolam, and glycopyrrolate within a structured perioperative analgesic plan effectively decreases early postoperative pain in infants and children without increasing adverse effects. This ketamine-based approach may provide a reliable strategy for improving postoperative comfort in the paediatric population.

Keywords: FLACC scale; paediatric premedication, ketamine, postoperative analgesia.

INTRODUCTION

Pain assessment and management in infants and young children remain among the most demanding responsibilities in perioperative care. Although the International Association for the Study of Pain (IASP) defines pain as a subjective sensation, it simultaneously emphasizes that the inability to articulate pain verbally does not exclude an individual from experiencing significant discomfort or needing appropriate treatment.[1] This statement is particularly relevant for infants and small children, who are developmentally incapable of expressing pain, fear or anxiety in a clear verbal manner. Their limited cognitive and linguistic abilities make conventional pain assessment difficult, necessitating reliance on behavioural cues, facial expressions and physiological responses.

Over the years, several behavioural pain assessment tools have been developed to address these challenges. Among these, the Face, Legs, Activity, Cry, Consolability (FLACC) scale has emerged as one of the most widely adopted instruments due to its simplicity, reproducibility and clinical applicability.[2] Validated for children between 2 months and 7 years, the FLACC scale allows providers to quantify postoperative discomfort in a structured manner in the post-anaesthesia care unit and during early recovery.[3] Its ability to combine observable behaviours into a numerical score makes it particularly suitable in settings where rapid and reliable assessment is required.

Adequate control of postoperative pain in paediatric patients is crucial not only to improve comfort but also to reduce physiological stress responses that can otherwise lead to complications.[4] Children experiencing significant postoperative pain may have delayed wound healing, prolonged hospitalization and behavioural disturbances.[5] Inadequate analgesia has also been associated with long-term consequences, including altered pain sensitivity and greater risk of chronic pain in later childhood. Conversely, over-reliance on potent analgesics—especially opioids—carries risks such as respiratory depression, sedation and potential misuse.[6] These concerns highlight the need for balanced, multimodal analgesic strategies that integrate multiple agents and techniques to improve safety and efficacy.

Despite growing awareness and the publication of multiple guidelines addressing paediatric perioperative pain management,[7–10] implementation of standardized postoperative analgesia protocols has been inconsistent across institutions. Variations in clinical expertise, resource availability, and individual practice patterns often influence perioperative pain strategies. Moreover, the heterogeneity of paediatric patients—with differences in age, development, surgical pathology and comorbidities—makes establishing a universally accepted approach particularly challenging.

Pharmacological options used for premedication and intraoperative analgesia must therefore be selected carefully. Ketamine has gained renewed interest in recent years because of its unique mechanism of action as an NMDA receptor antagonist, offering both analgesic and antihyperalgesic effects. At low doses, ketamine has been shown to modulate central sensitization, reduce postoperative pain intensity and decrease opioid requirements. In addition to its analgesic properties, ketamine can alleviate perioperative anxiety—an important factor because heightened preoperative anxiety has been correlated with increased postoperative pain in children.[11] Midazolam, commonly used for anxiolysis and sedation, complements ketamine's effects, while anticholinergic agents such as glycopyrrolate help counteract ketamine-induced secretions.

Given these considerations, a premedication protocol incorporating ketamine—especially when combined with agents such as midazolam and glycopyrrolate—may offer both anxiolytic and analgesic advantages. Integrating such a regimen into a structured perioperative pain management plan may therefore have meaningful implications for improving postoperative comfort in children.

The present study was undertaken to evaluate the effect of a defined premedication consisting of ketamine, midazolam and glycopyrrolate on postoperative pain intensity, measured by the FLACC scale, in infants and young children undergoing major elective surgery. The study further aimed to determine whether this approach reduces the need for rescue analgesia and enhances early postoperative comfort when compared with standard premedication practices.

MATERIALS AND METHODS

Study Design and Setting: This prospective, randomized, double-blind study was carried out in a tertiary-care teaching hospital after obtaining approval from the Institutional Ethics Committee. The study included infants and children scheduled for major elective surgical procedures over a period of two years.

Study Population: Children of either sex, aged up to 8 years, and planned for major elective surgeries under general anaesthesia were considered eligible.

Exclusion criteria included:

- emergency or life-saving procedures,
- history of prematurity,
- anticipated need for postoperative intensive care,
- known hypersensitivity to any study medication.

Informed written consent was taken from parents or legal guardians before enrollment.

Randomisation and Blinding: Participants were assigned to one of the two study groups—Group S or Group I—using a computer-generated random sequence. Group allocation was concealed in sequentially numbered, opaque, sealed envelopes, which were opened immediately before administering premedication. Care providers involved in postoperative assessment, as well as patient caregivers, remained blinded to group allocation. Premedication was administered by an anaesthesiologist who had no role in postoperative evaluations.

Study Groups

Group S (Standard Premedication)

- According to institutional practice:
  - infants <6 months received IV atropine 0.01 mg/kg
  - infants/ children >6 months received IV midazolam.

Group I (Ketamine-Based Premedication Cocktail)

- Midazolam 0.03–0.04 mg/kg IV
- Ketamine 0.5 mg/kg IV
- Glycopyrrolate 0.005-0.01 mg/kg IV

Anaesthesia and Perioperative Care: After premedication, all patients were transferred to the

operating room, where routine monitoring (pulse oximetry, ECG, non-invasive blood pressure, and temperature) was applied. General anaesthesia was induced and maintained using the institution's standard protocol.

A multimodal analgesic plan was used for every patient. Surgical wounds were infiltrated with 0.125% bupivacaine, and additional systemic analgesics were given intraoperatively and postoperatively according to procedure type and weight-based dosing. Local anaesthetic infiltration and intravenous analgesic combinations formed the core of the postoperative pain protocol.

Postoperative Assessment: Pain was evaluated using the FLACC (Face, Legs, Activity, Cry, Consolability) scale.[12] Physiological parameters—heart rate, mean arterial pressure, and oxygen saturation—were recorded at the following time points:

- Baseline (pre-intervention)
- 15, 30, 45, 60, 90, and 120 minutes postoperatively

Any adverse effects, such as excessive secretions, hallucinations, emergence agitation, nausea, vomiting, or respiratory depression, were documented.

Statistical Analysis: The Shapiro–Wilk test was used to determine normality of data distribution. Normally distributed continuous variables were presented as mean ± standard deviation (SD). The Independent Samples t-test was used for intergroup comparisons. Repeated measures across the postoperative timeline were analysed using one-way repeated measures ANOVA. When ANOVA indicated significant differences, Bonferroni or LSD post-hoc corrections were applied for pairwise comparisons.

Categorical data were analysed using the Chi-square test or Fisher's Exact test, depending on cell frequencies.

A p-value < 0.05 was considered statistically significant.

RESULTS

Subject Characteristics: In a 2 years duration, 136 infants and 168 children underwent major elective surgery in paediatric surgery, orthopaedic surgery and ophthalmic surgery operation theatres. These were randomly allocated to one of the two study groups. The mean age of infants in the two study groups was 6.121 ± 1.345 months and 6.189 ± 1.536 months respectively while the mean age of children in the two groups (S and I) were 4.22 ± 2.06 years and 4.32 ± 1.97 years respectively. The patients in the two study groups were similar in terms of their demographic profile (age, weight, height, ratio of males to females), the minor differences observed were found to be statistically insignificant, [Table 2].

Haemodynamic Parameters: The postoperative haemodynamic and other physiologic parameters, pulse rate, mean arterial pressure, respiratory rate, oxygen saturation (as assessed by SpO2) remained stable for all the patients, the minor variations were found to be statistically insignificant in patients of both study groups. The average baseline values in the two study groups were also similar.

Pain Relief: A majority (94.36%) of patients in the intervention group, who received the premedication cocktail of ketamine, midazolam and glycopyrrolate, remained comfortable (FLACC score < 3) throughout the 120-minute postoperative observation period. In contrast, patients in the standard premedication group who received intravenous atropine (0.01mg/kg) for infants less than 6 months and intravenous midazolam for infants/children more than 6 months, showed lower levels of comfort.

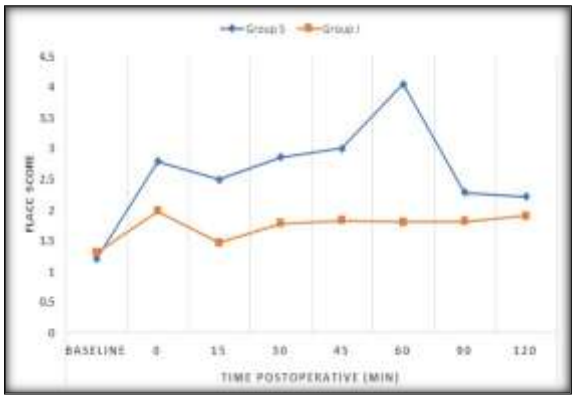
Table 1: FLACC Scale

Although the mean baseline and immediate postoperative FLACC scores were comparable between the two study groups for both infants and children, the scores in the intervention group (Group I) remained consistently stable during the entire postoperative observation period. However, in the standard premedication group (Group S), both infants and children demonstrated higher FLACC scores, often reaching ≥ 4 and necessitating rescue analgesia. The highest scores in Group S were observed at 45 and 60 minutes postoperatively. Consequently, the intergroup differences were significant at these points of time for both age subgroups. Beyond 60 minutes, the differences became statistically insignificant within the next 30 minutes and remained so throughout the rest of the observation period ($p = 0.21$).

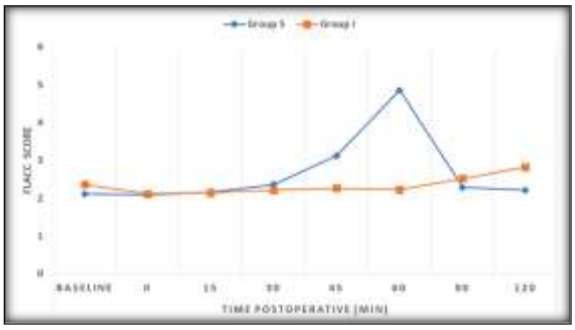
Among infants, FLACC scores in Group S were higher than those Group I at all postoperative time points except at baseline and at 90 and 120 minutes.

Safety Analysis

Safety analysis showed that approximately 2–3% of patients in each group experienced transient respiratory depression, defined as a ≥10% decrease in respiratory rate from baseline. All episodes resolved spontaneously without the need for any intervention. Additionally, one patient in each group demonstrated oversedation, with a Ramsay Sedation Score of 5 at 15 minutes postoperatively. Sedation levels returned to normal within the subsequent 5 minutes and remained stable for the rest of the study period.



(a) Infants



(b) Children

Figure 1 FLACC score variation – baseline and postoperative

Table 2: Baseline Haemodynamic and Demographic Parameters

Group		**Group S (n = 152)**		**Group I (n = 152)**	
Patient type		**Infants**	**Children**	**Infants**	**Children**
Number of patients (n)		67	84	69	82
Gender (M:F)		39: 28	40:44	39:30	42:40
Age (months / years)		6.121 ± 1.345	4.22 ± 2.06	6.189 ± 1.536	4.32 ± 1.97
Weight (kg)		5.02 ± 1.44	14.15 ± 7.23	4.98 ± 1.96	14.38 ± 7.11
Height (cm)		56.21 ± 10.44	86.28 ± 22.75	58.01 ± 9.86	83.38 ± 20.65
Procedure done	Abdominal	29	42	26	44
	Thoracic	16	12	17	15
	Ophthalmic	17	8	18	6
	Orthopaedic	5	24	8	17
Baseline heart rate (beat/min)		137.54 ± 4.17	97.54 ± 13.17	135.29 ± 5.77	98.04 ± 10.17
Baseline Mean Arterial Pressure (mm of Hg)		62.36 ± 4.51	69.24 ± 7.24	60.11 ± 4.32	70.61 ± 3.94
FLACC baseline		1.2 ± 0.73	2.11 ± 0.34	1.3 ± 0.63	2.36 ± 0.14

Table 3: Postoperative Parameters in Infants

		Time Postoperative (min)						
		0	**15**	**30**	**45**	**60**	**90**	**120**
Hear Rate (HR)	Group S	142.40 ± 8.17	138.04 ± 7.14	140.00 ± 7.32	137.40 ± 8.02	141.20 ± 8.07	139.94 ± 9.08	138.43 ± 9.10
	Group I	141.23 ± 8.17	119.81 ± 20.88	118.32 ± 14.71	114.64 ± 12.55	120.33 ± 11.71	120.31 ± 9.84	122.03 ± 12.24
Mean Arterial Pressure (MAP) (mmHg)	Group S	62.36 ± 4.51	61.59 ± 5.29	63.50 ± 5.92	62.16 ± 4.78	63.95 ± 4.38	61.17 ± 6.39	62.33 ± 5.34
	Group I	61.61 ± 5.01	58.34 ± 5.09	57.34 ± 4.29	57.46 ± 4.89	58.01 ± 4.96	58.14 ± 5.04	58.34 ± 5.29
FLACC Score	Group S	2.79 ± 1.23	2.49 ± 1.13	2.86 ± 1.53	3.00 ± 1.85	4.05 ± 3.11	2.28 ± 2.14	2.21 ± 1.53
	Group I	1.98 ± 1.43	1.46 ± 0.73	1.77 ± 0.65	1.82 ± 0.63	1.80 ± 0.70	1.81 ± 0.77	1.90 ± 0.12

Table 4: Postoperative Parameters in Children

		Time Postoperative (min)						
		0	**15**	**30**	**45**	**60**	**90**	**120**
Hear Rate (HR)	Group S	97.54 ± 13.17	99.28 ± 14.11	100.02 ± 12.87	102.64 ± 10.55	128.81 ± 20.88	130.94 ± 28.48	109.03 ± 12.24
	Group I	98.04 ± 10.17	97.04 ± 11.07	98.40 ± 9.64	97.87 ± 11.01	98.13 ± 9.76	98.43 ± 9.91	99.24 ± 10.32
Mean Arterial Pressure (MAP) (mmHg)	Group S	69.24 ± 7.24	69.78 ± 7.41	70.01 ± 6.89	70.50 ± 6.92	74.15 ± 8.03	69.17 ± 6.39	65.33 ± 10.34
	Group I	70.61 ± 3.94	69.34 ± 2.63	68.61 ± 2.97	68.53 ± 3.01	70.34 ± 2.32	70.47 ± 2.94	70.61 ± 3.38
FLACC Score	Group S	2.09 ± 1.43	2.16 ± 0.14	2.36 ± 0.33	3.12 ± 1.85	4.85 ± 3.11	2.28 ± 2.14	2.21 ± 1.53
	Group I	2.11 ± 0.34	2.14 ± 0.24	2.21 ± 0.14	2.26 ± 0.33	2.22 ± 0.42	2.51 ± 0.38	2.82 ± 0.41

DISCUSSION

The findings of the present study reinforce the importance of a structured approach to perioperative care in paediatric patients, particularly with regard to anticipatory analgesia and anxiolysis. The use of a predefined premedication regimen combining ketamine, midazolam and glycopyrrolate resulted in significantly better postoperative comfort during the first two hours of recovery, compared with standard

premedication practices. One of the key observations was the consistently low FLACC scores in children receiving the ketamine-based cocktail, suggesting that early modulation of anxiety and nociception has a meaningful influence on postoperative behaviour and perceived discomfort.

Ketamine has been widely used in paediatric anaesthesia for several decades, and its safety profile is well established. Earlier studies from the 1990s demonstrated its predictable onset, stable haemodynamic profile and relatively wide safety margin, especially in children.[11] These properties make ketamine a particularly useful agent in younger age groups where airway reflexes and cardiovascular stability are of paramount concern. The risk of severe complications such as laryngospasm, aspiration or significant respiratory depression remains exceedingly low when the drug is used in sub-anaesthetic doses, further supporting its applicability for premedication.[11]

Midazolam, another essential component of the combination used in this study, is recognised as a reliable anxiolytic and sedative in infants and children.[13] Although it may cause injection-site discomfort, thrombophlebitis or transient respiratory depression at higher doses, its overall safety profile is favourable. Midazolam's anxiolytic properties are particularly relevant in the paediatric population, where preoperative fear and separation anxiety can trigger exaggerated physiological stress responses. Studies have suggested that higher preoperative anxiety in children correlates with increased postoperative pain, behavioural disturbances and delayed recovery.[11] The inclusion of midazolam in the premedication protocol therefore serves both a psychological and a physiological purpose.

The complementary actions of ketamine and midazolam have been explored in multiple clinical trials. A comparative study in children aged 1–6 years reported that ketamine produced deeper sedation and superior anxiolysis compared with midazolam, with smoother postoperative recovery.[14] Although children receiving midazolam alone experienced quicker emergence from anaesthesia, their recovery was more frequently complicated by irritability and restlessness. Such findings support the hypothesis that combining ketamine and midazolam may yield the advantages of both drugs while minimising their individual limitations.

Funk et al,[15] further demonstrated that combining midazolam with ketamine provided notably better results in terms of anxiolysis, cooperation at parental separation and acceptance of mask induction when compared with using either drug alone. Their study documented success rates exceeding 90% with the combination, significantly higher than the rates observed with midazolam alone (approximately 70%) or ketamine alone (around 51%). Importantly, undesirable psychological effects—including excitation, hallucinations or excessive salivation—were found to be infrequent and typically short-lived. Recovery characteristics were similar across groups, and delayed psychological disturbances such as nightmares or restlessness were minimal in the combination group.

A later study by Erk et al,[16] supported these findings, reporting that ketamine as a sole anaesthetic, with or without midazolam, produced calm and safe anaesthesia in paediatric patients undergoing adenotonsillectomy. The combination of ketamine and midazolam resulted in better postoperative outcomes, including reduced emergence agitation and smoother transition to recovery. These observations further validate the use of ketamine and midazolam together, especially in children who are prone to anxiety and postoperative distress.

More recent retrospective analyses have also endorsed the efficacy of midazolam–ketamine combinations for premedication.[17,18] These studies highlight that the combination reliably produces cooperative behaviour preoperatively, attenuates fear during induction and contributes to improved perioperative stability. They also emphasise that psychological factors—especially preoperative anxiety, parental separation and fear related to surgical procedures—play an important role in shaping postoperative pain perception and overall recovery profile in children.

The addition of glycopyrrolate to the regimen serves a specific physiological purpose. Ketamine is known to increase salivary and tracheobronchial secretions, and anticholinergic agents such as glycopyrrolate effectively counter this effect.[19] Unlike atropine, glycopyrrolate does not cross the blood–brain barrier and therefore minimizes central nervous system side effects. Furthermore, anticholinergic premedication is often considered beneficial in infants and younger children due to their higher baseline vagal tone and increased susceptibility to bradycardia, particularly during induction or surgical stimulation.

The present study suggests that mitigating psychological distress before surgery may have a greater effect on postoperative comfort than previously appreciated. Children who were calmer and better sedated preoperatively were less likely to exhibit high FLACC scores postoperatively, and fewer children in the ketamine-based group required rescue analgesia during the observation period. Although postoperative analgesic regimens varied based on the surgical procedure and clinician preference, the overall trend indicated that pre-emptive modulation of nociception and anxiety delivered tangible benefits.

The significant differences in FLACC scores between groups at 45 and 60 minutes support the idea that the ketamine-based protocol plays an important role during the period when residual sedation wears off and surgical pain becomes more noticeable. By this time, children who were premedicated with only midazolam or atropine in the standard group displayed higher distress behaviours, whereas those in the intervention group maintained stable comfort scores.

Collectively, the results of this study underscore the value of adopting a structured, protocol-based approach to paediatric premedication. By combining anxiolysis, pre-emptive analgesia and physiological stabilization, the ketamine–midazolam–glycopyrrolate regimen appears to provide a more favourable perioperative experience for paediatric patients. These findings highlight the potential benefits of integrating such a protocol into routine clinical practice, particularly in institutions where postoperative pain control in children remains a challenge.

CONCLUSION

This study demonstrates that premedication with a combination of ketamine, midazolam and glycopyrrolate, when incorporated into a structured perioperative analgesic plan, provides superior early postoperative comfort in infants and young children undergoing major surgery. Children receiving this regimen consistently showed lower FLACC scores and required less rescue analgesia, without an increase in adverse events or haemodynamic instability.

These findings highlight the importance of addressing both anxiety and nociception before surgery. By offering reliable anxiolysis and pre-emptive analgesia, the ketamine-based protocol appears more effective than conventional premedication practices in reducing early postoperative distress. This suggests that the quality and structure of premedication may significantly influence postoperative pain outcomes in paediatric patients.

Implementing a uniform premedication protocol may therefore enhance perioperative care across diverse surgical settings. Thoughtful anticipatory management, aligned with multimodal analgesic strategies and paediatric expertise, can meaningfully improve postoperative recovery and comfort in this vulnerable population.

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