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Original Research Article

A Study Comparing Nebulised Ketamine and Midazolam as Premedicant in Pediatric Patients Undergoing Elective Surgery

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Conflict of interest: Nil

Abstract:

Background: Apprehension prior to clinical procedures in children is not uncommon and can end up with usage of complex anaesthetic induction, increased postoperative analgesic necessities, and inconsistent behavioural changes. Nebulised drug delivery offers a non-invasive route with optimal mucosal absorption and enhanced patient reception. Both midazolam and ketamine are employed worldwide as pediatric premedicants; nevertheless, very little clinical data is available in literature about their nebulised formulations.

Aim: To compare the sedative efficacy, ease of parental separation, mask acceptance, hemodynamic effects, and adverse events associated with nebulised ketamine and nebulised midazolam in pediatric patients undergoing elective surgery.

Methods: This study model was prospective and randomised along with double-blinding which included 60 children aged 2–12 years (ASA I–II) scheduled for elective surgeries under general anaesthesia. All willing patients were logically categorized into two groups: Group K received nebulised ketamine 2 mg/kg, and Group M received nebulised midazolam 0.2 mg/kg. All parameters related to Sedation were evaluated utilizing the Ramsay Sedation Score at 5-minute intervals up to 30 minutes. Secondary outcomes included parental separation score, mask acceptance score, hemodynamic parameters, and adverse events. Statistical significance was set at $p<0.05$.

Results: Results were highly imperative and stated that both groups confirmed significant time-dependent boosts in sedation scores ($p<0.001$), with no significant intergroup differences. However, Group M showed significantly better mask acceptance ($p=0.04$) and smoother parental separation. Heart rate and systolic blood pressure were significantly higher in Group K at 30 minutes ($p = 0.04$). Oxygen saturation and respiratory rate remained stable and comparable in both groups. No significant adverse events were observed.

Conclusion: Within the limitations of the study, authors concluded that both nebulised midazolam and ketamine are safe and effective premedicants in pediatric patients. Nebulised midazolam improves behavioural compliance and steadier hemodynamics, making it a preferable choice for facilitating smoother anaesthetic induction.

Keywords: Ketamine, Midazolam, Premedication, Pediatric Anaesthesia, Preoperative Anxiety, Conscious Sedation.

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Introduction

As we all are aware that hospitalisation and the preoperative surroundings could by extremely worrying for children. Strange environment, separation from parents, dealings with anonymous healthcare workers, and terror of surgery and pain contribute drastically to preoperative anxiety. [1]

This anxiety actually produces an acute stress response triggering sympathetic, parasympathetic and endocrine systems. All these events jointly end up with increased heart rate, blood pressure, and myocardial excitability.[2] Elevated preoperative anxiety not only obscures anaesthetic initiation but is also linked with increased postoperative analgesic necessities, higher occurrence of postoperative nausea and vomiting (PONV), emergence delirium (ED), and problematic behavioural alterations like sleep disturbances, violence, eating issues and nocturnal enuresis.[1] Different non-pharmacological tactics have been searched by different researchers in the literature to decrease preoperative anxiety in paediatric cases. These comprise primarily preoperative counselling, behavioural training programs, parental existence during initiation of anaesthesia and distraction procedures.[3] Parental presence throughout initiation gives psychological encouragement and can assist smoother adjustment to the unknown operating room settings. Accommodating caregiver actions, distraction, humour, and non–procedure-related discussion has been related with enhanced coping responses in children, but unnecessary encouragement and emotion-focused behaviours can illogically amplify distress. Distraction methodologies such as hospital clowns, smartphone based audiovisual means; guided imagery, hypnosis, and virtual reality have demonstrated inconsistent usefulness in diminishing preioperative distress. Many clinicians believe that pharmacological premedications are keystone in controlling pediatric preoperative anxiety. [4] Commonly employed pharmacological agents are benzodiazepines (midazolam, temazepam), α-adrenoceptor agonists (dexmedetomidine, clonidine), N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine), and opioids. A perfect premedicant must successfully diminish anxiety, fear and emotional stress; make easy and smooth separation from parents; and offer constructive conditions for the introduction of anaesthesia without noteworthy undesirable consequences.[5] conversely; no single agent or route of administration accomplishes all these criteria. Conventionally used drugs like morphine, paraldehyde, meperidine, diazepam, trimeprazine, promethazine, lorazepam, and barbiturates have mostly been substituted because of inauspicious side-effect reports. Premedication can be given through oral, rectal, sublingual, intranasal, or inhalational routes, each with changing levels of effectiveness and patient reception. The preference of premedicant solely based on numerous things including pharmacological properties, compositions, contraindications, the child's level of cooperation, and previous anaesthetic record. For accommodating but apprehensive children, oral or buccal midazolam is extensively used. If taste intolerance limits receiving, oral clonidine can be a preference. In children declining oral medication, intranasal dexmedetomidine offers a valuable option. Nebulised drug delivery characterizes a noninvasive and possibly successful alternative route. This evades venipuncture and is comparatively simple to control, and offers high mucosal bioavailability. [6] Nebulization creates fine particles that improve surface area coverage and assists speedy assimilation via nasal, buccal, and respiratory mucosa. It also seriously enhances central nervous system penetration and clinical effectiveness while maintaining good patient acceptability. [7-8] Ketamine, an NMDA receptor antagonist, creates dissociative anaesthesia by functionally separating the cortex from the limbic system. It also provokes sedation, analgesia, amnesia, and immobility while characteristically controlling airway reflexes and natural respiration. [9] Unlike several sedatives, ketamine maintains respiratory rhythm and functional residual capacity and creates gentle bronchodilation. Its adaptability permits introduction via multiple routes, making it predominantly helpful in obstinate children. On the other hand, unfavourable effects like emergence reactions, cognitive disturbances, postoperative behavioural changes, and delayed recovery may limit its use. Midazolam, a short-acting benzodiazepine, is commonly used for paediatric premedication because of its quick inception, anxiolytic properties, and positive safety profile. [10] Intranasal midazolam creates sensible sedation, assisting parental separation and anaesthetic initiation with no noteworthy respiratory issues. Vital parameters, including oxygen saturation, usually remain constant, and severe undesirable happenings are exceptional. It can also be joint with other agents for diagnostic and small surgical practices in children. Although both ketamine and midazolam are commonly used as pediatric premedicants, consensus regarding the optimal drug and route of administration remains lacking. Moreover, comparative evidence regarding nebulised formulations of these agents is limited.

Purpose of the Study: The present study was planned, designed and executed to compare the sedative efficacy, hemodynamic effects, and incidence of adverse events associated with nebulised ketamine and nebulised midazolam when used as premedication in pediatric patients undergoing elective surgical procedures.

Aim: To compare nebulized ketamine and midazolam as premedication in pediatric patients undergoing elective surgeries.

Objective

Primary Objective

1. To evaluate and compare the level of sedation between group Ketamine and group Midazolam.

The secondary objectives are to

1. Compare time of onset of action.
2. Compare ease of child-parent separation.
3. Study the ease of induction in operative room.
4. Effects of two drugs on intra-operative hemodynamics.
5. Study the adverse effects of two drugs if any.

Materials and Methods

Study Design and Ethical Approval: This prospective, randomized, double-blind, comparative study was conducted in the Department of Anaesthesiology and Critical Care, Pt. B. D. Sharma PGIMS, Rohtak, between July 2024 and October 2025. The study protocol was approved by the Institutional Ethics Committee [IRB number: BREC/24/651 and Research Registration Number: CTRI/2025/07/091128]. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrolment. Sixty pediatric patients of either sex, aged 2–12 years, belonging to American Society of Anesthesiologists (ASA) physical status I or II and scheduled for elective surgical procedures under general anaesthesia, were included in the study.

Exclusion Criteria

Children were excluded if they had:

1. Developmental delay
2. Significant systemic illness (cardiac, neurological, hepatic, or renal disease)
3. Known hypersensitivity to ketamine or midazolam
4. Refusal of parental consent

Sample Size Calculation and Preoperative Assessment/Preparation: The sample size was calculated based on data from a previous study by Narendra et al. In that study, sedation scores differed between the ketamine (36%) and midazolam (46%) groups. For the present study, a mean difference (δ) of 5.66 with a pooled standard deviation (SD) of 7.95 was considered clinically significant. The calculated sample size was approximately 30 patients per group. Therefore, a total of 60 children were enrolled, with 30 participants in each group. All patients underwent detailed pre-anesthetic evaluation one day prior to surgery, including medical history, general physical examination, and systemic examination. Routine investigations such as hemoglobin (Hb), random blood sugar (RBS), blood urea, and serum creatinine were performed. Preoperative fasting guidelines were followed as per standard recommendations:

- 6 hours for solids
- 4 hours for breast milk
- 2 hours for clear fluids

Baseline heart rate, respiratory rate, systolic blood pressure, and activity level were recorded in the preoperative area on the day of surgery.

Randomization and Blinding: Participants were randomly allocated into two groups (n=30 each) using a computer-generated random number table:

- **Group K:** Nebulized ketamine 2 $mg \cdot kg^{1}$
- **Group M:** Nebulized midazolam 0.2 $mg \cdot kg^{1}$

Double blinding was maintained. The study drug was prepared by a researcher not involved in patient assessment or data collection. The anesthesiologist responsible for evaluating sedation and recording outcomes was blinded to group allocation.

Intervention Protocol: The study drugs were diluted with 0.9% normal saline to a total volume of 3 mL. Nebulization was performed using a standard nebulizer connected to a wall oxygen source at 4 L/min. Drug administration lasted 15 minutes in the preoperative area before transfer to the operating room. In the operating room, standard monitoring was instituted, including electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse oximetry (SpO_2). Anesthesia was induced with inhalational sevoflurane. Intravenous access was subsequently secured, followed by administration of fentanyl (2 $\mu g \cdot kg^{1}$) and atracurium (0.1 $mg \cdot kg^{1}$) to facilitate tracheal intubation. Anesthesia was maintained with isoflurane. At the completion of surgery, patients were extubated upon meeting standard awake extubation criteria and shifted to the recovery room for postoperative monitoring.

Outcome Measures

Primary Outcome: Sedation level was assessed using the six-point Ramsay Sedation Score.[11] Sedation was evaluated at 5-minute intervals (5,10,15,20,25, and 30minutes) following drug administration.

Ramsay Sedation Score [11]

1. Anxious and agitated
2. Cooperative, oriented, tranquil
3. Responds to commands only
4. Brisk response to stimulus
5. Sluggish response to stimulus
6. No response

Secondary Outcomes

1. Separation Score[2]

After achieving adequate sedation, children were separated from their parents. Response to separation was graded using a 4-point scale:

Child unafraid, co-operative, asleep	excellent	1
Slight fear or crying, quiet with reassurance	good	2
Moderate fear, crying not quiet with reassurance	fair	3
Crying, need for restraint	poor	4

2. Mask Acceptance Score [12]

Calm, co-operative, or asleep	1
Moderate fear of mask, manageable with reassurance	2
Cries, combative, and needs restraining	3

Scores of 1–2 were considered satisfactory.

3. Hemodynamic Parameters

Heart rate, respiratory rate, and systolic blood pressure were monitored continuously and recorded every 5 minutes for 30 minutes following nebulization.

4. Adverse Events

Patients were observed for vomiting, excessive salivation, abdominal rigidity or movements, airway compromise, upper airway obstruction, respiratory depression, apnea, and oxygen desaturation. Any adverse events were managed according to standard institutional protocols.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables were expressed as mean ± standard deviation (SD) or median, as appropriate. Categorical variables were presented as frequency and percentage. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Parametric tests were applied for normally distributed data, while non-parametric tests were used when normality assumptions were not met. A p-value < 0.05 was considered statistically significant.

Results

Participant Characteristics: Sixty children were enrolled and randomized into two groups: Group K (nebulized ketamine, n = 30) and Group M (nebulized midazolam, n=30). All randomized participants completed the study and were included in the final analysis. The mean age in Group K was 6.87±2.79 years, while in Group M it was 6.00±3.14 years. The difference in age between the groups was not statistically significant (p=0.26). In Group K, 25 children (83.3%) were male and 5 (16.7%) were female. In Group M, 24 children (80%) were male and 6 (20%) were female. The sex distribution between groups was comparable, with no statistically significant difference ($p = 0.73$). These findings indicate that the groups were demographically similar at baseline.

Sedation Scores: Sedation was assessed using the Ramsay Sedation Score12 at baseline (0 minute) and at 5, 10, 15, 20, 25, and 30 minutes following nebulization. At baseline (0 minute), all children in both groups had a sedation score of 1 (awake and anxious).

In Group M, sedation scores increased progressively over time. By 10–15 minutes, the majority of children achieved a score of 2 (cooperative and tranquil). At 20–25 minutes, several children reached a score of 3 (responding to commands only). At 30 minutes, most children had sedation scores between 2 and 3.

In Group K, sedation scores also demonstrated a gradual increase over time. By 10–15 minutes, most children had scores between 1 and 2. At 25–30 minutes, a greater proportion of children achieved scores between 2 and 3.

Within-group analysis using the Friedman test showed a statistically significant increase in sedation scores over time in both groups ($p < 0.001$), indicating effective sedative action of both interventions. Between-group comparison at each time point using the Mann–Whitney U test revealed no statistically significant differences in sedation scores between Group M and Group K ($p > 0.05$ at all intervals).

Parental Separation Score: Parental separation was evaluated using a 4-point separation scale [2], where lower scores indicated easier separation. In Group M, 11 children (36.7%) demonstrated easy separation (score 1), 16 children (53.3%) had moderate separation (score 2), and 3 children (10%) exhibited difficult separation (score 3). The mean separation score in this group was 1.73 ± 0.64. In Group K, 3 children (10%) had easy separation, 21 children (70%) had moderate separation, and 6 children (20%) experienced difficult separation. The mean separation score was 2.03 ± 0.61. The distribution of separation scores suggested a greater proportion of children with lower (more favourable) scores in Group M compared to Group K.

Mask Acceptance: Mask acceptance scores ranged from 1 (easy acceptance) to 3 (major resistance/refusal). In Group M, 11 children (36.6%) had a score of 1, 17 (56.6%) had a score of 2, and 2 (6.6%) had a score of 3 (mean score 1.73). In Group K, 3 children (10%) had a score of 1, 24 (70%) had a score of 2, and 3 (20%) had a score of 3 (mean

score 2.0). The proportion of children with easy mask acceptance (score 1) was significantly higher in Group M compared with Group K (p=0.04).

Heart Rate: Baseline heart rate was comparable between Group M (97.70 ± 14.13 bpm) and Group K (97.37 ± 14.07 bpm) (p = 0.92). No significant intergroup differences were observed at 0, 5, 10, 15, 20, or 25 minutes (all p > 0.05). At 30 minutes, mean heart rate was significantly higher in Group K (101.63 ± 14.11 bpm) compared with Group M (94.07 ± 14.89 bpm) (p = 0.04).

Systolic Blood Pressure (SBP): Baseline SBP was similar in Group M (101.47 ± 12.63 mmHg) and Group K (101.87 ± 5.89 mmHg) (p > 0.05). No statistically significant differences were observed between groups from 0 to 25 minutes (all p > 0.05). At 30 minutes, SBP was significantly higher in Group K (103.80 ± 8.12 mmHg) compared with Group M (98.50 ± 11.40 mmHg) (p = 0.04).

Diastolic Blood Pressure (DBP): Baseline DBP was comparable between Group M (73.58 ± 3.39 mmHg) and Group K (74.88 ± 3.82 mmHg) (p = 0.11). No statistically significant differences were observed at any subsequent time interval (all p > 0.05).

Oxygen Saturation (SpO_2): SpO_2 values remained stable and comparable between groups throughout the study period. Baseline values were 99.97 ± 0.18% in Group M and 100% in Group K (p = 0.32). No statistically significant differences were observed at any time point.

Respiratory Rate: Baseline respiratory rate was similar between Group M (17.76 ± 3.55 breaths/min) and Group K (18.00 ± 3.03 breaths/min) (p = 0.75). Respiratory rates remained comparable between groups at all recorded time intervals up to 30 minutes, with no statistically significant differences (all p > 0.05).

Discussion

Our study results were highly imperative and exacting. Several researchers in the literature have put forwarded different conceptions and recommendations in these regards. The mean age of children in Group M and Group K was comparable (6.00 ± 3.14 years vs 6.87 ± 2.79 years), limiting the possible effects of age-related behavioural and pharmacodynamic inconsistency on outcomes. Sedation scores augmented increasingly over time in both groups. Within-group analysis confirmed a significant time-dependent increase in sedation scores. Children in Group M achieved moderate sedation (score 3) slightly earlier (approximately 20–25 minutes) compared with Group K; however, intergroup differences were not statistically significant. These conclusions were in agreements with the results of Yuen et al. [13], who stated continuing onset of sedation following pediatric premedication. Correspondingly, Sajedi et al. [14] noticed analogous sedation levels between dexmedetomidine and midazolam at later time intervals. Khoshrang et al. [15] also confirmed no significant difference in sedation scores between ketamine and midazolam groups. Their findings were in agreement and alignment aligns with the current study outcomes. Separation scores illustrated improved parental separation in Group M compared with Group K, with a considerably lower mean separation score in Group M. A higher proportion of children in Group M had acceptable separation scores. These outcomes are consistent with Mountain et al. [16], who reported smoother parental separation with midazolam, likely attributable to its anxiolytic and amnestic properties. Sheta et al. [17] noted that although ketamine offers sufficient sedation, children were less reactive to reassurance, perhaps due to dissociative effects. Mask reception was appreciably superior in Group M. A larger section of children in Group M showed simple reception (score 1), while Group K had an elevated section of children with resistance (score 3). Abdel-Ghaffar et al. In their work illustrated higher mask acceptance with midazolam compared to ketamine somewhat comparable with our study results. Kain et al. [1] recommended that even if ketamine offers cardiovascular and respiratory stability, it cannot constantly recover behavioural issues throughout introduction. Comparable results were showed by Vaishnavi et al [18], who noticed noteworthy dissimilarities in mask reception at 30 minutes. From 15 minutes onward, Group K confirmed superior heart rates, getting statistical significance at 30 minutes. All such events are maintained by Koroglu et al. [19], who demonstrated augmented heart rate after ketamine administration, possibly associated to its sympathomimetic entities. Malinovsky et al. [20] notices steady heart rate profiles with midazolam, regular with minimal cardiovascular stimulation. Systolic blood pressure (SBP) was equivalent at baseline. From 10 minutes onward, SBP tended to be lower in Group M and higher in Group K, reaching statistical significance at 30 minutes. These findings are consistent with the meta-analysis by Lang et al [21], which reported higher mean blood pressure values and greater variability with ketamine compared to midazolam. Diastolic blood pressure (DBP) values were similar at baseline and showed no statistically significant differences throughout the observation period. These findings are in agreement with Sheta et al. [17], who reported hemodynamic stability with both agents. Green et al. [22] also reported only minor, clinically insignificant changes in DBP with ketamine sedation in children. Oxygen saturation remained stable and within normal limits in both groups at all time intervals, with no episodes of desaturation. These findings are consistent with

previous studies by Yuen et al. [13] and Sheta et al. [17], which reported preserved respiratory function with pediatric sedative premedication. Narendra et al. [8] similarly found no significant differences in oxygen saturation between ketamine and midazolam groups. A systematic review comparing sedative agents in pediatric patients also reported no clinically significant respiratory depression. [18] Respiratory rate remained comparable between groups throughout the study period, with no statistically significant differences. Transient variations were observed but were not clinically significant. Similar findings have been reported by Malinovsky et al. [20] and Green et al. [22], who observed minimal respiratory compromise with either midazolam or ketamine when administered in appropriate doses.

Limitations

This study has several limitations. The sample size was relatively small, which may limit statistical power. The study was conducted at a single centre, potentially affecting generalizability. The age range of participants was broad, which may introduce variability in behavioural responses. Some outcome measures were observer-dependent, introducing potential assessment bias. Additionally, only short-term preoperative outcomes were evaluated; postoperative and long-term effects were not assessed.

Conclusion

Authors have concluded highly significant and exacting remarks with clinical applicability. They stated that both midazolam and ketamine provided effective preoperative sedation with stable hemodynamic and respiratory parameters. Nevertheless, midazolam was related with earlier attainment of moderate sedation, smoother parental separation, and improved mask acceptance. Ketamine illustrated comparable safety but showed relatively higher heart rate and systolic blood pressure values at later time intervals. Both agents may be considered safe and effective options for pediatric premedication, with selection guided by clinical priorities and desired behavioural outcomes.

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