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Comparative Evaluation of Oral Ketamine-Dexmedetomidine Versus Oral Ketamine-Midazolam as Premedication in Pediatric Patients Undergoing Elective Surgery Under Anaesthesia

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Abstract: ***Background: Preoperative anxiety is a significant challenge in pediatric anaesthesia, necessitating effective premedication strategies. Oral drug combinations offer a non-invasive and child-friendly approach to achieving adequate sedation and anxiolysis. This study evaluates two commonly employed oral premedication regimens- ketamine combined with dexmedetomidine (KD) and ketamine combined with midazolam (KM)—in children aged 2–10 years scheduled for elective procedures. Methods: A prospective observational study was conducted at a tertiary care hospital over 14 months (March 2024 – May 2025). Sixty pediatric patients (ASA I–III, aged 2–10 years) were allocated into two groups of 30 each. Group KM received oral ketamine 3 mg/kg + midazolam 0.3 mg/kg, and Group KD received oral ketamine 3 mg/kg + dexmedetomidine 3 mcg/kg, each diluted in mango juice and administered 50 minutes before surgery. Sedation was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAAS) scale, parental separation anxiety score, mask acceptance scale, and hemodynamic parameters. Results: At the 50-minute time point, Group KD showed significantly deeper sedation (MOAAS: 2.1 ± 0.64) compared to Group KM (2.6 ± 0.60; $p < 0.05$). Parental separation was rated excellent in 90% of KD patients versus 56.7% in KM ($p < 0.001$). Mask acceptance was superior in KD (83.3% excellent) compared to KM (46.7% excellent; $p = 0.006$). Hemodynamic parameters remained clinically stable in both groups with no significant intergroup differences. No adverse events were recorded in either group. Conclusion: Both premedication regimens demonstrated acceptable sedative profiles; however, the ketamine-dexmedetomidine combination provided superior sedation depth, smoother parental separation, and better mask acceptance with a comparable safety profile. These findings support ketamine-dexmedetomidine as a preferred oral premedication option in pediatric patients undergoing elective surgery.***

Keywords: Oral premedication, Pediatric anaesthesia, Ketamine, Dexmedetomidine, Midazolam, Sedation, Parental separation anxiety, Mask acceptance.

1. Introduction

Preoperative anxiety is a well-documented phenomenon in pediatric patients scheduled for surgical procedures. A significant proportion of children manifest psychological and physiological stress responses during the perioperative period, manifesting as agitation, refusal of parental separation, and resistance to anaesthetic induction. Evidence suggests that unmanaged preoperative anxiety is associated with delayed postoperative recovery, increased analgesic requirements, and long-term behavioral disturbances including sleep disruption and separation anxiety.[1]

Effective pharmacological premedication plays an integral role in paediatric anaesthetic management by facilitating anxiolysis, sedation, and smooth induction without compromising hemodynamic stability or respiratory function. The oral route is the preferred mode of premedication delivery in children owing to its non-invasive nature, ease of administration, and superior acceptability compared to parenteral routes.[2]

Among the agents available for paediatric premedication, midazolam, ketamine, and dexmedetomidine are widely employed either as single agents or in combination. Midazolam, a short-acting benzodiazepine, produces rapid anxiolysis and amnesia but may be associated with paradoxical excitation or prolonged sedation in select patients.[3] Ketamine, a dissociative anaesthetic agent, offers the advantage of profound analgesia and airway reflex preservation but carries the risk of hypersalivation, sympathomimetic stimulation, and emergence phenomena.[4] Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, has garnered increasing interest due to its sedative and analgesic properties with minimal respiratory depression, though its potential to cause bradycardia and hypotension warrants monitoring.[5]

Combination regimens at reduced individual doses aim to exploit synergistic pharmacodynamic effects while attenuating dose-dependent adverse reactions. Ketamine and midazolam in combination provide complementary effects—ketamine contributing analgesia and airway preservation while midazolam counters the excitatory and hallucinogenic sequelae of ketamine.[3] The ketamine-dexmedetomidine pairing offers sedation with relative hemodynamic stability, an attribute particularly beneficial in younger pediatric populations.[6]

Despite the theoretical rationale supporting these combinations, comparative institutional data evaluating their clinical performance across standardized parameters—including sedation depth, parental separation, mask acceptance, and adverse effects- remain limited. The present

study was, therefore, undertaken to systematically compare the efficacy and safety of oral ketamine-dexmedetomidine versus oral ketamine-midazolam as premedication agents in children aged 2–10 years posted for elective surgery under anaesthesia.

2. Aims and Objectives

Primary Objectives:

- To assess the level of sedation following oral premedication using the Modified Observer's Assessment of Alertness/Sedation (MOAAS) scale.
- To evaluate ease of parental separation using a standardized parental separation anxiety scale.
- To determine mask acceptance during anaesthetic induction using a four-point mask acceptance scale.

Secondary Objectives:

- To compare hemodynamic parameters (pulse rate, systolic blood pressure, diastolic blood pressure) between the two groups.
- To document and compare adverse effects observed in both groups during the perioperative period.

3. Materials and Methods

Study Design and Setting:
This was a prospective, observational, comparative study conducted at the Department of Anaesthesiology, Government Medical College and New Civil Hospital, Surat, Gujarat, India. The study was conducted over 14 months from March 2024 to May 2025, following approval from the Institutional Review Board.

Study Population:
A total of 63 pediatric patients were initially enrolled; however, 3 patients were excluded due to vomiting of the premedication drug (2 from Group KM and 1 from Group KD), resulting in a final study population of 60 children (n = 30 per group). Convenient sampling was employed for patient allocation.

Inclusion Criteria:
Children aged 2 to 10 years of either sex; posted for elective surgery under general anaesthesia; ASA physical status I, II, or III; with written informed parental consent and assent from children above 8 years of age.

Exclusion Criteria:
Children with known airway anomalies, cardiovascular, gastrointestinal, endocrine, mental, or developmental disorders; known allergy to any of the study drugs; and children who refused to swallow or vomited the premedication.

Drug Preparation and Administration:
Group KM (n = 30): Oral ketamine 3 mg/kg + oral midazolam 0.3 mg/kg diluted in 0.4 ml/kg of mango juice (Tang), administered 50 minutes prior to surgery.
Group KD (n = 30): Oral ketamine 3 mg/kg + oral dexmedetomidine 3 mcg/kg diluted in 0.4 ml/kg of mango juice (Tang), administered 50 minutes prior to surgery.
Drug allocation was determined by the attending consultant anaesthesiologist (excluding the guide). The time of premedication administration was designated as 0 minutes.

Monitoring and Assessment:
Baseline vitals including pulse rate, non-invasive blood pressure (systolic and diastolic), and SpO_2 were recorded prior to premedication. Reassessment was performed at 10-minute intervals up to 50 minutes. Sedation was quantified using the six-point MOAAS scale, with scores 2–3 considered satisfactory and a score of 1 deemed as excessive sedation. Upon transfer to the operating room, parental separation anxiety and mask acceptance were scored by a blinded observer using standardized scales.

Statistical Analysis:
Data were analyzed using Jamovi version 2.3.28 and SPSS version 20. Continuous variables were compared using the independent samples t-test and expressed as mean ± standard deviation. Categorical variables were analyzed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

4. Observations and Results

4.1 Demographic Profile

Sixty pediatric patients were enrolled and evenly distributed into Group KM (n = 30) and Group KD (n = 30). The overall cohort comprised 41 males (68.3%) and 19 females (31.7%). The two groups were comparable across gender, age, weight, type of surgery, and ASA classification with no statistically significant differences ($p > 0.05$), confirming baseline homogeneity.

Table 1: Gender Distribution of Study Population (n = 60)

Gender	Group KM (n=30)	Group KD (n=30)	Total (n=60)
Male	23 (76.7%)	18 (60.0%)	41 (68.3%)
Female	7 (23.3%)	12 (40.0%)	19 (31.7%)
P value	0.210 (p > 0.05)		

Chi-square test; p = 0.210 (p > 0.05) – Not significant

The majority of patients (58.3%) were in the 2–4 years age group. Mean age was 4.1 ± 2.4 years in Group KM and 4.9 ± 2.7 years in Group KD (p = 0.235). Mean weight was 13.6 ± 4.2 kg in Group KM and 14.7 ± 5.2 kg in Group KD (p = 0.377). Most patients were classified as ASA II (73.3% in each group).

Table 2: Age Group Distribution of Study Population (n = 60)

Age Group	Group KM (n=30)	Group KD (n=30)	Total (n=60)
2–4 years	18 (60.0%)	17 (56.7%)	35 (58.3%)
5–7 years	7 (23.3%)	7 (23.3%)	14 (23.3%)
8–10 years	5 (16.7%)	6 (20.0%)	11 (18.3%)
Mean Age (yrs)	4.1 ± 2.4	4.9 ± 2.7	P = 0.235 (NS)

Independent t-test; p = 0.235 – Not significant

4.2 Sedation Level (MOAAS Scale)

The MOAAS scale was employed to evaluate the depth of sedation at baseline and at 10-minute intervals up to 50

minutes post-premedication. Both groups exhibited progressive increases in sedation depth over time. At baseline, scores were comparable between Group KM (5.7 ± 0.44) and Group KD (5.8 ± 0.40; p = 0.549). Intragroup analysis revealed highly significant sedation progression in both groups from baseline to 50 minutes (p < 0.001).

A statistically significant intergroup difference emerged at the 50-minute assessment, where Group KD demonstrated a lower mean MOAAS score (2.1 ± 0.64) compared to Group KM (2.6 ± 0.60; p < 0.05), indicating deeper sedation with the ketamine-dexmedetomidine combination. The onset of satisfactory sedation (MOAAS score of 2–3) appeared approximately 10 minutes earlier in Group KD (at 40 minutes) compared to Group KM.

Table 3: Modified Observer's Assessment of Alertness/Sedation (MOAAS) Scale (n = 60)

Time Point	KM Mean	KM SD	KD Mean	KD SD	P value (Intergroup)
0 min	5.7	0.44	5.8	0.4	0.549
10 min	5.2	0.5	5.2	0.58	0.814
20 min	4.3	0.84	4.6	0.49	0.142
30 min	3.7	0.91	3.7	0.56	0.736
40 min	3.2	0.8	2.8	0.62	0.079
50 min	2.6	0.6	2.1	0.64	< 0.05*

** p < 0.05 significant; ** p < 0.001 highly significant (intergroup comparison via independent t-test)*

4.3 Parental Separation Anxiety

Parental separation anxiety was assessed at the time of transfer to the operating room after 50 minutes of premedication. The KD group demonstrated significantly superior parental separation outcomes. A total of 27 patients (90%) in Group KD achieved an 'Excellent' score (unafraid, cooperative, or asleep), compared to only 17 patients (56.7%) in Group KM. The remaining 13 patients (43.3%) in Group KM scored 'Good' versus 3 patients (10.0%) in Group KD. The difference was statistically highly significant (p = 0.007, p < 0.001).

Table 4: Parental Separation Anxiety Scale Scores (n = 60)

Score	KM n	KM %	KD n	KD %
Excellent	17	56.70%	27	90.00%
Good	13	43.30%	3	10.00%
P value	0.007 (p < 0.001)**			

*** p < 0.001 highly significant (Chi-square test)*

4.4 Mask Acceptance

Mask acceptance was evaluated at the time of induction in the operating room. The mean mask acceptance score in Group KD (1.1 ± 0.37) was significantly lower than in Group KM (1.5 ± 0.50; p < 0.001), where a lower score reflects superior cooperation. In the categorical analysis, 25 children (83.3%) in Group KD received a score of 1 (Excellent), compared to 14 children (46.7%) in Group KM. A score of 2 (Good) was observed in 16 patients (53.3%) of Group KM versus only 5 patients (16.7%) in Group KD. Notably, no patient in either group received a score of 3 (Poor), indicating that restraint was not required in any case.

Table 5: Mask Acceptance Scale (n = 60)

Score	KM n	KM %	KD n	KD %	P value
1 (Excellent)	14	46.70%	25	83.30%	0.006**
2 (Good)	16	53.30%	5	16.70%	
3 (Poor)	0	0%	0	0%	
Mean ± SD	1.5 ± 0.50		1.1 ± 0.37		0.002**

*** p < 0.001 highly significant (Chi-square test)*

4.5 Hemodynamic Parameters

Hemodynamic monitoring was carried out at baseline and every 10 minutes up to 50 minutes. Pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) all showed a gradual decline in both groups across the study period; however, no statistically significant intergroup differences were identified at any time point (p > 0.05). Within each group, intragroup comparisons revealed statistically significant declines at later time intervals; however, these changes were clinically non-significant and did not necessitate any medical intervention. SpO_2 values remained stable in both groups throughout the observation period.

Table 6: Summary of Hemodynamic Parameters – Baseline to 50 Minutes (n = 60)

Parameter	Group KM (Baseline → 50 min)	Group KD (Baseline → 50 min)	P value (Intergroup)
Heart Rate (bpm)	110.3 ± 12.5 → 104.1 ± 12.7	108.6 ± 12.2 → 102.9 ± 13.2	> 0.05 (NS)
SBP (mmHg)	93.1 ± 5.6 → 89.6 ± 6.9	94.8 ± 4.9 → 92.6 ± 5.0	> 0.05 (NS)
DBP (mmHg)	64.6 ± 6.3 → 60.3 ± 5.7	64.3 ± 5.2 → 62.2 ± 5.4	> 0.05 (NS)

Independent t-test; NS = Not significant (p > 0.05); SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

4.6 Adverse Effects

No clinically significant adverse events- including hypoxia, excessive salivation, nausea, vomiting, emergence reactions, or shivering- were documented in either group throughout the observation period. Two patients in Group KD achieved a MOAAS score of 1 (deep sedation) without requiring supplemental oxygen or respiratory support, and both recovered uneventfully. The safety profile was comparable between the two regimens.

5. Discussion

The results of this prospective observational study affirm that both oral ketamine-midazolam and oral ketamine-dexmedetomidine combinations are effective and safe premedication strategies in the pediatric population. However, the ketamine-dexmedetomidine combination demonstrated a distinct advantage in multiple domains, including depth of sedation, parental separation, and mask acceptance.

The observed superiority of the KD combination in achieving deeper sedation at 50 minutes aligns with the pharmacological rationale of dexmedetomidine. Being a highly selective alpha-2 adrenergic agonist, dexmedetomidine produces a natural sleep-like sedation by acting on the locus coeruleus, thereby reducing norepinephrine release and inducing physiologically coherent sleep without significant respiratory depression.[5] Qiao et al. (2017) similarly reported enhanced sedation with ketamine-dexmedetomidine in a double-blind randomized trial of pediatric premedication, supporting the synergistic sedative effects of this combination.[6]

The significantly better parental separation scores observed in Group KD (90% excellent vs. 56.7% in Group KM) are clinically meaningful. Parental separation is a critical milestone in the perioperative pathway of pediatric patients, and failure to achieve adequate separation may result in distress for both the child and caregivers. The deeper and earlier sedation produced by the KD combination likely contributed to its superior performance in this domain. Similar findings were reported by Malhotra et al. (2016), who noted that dexmedetomidine-based sedation resulted in greater anxiolysis and cooperative behavior in children undergoing dental procedures.[2]

Mask acceptance, a key determinant of smooth anaesthetic induction, was markedly superior in the KD group (83.3% excellent vs. 46.7% in KM). This observation is consistent with the existing literature suggesting that deeper preoperative sedation facilitates a smoother transition to inhalational induction. Darlong et al. (2004) found that combination oral premedication regimens yielded better mask acceptance than single-agent administration, underscoring the benefit of pharmacological synergy.[3]

Hemodynamic stability was maintained in both groups throughout the study duration, with no clinically significant differences between the groups. Although statistically significant intragroup reductions in heart rate and blood pressure were noted at later time points in Group KD, these were not associated with any clinical sequelae and did not require intervention. This finding is consistent with the known cardiovascular effects of dexmedetomidine, which may produce modest decreases in heart rate and blood pressure at therapeutic doses through central sympatholysis.[5] The absence of adverse events in both groups highlights the clinical safety of these drug combinations when used within the recommended dose ranges.

The limitations of the present study include its observational design, the relatively small sample size, and the absence of blinding. A blinded randomized controlled trial with a larger cohort would provide stronger evidence. Additionally, long-term behavioral outcomes beyond the immediate perioperative period were not assessed.

6. Conclusion

Both oral ketamine-midazolam and oral ketamine-dexmedetomidine combinations provide effective preoperative sedation in pediatric patients scheduled for elective surgery. The ketamine-dexmedetomidine regimen demonstrated superior sedation depth with earlier onset, significantly better parental separation (90% vs. 56.7% excellent), and markedly improved mask acceptance (83.3% vs. 46.7% excellent), with comparable hemodynamic safety and absence of significant adverse events. These findings collectively support the oral ketamine-dexmedetomidine combination as a favorable premedication option in pediatric anaesthesia practice. Larger multicenter randomized controlled trials are warranted to corroborate these findings and establish evidence-based guidelines.

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