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Sweet Sedation: Honey Based Midazolam versus Ketamine in Pediatric Anesthesia Premedication

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Abstract

Background: Surgeries in pediatric age group is more challenging, stressful as compared to adult population. Anxiety and separation from parents is worrisome and there are no ideal premedications to calm the pediatric patients. Hence this comparative study of effects of Midazolam with honey & Ketamine with honey as oral premedication.

Methods: This study was undertaken in different specialties of surgery department, 100 patients of either sex, aged between 2-8 years were taken and randomly assigned into 2 groups of 50 patients each; patients were selected by process of exclusion at every step for any variation from normal. Patients of both groups were premedicated orally with parenteral preparation of midazolam & ketamine mixing with honey (0.2ml/kg body weight).

Group M Midazolam 0.75 mg/kg body weight.

Group K Ketamine 6mg/kg body weight.

Both the drugs were given 30 minutes prior to proposed time of induction.

Patients were observed and compared in between the two groups and results were tabulated.

Results: Onset of sedation in midazolam group was 16.2± 3.6mins & in ketamine group 19.4 □3.2 mins, 66% patients were calm & sleepy compared to 56% with ketamine during separation from their parents, 54% patients in midazolam group were unafraid and cooperative during application of facemask compared to 44% in ketamine group, level of sedation was satisfactory & similar in both groups.

In group M patients who received midazolam orally; onset of sedation was quicker ($P < 0.001$), number of patients calm and sleepy during separation from their parents and at the time of venepuncture were more silent ($P > 0.05$) and degree of induction score was superior ($P < 0.05$). Undesired effects like increased secretion, vomiting, nystagmus, random limb movement, and excitement before & after surgery were more in ketamine group.

Conclusion: Both midazolam (0.75mg/kg) and ketamine (6mg/kg) can be used as oral premedicants for children. However, midazolam may be preferred because of its early onset of action, better effect on allaying anxiety during separation from parents and lesser side effects.

Keywords: Premedication; Pediatrics; Psychosis; Midazolam; Ketamine; Honey; Anxiety; Psychosis

Introduction

Surgery is a terrifying and intimidating experience for all ages. The fear psychosis of surgery in children is a traumatic experience because of unfamiliar and intimidating environment of the operation theatre and separation of the child from his/her parents. The objective of the anesthesiologist in planning the preoperative care and premedication of pediatric patients is to ensure as far as possible, to minimize the potential adverse physiological and psychological effects of anesthesia and surgery. The goal is achieved only, fully recognizes the problems, and then

orders appropriate preoperative care. Premedicating a pediatric patient has become unavoidable and remains to be a challenge to the anesthesiologist. A wide variety of drugs and routes have been tried and described. But the perfect drug or combination and the route of premedication especially in children is not yet available.

The ideal premedication for children should be

1. Safe and reliable
2. Easy to administer
3. Acceptable to children
4. Ensure a rapid level of short-term sedation to facilitate a smooth separation from parents.
5. Smooth anesthetic induction should have minimal undesirable side effects. Several significant changes in clinical practice have changed the focus of traditional premedication techniques, and there has been a definite shift towards oral, oro-transmucosal, nasal and rectal administration of drugs. Of these, the oral route is definitely most popular and acceptable.

Aims and Objective

General objectives

The objective of the study was to compare the effects of oral Midazolam and oral ketamine with honey preparation as pre-anesthetic medication among 100 patients of either sex in the age group of 2-8 years for elective surgery under general anesthesia in different specialties.

Specific objectives

To compare the effectiveness of oral ketamine and oral midazolam in achieving:

1. Ease of parent-child separation.
2. Ease of intravenous cannulation
3. Ease of induction of general anaesthesia
4. Safe post anaesthetic recovery

One hundred patients of either sex (ASA-I&II) in the age group of 2 to 8 years posted for elective surgery under general anaesthesia, in different specialties during this study with due permission from the institutional authorities and ethical committee.

Informed consent was obtained from parents of the patients before being included in the study.

Preoperative Assessment

Prior to taking up the cases for the study a detailed clinical assessment of each patient was done to exclude any underlying systemic disease. Detailed case history was taken in all cases. Pulse rate and blood pressure was checked and the weight of each patient was taken. Routine laboratory investigations such as hemogram, routine and microscopic examination of stool and urine was done. Investigations like chest X-ray, Mantoux test, blood sugar, serum urea and creatinine , liver function test, serum electrolytes were advised if required. Any case showing gross deviation from normal was excluded from the study.

Exclusion criteria

History of intolerance to oral administration of drugs, Hypersensitivity to either drug, Cyanotic heart disease, Convulsive disorders, Liver diseases, Respiratory diseases, Renal diseases, Neurological disorders, Emergency surgeries were excluded

Grouping

For the purpose of this study patients were randomly allocated to two groups of 50 each to receive either Midazolam or Ketamine mixed with honey as oral premedication.

Group M : Midazolam 0.75 mg/kg body weight

Group K : Ketamine 6 mg/kg body weight.

Preparation

All the patients were visited in the evening before operation. During this time a detailed clinical reevaluation was done. Parents were explained about the pre-operative preparations. Patients were not allowed to take milk or solid diet orally for 8 hours prior to administration of premedication. But, oral intake of clear fluids, such as glucose water, and green coconut water were permitted up to 4 hours prior to premedication.

Anaesthetic Procedure

On the day of surgery, the patients were brought to the preanaesthesia room near the operation theatre about 45 minutes before operation. In the pre-anaesthesia room necessary arrangements were made for administration of the studied drugs, monitoring of the child, emergency drugs and equipment's to tackle any untoward effects of the drugs. Patient's pulse, BP and body weight were recorded.

Premedication

In the pre-anaesthesia room, premedicants were given in presence of parents 30 minutes prior to proposed time of induction time of 6mg/kg body weight. Here, parenteral (Intravenous or intramuscular) preparations of midazolam containing 5mg of midazolam hydrochloride per ml and ketamine containing 50 mg of ketamine hydrochloride per ml were used. Though the suggested oral dose of midazolam varies from 0.45 to 0.75 mg/kg body weight and ketamine varies from 3 to 10mg/kg body weight; midazolam 0.75mg/kg and ketamine 6mg/kg body weight were

selected as they appeared to fulfil the criteria of a safe and satisfactory premedicants without increasing untoward side effects. Calculated dose of the drugs and honey were measured with the help of a plastic 2ml syringe, mixed by the anesthetist and administered by the mother with the help of a teaspoon having approximate measurement of 5ml. Thirty minutes following premedication patients were separated from their parents and brought to the operation theatre. Intravenous cannulation was done with appropriate size I.V.canula, pedolyte infusion was started and drip rate was adjusted according to calculation on body weight basis. Pulse oximeter, NIBP, and ECG.

Table 1: *Patient Demography.*

Group	No of patients	Mean Age (yr.± SD)	Sex		Mean body Wt.KG.(±SD)
			Male	Female	
M	50	5.6 ±1.4	30(60%)	20(40%)	15.8±3.06
K	50	5.7±1.2	28(56%)	22(44%)	16.02±3.07

Table 2: *Type of Operation.*

OPERATION	GROUP M	GROUP K
Tonsillectomy	12	15
Mastoidectomy	18	14
Circumcision	6	4
Cleft clip & Cleft palate	12	14
Repair of inguinal hernia	2	3
Total	50	50

Table 3: *Level of Sedation.*

Time interval	Before premedication	5 min	10 min	15 min	20 min	25 min	30 min
Group M							
Score 5	12	-	-	-	-	-	-
Score 4	38	50	44	15	3	-	-
Score 3	-	-	6	35	34	17	10
Score 2	-	-	-	-	13	31	33
Score 1	-	-	-	-	-	2	7
TOTAL	50	50	50	50	50	50	50
Group K							
Score 5	10	-	-	-	-	-	-
Score 4	40	50	50	33	11	-	-
Score 3	-	-	-	17	35	24	13
Score 2	-	-	-	-	4	26	32
Score 1	-	-	-	-	-	-	5
Total 50	50	50	50	50	50	50	50

Table 4: *Distribution of Anxiolysis Score during Separation from Parents.*

EMOTIONAL SCALE	GROUP – M	GROUP – K
SCORE -1(Calm & sleepy)	33	28
SCORE -2(Apprehensive)	10	11
SCORE -3(Crying)	5	7
SCORE -4(Thrashing)	2	4
TOTAL	50	50

Table 5: *Effect of Premedication on Vital Parameters.*

GROUP	PULSE RATE PER MINUTE	BLOOD PRESSURE (mm Hg)		Resp. Rate per min
		Systolic	Diastolic	
Group M				
Before premedication	106±5.3	98±9.6	68±6.4	21±2
15 minutes after premedication	101±3.6	96±8.8	64±4.8	22±4.3
30 minutes after premedication	103±8.5	101±5.4	70±3.1	20±2.7
Group K				
Before premedication	101±7.6	98±8.4	70±5.3	20±3.8
15 minutes after premedication	108±6.4	104±5.7	74±7.4	21±4.4
30 minutes after premedication	105±4.8	100±4.6	72±6.3	22±2.5

Table 6: *Incidence Of Side Effects Seen In Pre-Operative Period.*

Parameters	No. of patients	
	Group M	**Group K**
Increased secretions	3 (6%)	12 (24%)
Vomiting	2 (4%)	7 (14%)
Nystagmus	0 (0%)	28 (56%)
Random limb movement	3 (6%)	8 (16%)
Airway support required	2 (4%)	3 (6%)
Hallucinations	-	-

Table 7: *Distribution of Anxiolysis Score at the Time of Venepuncture.*

EMOTIONAL SCALE	GROUP – M	GROUP – K
Score – 1(calm & sleepy)	26	23
Score – 2 (Apprehensive)	11	10
Score – 3 (Crying)	10	11
Score – 4(Thrashing)	03	06
TOTAL	50	50

Table 8: *Quality of Induction.*

INDUCTION SCORE	GROUP – M	GROUP - K
Poor – 1	3	5
Fair – 2	4	6
Good – 3	16	17
Excellent – 4	27	22
TOTAL	50	50

Table 9: *Comparsion of Findings during Anaesthesia.*

Parameters	No. of Patients	
	Group M	**Group K**
Intravenous cannulation (Positive)	40(80%)	36(72%)

Increased secretions	5(10%)	19(38%)
Anaesthesia time (min)	58.4 ± 4.6	53.3 ± 6.8

Table 10: *Adverse Effect during Post – Anaesthetic Period.*

Parameters	No. of patients	
	Group M	Group k
Vomiting	5(10%)	8(16%)
Nystagmus	0(0%)	6(12%)
Crying	27(54%)	30(60%)
Excitement	4(8%)	6(12%)
Airway support required	2(4%)	4(8%)
Hallucinations	0(0%)	0(0%)

Table 11: *Results of Post – Operative Questionnaires.*

Group	Parental response				Child response			
	Total	1	2	3	Total	1	2	3
Midazolam (Group M)	50 (100%)	39 (78%)	11 (22%)	0 (0%)	50 (100%)	32 (64%)	18 (36%)	0 (0%)
Ketamine (Group K)	50 (100%)	30 (60%)	20 (40%)	0 (0%)	50 (100%)	26 (52%)	24 (48%)	0 (0%)

Table 12: *Child's ability to recall going to sleep.*

Groups	Total	#Going to sleep		* Face Mask	
		Yes	No	Yes	No
Midazolam (Group – M)	50 (100%)	31(62%)	19(38%)	32(64%)	13(36%)
Ketamine (Group- K)	50 (100%)	12(24%)	38(76%)	22(44%)	28(56%)

Induction and Maintenance

After pre-oxygenation with 100% O2 for 5 minutes, patients were induced with propofol 3-5 mg/kg body weight followed by succinylcholine 1.5 mg/kg i.v. and ventilation was supported till sufficient relaxation occurred as observed by jaw relaxation. After visualizing the laryngeal inlet under direct laryngoscopy patients were intubated with appropriate sized uncuffed/ cuffed (according to age) endotracheal tubes. All the patients were ventilated with 100% oxygen via endotracheal tube till return of spontaneous respiration. Jackson-Ree's modification of Ayre's T-piece was used in patients weighing less than 20 kg. Maintenance of anaesthesia was done with nitrous oxide (50%), Oxygen (50%), non-depolarizing muscle relaxants & sevoflurane was used as maintenance of anesthesia.

Recovery

At the end of surgical procedure patients were reversed with neostigmine 0.05mg/kg and atropine 0.02 mg/kg. Thorough suctioning of the oral cavity and pharynx was done and patients were extubated after presence of all protective reflexes were guaranteed. Then 100% oxygen was administered for 5-10 minutes. All the patients left the operating room awake.

Monitoring

Heart rate, ECG, and oxygen saturation was monitored by using pulse oximeter, NIBP, Capnography and continuous visual vigilance and intermittent auscultation of the chest.

Recording

Heart rate blood pressure and respiratory rate before administration of premedication were recorded as base line (pre-drug) values and findings.15 minutes and 30 minutes after premedication i.e. just before induction findings were again recorded. Continuous monitoring for HR, ECG and Oxygen saturation was done perioperatively.

Parameters to be Observed

Preinduction observations

These observations were done in the pre-anaesthesia room during the interval between administration of drug and induction of anaesthesia. These were as follows:

Level of sedation

This was assessed at 0, 5, 10, 15,20,25,30 minute after premedication by using a 5-points sedation scale.

Scale used to assess sedation

Score1- Barely arousable (Sleep, needs shaking or shouting to arouse).
Score2- Asleep (Eyes closed, arousable with soft voice or light touch).
Score3- Sleepy (Eyes opened but less active and responsive).
Score4- Awake.
Score5- Agitated.
Scores up to 3 was considered as acceptable level of sedation

Time of onset of sedation

It is the time from oral premedication till the child is sleepy (Score 3)

Anxiolysis (Emotional state)

Emotional state of the children were observed during separation from their parents and at the time of venepuncture by using a 4-point scale

Emotional scale

Score1 - Calm and sleepy
Score2 - Apprehensive (not smiling) behaviour and withdrawn.
Score3 - Crying
Score4 - Thrashing

Undesired effects

Patients were also observed for presence of
Increased secretion
Vomiting
Nystagmus
Random limb movement
Hallucinations
Airway obstruction.
Increased secretion was determined by presence of dribbling of saliva from the angle of mouth of a sedated child or noisy respiration, which became normal after suction of oral cavity.

Peri-Anaesthesia Observations

Intravenous Cannulations: In the operation theater, reaction to placement of intravenous catheter was observed, if it was possible without much resistance from the child it was considered as evidence of analgesia.

Quality of Induction: It was assessed by noting child's response to application of facemask and i.v. administration of drugs during induction by using a 4-point scale.

Induction scale:			Score
Poor	-	Afraid, combative, crying	1
Fair	-	Moderate fear at mask, not easily calmed	2
Good	-	Slight fear at mask, easily calmed	3
Excellent	-	Unafraid, co-operative, accepts mask readily	4

Increased secretions: Patients were observed for presence of any increased secretions during direct laryngoscopy.

Anaesthesia time: Total time in minutes from beginning of indication to eye opening and return of protective reflexes after cessation of anesthetic agents was noted.

Post Anaesthesia Observations

Observations made during recovery when patient were placed in recovery room (post anaesthesia care unit), before transfer to respective wards.

Crying: After awakening whether crying without any external stimulation was marked or not.

Other observations: Patients were also observed for Airway support, Nystagmus, Incidence of postoperative nausea & vomiting, Excitement or restlessness, Presence of laryngospasm, Emergence phenomena.

Post-Operative Questionnaire

24 Hours after surgical procedure, parents were asked following questions like:

1. Did you feel that your child was adequately relaxed awaiting for operation?
2. Did you feel that your child was adequately relaxed at the time of he or she was separated from you to enter the operation room?

Based on these parental responses, it was 1) pleasant, 2) Acceptable and 3) unpleasant.

Similarly, every child was also enquired about his/her pre &Postoperative experiences like:

Would you choose these drugs in future?

Answers of child's responses were also marked as 1) Pleasant 2) acceptable and 3) unpleasant. The children were also asked "if he or she remembered going to sleep" before the operation or remembered the application of "facemask".

Results

The study was carried out in 100 patients in two different groups of 50 patients each, meant for elective surgery of 40-60 minutes duration. The two groups were premedicated with midazolmam

0.75-mg/kg body weight (group M) or ketamine 6mg/kg body weight (group K). Both the drugs are given orally 30 min prior to proposed time of induction. In this study honey was used to mask the bitter taste of ketamine and to make it acceptable to children. It is chemically inert, can prevent interfere hypoglycaemia and does not interfere with gastric pH, and volume. Moreover it is easily available, cheap and of better taste and flavour.

Patients were observed in relation to

1. Age, sex & weight
2. Type of operation
3. Level of sedation
4. Onset of sedation
5. Emotional state (Anxiolysis) during separation from parents and at the time of venepuncture,
6. Observations made before induction of anaesthesia (Vital parameters, side effects)
7. Quality of induction
8. Evaluation of parameters observed during anaesthesia,
9. Evaluation of post anaesthetic side effects
10. Post-operative questionnaire

The above table shows the demographic patterns of patients in the two groups according to their age, sex and body weight. The mean ages in the two groups are almost identical. The male: female ratio in each group and average body weight was also similar in both the groups. Thus both groups were comparable with respect to age, sex and weight.

The above table shows no of patients according to the type of surgery. It is evident that no of particular operations in both groups were comparable.

The above table shows sedation score at different time intervals in both groups. Score 3 was considered as an acceptable level of sedation, After 25 minutes of premedication i.e. before the time of separation of the children from their parents all of them in both groups were sleepy (Achieved score 3 or less).

The above table shows in midazolam group 33 (66%) children were calm and sleepy during separation from their parents where as it was 28(56%) with ketamine. Midazolam found to have better anxiolytic action than ketamine ($p<0.05$)

The above table shows effect of midazolam and ketamine premedication on vital parameters before induction of anaesthesia. There were no significant changes in the cardiorespiratory status of the patients in both the groups. As seen in the table, there were side effects like increased secretions, vomiting, nystagmus and random limb movement in ketamine groups compared to midazolam group in the preoperative period.

The above table shows 26(52%) children in midazolam group were calm & sleepy during venepuncture compared to 23(46%) children in ketamine group ($P < 0.05$)

The above table shows distribution of induction score in both groups. Midazolam had a superior degree of induction, excellent in 27(54%) children compared to 22(44%) with ketamine. So midazolam is significantly better ($P<0.05$)

Above table shows there was increased secretions during direct laryngoscopy more in ketamine group seen in 19 (38%) children compared to midazolam group where it is seen in 5(10%) children ($P < 0.005$)

The above table shows the incidence of side effects during post - anaesthesia period. Findings appear to be in favour of midazolam as incidence of side effects were more with ketamine (Tables 1-12).

Child's ability to recall going to sleep.

* Child's ability to recall application of face mask.

Response score refer to

1 = Pleasant
2 = Acceptable
3 = Unpleasant

Group M had better response compared to Group K.

Discussion

The results show that oral ketamine produced sedation levels comparable to midazolam, with a faster onset of action, indicating its potential as a valuable sedative option for pediatric patients undergoing surgical procedures. Although the side effects of the ketamine were recorded and noted such as increased secretions, nystagmus, increased muscle tone and post-operative nausea and vomiting 10. Onset of sedation in midazolam group was 16.2± 3.6mins & in ketamine group 19.4 ±3.2 mins, 66% patients were calm & sleepy compared to 56% with ketamine during separation from their parents, 54% patients in midazolam group were unafraid and cooperative during application of facemask compared to 44% in ketamine group, level of sedation was satisfactory & similar in both groups. In group M patients who received midazolam orally; onset of sedation was quicker ($P < 0.001$), number of patients calm and sleepy during separation from their parents and at the time of venepuncture were more silent ($P > 0.05$) and degree of induction score was superior ($P <0.05$). Midazolam undergoes extensive first-pass hepatic extraction [1,2]. Therefore, the bioavailability of midazolam has appeared to be less than 50 % after enteral administration [1,3] and about 30 % after administration by mouth [3]. On this basis, the dose range used here was comparable to a rectal dose of 0.3 mg /kg^2. The anxiolytic effect of midazolam in the present study seemed also to be comparable to the results obtained by Saint-Maurice and colleagues [4-6]. Dilip Kothari, compared the dose of oral midazolam between 0.5mg/kg & 0.75mg/kg [7-11]. They found oral midazolam in a dose of 0.75mg/kg offer effective sedation and, better emotional control without fear of needle prick and side effects. This study was comparable with the present study. W. Funk, observed and recommended the dose of 6mg/kg

as satisfactory & ketamine alone is safe for premedication for pediatric population without side effects [12].

Emergence phenomena have been reported, albeit sporadically, after parenteral ketamine in children. To date, none have been reported after oral administration of ketamine [2,4,5]. The absence of emergence phenomena after oral ketamine may be explained by (a) an increased ratio of Nor ketamine to ketamine after oral ketamine [6,7] (b)blockade of the side effects of N-methyl-D-aspartate receptor antagonists (such as ketamine) with barbiturates or anticholinergics [7,8] and (c) too limited an experience oral ketamine to comment on a rare phenomenon. These explanations individually or in combination may explain the absence of emergence phenomena after oral ketamine in this study. Honey was used as the vehicle of administration for both ketamine and midazolam to counteract the bitter taste and to make it acceptable to children. It is chemically inert, can prevent interfere hypoglycaemia and does not interfere with gastric pH, and volume. Different authors has used orange juice, apple juice, flavouring extracts (cherry & banana), coke and flavoured gelatin with or without sugars [9]. Hence honey was used in this study, since it is easily available, cheap and of better taste and flavour.

Conclusion

Both midazolam (0.75mg/kg) and ketamine (6mg/kg) can be used as oral premedicants for children. However, midazolam may be preferred because of its early onset of action, better effect on allaying anxiety during separation from parents and lesser side effects. Honey is the preferrable choice as a vehicle of administration as its cheap, easily available, cost effective, easily palatable and acceptable in pediatric population.

References

1. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. Cli Pharmacol Therapeutics. 1981; 30: 653-661.
2. Saint-Maurice C, Mistelman C, Rey E, Esterec C, DeLauture D, Olive G. The pharmacokinetics of rectal midazolam for premedication in children. Anesthesiol. 1986; 65: 536-538.
3. Crevoisier CH, Ziegler WH, Eckert M, Heizmann P. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. British J Pharmacol. 1983; 16: 51-61.
4. Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. Anesthesiol. 1992; 76: 28-33.
5. Lin YC, Moynihan R J, Hackel A. A comparison of oral midazolam, oral ketamine, and oral midazolam combined with ketamine as preanesthetic medication for pediatric outpatients. Anesthesiol. 1993; 79: A1177.
6. Grant LS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth. 1981; 53: 805-809.
7. Olney JW, Labruyere J, WangG, Wozniak DE Price MT, Sesma MA. NMDA antagonist neurotoxicity: mechanism and prevention. Sci. 1991; 254: 151
8. AIderson PJ, Lern'lan J. Oral premedication for paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. CAN J ANAESTH. 1994; 41: 221-226.
9. Isik B, Baygin O, Bodur H. Effect of drinks that are added as flavoring in oral midazolam premedication on sedation success. Pediatric Anesth. 2008; 18: 494-500.
10. Hollister GR, Burn J. Side Effects of Ketamine in Pediatric Anesthesia. Anesth Analgesia. 1974; 53: 264-267.
11. Kothari D, Kothari S, Agarwal J. Dental anaesthesia: an overview. Associate professor Article Annals Essences Den. 2023.
12. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. British J Anaesth. 2000; 84: 335-340