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ORIGINAL ARTICLE

A COMPARISON OF MIDAZOLAM AND KETAMINE PLUS MIDAZOLAM COMBINATION AS AN ORAL PREMEDICANT IN PAEDIATRIC PATIENTS

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ABSTRACT: INTRODUCTION: Effective premedication in pediatric patients posted for elective surgeries allays patients' anxiety and reduces risk of post-operative behavioral problems. Oral midazolam and oral ketamine are tried in different doses as pediatric premedicant, but addition of 3mg/kg of oral ketamine with 0.5 mg/kg of oral midazolam resulted in better premedication when compared to oral midazolam 0.5mg/kg or oral ketamine 6mg/kg given alone. **MATERIAL AND METHODS:** 60 healthy children under 1-8 yrs. age group posted for elective surgeries chosen for this study were randomly divided into two groups of 30 each. Double blinding was done using sealed envelope technique to prevent observer bias. Children with other co-existing illnesses were excluded from the study. Group KM received Ketamine 3 mg/kg and midazolam 0.5 mg/kg + atropine 20 µg/kg (oral route) and Group M received midazolam 0.5 mg/kg and atropine 20 µg/kg (oral route) 30 minutes before proposed induction time. Sedation score, anxiolysis score, parental separation and mask tolerance was assessed in all the patients 30 minutes after administration of the drug. **RESULTS:** The data collected was analyzed using SPSS statistical software. There was a statistically significant increase in sedation score at 15 and 30 minutes in group KM compared to group M. Parental separation at 30 minutes is peaceful in 30 children (100%) in group KM compared to 24 children (80%) in group M. **CONCLUSION**: The oral ketamine and midazolam combination produces significantly better anxiolysis, sedation, parental separation and mask tolerance, without hemodynamic alteration, when compared to oral midazolam (0.5mg/kg) given alone.

KEYWORDS: Premedication, anxiolysis, sedation, ketamine, midazolam.

INTRODUCTION: A stormy anesthetic induction in children leads to an increased incidence of postoperative behavioral problems. These problems can be reduced by psychological preparation. However a pharmacological adjunct is more reliable and better.[1] Pre-operative administration of sedative premedication decreases the incidence of post-operative behavioral changes. Effective pre-anesthetic medications in children undergoing surgery should allay apprehension regarding anesthesia and surgery and should lessen the trauma of separation from family. Ideal pre-medication for children should:

a. Be available in a preparation that is readily accepted by the children.
b. Have a relatively rapid and reliable onset.
c. Provide anxiolysis and sedative effects of sufficient duration to accommodate delays in operating room schedule and without delay in discharge.
d. Be free of side effects.
e. Provide a rapid recovery and return to alertness post-operatively.

Oral promethazine, trimeperazine, midazolam, ketamine, chloral hydrate and other various drugs has been used with different success rates.[2]

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Oral midazolam when used alone as a premedicant meets these criteria, with an onset time of 20 min, duration of action of approximately 30min and no interference with vital signs.[3] However, good results were seen in only 60-80% of cases. Midazolam 0.5 to 0.75 mg/kg can be used as an effective oral dose for premedication in pediatric patients.[4] Studies shows that administration of small amounts of fluid (5-10ml) to children prior to induction of anesthesia does not pose a significant risk with respect to aspiration of abdominal contents.[3, 4]

Oral ketamine has been investigated as an alternative premedication with a high overall success rate. The dose of oral ketamine that would facilitate induction of anesthesia without causing significant side effects was defined. It was concluded that an oral dose of 6mg/kg ketamine is easily administered and well accepted in young children and provides predictable, satisfactory premedication without significant side effects. It is widely acknowledged that ketamine causes hallucinations, increased secretions and dysphoria in many patients when given orally at dose of 6mg/kg. But studies have reported severe emergence reaction associated with the use of oral ketamine premedication.[5]

The combination of oral ketamine with oral midazolam provides better premedication, prevents delirium compared with oral midazolam 0.5mg/kg or oral ketamine 6mg/kg given alone.[6] Success rate for anxiolysis and behavior at separation were greater than 90% with the combination, approximately 70% with the midazolam and only 51% with ketamine alone.

Significantly better anxiolysis and sedation were observed with a combination of ketamine and midazolam.[7, 8] But ketamine 6mg/kg with oral midazolam 0.5mg/kg was associated with deeper sedation which was unfavorable for monitoring in holding area. We therefore designed the following study to compare the advantages of oral ketamine 3mg/kg + oral midazolam combination, and oral midazolam given alone as premedicant in pediatric patients.

METHODS: This study was conducted in our institute after obtaining ethical committee and scientific committee approval. Sixty children belonging to ASA I and II in the age group 1 to 8 years of either sex posted for elective surgery in department of pediatric surgery were taken up for the study. Children with systemic illnesses, allergy to ketamine and midazolam, children on anti-convulsants were excluded from the study. All the patients were examined pre-operatively and informed parental consent was obtained for inclusion in this study.

This study was a randomized, double-blinded, prospective study. Sixty patients posted for elective surgery who fulfilled the inclusion criteria were included in the study. They were allocated to two groups of 30 each, depending on premedication administered. Group KM: Ketamine 3 mg/kg and midazolam 0.5 mg/kg + atropine 20 µg/kg (oral route). Group M: Midazolam 0.5 mg/kg and atropine 20 µg/kg (oral route).

30 labels each of midazolam 0.5 mg/kg and ketamine 3 mg/kg plus midazolam 0.5 mg/kg combination were prepared with covered envelopes and thoroughly shuffled. A staff-nurse in the operation theatre picked up an envelope, read the label and administered the drug outside the theatre. Calculated volumes of drugs were mixed with 5ml of orange flavored drink to mask the bitter taste.

The mixture was stirred well and administered orally and drug acceptance was noted. Atropine 20 µg/kg was added in ketamine plus midazolam group, to reduce secretions.

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Atropine 20µg/kg was added in midazolam group for blinding. Children were assessed before premedication and at 15 and 30 minutes after premedication.

Parameters assessed were, Heart rate, Respiratory rate,
Sedation score – using a 5 point scale,

[1. Agitated (uncomfortable, crying), 2. Awake (alert, comfortable), 3. Sleeping intermittently, 4. Asleep, wake up on touch, 5. Asleep, not arousable by touch.]

Anxiolysis score- using a 4 point scale,
[1. Combative, 2. Tearful (crying), 3. Apprehensive, 4.Calm]

Mask tolerance- using a 4 point scale
[1. Poor, 2. Fear to mask, 3. Good, 4. Excellent]

Blood pressure before premedication and 30 min after premedication. Blood pressure was not recorded at 15 minutes to avoid disturbing the sleeping child.

Parental separation was assessed 30 min after premedication as peaceful or not peaceful.

The name, hospital number of the child and data collected were written on the same label and put inside the envelope. The envelope was sealed and handed over to the investigator. The sealed envelopes were opened at the end of the study and the data's were then compiled.

RESULTS: The envelopes were opened at the end of the study and data was analyzed using SPSS statistical software. The change in heart rate, blood pressure and respiratory rate variables in a particular group over time was analyzed by paired 't' test. The changes in the above variables between the two groups with progression of time were analyzed by unpaired 't' test. Sedation score, anxiolysis score, parental separation, and mask tolerance were analyzed by chi-square test. A 'p' value of <0.05 was considered statistically significant.

The patients were comparable in both groups regarding age and sex. Patients in group KM were aged between 1-7 years. Median age in this group was 4 years. Patients in group M were aged between 1-6 years. Median age in this group was 3 years. 23 patients in group KM and 22 patients in group M were males. Remaining were females. [Table 1]

Baseline heart rate was comparable between the groups. The mean basal heart rate varied from 112.47 ±19.06 in group KM and 115.80±21.71 in group M. With progression of time after administration of premedication, there was no significant change in heart rate between groups (P value = 0.857). [Table 2 and Figure 1]

Baseline blood pressure was comparable between groups. The mean basal systolic blood pressure in group KM was 98.80±7.27 and diastolic blood pressure was 63.67±9.95. The mean basal systolic blood pressure in group M was 96.73±12.05 and diastolic blood pressure was 63.00±12.92. There was no significant change in blood pressure between groups with progression of time after administration of the premedication (P = 0.824). [Table 3]

Baseline respiratory rate was comparable between the groups. The mean basal respiratory rate was 26.47 ±9.15 in group KM and 26.17±9.93 in group M. With progression of time after

administration of premedication there was no significant change in respiratory rate between the groups (P = 0.985). [Table 4 and Figure 2]

Baseline sedation score was comparable between the groups. With progression of time each group had statistically significant increase in the sedation score (p=0.000).There was statistically significant increase in sedation score in group KM compared to group M at 15 minutes and at 30 minutes (p=0.029). [Table 5 and Figure 3]

Baseline anxiolysis score was comparable between the groups. There was statistically significant increase in anxiolysis score in both the groups at 15 and at 30 minutes compared to baseline (p=0.000). There was statistically significant increase in anxiolysis score in group KM compared to group M at 15 and 30 minutes (p=0.036). [Table 6 and Figure4]

Parental separation was 100% successful in children in group KM and 80% in group M. The values were statistically significant between the groups (P=0.010; chi-square value=6.667). [Table 7 and Figure 5]

Application of facemask was excellent in 30% of children in group KM and 20% in group M while it was good in 54% of children in group KM and 27% in group M. Acceptance to facemask was statistically significant in group KM compared to group M (P=0.025; chi-square value = 9.321). [Table 8 and Figure 6]

DISCUSSION: Anxiolysis and sedation using pre-operative medication is a common practice in pediatric anesthesia. Stormy anesthetic induction leads to unfavorable hemodynamic at induction and also post-operative behavioral problems in children. Conscious sedation to facilitate parental separation in young children is often problematic. The intravenous and intramuscular routes are traumatic.[9]

The disadvantages of intramuscular medications are that they are painful to administer and threatening to child, chance of infection at injection site and often the child remembers the injection he had received. The rectal route is marked by variable absorption.[10,11] The intranasal route is similarly marked by variable absorption, may be irritating to nasal mucosa and drugs administered may traverse directly into the central nervous system through the cribriform plate by traveling alone the olfactory nerves.[12,13]

The oral route provides the least anxiety for sedation of young children.[14] Chloral hydrate in dose of 75 mg/kg was used as premedication, but it was associated with delayed onset of sedation and delayed recovery in post-operative period. Chloral hydrate is less palatable than other drugs.[15]

Promethazine 1mg/kg is used as a premedicant in our institute. But it produces poor sedation and anxiolysis. Midazolam, a benzodiazepine has drawn more attention as an ideal premedicant by oral route.[16] It has been studied extensively for premedication in children in comparison with other drugs.[17] Oral ketamine 3 to 6mg/kg is another alternative premedicant.

In a study which compared oral premedication with ketamine 3 and 6mg/kg, 73% of the children were sleepy with 3mg/kg ketamine as compared to 100% with 6mg/kg. But ketamine 6mg/kg produced side effects such as nystagmus, vomiting and increased secretions.[18]

Oral midazolam at the dose of 0.5mg/kg is an alternate to ketamine with negligible side effects, but with less satisfactory sedation.[19] In our setup parental separations after oral midazolam or oral ketamine premedication were less satisfactory and prompted us to investigate another regimen.

Our study evaluated the efficacy of combination of oral ketamine and midazolam, and oral midazolam alone as premedicant in pediatric patients. Oral midazolam has got a bitter taste and it is non-palatable.[20] The bitter taste of ketamine and midazolam was masked with 5 ml of orange flavored drink added to the drugs.

Majority of the patients accepted the oral preparation without any difficulty, while five children made facial expressions that suggested that the taste was unpleasant and two complained about the bitter taste of the mixture. It is observed that administration of 5-10 ml fluid to children prior to induction of general anesthesia does not pose a significant risk with respect to aspiration of gastric contents.[9]

In our study, Group KM received oral ketamine 3mg/kg, oral midazolam 0.5 mg/kg and oral atropine 20 microg/kg; Group M received oral midazolam 0.5 mg/kg and oral atropine 20 microg/kg. Atropine was added in Group KM to reduce ketamine induced secretions. Atropine was added in Group M for blinding (atropine induced tachycardia in Group KM).[21]

We did not include placebo group, as the effectiveness of both oral ketamine and midazolam were compared with placebo and were found to be superior to placebo in the previous studies. The study conducted by Alderson et al questioned the inclusion of placebo, where superiority of these medications over placebo for preanesthetic sedation and anxiolysis had been established.[22]

Patients in both the group were comparable regarding age and sex. Baseline sedation and anxiolysis for children in both groups were comparable. We compared sedation and anxiolysis score at 15 minutes and 30 minutes after administration of premedication. Sedation and anxiolysis score increased in each group with progression of time, which was both statistically and clinically significant.

There was a statistically significant increase in sedation score at 15 and 30 minutes in group KM compared to group M. The combination of ketamine and midazolam produced early onset of sedation. 28(93%) children in group KM and 22(73%) children in group M were calm at 30 minutes. Anxiolysis in group KM was significantly better when compared to group M.

Parental separation at 30 minutes is peaceful in 30 children (100%) in group KM compared to 24 children (80%) in group M which was statistically significant. 25 (84%) children in group KM and 14(47%) children in group M had acceptable mask tolerance at 30 minutes. Mask tolerance was better (statistically and clinically) in group KM compared to group M.

Increase in heart rate was observed in both the groups compared to baseline which was insignificant. This could be due to use of oral atropine as its action starts within 30 minutes, peaks at one hour and lasts for two hours. There was no significant change in blood pressure between groups with progression of time after administration of the premedication.

Oral ketamine and oral midazolam, when used alone as premedicant have negligible effect on cardio respiratory system.[23,24] The combination of oral ketamine and oral midazolam has no significant effects on cardio respiratory system and also has minimal side effects like nightmares, restless, or negative memories.[22]

In both of our study groups there were no side effects like loss of balance, vomiting, dysphoria or increased secretions. There was no incidence of regurgitation or aspiration in any of the patients. Loss of balance was seen in previous studies, where midazolam 1mg/kg was used orally as premedicant. Restlessness, dysphoria, vomiting were seen in previous studies were oral ketamine 6mg/kg was used as premedicant.

We observed that all children had an oxyhaemoglobin saturation of 98-100% (30-45) minutes after premedication; and there was no delayed recovery from anesthesia in any patient.
In summary, significant increase in sedation and anxiolysis scores were seen in both the groups at 30 minutes compared to baseline.

There was significant increase in sedation score and anxiolysis score in group KM at 15 minutes and at 30 minutes compared to group M. Parental separation was 100% successful in group KM and 80% in group M, which was statistically and clinically significant. Acceptance of facemask was better in group KM as compared to group M. Drug acceptance was better in both the groups.

There were no side effects like loss of balance, vomiting, dysphoria or increased secretions. There was no incidence of desaturation, regurgitation, aspiration or airway obstruction in any of the patients.

CONCLUSION:

1. Combination of oral ketamine (3mg/kg) and midazolam (0.5mg/kg) produces significantly better anxiolysis, sedation, parental separation and mask tolerance, without any clinically significant effect on cardio respiratory variables, when compared to oral midazolam (0.5mg/kg) given alone.
2. Optimum time interval for excellent anxiolysis, and parental separation from administration of oral premedication, both combination of ketamine plus midazolam and midazolam given alone is 30 minutes.

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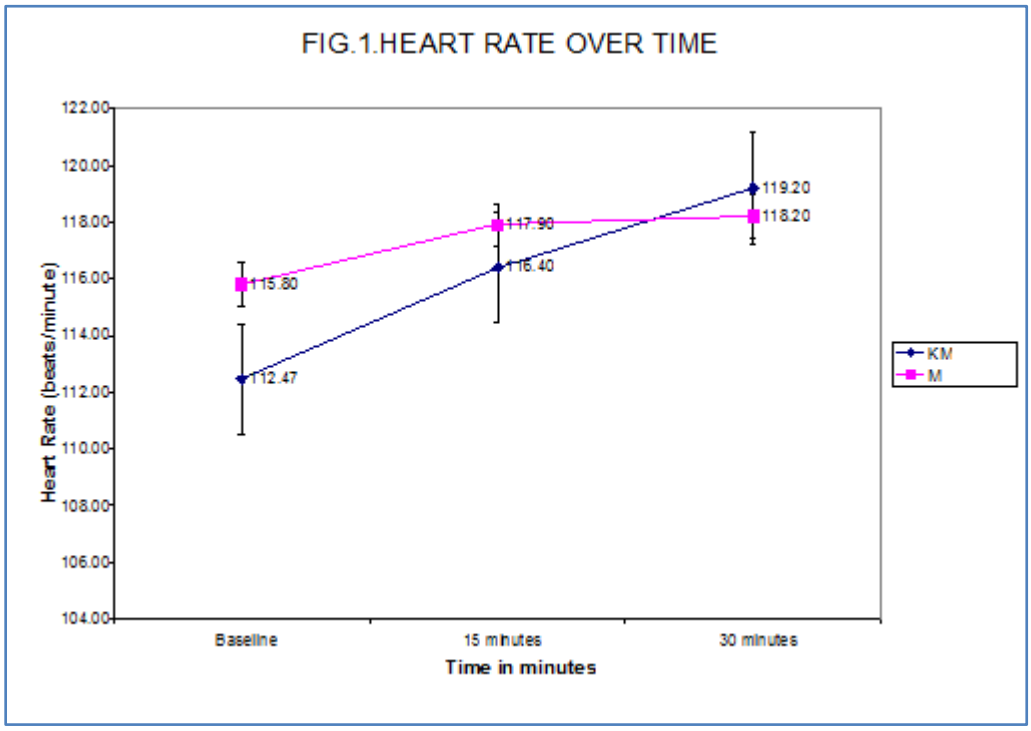

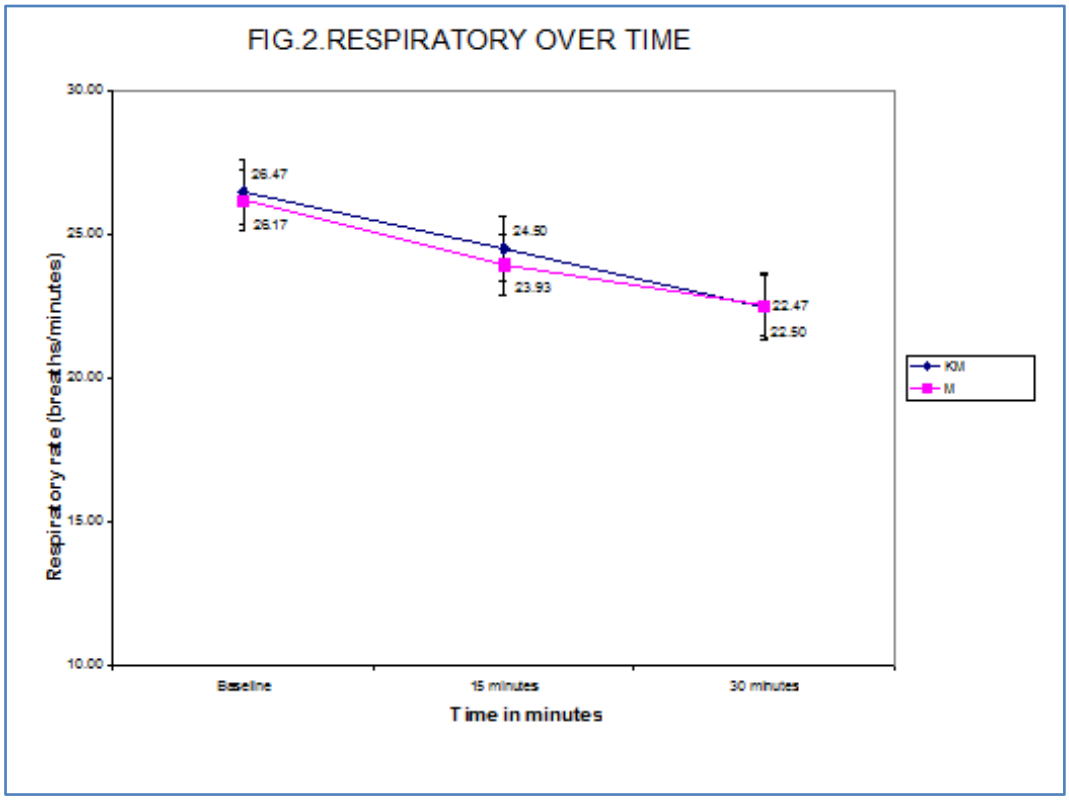

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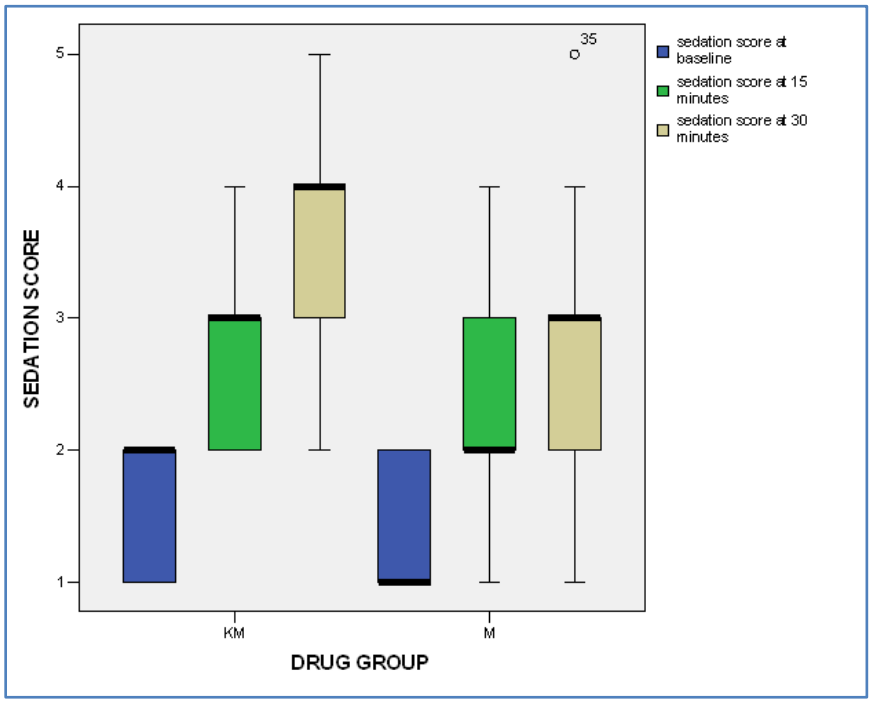

FIG. 3: SEDATION SCORE OVER TIME

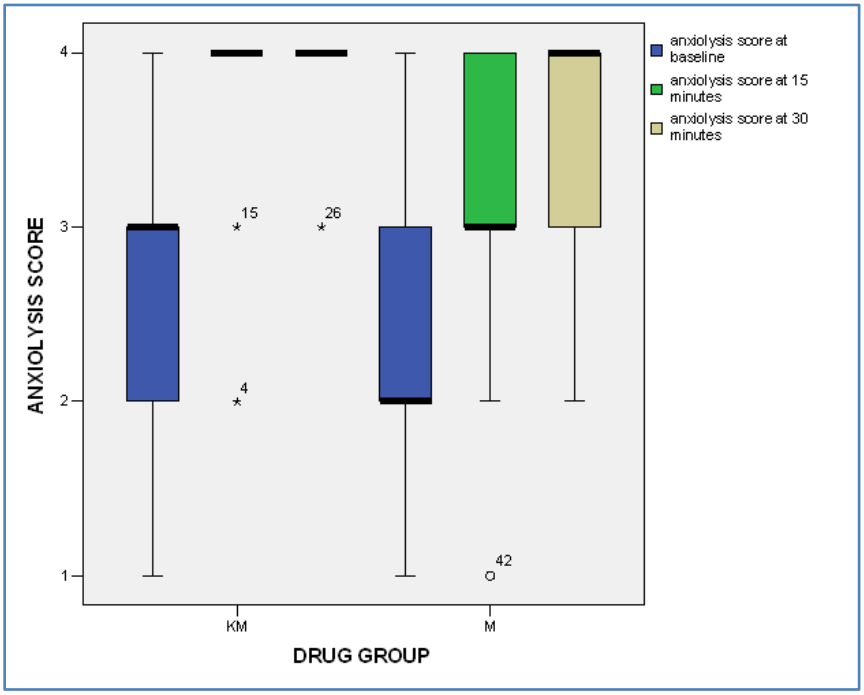

FIG. 4: ANXIOLYSIS SCORE OVER TIME

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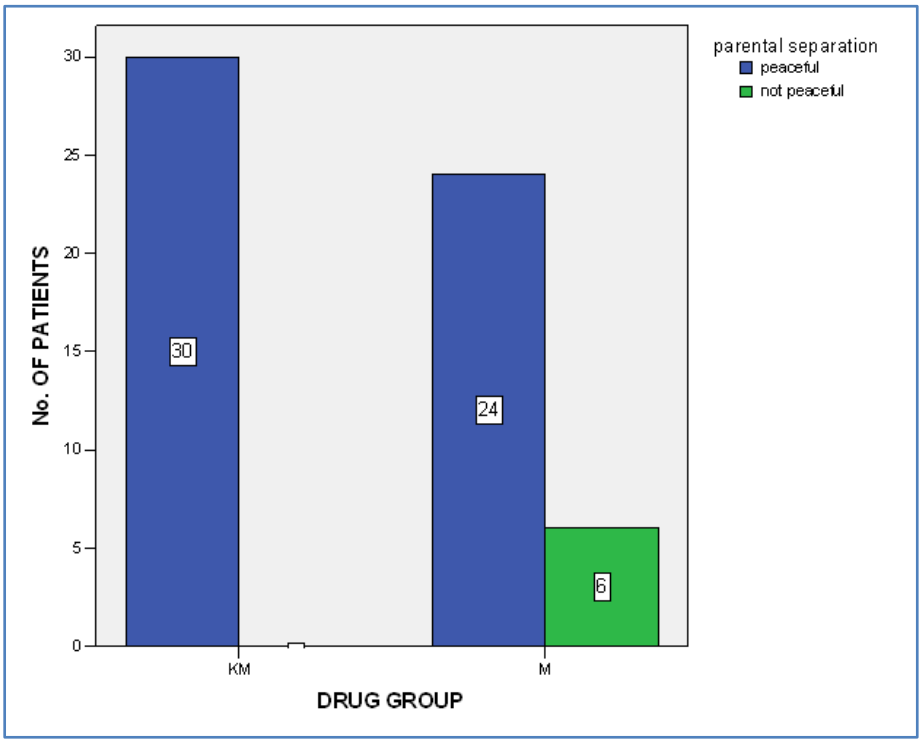

FIG. 5: PARENTAL SEPARATION

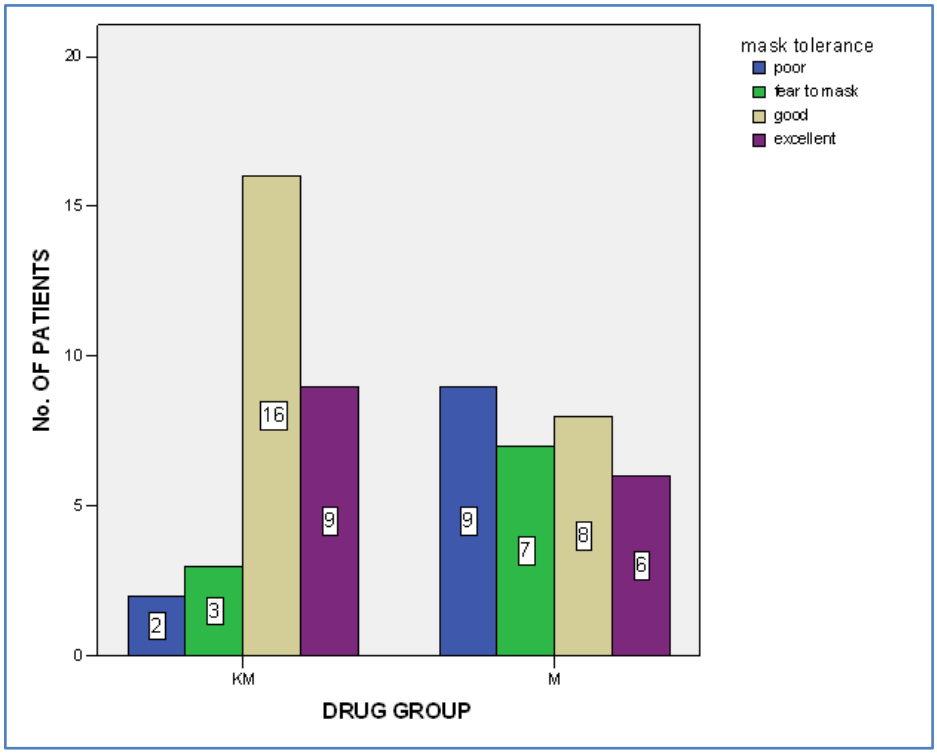

FIG. 6: MASK TOLERANCE

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Data	Group KM (Mean±S. D)	Group M (Mean±S. D)
AGE (years)	4.10±1.69	3.18±2.00
SEX (M/F)	23/7	22/8

Table 1: Demographic data

HEART RATE (HR)	GROUP KM (MEAN±S.D) Heart rate/min	GROUP M(MEAN±S.D) Heart rate/min
HR BASELINE	112.47±19.06	115.80±21.71
HR 15 MIN	116.40±21.07	117.90±22.81
HR 30 MIN	119.20±21.83	118.20±20.94

Table 2: Heart rate over time

BLOOD PRESSURE	GROUP KM (MEAN±S.D) B.P. in mmhg	GROUP M (MEAN±S.D) B.P. in mmhg
SYSTOLE 0min	98.80±7.27	96.73±12.05
SYSTOLE 30min	102.37±10.11	94.00±11.21
DIASTOLE 0min	63.67±9.95	63.00±12.92
DIASTOLE 30min	64.80±10.84	60.43±11.49

Table 3: Blood pressure changes over time

RESPIRATORY RATE(RR)	GROUP KM (MEAN±S.D) (Rate per minute)	GROUP M (MEAN±S.D) (Rate per minute)
RR basal	26.47±9.15	26.17±9.93
RR 15 min	24.50±7.88	23.93±8.97
RR 30 min	22.47±6.50	22.50±7.37

Table 4: Respiratory rate over time

SCORE	0 min		15 min		30 min	
	GROUP KM (n=30)	GROUP M (n=30)	GROUP KM (n=30)	GROUP M (n=30)	GROUP KM (n=30)	GROUP M (n=30)
1	12	18	0	2	0	1
2	18	12	10	19	6	12
3	0	0	15	7	8	10
4	0	0	5	2	11	4
5	0	0	0	0	5	3

Table 5: Sedation score over time

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SCORE	0 min		15 minutes		30 minutes	
	GROUP KM(n=30)	GROUP M(n=30)	GROUP KM(n=30)	GROUP M(n=30)	GROUP KM(n=30)	GROUP M(n=30)
1	7	6	0	2	0	0
2	7	10	1	5	0	1
3	11	13	6	9	2	7
4	5	1	23	14	28	22

Table 6: Anxiolysis score over time

DATA	GROUP KM (n=30)	GROUP M (n=30)
PEACEFUL	30(100%)	24(80%)
NOT PEACEFUL	0	6(20%)

Table 7: Parental separation

MASK TOLERANCE	GROUP KM (n=30)	GROUP M (n=30)
1	2(6%)	9(30%)
2	3(10%)	7(23%)
3	16(54%)	8(27%)
4	9(30%)	6(20%)

Table 8: Mask tolerance

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