CLINICAL EVALUATION OF ORAL KETAMINE AND ORAL MIDAZOLAM FOR PREMEDICATION IN PAEDIATRIC SURGICAL OUTPATIENTS

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ABSTRACT

BACKGROUND

Forty children of ASA grade I, aged 1 to 8 years, both males and females undergoing elective surgery under general anaesthesia and regional anaesthesia for procedures such as herniotomy and circumcision were included in the study.

MATERIALSAND METHODS

Children were allocated randomly into 2 groups. In order to get statistically significant results, a sample size of 20 was allotted to each groups. Group 1 children in this group received oral midazolam 0.5 mg/kg as premedication and group 2 children received oral ketamine 5 mg/kg as premedication. Parenteral formulation of both the drugs was given to the children after mixing with honey. All children were observed and scores allotted by the investigator. Child's emotional reaction and sedation status were noted on arrival in operation theatre on insertion of IV cannula and on acceptance of facemask. The children were separated from their parents 30 minutes after ingestion of the drug. Any side effect after ingestion of the drug until 4 hours in the postoperative period was looked for. Time of recovery from anaesthesia was noted. It was observed that both the drugs were well accepted by the children.

RESULTS

Sedation and anxiolysis was better in ketamine group during separation from parents at IV cannulation and facemask application. Both oral midazolam and oral ketamine are excellent agents for premedication in paediatric outpatient surgeries. Considering sedation and emotional scores during arrival in OT, IV cannulation and facemask application, oral ketamine is superior to oral midazolam. No significant adverse effects were found in both the groups. In the recovery room, the 2 groups did not differ significantly with respect to side effects like nausea, vomiting, emergence phenomenon and need for airway support. No haemodynamic instability was recorded. The time of discharge was not delayed in both the groups.

CONCLUSION

Considering sedation and emotional scores during arrival in OT, IV cannulation and facemask application, oral ketamine is superior to oral midazolam.

KEYWORDS

Paediatric Anaesthesia, Oral Premedication, Ketamine, Midazolam.

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BACKGROUND

Anaesthetic management begins with the preoperative psychological preparation of patient and administration of a drug or drugs selected to produce specific pharmacological responses prior to induction of anaesthesia.

Hospital admission, anaesthesia and surgery are stressful experience for children, which may lead to psychological trauma and personality changes. Pre anaesthetic medication in children is to allay anxiety, to prevent pain and to control the reflex effects of vagal stimulation.

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During the past twenty years, numerous pre anaesthetic medications have been advocated to produce sedation, anxiolysis and to facilitate separation of children from parents. But, no single premedication has achieved universal acceptance each as has its own disadvantages.

The route of administration for premedication should also be carefully considered. Intramuscular injections are painful and are avoided whenever possible. The rectal route is ideal for small children and oral route for children above one year.

The ideal pre anaesthetic medication for ambulatory anaesthesia in children should possess the following attributes-

1. Acceptable, atraumatic route of administration.
2. Rapid and reliable onset.
3. Minimal side effects.
4. Rapid elimination.

Recent reports have indicated that both oral midazolam and oral ketamine fulfil many of these characteristics.

In anaesthesiology, there has been a growing interest in the psychometric assessment of recovery after drugs often involving the use of tools more commonly found in the hands of a psychologist. Two factors account for this relatively new state of affairs. Patients are now encouraged to be active as soon after surgery as they can. New rapidly-acting anaesthetic agents that are metabolised fast, usually enable patients to be ambulatory within hours following surgery. The second development that has fuelled interest in psychometric testing is the increasing number of procedures now done on a day basis. The anaesthetic drugs cause impairment of cognitive and psychomotor functions hindering overall performance. Assessment of recovery of psychomotor function is not possible in case of paediatric patients. The preoperative and intraoperative responses are assessed by noting the emotional and sedation scores after oral premedication.

Objectives

To compare the sedative and anxiolytic effects of oral ketamine and oral midazolam during-

1. Acceptance of premedication.
2. Separation from parents.
3. Arrival in operation theatre.
4. On intravenous cannulation and facemask application.

MATERIALS AND METHODS

This is a prospective randomised comparative study conducted at Sree Avittom Thirunal Hospital, Thiruvananthapuram. The study design was similar to randomised control trial. The setting of the study was Department of Anaesthesiology, Sree Avittom Thirunal Hospital, Thiruvananthapuram. Populations under study included paediatric patients of ASA grade I for outpatient surgeries during the study period.

Those patients are belonging to ASA I physical status in the age group of 1 to 8 years, both males and females undergoing elective surgery under general anaesthesia and regional anaesthesia for procedures such as herniotomy and circumcision were included in the study.

Inclusion Criteria

1. Children of 1 to 8 years.
2. ASA I physical status.
3. Children of weight less than 20 kg.
4. Children for outpatient surgeries (herniotomy and circumcision).

Exclusion Criteria

1. Children with history of seizures.
2. Patients with intracranial space occupying lesion.
3. Patients of ASA II,II and IV.
4. Children of weight more than 20 kg.

Intervention

Children were allocated randomly into 2 groups. In order to get statistically significant results, a sample size of twenty was allotted to each groups.

Group I- Children in this group received oral midazolam 0.5 mg/kg as premedication.

Group II- Children in this group received oral ketamine 5 mg/kg as premedication.

Primary data was collected with the help of a prestructural and pretested proforma by the investigator.

Method

Children were seen preoperatively by the investigator. Detailed history with reference to history of congenital heart disease, drug allergy, bronchial asthma, history of neonatal asphyxia, previous history of anaesthesia and respiratory infection were taken. Clinical examination was done by the investigator. Blood routine was done routinely to all children. Informed consent was taken from parents and clearance from the Hospital Ethical Committee was obtained.

Children were randomly allocated into 2 groups of 20 children each. Group 1 received oral midazolam 0.5 mg/kg (5 mg/mL parenteral formulation) mixed with honey made to a total volume of 0.2 mL/kg. Group 2 received oral ketamine hydrochloride 5 mg/kg (50 mg/mL parenteral solution) mixed with honey made to a total volume of 0.2 mL/kg.

Scores Allotted to Different Parameters

Acceptance of premedication-

0 - Spits or vomits.
1 - Accepts, but not vomit.
2 - Enjoys.

Sedation score.

5 - Barely arousable.
4 - Asleep.
3 - Sleepy.
2 - Awake.
1 - Agitated.

Emotional score.

4 - Calm.
3 - Apprehensive.
2 - Crying.
1 - Thrashing.

The efficacy of premedication was evaluated by obtaining a composite score, which has arrived at by adding sedation and emotion score.

Composite Score	Response
2-5	Unsatisfactory
6-8	Satisfactory
9	Unacceptable

All children were observed and scores were allotted by the investigator. Child's emotional reaction and sedation status were noted on arrival in operation theatre on insertion of IV cannula and on acceptance of facemask.

On arrival in operation theatre, an IV cannula was inserted in the peripheral vein. All patients were induced with oxygen and nitrous oxide and with incremental concentration of sevoflurane by facemask. Surgeries were done under caudal blockade with 1% lignocaine and 0.25% bupivacaine. Intraoperative period was uneventful.

Patients were assessed for these criterions every half an hour in the recovery room. Amnesia was assessed in children above 5 years at the time of discharge by asking them if they remembered application of facemask in the operation theatre.

Method of Statistical Analysis

The data collected were entered into a master sheet and the statistical constants like mean, standard deviation and percentage were computed. The hypothesis formulated was tested statistically using Student's t-test in the case of quantitative data. To find out association between variables the 'Chi-square test' was used.

Diagrams and chart were drawn wherever necessary to substantiate the important findings. All statistical computations were done by using SPSS computer package.

Observation and Analysis

In the present study, 40 ASA grade I patients were registered into 2 groups of 20 each.

Group I- Children who have received oral midazolam 0.5 mg/kg.

Group II- Children who have received oral ketamine 5 mg/kg.

Distribution of Cases According to Type of Surgery

Type of Surgery	Number of Cases
Herniotomy	12
Circumcision	8
Total	**20**
Group I	

Type of Surgery	Number of Cases
Herniotomy	10
Circumcision	10
Total	**20**
Group II	

Attempts were made to see whether the 2 groups were identical with respect to general characteristics like age, weight, sex and duration of surgery before assessing the changes in different variables.

Age	Number of Cases	Mean	SD
Group I	20	2.675	0.866
Group II	20	1.95	0.484
Table 1. Mean and Standard Deviation of Age			

Mean difference = 0.7250.

Levene's test for equality of variances- F = 9.272, P = 0.004.

It is observed that numerically the mean age was slightly higher in midazolam group compared to ketamine. However, statistical test revealed that the difference noted was only due to sampling variation. Since, the test happened to be insignificant. Therefore, it is inferred that both the groups were identical with respect to age and hence age will not have any influence over the final outcome measures.

Gender	Number of Cases	Mean	SD
Group I	20	1.25	0.444
Group II	20	1.4	0.503
Table 2. Mean and Standard Deviation of Sex			

Mean difference=0.150.

Levene's test for equality of variances- F=3.709, P=0.062.

Group	Sex of Patients				Total
	Male		Female		
	Number	Percentage	Number	Percentage	
Midazolam	15	75	5	25	20
Ketamine	12	60	8	40	20
Table 3. Distribution According to Sex					

While considering the sex of the patients in midazolam group, 75% were males and 25% were females and in ketamine group, males 60% and females 40%. There will not be any difference in final outcome measures due to sex difference.

Weight	Number of Cases	Mean	SD
Group I	20	12.4	2.415
Group II	20	11.8	1.322
Table 4. Mean and Standard Deviation of Weight			

Mean difference=0.6.

Levene's test for equality of variances- F=5.861, P=0.020.

In this variable, there is only negligible difference between two groups from the mean weight. It has been statistically established that both the groups were identical.

Acceptance ofPremedication	Number of Cases	Mean	SD
Group I	20	1.25	0.444
Group II	20	1.15	0.366

Table 5. Mean and Standard Deviation of Acceptance of Premedication

Mean difference=0.1.

Levene's test for equality of variances- F=2.502 P= 0.122.

Despite somewhat bitter taste of ketamine and midazolam, which was masked by honey, none of the children spit it out. Both the groups accept premedication well.

Emotional Score During Parental Separation	Number of Cases	Mean	SD
Group I	20	2.75	0.444
Group II	20	2.95	0.394

Table 6. Mean and Standard Deviation of Emotional Score During Parental Separation

Mean difference=0.2.

Levene's test for equality of variances- F=4.109, P=0.050.

Sedation Score During Parental Separation	Number of Cases	Mean	SD
Group I	20	2.7	0.470
Group II	20	2.95	0.394

Table 7. Mean and Standard Deviation of Sedation Score During Parental Separation

Mean difference = 0.25.

Levene's test for equality of variances- F=6.932, P=0.012.

From the above given data, it is concluded that there was no statistically significant difference between the two groups.

Emotional Score on Arrival in OT	Number of Cases	Mean	SD
Group I	20	2.25	0.444
Group II	20	2.55	0.510

Table 8. Mean and Standard Deviation of Emotional Score on Arrival in OT

Mean difference=0.3.

Levene's test for equality of variances- F=5.544, P=0.024.

Sedation Score on Arrival in OT	Number of Cases	Mean	SD
Group I	20	2.25	0.444
Group II	20	2.45	0.510

Table 9. Mean and Standard Deviation of Sedation Score on Arrival in OT

Mean difference = 0.2.

Levene's test for equality of variances- F = 5.544, P = 0.024.

From the above data, sedation and emotional score are high with ketamine group. On arrival in OT, children received ketamine were calmer than those received midazolam.

Emotional Score onIV Cannulation and Facemask Application	Number of Cases	Mean	SD
Group I	20	1.65	0.489
Group II	20	1.95	0.394

Table 10. Mean and Standard Deviation of Emotional Score on IV Cannulation and Facemask Application

Mean difference=0.3.

Levene's test for equality of variances- F=10.118, P = 0.003.

Sedation Score on IV Cannulation and Facemask Application	Number of Cases	Mean	SD
Group I	20	1.65	0.489
Group II	20	1.9	0.447

Table 11. Mean and Standard Deviation of Sedation Score on IV Cannulation and Facemask Application

Mean difference = 0.25.

Levene's test for equality of variances- F = 4.724, P = 0.036.

It is observed that the ketamine group shows higher scores on both emotional and sedation than the midazolam group on IV cannulation and facemask application.

RESULTS

There was no statistically significant difference between the 2 groups with respect to age, weight and time from premedication to skin incision and time from discontinuation of anaesthesia to spontaneous eye opening.

Comparing the acceptance of medication in either group showed no significant difference.

Time of onset of sedation, maximum sedation achieved, time for gaseous induction in both the groups showed no significant difference.

The children were asleep were more in ketamine group. The ketamine group showed higher emotional score than midazolam group on reactions when they are separated from parents (F = 4.1; p=0.05), on arrival in OT (F=5.5; p= 0.05), on IV cannulation and on facemask application (F=10; p= 0.01).

The ketamine group showed better sedation scores than the midazolam group on reactions when separated from parents (F=6.9; p=0.01), on arrival in OT (F= 5.5; p

=0.05), on IV cannulation and facemask application (F=4.7; p= 0.05).

In the recovery room, the 2 groups did not differ significantly with respect to sideeffects like nausea, vomiting, emergence phenomenon and need for airway support. No haemodynamic instability was recorded. The time of discharge was not delayed in both the groups.

DISCUSSION

Up to 1988, no investigations have clearly demonstrated any psychological benefits of premedication in children of any age. This finding is significant in the study by Jackson K[1](1951) demonstrated the value of psychological preparation in a variety of circumstances.

It has been reported correlation between pulse rate, blood pressure and behavioural rating of anxiety.[2] Thus, to allay anxiety, various premedication are given in preoperative period.

The route of administration is also carefully considered. In a study by Korsch BM[3](1975) found that oral route is more appropriate for many patients.

Pecazine (Doughty AG[4] 1959) methylpentynol (Rendell 1954; Doughty 1959) and quinalbarbitone sodium (Cope and Glover 1959) enjoyed passing popularity until great interest was shown in trimeprazine tartrate (Doughty 1962[5]; Haq and Dundee[6] 1968). This drug belongs to phenothiazine group.

Later hyoscine was added to premedication.

Diazepam was evaluated as oral premedication in children by Bush (1968), Dowel (1968), Haq and Dundee[6] (1968) and Gordon and Turner (1969).

Alderson PJ[7]compared clinical characteristics of oral ketamine and midazolam in 40 children. He found that midazolam and ketamine offer similar clinical characteristics in children.

Austuto M and Dimsa N[8] conducted double-blind study on 120 patients aged between 2 and 6 years and are divided into 2 groups. First group received midazolam 0.3 mg/kg and ketamine 1mg/kg; second group received midazolam 0.3mg/kg and ketamine 2mg/kg. He found the second group has better sedation and emotional scores.

Oral route is easiest mode for premedication, onset is slow and requires 30-40 minutes for sedation and according to McMillan[9] dose is 0.5mg-0.75mg for oral route. Combination of midazolam and ketamine given orally or rectally offer results better than either drug used alone.

Roelofse JA[10] compared the effectiveness of oral ketamine with standard oral premedication in 60 children for dental procedures. He found ketamine group were better sedated than the other group.

Riva J[11] conducted study to assess the sedation and emotional scores with oral midazolam in paediatric patients and showed a better level of sedation.

Parnis SJ[12]conducted a double-blind study. He compared midazolam 0.25mg/kg, 0.5mg/kg and 0.5mg/kg diazepam and found that 0.5mg/kg midazolam showed a better level of sedation.

McGraw T[13] studied the effect of oral midazolam on postoperative behaviour of children. He found that children received midazolam were less likely to cry and fight.

Ketamine lollipop (50mg) was evaluated as premedication in children by Horiuchi T[14] and showed good emotional state and no typical side effects.

Tobias SJ[15] prospectively evaluated the efficacy of oral ketamine in alleviating procedure-related distress in paediatric oncology patients. Procedure-related distress evaluated by Observational Scale of Behavioural Distress (OSBDR) and found to be effective in reducing distress.

In this study, no side effects like nystagmus, vomiting and increased salivation was observed with ketamine as found by Gutstein et al[16] in 1992, probably because, we used lower dose of 5mg/kg compared to 6mg/kg used by them.

In the present study, midazolam 0.5mg/kg also was not associated with any side effects. Thus, in conclusion, both oral midazolam 0.5mg/kg and oral ketamine 5mg/kg are equally safe and effective for premedication in paediatric outpatient surgeries.

CONCLUSION

Both oral midazolam and oral ketamine are excellent agents for premedication in paediatric outpatient surgeries. Considering sedation and emotional scores during arrival in OT, IV cannulation and facemask application, oral ketamine is superior to oral midazolam. No significant adverse effects were found in both the groups.

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