

Premedication with a Combination of Ketamine and Midazolam in Pediatric Cardiac Surgical Patients: A Comparison of Nasal versus Oral Route.

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Abstract

Background

Premedication remains the most debating thought in anaesthesiologist's mind, while preparing paediatric patients for anaesthesia. Paediatric patients whether cyanotic or acynaotic planned for cardiac surgical procedures poses most challenging task, as maintaining haemodynamic stability remains of paramount importance. Even subtle variation in vitals as compare to normal paediatric patients, may result in haemodynamic compromise and devastating consequences.

Method

Around 100 pediatric cases undergoing cardiac surgery with diagnosis of cyanotic or acynotic heart disease were randomized into oral vs nasal group using computer randomization. In this study children included, were of age 3 months to 5 years, weight more than 5 kgs, suffering from congenital heart disease (cyanotic or acyanotic). Patients with known h/o allergy to Ketamine and Midazolam and known ear nose throat disease were excluded.

After informed written consent from parents and approval of Hospital ethical committee, premedicament a combination of Midazolam (100 ug/kg) and Ketamine (5 mg/Kg) were administered, nasally or orally as per group assigned.

The collected data was analyzed by using epi-info statistical software and Mann-Whitney or Wilcoxon Two-Sample Test (Kruskal-Wallis test for two groups) was applied for analysis.

Result

Analysis of collected data was done to compare the results in term of clinical effects, of combination of Ketamine and Midazolam in oral versus nasal route in Premedication.

There is no significant variation of pulse rate, respiratory rate and oxygen saturation from baseline data in both nasal as well as oral group after 30 minutes. There was significant difference for separation timing between routes of administration of drugs. Nasal was faster than oral as within 30 minutes of drug administration around 74.50% in nasal group got separated, whereas in oral group it was only 42.85%, where as regarding acceptance, it was better in oral route that is 85.71% in comparison to nasal group in which it was only 43.13%.

The collected data was analyzed by using epi-info statistical software and Mann-Whitney or Wilcoxon Two-Sample Test (Kruskal-Wallis test for two groups) was applied for analysis.

Conclusion

Combination of Ketamine (5mg/kg) and Midazolam 0.1 mg/kg is better than individual drugs alone as described by earlier studies. They counter each other's side effects hence this combination has good desired clinical outcome with least side effects. Although acceptability is better in oral route but nasal route offers distinct advantage over oral route as premedication, in term of reliability and rapid onset. Reason behind this is nasal mucosa is rich in venous plexus which facilitates rapid and more reliable absorption. It also helps in more bioavailability due to its hepatic bypass metabolism.

Key words

Oral, Nasal, Premedication, Cardiac surgery

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Received: 23.03.17

Accepted: 26.08.19

Introduction

Premedication in paediatric patients undergoing surgery is least practiced in the past due to ignorance, fear and misbeliefs. It was common belief among physicians that neonates, infants and pediatric patients, don't appreciate or perceive pain, anxiety and separation from parents [1].

Even today, most of the paediatric centres do not have uniform protocol for premedication [2]. It is a well established fact that paediatric patients perceive pain and are apprehensive of

- a) Fear of separation from the parents;
- b) Fear of pain;
- c) Fear of unknown and unfamiliar surroundings;
- d) Uncertainty of limits of behaviour;
- e) Fear regarding loss of control, autonomy and privacy.

Separation from parents of the pediatric cardiac surgical patients just prior to surgery is one of the most traumatic ordeals [3]. These patients are prone to develop pulmonary hypertensive crisis, cyanotic spells and life threatening arrhythmias, amongst other complications, at the slightest of provocation [4,5]. Therefore, a well-sedated child in the preoperative period is an essential prerequisite in paediatric cardiac surgery. Achieving this goal is one of the most challenging and vital tasks faced by Anaesthesiologists [3].

Premedication facilitates child to undergo a smooth anaesthetic induction. This reduces incidence of behavioral and personality changes e.g. nightmares, irritability, enuresis and nocturia from 57% to 17% [6].

Premedication with sedatives and anxiolytic agents may minimize these problems. An ideal premedicant should have the following properties [7].

- a) Sedation and anxiolysis;
- b) Least traumatic in administration;
- c) Rapid and reliable onset of action;
- d) Reduce the requirement of anaesthetic agent;
- e) Minimal side effects;
- f) Rapid elimination;

Common routes of premedication widely practised are oral, nasal, rectal, intramuscular and intravenous. Premedication by oral route is one of the most popular routes, but it has drawbacks like slow onset, poor absorption, noncompliance in form of spitting, regurgitation and vomiting due to its unpleasant taste. Intranasal is another route practiced, which counters, some drawbacks of oral route. Quest for an ideal sedative premedication is still on. This study was undertaken to

evaluate and compare the safety and efficacy of combination of Ketamine and Midazolam as preanaesthetic medication in paediatric cardiac surgical patients.

Objectives of this study was to assess and compare the acceptability level of sedation, anxiolysis, ease of separation from parents, onset of desired clinical outcome and safety profile by studying side effects of above combination of drugs.

Material and Methods

Prospective, randomized, placebo controlled, double blinded, study was carried out with total of 100 children, of age 3 months to 5 years, of body weight more than or equal to 5 kg, of both sexes were included in study. These patients were suffering from cyanotic or acyanotic congenital heart disease. Patients with known h/o allergy to Ketamine and Midazolam and known ear nose throat disease which might affect intake of drug and its absorption were excluded from the study.

After informed written consent from parents and approval of Hospital ethical committee, selection of children were done. Allocation to nasal group and oral group was carried out by computer generated random numbers. Medications were prepared by the OR technician which was combination of Ketamine -5 mg/kg and Midazolam -100ug/kg and placebo was same volume of 25% Dextrose administered by another OT technician.

Nasal group was administered premedication nasally and placebo orally of equal quantity whereas in oral group, premedication was administered orally and placebo nasally by another OT technician, unaware of drug composition, 30 minutes before separation of child from mother for administration of anaesthesia.

Patients were induced by using Fentanyl 7µg/kg and Midazolam 100µg/kg. Intubation was carried out using, Vecuronium bromide 0.1-0.2 mg/kg body weight, with ETT tube, as per patient's age. Rest of surgery was performed under GA.

Study was carried out to assess the safety and therapeutic efficacy of combination of Ketamine and Midazolam as premedication agent using oral and nasal route in paediatric cardiac surgical patients.

The reactions of the children to the taste of the premedication were noted by independent observer not aware of cohort. Subjects were assessed score-wise for acceptance of medicine, anxiety, sedation and compliance in establishment of peripheral line. Monitoring of Pulse, Respiratory rate, Oxygen saturation at every five minutes

Table 1: Various scales and grades applied to assess the patients

Level	Acceptance	Anxiety	Sedation	Compliance in IV
1	Accepts with enthusiasm	None	Asleep not easily arousable	Excellent – fully co-operative
2	Accepts	Little – slight expression of fear / apprehension, easily reassured	Asleep – slowly responds to verbal commands or gentle stimulation	Good – mostly co-operative, responds to reassurance
3.	Accepts but needs encouragement / persuasion	Moderate – clearly fearful cries but becomes quiet with reassurance	Drowsy readily responds to verbal commands	Fair – moderate fear / crying, not quiet with reassurance
4.	Accepts-but rejects or spits out	Excessive – crying, uncooperative, combative	Awake – calm and quiet	Poor – stormy, crying, need for restraint.
5	Refuses	-	-	-

Table 2: Demographic profile of two cohorts of nasal and oral groups

Attributes		Route of adm of drug		Total	Chi Square (p Value)
		Nasal	Oral		
Gender	Female	30	34	64	Chi square = 0.59 p value = 0.443299
	Male	21	15	36	
Age Group	<3 yrs	29	31	60	Chi square = 0.103 p value = 0.747951
	>3 yrs	22	18	40	
Weight	<15 kgs	43	43	86	Chi square = 12.57 p value = 0.560861
	>15 Kgs	8	6	14	
Cardiac Condition	Cyanotic Heart Disease	24	22	46	Chi square = 12.57 p value = 0.560861
	Acyanotic Heart Disease	27	27	54	

Table 2- Upon demographic comparison and statistical analysis no significant variation in baseline characteristics with respect to gender, age group, weight and cardiac condition between two groups i.e. nasal versus oral route were observed.

Comparison of parametres

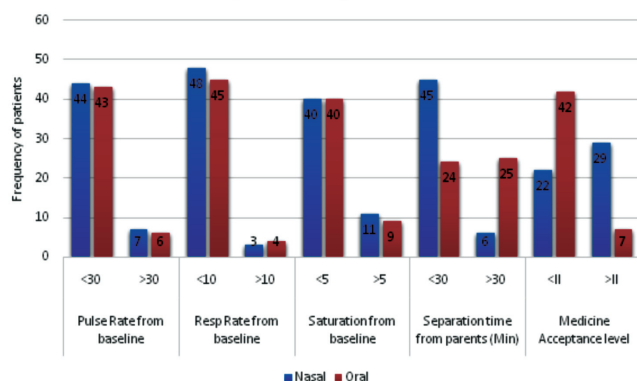


Fig. I: Comparison of Parameters in Various Groups as per Objectives

Figure I : There is no significant variation of pulse rate, respiratory rate and oxygen saturation from baseline after 30 minutes. There is no significant variation in both nasal as well as oral group. There was significant difference between separation timing in less than 30 minutes duration and it was 74.50% in nasal group whereas it was 42.85 %, in oral group. This distinctly implies that, separation timing from parents was much faster in nasal group than oral. Whereas acceptance level (\leq II) was better in oral group whereas was better in oral than nasal group i.e 85.71% vs 43.13 %.

Table 3 : Comparison of Parameters in various groups as per objectives

Attributes		Nasal	Oral	Total	Chi Square (p Value)
Pulse Rate from baseline	≤30	44	43	87	Chi square = 0.021 p value = 0.88549
	>30	07	06	13	
Resp Rate from baseline	≤10	48	45	93	Chi square = 0.330 p value = 0.565571
	>10	03	04	07	
Saturation from baseline	≤5	40	40	80	Chi square = 0.017 p value = 0.897077
	>5	11	09	20	
Separation time from parents (Min)	≤30	45	24	69	Chi square = 25.355 p value = 0.000000
	>30	06	25	31	
Medicine Acceptance level	≤II	22	42	64	Chi square = 24.306 p value = 0.000001
	>II	29	07	36	

interval was done. Children were induced by using Fentanyl 7 ug/kg and Midazolam 100ug/kg. Intubation was carried out using, Vecuronium bromide 0.1-0.1.2 mg/kg body weight, with ETT tube, size as per patients age.

The randomization code was assigned to the next child enrolled in study. Subjects were assessed in the following scores adopted from published studies investigating paediatric premedication [8].

Other events which were noted was

- 1.) Time of premedication;
- 2.) Separation from parents;
- 3.) Time in operation theatre;
- 4.) Time of induction, intubation;
- 5.) Any unusual event.

Analysis of collected data was done to compare the results in term of clinical effects, of combination of Ketamine and Midazolam in oral versus nasal route in premedication. The collected data was analyzed by using epi-info statistical software and Mann-Whitney or Wilcoxon Two-Sample Test (Kruskal -Wallis test for two groups) was applied for analysis.

Results

Around 100 patients were included in the study applying exclusion and inclusion criteria. All these patients underwent paediatric cardiac surgery at Armed Forces Cardiothoracic centre. All 100 patients after selection and randomisation were divided in two study groups. Oral group were administered premedication orally and placebo nasally whereas Nasal group were administered premedication Nasally and placebo orally.

Drug used for premedication were combination of Ketamine with dosage 5mg/kg body weight and Midazolam with dosage of 100mcg/kg body weight as syrup with 25% dextrose and placebo was of similar volume of 25% dextrose.

After administration of premedication drug in front of parents, all the parameters were recorded at every 5 minutes interval till next 30 minutes.

As shown in Table no III and Fig No I, there is no significant variation in pulse rate from baseline after 30 minutes in each group as well as no significant intra group significant variation. Although ketamine and midazolam may cause respiratory depression but there was no significant fall or rise in respiratory rate in each group from baseline after 30 minutes neither any significant intra group variation in respiratory rate.

Saturation was monitored by using pulse-oximeter which again recorded no significant variation in saturation from baseline after 30 minutes in both the groups or intra group variation. Anxiety level on assessment using Table no II, adequate anxiolysis was achieved in both groups after 30 minutes with no significant variation when both routes were compared.

After 30 minutes children were separated from their parents after achieving adequate anxiolysis (scale 1 & 2) and sedation (scale 3 & 4). There was significant variation, noted in time of separation in nasal versus oral route as shown by Mann-Whitney or Wilcoxon Two-Sample Test (Kruskal - Wallis test for two groups) which can be seen by Table No. III and Fig. - I [9].

On operation table, during establishing IV access after 30 minutes, compliance and cooperation of child in establishing IV Line was assessed. There was no significant variation in sedation in nasal versus oral route as shown by Kruskal - Wallis test which can be seen by graph.

Onset of action was faster in nasal route, but acceptance of medicine was lesser in nasal route than oral route as shown by Table no. III and Fig No I and there is a significant statistical variation in both groups as shown by Kruskal-Wallis test.

There were no significant side effects observed in the both

the groups except mild salivation. There were no important circulatory, respiratory or long-term residual neurological effects observed in any of the children.

Discussion

Despite several reservation and apprehensions regarding premedication in paediatric patients, various studies have reported that pre-anaesthetic medication in children can allay anxiety and facilitate separation of children from their parents as they enter the surgical suite [10-12].

Drugs like Chloral hydrate, midazolam, ketamine, dexmedetomidine and fentanyl have been used as effective preanesthetic medication either solely or in combination. These premedications were administered through various routes i.e intramuscularly, rectally, intranasal or orally in paediatric age group [13-16].

A comparative study involving children (1-9 yr of age) receiving Midazolam or chloral hydrate po (in combination with atropine) 65 ± 12 min before induction of general anaesthesia, reported that midazolam 0.4-0.6 mg/kg po provided only "Fair" anxiolysis in children younger than 5 yrs. of age. In contrast, midazolam 0.4-0.6 mg/kg po, produced good anxiolysis in older children (>5 yrs. of age). In the younger children, restlessness was noted with both the lowest and highest doses of Midazolam.

In preliminary study, the effects of oral Midazolam 0.25 or 0.5 mg/kg po and Midazolam 0.1 or 0.2 mg/kg im were compared. Conclusion drawn that Midazolam 0.5mg/kg po was as effective alternative to intramuscular injections for pediatric outpatients requiring preanesthetic medication [16].

Midazolam 0.75 mg/kg po produced an increased level of sedation in children 1-10 yrs. of age within 30 min after oral administration. Furthermore, midazolam 0.75 mg/kg facilitated separation of the child from parents and provided a better quality of induction.

The limited bioavailability of oral Midazolam may explain the high-dose requirement for sedation and anxiolysis after the oral route of administration. The bioavailability of midazolam was only 27% after a dose of 0.15 mg/kg and 15% after 0.45 and 1.0 mg/kg, as a result of incomplete absorption and extensive first-pass metabolism [17-18].

In study of oral Midazolam with dosages of 0.25, 0.5 and 0.75 mg/kg, were found to be equally effective for sedation and anxiolysis, although the separation of the children from their parents was excellent in less than 10% of cases. It detected a 25% improvement in separation / anxiolysis scores between 0.75 and 1.0 mg/kg whereas midazolam, at dosages of 0.5, 0.75 and 1.0 mg/kg are equally effective in providing sedation and anxiolysis in

children at the time of separation from their parents 30 min after administration of the premedication almost 80% [18].

The untoward effects noted (loss of balance, blurred vision, dysphoria) occurred only in children who received 0.75 and 1.0 mg/kg. These data combined with the results of five different studies indicate that the incidence of serious complications after oral Midazolam (0/400 children) is low [9,13,18].

Although our patients accepted the oral drug mixture without difficulty, some of the children stated that the mixture was bitter (or made a facial expression which suggested that the taste was unpleasant)[19].

Concern regarding volume of drug and chances of aspiration studies suggested that administration of small volume of fluid e.g. 5-10ml to children prior to induction of general anaesthesia does not pose a significant risk of aspiration of abdominal contents (20). In this study, total volume combined used in both routes i.e placebo and premedication never exceeded more than 10 ml.

With 6 mg/kg of Ketamine onset time of sedation was 13.16 ± 2.50 min; 77% patients achieved sedation within 30 min, 90% of children were calm when separated from parents and 80% did not cry at IV cannulation. (27.3 ± 6.15 min in comparison to 11.2 ± 2.4 min by other study). Similar results were seen with 6mg/kg of Ketamine given orally in another separate study [21]. A dose of 6mg/kg of ketamine made better sedation and anxiolysis than 0.5 mg/kg of midazolam and to achieve better results higher dosages like 0.75 mg / kg were required [9,22-24]. Premedication with higher dosages of ketamine and midazolam resulted in better sedation, anxiolysis and earlier separation but at the cost of safety profile. Increased drug dosages have reported side effects and stormy post - operative recovery due to irritability [25-26].

Hence combining of drugs to decrease individual drugs dosages, not only minimizes side effects but counteracts each other's side effects. Similarly, ketamine combined with midazolam given nasally reported no discernable cardiovascular effects. Even intravenous use of ketamine combined with benzodiazepines proved to have a good safety profile. The cardiovascular stability with ketamine alone or with other drugs, has led to its use as an induction drug for patients with unstable cardiovascular physiology. Combination of ketamine and midazolam has been used successfully in cardiac catheterization procedures in children. In this study nasal ketamine combined with midazolam provided sedation without cardiac or respiratory effects. Although, we initially began to use this regimen primarily with retarded or uncooperative older

children, these data reveal that ketamine /midazolam may be a useful regimen for children with tenuous cardiovascular status. Poor acceptance of the intranasal administration of this medication, however, may prevent widespread use. In most of studies assessments of sedation/anxiolysis at separation were made at after 30 minutes of premedication irrespective of timing of commencement of surgery [26-27]. Premedication with oral Midazolam is used consistently in day care surgeries with good results and recovery profile and is used frequently in ambulatory surgery unit [19].

There were no important circulatory, respiratory or long-term residual neurological effects observed in any of the children.

A number of drugs are available today to provide preanaesthetic sedation in children. Most of these are given by oral, intramuscular, intravenous, intranasal or per-rectal route. There are certain advantages as well as disadvantages of each route. Combination of both the drugs will acts as synergistic effect and reduces side effect of each other. Intranasal ketamine, like midazolam, is clearly superior to placebo for sedation prior to painful or frightening procedures. Most studies have used doses of 3 to 5mg/kg for sedation, few have even larger doses used for preoperative induction. In the studies where ketamine and midazolam have been directly compared, they appear to be similar in efficacy and bioavailability (ketamine is 50% bioavailable through the nose, 25% via the rectal route). Ketamine in combination with midazolam may actually be even more efficacious, with one study showing superior sedation, low toxicity and excellent amnesia [1,9].

There are certain advantages as well as disadvantages of each route. Oral route though being atraumatic, certain non palatable drugs with bitter taste, may result in lower acceptability, nausea and vomiting. It under goes hepatic first by pass metabolism hence may require larger doses. Per-rectal route is uncomfortable and embarrassing in paediatric age group. Its unpredictable absorption due to faeces may require larger volume of drug. Absorption via intramuscular route is complete but it is not only traumatic but also slow in onset.

Summary

An ideal premedication in children is the one that can be easily administered, should be atraumatic, reliable, rapid in onset with minimum side effects. No drug as on date can fulfill these criteria but this combination of Ketamine (5mg/kg) and Midazolam (100mcg/kg) is very near to an ideal premedicant. As we have seen in our 100-paediatric cardiac surgical cases there was least haemodynamic disturbance irrespective of route. If each

drug is given alone, higher dosages required to produce the desired clinical outcome, as compared to dosage in combination, similarly side effect of drug also increases. Combination of Ketamine and Midazolam has minimum side effects because first, dosage of each drug [27-32].

Conflict of interest:	All authors declare no COI
Ethics:	There is no ethical violation as it is based on voluntary anonymous interviews
Funding:	No external funding
Guarantor:	Col. (Dr.) P. S. Bedi will act as guarantor of this article on behalf of all co-authors.

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