Comparison of intranasal ketamine and intranasal midazolam for pediatric premedication in patients undergoing congenital heart disease surgery

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Background
Premedication via intranasal route has been studied for various types of surgeries, but there are only few studies reported in patients undergoing congenital heart disease correction surgeries. Intranasal premedication in pediatric patients undergoing congenital heart disease surgery is much more useful, as there is no need for intramuscular and intravenous injections that will cause pain and anxiety to patients and cause the child to cry, thus creating hemodynamic instability in compromised heart patients. In our study, the authors compared the efficacy and side effects of ketamine and midazolam administered with a nasal mucosal atomizer (MAD).
Methods
A total of 60 patients with ASA grade II and III undergoing congenital heart disease surgeries were randomly allocated into two groups: group A (ketamine) and group B (midazolam). These drugs were given intranasally on the mucosal surface with an atomizer. The primary variables were onset of sedation, separation from parents, degree of sedation, response to venipuncture, and acceptance of face mask.
Results
The sedation score was higher in the midazolam group as compared with the ketamine group ($P<0.05$) and the mean time of onset of sedation in the midazolam group was 10.66 min as compared with 15.16 min in the ketamine group which was statistically significant, with the P value of 0.005.
Conclusion
Midazolam has an early onset of sedation and is associated with no side effects.

Keywords:
congenital heart disease, intranasal mucosal atomizer (MAD), ketamine, midazolam

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Introduction

The fear of the operation room, needle prick, and the operation room staff can cause a lot of distress and psychological effect on a child, which can be long lasting by being carried as bad memories in the child's future. Preanesthetic medication allay the stress, fear, and anxiety of surgery and also ease the child – parent separation, providing a smooth induction. Preoperative anxiety has been reported to have correlations between heart rate (HR), blood pressure (BP), and behavioral ratings [1]. Preoperative anxiety in children can lead to postoperative behavioral changes, such as bad dreams, enuresis, and increased fear of doctors and operation room staff. Premedication or the presence of parents in the preoperative room can relieve the anxiety [2]; hence, all pediatric patients need to be premedicated.

Many premedications have been used in the separation of children from their parents and to reduce the anxiety associated with surgical procedures before general anesthesia. An ideal preanesthetic medication should be easy to administer, with a tendency of rapid and smooth induction of sedation, faster recovery in short procedures, and with minimal side effects [3]. Previously, the routes of premedication used were oral (p.o.), intramuscular (i.m.), intranasal (IN), and lately, sublingual (SL) [4–8]. Rectal administration of drugs for premedication in children have been used [9], but many of the children would be very reluctant to allow this sedation technique, which could be very traumatic. Oral route takes longer time for sedation and is associated with nausea and vomiting.

Crying of the anxious and distressed children can increase the myocardial oxygen consumption and work, which is poorly tolerated in these patients as they have little cardiac reserve. This increase in

myocardial oxygen consumption can be prevented by sedating these children with a premedication to allow for a smooth induction.

In recent years, IN use of premedications has become the choice of many anesthetists, as it is a noninvasive route of administration [10]. The nasal cavity has a rich vascular plexus with a broad surface area communicating with the subarachnoid space via the olfactory nerve. Therapeutic levels can be achieved by the mucosal atomizer device (MAD). It delivers the drug via a fine spray over a broad surface area in the nasal cavity. It also reduces coughing and sneezing, which are associated with other devices. Nasal premedication via an atomizer has the advantage of rapid onset, avoidance of painful needle pricks, and ease of administration. The disadvantages are the association of irritation to the nasal mucosa with burning sensation and patient irritability.

Midazolam, a short-acting drug, causes anterograde amnesia and sedation, decreases anxiety with reduction of adrenergic response to surgical stress, is useful for separation, and facilitates a smooth induction [11–14]. Ketamine possesses a lot of properties of an ideal premedication drug like rapid onset, low-grade respiratory depression, sedation, and analgesia. However, emergence reactions, excessive salivation, and prolonged recovery time are cited as reasons to limit its routine use. Ketamine has previously been used in premedication as either IM [11] or PR [12]. The IM or PR route causes mental and physical trauma to the children.

This study aimed to determine the efficacy of IN midazolam and ketamine with the use of an atomizer in children with various congenital heart disease with respect to onset time and level of sedation, anxiety, hemodynamic changes, and side effects.

Our study is probably the only one of its kind in using an IN sedation through a MAD in patients undergoing various cardiac surgeries for correction of congenital heart disease.

Materials and methods

After approval from the Institutional Ethics Committee and Review Board (registration number: 33/MC/EC/2019), written informed consent was taken from parents of all children. A total of 60 eligible cases having congenital heart defects posted for elective cardiac surgery of American Society of Anesthesiologists (ASA) grade II and III, within the age group 1–12 years, and with a body weight up to 30 kg were allocated into two study groups using the sealed envelope method of randomization. The manuscript adheres to the consort guidelines. The anesthetist who would give anesthesia was different from the anesthetist who would observe the study variables. This study was conducted at a tertiary level of hospital. It is a prospective, randomized, double-blind, interventional study. The study period included from the date of approval till the sample size completion.

The sample size required was 30 in each group at 95% confidence and 80% power to verify the expected difference of 3.72±2.06 in early onset of sedation in both groups.

All the patients were randomly allocated into two groups (30 patients in each group).

(1) Group A (n=30): patients received ketamine 5 mg/kg IN (50 mg/ml vial)
(2) Group B (n=30): patients received midazolam 0.2 mg/kg IN (1 mg/ml vial).

Patients with renal failure, congestive heart failure, with a known allergy to the study drugs, with a history of neurological, psychiatric illness, and nasal anomalies or diseases (rhinitis) were excluded from the study. Patients having relative or absolute contraindication to the use of ketamine (arterial hypertension), increased intracerebral pressure, and convulsions were excluded.

Children were given ketamine and midazolam through a nasal atomizer in the presence of their parents in the preoperative room. Baseline HR, systolic BP, diastolic BP, and peripheral (SpO_2) by a monitor were recorded and subsequent readings were recorded at 5, 10, 15, 20, and 30 min after the drug instillation. After 30 min, the child was separated from his parents and taken into the operating room. In the mean time, children were observed for any side effects like nausea, vomiting, salivation, and respiratory depression. The separation score, sedation score, intravenous (i.v.) cannulation score, and score for face mask acceptance were also noted simultaneously after 30 min. Children with a score of 3 and 4 were considered good and excellent.

Drugs were administered by an independent anesthetist not involved in the study. The child's response to the drugs was observed by the sedation score adapted by Wilton and colleagues.

(1) Agitated

(2) Alert
(3) Drowsy
(4) Calm
(5) Asleep.

The separation score included the following:

(1) Crying/clinging.
(2) Crying but not clinging.
(3) Good.
(4) Awake excellent.

The i.v. cannulation score was graded as follows:

An empirical four-point scoring system was used for evaluation of acceptance of the i.v. cannula.

(1) Poor – 1 (terrified, crying)
(2) Fair – 2 (fear of needles, not assured)
(3) Good – 3 (slight fear of needle, easily reassured)
(4) Excellent – 4 (unafraid, accepts intravenous cannula).

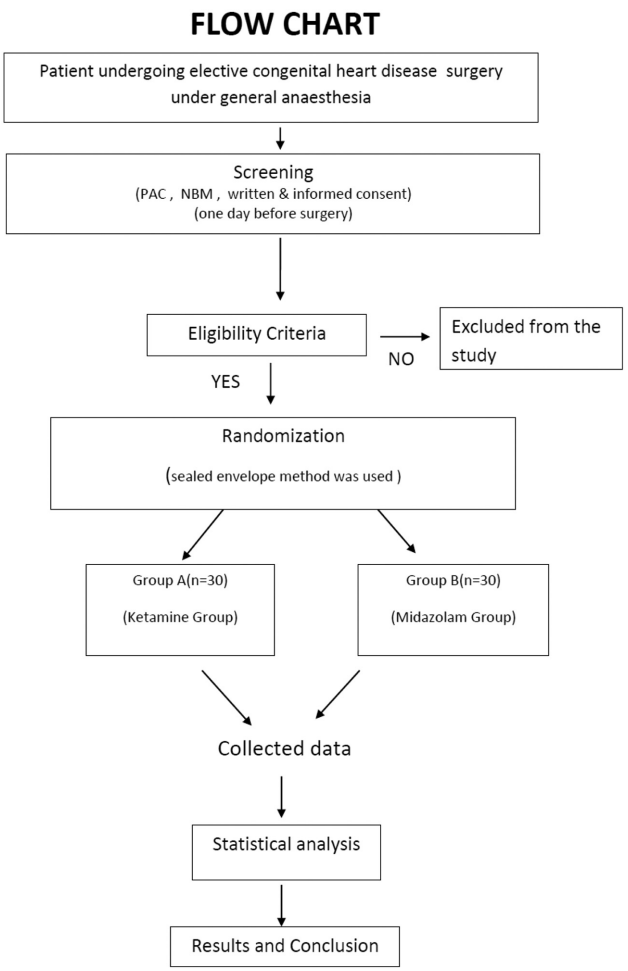
Face mask acceptance score was as follows:

(1) Agitated: refusal to accept.
(2) Fair: accepting after persuasion.
(3) Good: easily accepting.

General anesthesia was induced with etomidate 0.3 mg/kg, fentanyl 2 μg/kg, and rocuronium 0.9 mg/kg with appropriate size endotracheal tube placement. Maintenance of anesthesia was done with fentanyl 2 μg/kg/h, midazolam 0.15 mg/kg/h, vecuronium bromide, and sevoflurane inhalational agent. After total surgical correction, the patients were shifted to cardiac surgery intensive care unit for postoperative ventilation and care.

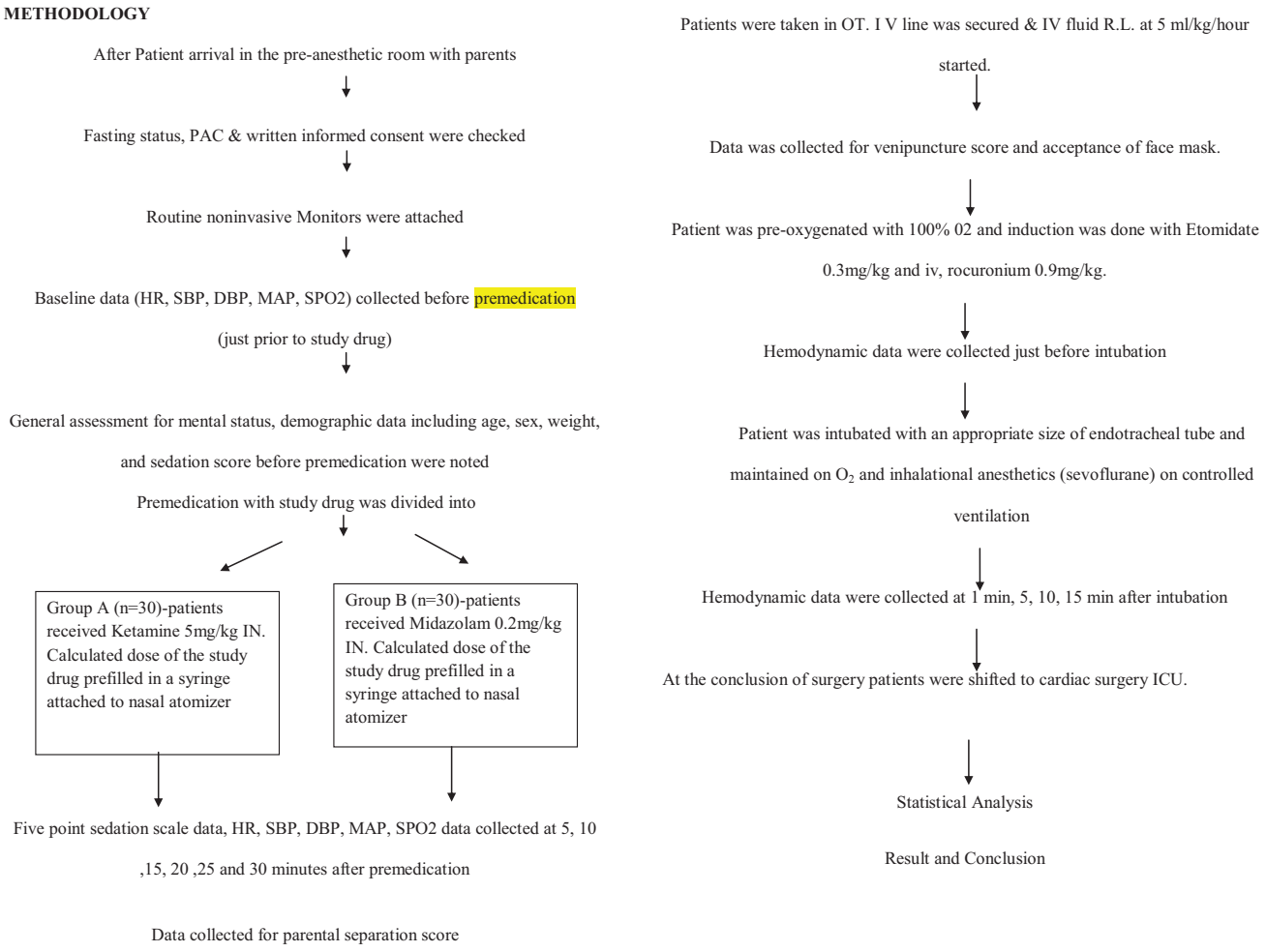
Statistical analysis

Statistical analysis was performed with the SPSS version 21 for windows statistical software package (SPSS Inc., Chicago Illinois, USA) after approval from the Institutional Ethical Committee and Review Board. The categorical data were presented as numbers (percent) and were compared among groups using χ^2 test. The quantitative data were presented as mean and SD and were compared by Student's *t*-test. Probability was considered significant if less than 0.05.



PAC, preanaesthetic checkup; NBM, nothing by mouth.

Methodology



Outcome variables

The outcome variables were as follows:

(1) Onset of sedation.
(2) Degree of sedation.
(3) Response to venipuncture.
(4) Acceptance of mask.

Results

Demographic profile

The demographic profile of the children in both groups was similar in terms of age, sex, weight, and ASA grade, without any statistically significant difference, as shown in Table 1. The most frequently performed procedure in this study was tetralogy of Fallot, as shown in Table 2.

Sedation score

The sedation scores were measured at baseline, 5, 10, 15, 20, 25, and 30 min. The mean sedation scores in ketamine group were 1.17, 1.97, 2.30, 2.73, 3.27, 3.60, and 3.77, respectively, whereas in the midazolam group, they were 1.07, 1.83, 2.70, 3.33, 3.77, 3.87, and 3.97, respectively. The values in both groups were compared, and the values at 10, 15, and 20 min showed significant differences in midazolam group compared with ketamine group ($P<0.05$). The midazolam group showed higher sedation score at 10 min, 15 min, and 20 min, as shown in Fig. 1.

Mean time of onset of sedation

In group B, 10% of cases showed onset of sedation within 5 min. Overall, 66.67% patients showed onset of sedation within 10 min and 23.33% of patients at 15 min. By 15 min, all the patients were sedated in group B as compared with group A, which showed complete sedation at 25 min of drug instillation ($P=0.0005$), which is statistically significant, as shown in Fig. 2.

Separation score

The mean separation score in the ketamine group was 2.83 and in the midazolam group was 3.00 ($P>0.05$).

Table 1 Demographic profiles and ASA grade of patients

	Group A		Group B		*P* value
	Mean	SD	Mean	SD	
Mean age (years)	7.37	3.83	6.92	3.62	0.644
Sex					
Male	20	66.67%	17	56.67%	
Female	10	33.33%	13	43.33%	
Mean weight (kg)	16.44	6.71	15.89	6.22	0.743
ASA					
Grade II	27	90.00%	25	83.33%	0.704
Grade III	3	10.00%	5	16.67%	

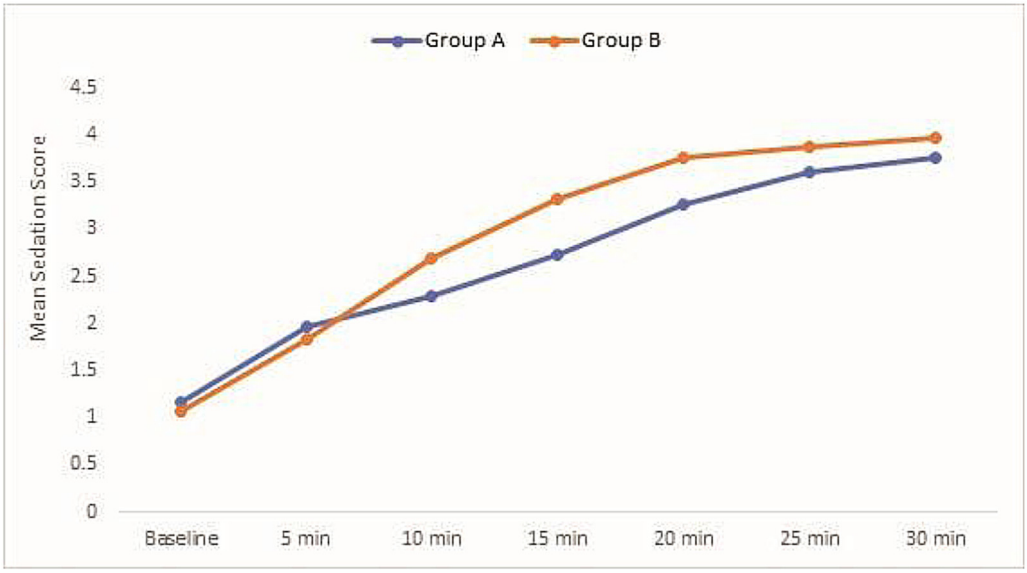
This table shows the demographic profile and ASA grade of patients, which were comparable without any statistical significance. ASA, American Society of Anesthesiologists.

Table 2 Distribution of surgical procedures

Sl. No.	Type of surgery	Group A: ketamine, *n* (%)	Group B: midazolam, *n* (%)	Total
1	TOF	10 (33.33)	8 (26.66)	18
2	VSD with PS	2 (6.66)	1 (3.33)	3
3	ASD with VSD	1 (3.33)	–	1
4	VSD	6 (20)	5 (16.66)	11
5	ASD with PS	2 (6.66)	1 (3.33)	3
6	DORV	2 (6.66)	–	2
7	TAPVC	1 (3.33)	1 (3.33)	2
8	ASD	4 (13.33)	6 (20)	10
9	COA	1 (3.33)	–	1
10	PDA	1 (3.33)	4 (13.33)	5
11	Tricuspid atresia	–	1 (3.33)	1
12	Severe PS	–	1 (3.33)	1
13	DORV with PS	–	1 (3.33)	1
14	TOF with PDA	–	1 (3.33)	1
	Total	30 (100)	30 (100)	60

This table shows distribution of surgical procedures; majority of patients underwent TOF surgeries. ASD, Atrial septal defect; COA, Co-arctation of aorta; DORV, double outlet right ventricle; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Figure 1



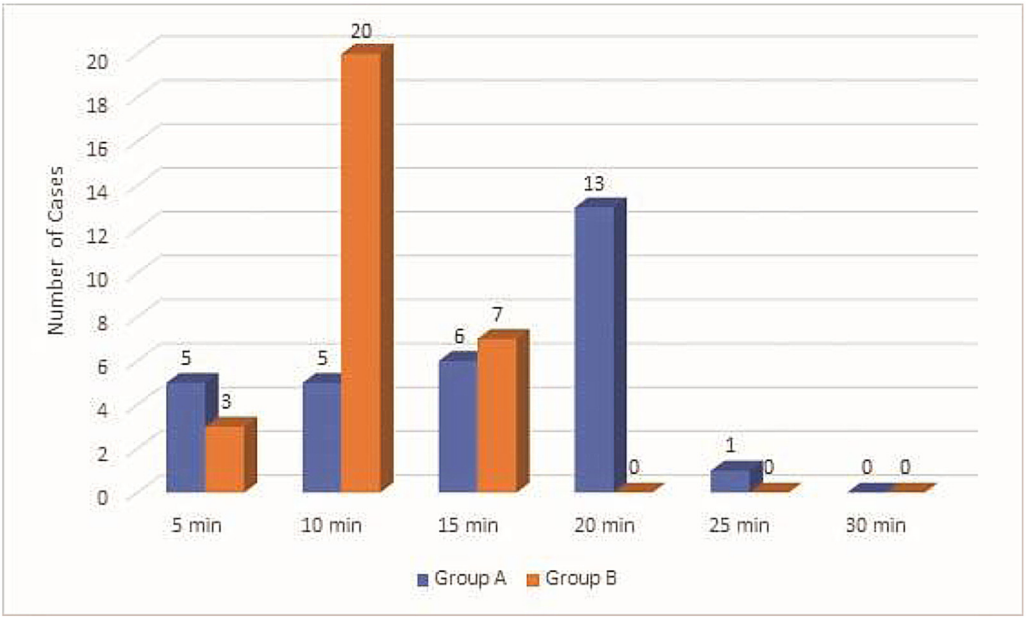
Comparison of sedation scores in both the groups. The value in both the groups were compared and the value at 10, 15, and 20 min showed significant differences in the midazolam group compared with the ketamine group ($P<0.05$). The midazolam group shows higher sedation score at 10, 15, and 20 min.

The separation score at 30 min were similar in both groups and did not show any statistical significance ($P>0.05$).

Intravenous cannulation score

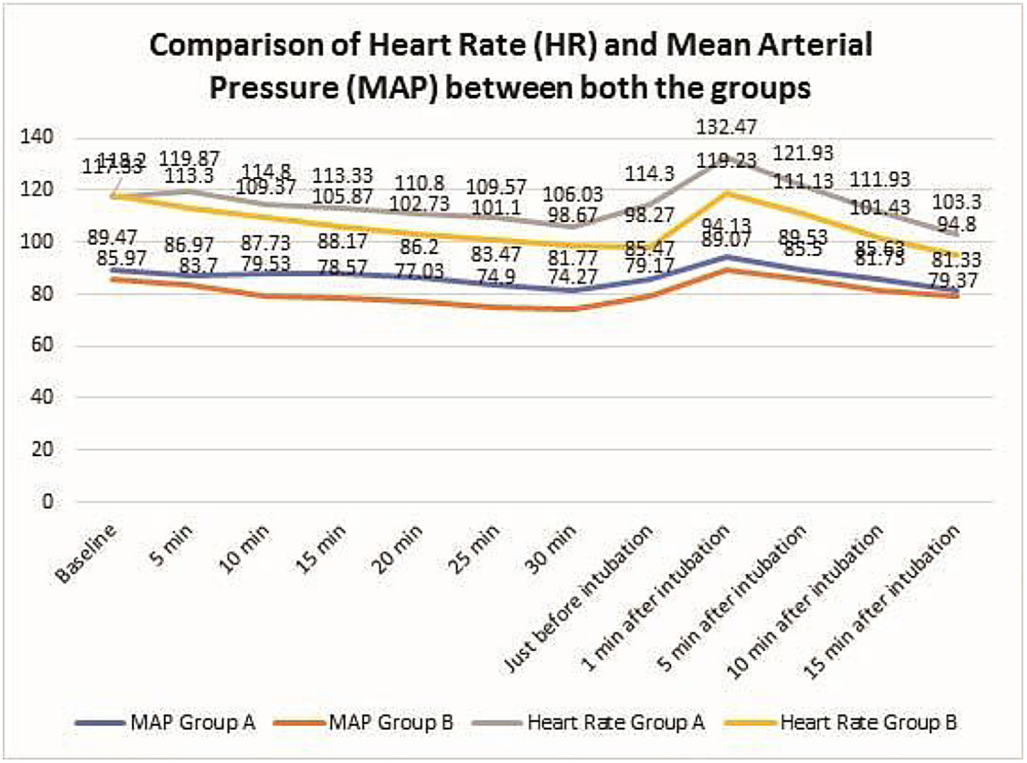
The mean i.v. cannulation score for ketamine group was 2.7 and for midazolam group was

Figure 2



Mean time of onset of sedation in both the groups. Mean time of onset of satisfactory sedation in the midazolam group was 10.66 min and in the ketamine group it was 15.16 min, which was statistically highly significant, as the *P* value was 0.0005 ($P<0.05$).

Figure 3



Comparison of heart rate and mean arterial pressure between both the groups.

3.03, which was statistically not significant (P=0.183).

The i.v. cannulation score at 30 min also did not show any significant difference (P>0.05).

Acceptance of face mask

Score for acceptance of facemask in ketamine group was 2.83 and was not statistically significant compared with midazolam group, which was 3.00 (P=0.528).

Heart rate

The baseline mean HR in group A was 117.33±16.61 and 118.20±17.12 beats per minute in group B. The mean HR was elevated in the group A after 5 min of IN administration and 1 and 5 min after intubation. It was elevated at all the levels as compared with the group B, with P value less than 0.05, as shown in Fig. 3.

Mean arterial pressure

The baseline mean arterial pressure (MAP) in group A was 89.47±11.78 and 85.97 in group B. The MAP showed a decrease in group B after 10, 15, 20, 25, 30 min, and just before intubation. The fall in mean MAP was from 89.47±11.78 mmHg to 81.33±7.59 mmHg in the group A and from 85.97±9.40 to 79.37 ±7.56 mmHg in the group B. This showed that the mean MAP remained clinically stable throughout the procedure. However, on intergroup comparison, group B showed significant fall in MAP at different time intervals till the time period just before intubation (P<0.05), as shown in Fig. 3.

Table 3 Side effects

	Group A (n=30), n (%)	Group B (n=30), n (%)
Nausea	6 (20.00)	0
Vomiting	6 (20.00)	0
Salivation	9 (30.00)	0
Res. Dys.	0	0

Res. Dys., respiratory depression.

Side effects

Group A showed a 20% incidence of patients with nausea and vomiting as compared with group B, which showed none (P=0.031). Overall, 30% of patients in group A had salivation and none in group B (P=0.004), which was statistically significant, as shown in Table 3.

Peripheral saturation

The mean baseline SpO_2 in group A was 87.63±14.50 and 90.53±11.72% in group B. There was no fall in the saturation from the baseline in both the groups, and this was statistically not significant, as shown in Table 4.

Discussion

The IN route of drug administration has been previously used for a variety of medications, like vaccines, antihistaminic, decongestants, opioids, benzodiazepines, and migraine therapies. There are commercial preparations of IN therapies with an in-built atomizer (IN decongestants, topical steroids or Flumist vaccine), or parenteral preparations of certain medications may be administered using a MAD. However all parenteral drugs cannot be administered IN, as the chemical property, pH, and concentration vary individually which affects the absorption and effect of the drugs.

The nasal turbinates have a large vascular surface area through which drugs or medications can be absorbed directly into the bloodstream. The olfactory region of

Table 4 SpO_2

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	87.63	14.50	90.53	11.72	0.397
5 min	88.40	13.16	90.97	11.28	0.420
10 min	88.87	12.42	91.07	11.03	0.471
15 min	89.40	11.60	91.60	10.46	0.443
20 min	89.87	11.32	91.77	10.16	0.496
25 min	89.90	11.22	91.93	9.88	0.459
30 min	89.90	11.73	92.43	9.11	0.354
Just before intubation	92.90	9.83	93.00	8.67	0.966
1 min after intubation	93.97	8.11	93.27	8.43	0.744
5 min after intubation	94.43	7.72	93.83	7.97	0.768
10 min after intubation	94.57	7.42	93.90	7.97	0.738
15 min after intubation	91.87	17.01	93.93	7.83	0.547

There was no significant differences in SpO_2 in both the groups.

the roof of the nasal cavity also has a role in the transmission of medications directly into the CNS.

Advantages of IN drug administration over oral medication are that, they are noninvasive, easily administered, generally well tolerated and have a rapid onset of sedation due to higher bioavailability and bypassing the first - pass hepatic metabolism. As compared with the SL route, it is better in terms of consistency and bioavailability (as seen in patients who cannot swallow and have excessive salivary secretions).

IN route is also an alternate route when i.v. access is not available. It is preferred to subcutaneous and i.m. routes during crises when there is impaired circulation to the extremities and subcutaneous tissue. Limitations include use of lipophilic drugs, medications outside the pH range of nasal mucosa (5.0–7.0), nasal congestion, bleeding, or obstruction in the nose.

Study by Baldwa *et al*. has suggested that the ideal volume per nostril is 0.2–0.3 ml. In practice, 0.5-ml volume for single administration into one nostril (in adults and children) and 0.1 in neonates is advised. Larger volume should be divided, that is, half in each nostril.

IN medication is contraindicated in patients with upper respiratory infection, recent exposure to radiation to head and neck, having coagulopathy, thrombocytopenia, neutropenia, and having a friable mucosa.

According to Frank *et al*. [10], there was an increase in HR in the midazolam (0.2 mg/kg) alone and midazolam (0.2 mg/kg) with ketamine (1 mg/kg) combination as compared with midazolam (0.2 mg/kg) with ketamine (2 mg/kg) combination groups at induction and after arrival in the recovery room. Audenaert *et al*. [15] and colleagues showed that IN dose of racemic ketamine 5 mg/kg and midazolam 0.2 mg/kg did not produce significant cardiovascular and respiratory side effects.

Shreyathi *et al*. [11] showed decrease in heart rate of approximately 10% in the midazolam group. Moreover, the respiratory rate was decreased in this group. However, ketamine group showed no change.

Chakravarthy *et al*. [12] showed that IN midazolam achieved better sedation and separation scores as compared with the p.o. route. Therefore, IN route is superior to p.o. route for midazolam administration in pediatric day care surgeries. Ghajari *et al*. [16] showed that IN midazolam and ketamine combination produced a satisfactory sedation level in children for dental procedures as compared with the p.o. route.

Gharde *et al*. [14] showed that IN midazolam produced a decrease in BIS values and increase in sedation scores and also was seen in the ketamine and midazolam combination. BIS value remained high in the ketamine group even though they were asleep (excellent sedation).

In our study, midazolam showed earlier onset of sedation as compared with ketamine. The sedation score was higher in the midazolam group at 15 min than ketamine group (P=0.01). Onset of sedation started at 5 min, and all the patients were completely sedated by 15 min. However, in the ketamine group, the onset of sedation started at 5 min and was completed in all the patients by 25 min. Similar results were found by Pant *et al*. [7] and Khatavkar and Bakshi *et al*. [17]. Wilton *et al*. [6] found that significant sedation developed from 5 min with 0.2 mg/kg to 10 min with 0.3 mg/kg with midazolam. Otsuka *et al*. [18] reported onset of sedation of 4 min with 0.2 mg/kg, whereas Malinovsky *et al*. [19] found that adequate sedation with midazolam developed in 7.7±2.4 min with nasal and 12.5±4.9 by rectal routes. They also showed that plasma concentration of midazolam was 100 ng/ml within 6 min and maximum concentration at 12 min with midazolam 0.2 mg/kg. Mean plasma concentration of ketamine peaked at 496 ng/ml at 20 min with 3 mg/kg and 2104 ng/ml at 21 min with 9 mg/kg nasally [20]. However, Shreyathi *et al*. [11] concluded that IN ketamine achieved better quality of sedation enabling easier parenteral separation. Midazolam is rapidly absorbed from the highly vascular nasal mucosa directly into the systemic circulation and produces onset of sedation action within minutes. It produces rapid onset of action because of the direct links between the nasal mucosa and brain via the perineurium of the trigeminal and olfactory nerves [20].IN ketamine was associated with more side effects like salivation, nausea, and vomiting.

A single disadvantage of atomized midazolam is that it produces a moderate transient burning of the nasal mucosa, which is attributed to the acidic pH, which can be overcome by using it as a solution in cyclodextrin [21].

Conclusion

Both midazolam and ketamine nasally are an effective pediatric premedication. Midazolam has an early onset of sedation and is associated with fewer side effects and

can be safely used in patients having congenital heart disease undergoing cardiac surgery.

No data, text, or theories by others are presented as if they were the author's own. Proper acknowledgements of other's work have been given (this includes material that is closely copied, summarized, and/or paraphrased), and quotation marks are used for verbatim copying of material. Permissions have been secured for material that is copyrighted.

The authors confirm that all authors have made substantial contributions to all of the following: the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted, and sound scientific research practice.

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Conflicts of interest
There are no conflicts of interest.

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