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Intranasal Drops Of Ketamine versus Midazolam for Preoperative Pediatric Sedation In General Surgical Procedures

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A B S T R A C T

Premedication in pediatric age group presents challenging situation. The young children are not fully able to understand the necessity for their surgery. Fear of operating theater, injections and separation from parents prior to anesthesia produce traumatic experiences in tend mind of young children. In the past, psychological preparation was only used before surgery. Later on, many drugs like morphine, paraldehyde, meperedine, diazepam and barbiturates have been used.

The aim of this study is to compare the effects and the side effects of intranasal ketamine versus midazolam administrated for pediatric premedication.

In this study we evaluate and compare intranasal ketamine versus midazolam as premedication in pediatric anesthesia according to the onset of sedation, degree of sedation , easy cannulation, acceptance of mask before intubation, hemodynamic changes regarding heart rate, mean blood pressure, respiratory rate and intraoperative oral secretion grading.

This study was a double blinded randomized controlled study which was carried out at ibn sina Hospitals from February 2018 to January 2020. This study included 54 Child aged from 5 to 8 years admitted to the ibn sina Hospitals for general surgical procedures e.g herniotomy, tonsillectomy and hypospadias etc. All the patients completed the study.

Regarding the onset of sedation: the result of this study found that onset of sedation was earlier in the intranasal midazolam as The onset of sedation for ketamine group and midazolam group was respectively 14.96 ± 3.1 and 8.16 ±2.1. Most patients became sedated 6-10 minutes when compared to intranasal ketamine as most patients sedated after 16-20 minutes.

We recommend the use of intranasal ketamine and midazolam as preoperative pediatric sedatives to decrease anxiety of children before start of general anesthesia to overcome drawbacks of pediatric anxiety and fear postoperatively and Intranasal midazolam was better than ketamine according to onset of sedation which started earlier and intraoperative secretions were scanty with midazolam in comparison with ketamine.

1.0 Inroduction

Premedication in pediatric age group presents challenging situation. The young children are not fully able to understand the necessity for their surgery. Fear of operating theater, injections and separation from parents prior to anesthesia produce traumatic experiences in tend mind of young children (Beeby and Hughes, 1980).In the past, psychological preparation was only used before surgery. Later on, many drugs like morphine, paraldehyde,

meperedine, diazepam and barbiturates have been used. Various routes of administration (oral -intramuscular-rectal) have been tried. There is still no ideal premedication or route of administration has been described (Narendra et al., 2015). An ideal premedicant should act rapidly with adequate sedation and analgesia; cause less respiratory depression, no postoperative sickness and no hypersensitivity reaction. Likewise the ideal route should be atraumatic, less unpleasant and should require little co-operation (Louon and Reddy., 1994). Intranasal premedication provides good condition for induction of anesthesia in preschool children. (Wilton et al. 1988) was the first one who described intranasal midazolam. Premedication with intranasal ketamine or midazolam provide good condition for sedation in preschool age (Weber et al, 2003). The aim of this study is to compare the effects and the side effects of intranasal ketamine versus midazolam administrated for pediatric premedication. In this study we evaluate and compare intranasal ketamine versus midazolam as premedication in pediatric anesthesia according to the onset of sedation, degree of sedation, easy cannulation, acceptance of mask before intubation, hemodynamic changes regarding heart rate, mean blood pressure, respiratory rate and intraoperative oral secretion grading.

Pediatric Anxiety

Anxiety in children undergoing surgery is considered challenging situation for anesthesia. It is characterized by feeling of nervousness, apprehension, tension, and worry that may be represented in various forms (Kain et al., 1996). Postoperative behaviors such as new onset enuresis, feeding difficulties, apathy, withdrawal, and sleep disturbances, may also result from anxiety before surgery (Perry et al., 2012). In fact, studies have indicated that up to 60% of all children undergo surgery may present with negative behavioral changes two weeks postoperatively (Kotiniemi et al., 1997). Variable factors such as age, temperature, and anxiety of the child and parent in the preoperative period have been identified as predictors for these behavioral changes. Preoperative Preparation of Pediatric Anxiety Anxiety is the most commonly reported emotion of children when confronted with surgery or stressful medical procedures and a risk factor for pre, intra and post-operative complications (Franck and Spencer 2005). It is estimated that 60% of children suffer from anxiety in the preoperative period (Vagnoli et al., 2005). Excessive anxiety and stress can affect children's physical and psychological health and it has been associated with number of negative behaviors (e.g. agitation, crying and spontaneous urination), also it hinders their ability to cope with surgery and may also inhibit their post- operative recovery (Li and Lopez 2007). Parental presence during induction of anesthesia is very important. Parents and children prefer to stay together during medical procedures such as immunizations, dental treatment, and induction of anesthesia. However, examination of Holter data revealed no signs of ischemia or rhythm disturbance during this period on both child and parents.

Mods of preoperative pediatric sedation

1-Non-Pharmacological Management: Several behavioral interventions have been used successfully to reduce preoperative anxiety and among them development of coping skill was found to be most effective, Other modes include modeling, therapeutic play, operating room tour and printed material, music therapy, clown nurse or clown doctors therapy (Yun et al., 2015). Coping therapy may include deep breathing, counting, watching a video or handheld game. Distraction is very effective form of coping for young children (Moadad et al., 2015).A child-life specialist (or play specialist) may have an important role in this respect . 2- Pharmacological Agents: Numerous sedative pharmacological agents currently administered to children as premedicants to facilitate the induction of anesthesia. Their appropriateness in different clinical situations is dispersed widely within the literature and therefore not easily comparable (Cote and Wilson 2006). Premedication is drug treatment given to a patient usually before medical or surgical procedures. The aim of premedication in children and young people is to produce a relaxed state with reduced anxiety and increased compliance, allowing the patient to tolerate and co-operate with the necessary procedure (Yuen et al., 2008). Ketamine Ketamine is considered a dissociative anesthetic. This means that the drug distorts the users' perception of sight and sound and produces feelings of detachment from the environment and the one himself (Dotson et al., 1995). Ketamine is phencyclidin agent acting on the central nervous system as antagonist at N-Methyl- D- Aspartate (NMDA) receptors inhibiting cerebral excitatory pathways (Turhanoglu et al., 2003). Ketamine also interacts with opioid receptors and has some local anesthetic action. It can be used to induce general anesthesia and to provide effective analgesia in both acute and chronic pain. It has cardiovascular stimulation with mild respiratory depression but with preservation of both pharyngeal and laryngeal reflexes (Pai and Heining 2007). Intranasal ketamine After IV, intranasal is the second-most common route of administration for ketamine. Intranasal ketamine attenuates pain in the emergency room in children (Graudins et al., 2015). Intranasal ketamine also reduces the severity of pain in migraine (Afridi et al., 2013). Wink et al. reported a 29-year-old woman with autism who was treated with intranasal ketamine (20–60 mg) on 12 dosing occasions across 6 weeks. She showed improvements in mood, social interactions, flexibility, tolerance of changes in routine, motivation and concentration. Adverse events were mostly mild; the most prominent was headache, which lasted for up to 10 hours after a treatment. A case report also showed benefits with intranasal ketamine in depression (Wink et al., 2014). In a randomized, double-blind, saline-controlled, crossover trial conducted in 20 patients with major depression, Lapidus et al. found that a single intranasal dose of ketamine (50 mg) outperformed saline by 7.6 points on the Montgomery-Asberg Depression Rating Scale as assessed 24 hours after dosing; the response rate was 44% vs 6%, respectively. Anxiety ratings also decreased significantly more with ketamine. However, there was no

significant separation between ketamine and saline at 3 and 7 days post-treatment. In this study, intranasal ketamine was well tolerated, with few, mild, and very transient adverse effects such as feelings of unreality. There was also a small and transient increase in systolic blood pressure (by 7.6 mm Hg at 40 minutes) (Lapidus et al., 2014). Dose: The dose of intanasal ketamine 5 mg per kilogram. The calculated dose for each patient was administered in each nostril divided equally 30 min. before induction of anesthesia containing respective drugs were administered drop by drop slowly over 3–4 min and children were asked to put their tongue out and instructed not to swallow. For the next30 min patients were asked to maintain supine position with slight head low (Narendra et al., 2015). MIDAZOLAM Midazolam is a water-soluble benzodiazepine available as a sterile, non-pyrogenic parenteral dosage form for intravenous or intramuscular injection. Each mL contains midazolam hydrochloride equivalent to 1 mg or 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% edetate disodium with 1% benzyl alcohol as preservative, and sodium hydroxide and/or hydrochloric acid for pH adjustment. PH 2.9-3.7.Midazolam is a white to light yellow crystalline compound, insoluble in water. The hydrochloride salt of midazolam, which is formed in situ, is soluble in aqueous solutions. Midazolam is a short-acting benzodiazepine in adults with an elimination half-life of 1.5-2.5 hours. In the elderly, as well as young children and adolescents, the elimination half-life is longer (Rosenbaum et al., 2009). Midazolam is metabolized into an active metabolite alpha1-hydroxymidazolam. Intranasal Midazolam Intranasal midazolam is a new route for pediatric sedation preoperatively .Intranasal midazolam has been used as a sedative/anxiolytic and an antiepileptic (Wolfe and Braude 2010). It has become well accepted as a means of providing sedation for radiologic imaging and prior to induction of anesthesia, alone or in combination intranasal regimens. In 2012, Baldwa and colleagues compared the effects of intranasal midazolam doses of 0.2 and 0.3 mg/kg as a premedication in 60 children undergoing elective surgery. The two doses were compared for the level of sedation and ease of parental separation. Patients were also graded according to their acceptance of the dose and willingness to have their face mask placed. Overall, acceptance of the intranasal route was rated as good in 23.4% of children, fair in another 43.4%, and poor in 33.4%. There was a significantly higher percentage of patients in the 0.3 mg/kg group who were adequately sedated at 10 minutes (70% versus 40% in the 0.2 mg/kg group, $p = 0.04$). Separation from parents was also rated as easier in the higher dose group, with 66.7% of patients achieving a score of excellent, good, or fair at 10 minutes, compared to only 30% of the children given the lower dose ($p = 0.005$). Transient adverse effects were common, with 60% of children experiencing nasal irritation, 42% having conjunctival congestion, and 30% having increased salivation. There were no cases of oxygen desaturation or bradycardia (Baldwa et al., 2012).

Patients and Methods

Site of the study: This study was a double blinded randomized controlled study which was carried out at ibn sina Hospitals from February 2018 to January 2020.

A- Patient: Population of the study:
This study included 54 Child aged from 5 to 8 years admitted to the ibn sina Hospitals for general surgical procedures e.g herniotomy, tonsillectomy and hypospadias etc. All the patients completed the study.
Sample Size:
95% Configuration
80% Power
1:2 Unexposed: Exposed
58% Disease in exposed
3,87 Risk ratio
7,83 Odds ratio
18 Sample size unexposed
36 Exposed
54 Total

Inclusion criteria:
1. Age: children from 5 to 8 years ASA class I and II .
2. Sex: male & female.
3.Children undergoing different surgical procedures.
Exclusion criteria:
1-Refusal of the parents or caregivers.
2-Patients with known allergy to study
3- Congenital anomalies in the nose.
4-Rhinorrhea and upper respiratory tract infection.
5- Patients with heart diseases.

B- Method: After approval by ethical committee and obtaining informed parents' consent, Children would be assigned randomly to receive either ketamine 5 mg/kg or midazolam 0.2mg/kg intranasal drops or intranasal normal saline. All patients would undergo general assessment for mental status, weight, pulse, blood pressure, nasal condition and every child will be investigated by routine laboratory investigations (CBC, PT, PTT, INR, liver and kidney functions).
The patients were randomly allocated into 3 equal groups (18 patients each) using closed envelops.
Group I: Ketamine group (K group) (18 patients): patients received intranasal ketamine drops as premedication (5mg / kg intranasal drops in 2 ml syringe) 30 minutes preoperatively.
Group II: Midazolam Group (M group) (18 patients): patients received intranasal midazolam drops as premedication (0.2 mg/kg intranasal drops in 2 ml syringe) 30 minutes preoperatively.
Group III: Control Group (C group) (18 patients): patients received intranasal normal saline drops (in 2 ml syringe) 30 minutes preoperatively.
The calculated dose for each patient would be administrated in each nostril divided equally 30 minutes before induction of anesthesia containing respective drugs. The drug would be administrated drop by drop slowly over 3-4 minutes and the child would be asked to put his tongue out and not to swallow. For the next period, patients would

be asked to maintain supine position with slight head down.Before induction of anesthesia in the operating theater, each patient would be observed for onset of sedation, degree of sedation, hemodynamic changes, response to venipuncture and acceptance of the mask whether readily, with persuasion or refuse. If any child did not achieve at least grade II of ramsay sedation scale, we would start to introduce face mask with sevoflurane to achieve sedation at least grade II. General anesthesia was standardized for all patients to minimize conflicting factors. Preoxygenation for 1 minute and induction with 1-2 mg propofol followed by suxamethoniuin 2mg per Kg. All patients were maintained with oxygen isoflurane (MAC 1-2%), pancronium 0.08 mg per kg. The lungs were ventilated mechanically(tidal volume 5- 6 ml per kg, RR 14 per minute and I:E ratio 1:2) and maintained P CO2 between 32-36) .At the end of the surgery ,reversal done with atropine 0.02 mg per kg and neostigmine 0.05 mg per kg and endotracheal tube were removed. Intraoperatively, oral Secretions were observed.
Points of evaluation will include:

1-Onset of sedation from time of administration of the drug intranasal.

2-Hemodynamic changes regarding heart rate , mean blood pressure and respiratory rate.

3-Degree of sedation according to Ramsey sedation scale :

Score	Observation
1	Anxious, agitated or restless
2	Cooperative, oriented and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

Fig. 10: Ramsay sedation scale De Jonghe B et al.,(2003)

4-Response to venipuncture:
Grade I: Crying, uncooperative, not able to start IV line.
Grade II: Withdrawal for painful stimuli but allows to cry.
Grade III: Calm no quantity, no-withdrawal for painful stimuli and IV cannulation.
Grade IV: Asleep - No response to painful stimuli and IV cannulation (Narendra et at, 2015).
5-Acceptance of the mask (Refuse- Accepts with persuasion- Accepts readily).
6-Intraoperative oral secretion grading (copious-moderate-mild-no secretions).

Statatical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann Whitney U test was used to compare between two groups of non-normally distributed variables. One Way ANOVA test was used to compare between more than two groups of normally distributed variables while Kraskall Wallis H test was used for non- normally distributed variables. Levene's test was used for testing homogeneity of variance; Post hoc comparison was done by Tamhane's T2 test according to homogeneity of variance. Repeated measures ANOVA test was used to compare more than two repeated measurements of normally distributed variables while Friedman's test was used for non- normally distributed variables; pairwaise comparison with baseline level was done by paired t-test or Wilcoxon signed ranks test according to normality. Percent of categorical variables were compared using Chi-square test. All tests were two sided. p-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥0.05 was considered statistically insignificant (NS).

Results

Table (1): Comparison between studied groups as regard age (years).

	Placebo (N=18)	Ketamine (N=18)	Midazolam (N=18)	p-value (Sig.)	p1- value (Sig.)	p2- value (Sig.)	p3- value (Sig.)
Age (years)							
Mean±SD	6.50 ± 1.09	5.94 ± 1.05	6.17 ± 1.20	0.310··	0.344	0.774	0.914
Median (Range)	6.50 (5 – 8)	6 (5 – 8)	6 (4 – 8)	(NS)	(NS)	(NS)	(NS)

Kraskall Wallis H test- p-value <0.05 is significant
Sig.: significance-
p1-value: difference between Placebo and Ketamine
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.

Table (2): Comparison between studied groups as regard types of operations.

Type of operation	Placebo (N=18)		Ketamine (N=18)		Midazolam (N=18)		p-value (Sig.)	p1- value (Sig.)	p2- value (Sig.)	p3- value (Sig.)
	No.	%	No.	%	No.	%				
Abscess	0	0%	1	5.55%	0	0%	0.031‡	0.172	0.066	0.106
Arthroscope	0	0%	0	0%	1	5.6%	(NS)	(NS)	(NS)	(NS)
Circumcision	0	0%	0	0%	2	11.1%				
Fracture radius	0	0%	2	11.1%	0	0%				
Hernia	7	38.9%	3	16.7%	3	16.7%				
Hirshspring	0	0%	0	0%	1	5.55%				
Hydrocele	0	0%	0	0%	1	5.55%				
Hypospedius	0	0%	1	5.55%	3	16.7%				
Mastoid	5	27.8%	2	11.1%	1	5.55%				
Orchipexy	4	22.2%	3	16.7%	3	16.7%				
PCNL	0	0%	0	0%	2	11.1%				
Splenectomy.	0	0%	0	0%	1	5.6%				
Tonsillectomy	2	0%	6	33.3%	0	0%				

‡ Chi-square test.
p-value >0.05 is non-significant. Sig.: non-signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam

Table (3): Comparison between studied groups as regard Onset of sedation (min.).

Onset of sedation (after 10min.)	Placebo© (N=18)	Ketamine (k) (N=18)	Midazolam(M) (N=18)	p- value (Sig.)	p1- value (Sig.)	p2- value (Sig.)	p3- value (Sig.)
Mean±SD	---	16.61 ± 2.97	10.78 ± 2.64	---	---	---	<0.001
Median (Range)	0	18 (12 – 20)	12 (7 – 14)				(HS)

Mann Whitney U test.
p-value <0.05 is significant Sig.: signficance.
p1-value: difference between Placebo and Ketamine. p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.

Table (4): Comparison between studied groups as regard degree of sedation after 10 minutes.

Degree of sedation	Placebo (N=18)		Ketamine (N=18)		Midazolam (N=18)		p-value (Sig.)	p1- value (Sig.)	p2- value (Sig.)	p3- value (Sig.)
	No.	%	No.	%	No.	%				
No sedation	18	100%	0	0%	0	0%	<0.001 ‡	<0.001	<0.001	0.940
Score 1	0	0%	1	5.6%	1	5.6%	(HS)	(HS)	(HS)	(NS)
Score 2	0	0%	6	33.3%	4	22.2%				
Score 3	0	0%	9	50%	10	55.6%				
Score 4	0	0%	1	5.6%	2	11.1%				
Score 5	0	0%	1	5.6%	1	5.6%				
Mean±SD	0 ± 0		2.72 ± 0.89		2.89 ± 0.90		<0.001	<0.001	<0.001	0.927
Median (Range)	0 (0 – 0)		3 (1 – 5)		3 (1 – 5)		(HS)	(HS)	(HS)	(NS)

‡ Chi-square test.
Kraskall Wallis H test.
p-value <0.05 is significant Sig.: signficance.
p1-value: difference between Placebo and Ketamine. p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam

Table (5): Comparison between studied groups as regard Venipucture grading**.**

Venipucture grading	Placebo (N=18)		Ketamine (N=18)		Midazolam (N=18)		p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
	No.	%	No.	%	No.	%				
0	18	100%	0	0%	0	0%	<0.001‡	<0.001	<0.001	0.710
Grade 1	0	0%	1	5.6%	1	5.6%	(HS)	(HS)	(HS)	(NS)
Grade 2	0	0%	11	61.1%	10	55.6%				
Grade 3	0	0%	5	27.8%	7	38.9%				
Grade 4	0	0%	1	5.6%	0	0%				

‡ Chi-square test.
p-value <0.05 is significant Sig.: signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.

Table (6): Comparison between studied groups as regard acceptance of mask**.**

Acceptance of mask	Placebo (N=18)		Ketamine (N=18)		Midazolam (N=18)		p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
	No.	%	No.	%	No.	%				
Refuse	18	100%	1	5.55%	0	0%	<0.001‡ (HS)	<0.001 (HS)	<0.001 (HS)	0.533 (NS)
Accept with persuation	0	0%	7	38.9%	6	33.3%				
Accept readily	0	0%	10	55.6%	12	66.7%				

‡ Chi-square test.
p-value <0.05 is significant Sig.: signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam,.
p3-value: difference between Ketamine and Midazolam.

Table (7): Comparison between studied groups as regard intraoperative secretion grade**.**

Intraoperative secretion grade	Placebo (N=18) No.	%	Ketamine (N=18) No.	%	Midazolam (N=18) No.	%	p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
No	18	100%	1	5.55%	9	50%	<0.001	<0.001	0.002	0.002
Mild	0	0%	6	33.3%	5	27.8%	(HS)	(HS)	(S)	(S)
Moderate	0	0%	3	16.7%	4	22.2%				
Copious	0	0%	8	44.4%	0	0%				

‡ Chi-square test.
p-value <0.05 is significant Sig.: signficance.
p1-value: difference between Placebo and Ketamine
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.

Table (8): Comparison between studied groups as regard mean arterial blood pressure (mmHg).

MAP (mmHg)	Placebo (N=18)	Ketamine (N=18)	Midazolam (N=18)	p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
0 min							
Mean±SD	71.66 ± 6.30	77 ± 2.84	65.22 ± 3.19	<0.001	0.010	0.002	<0.001
Median (Range)	73.50 (60 – 80)	76.50 (72 – 85)	65.50 (60 – 70)	(HS)	(S)	(S)	(HS)
10 min							
Mean±SD	71.66 ± 6.30	79.83 ± 3.27†	65.05 ± 3.03	<0.001	<0.001	0.002	<0.001
Median (Range)	73.50 (60 – 80)	79.50 (75 – 88)	65 (61 – 72)	(HS)	(HS)	(S)	(HS)
20 min							
Mean±SD	71.66 ± 6.30	82.27 ± 3.54†	65.61 ± 2.61	<0.001	<0.001	0.003	<0.001
Median (Range)	73.50 (60 – 80)	81 (78 – 90)	65 (61 – 72)	(HS)	(HS)	(S)	(HS)
p-value (Sig.)	1.000§ (NS)	<0.001§ (HS)	0.310** (NS)				

Kraskall Wallis H test.
* One Way ANOVA test.
§ Friedman's test.
** Repeated measure ANOVA test. p-value <0.05 is significant
Sig.: signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.
† significant difference when compared to baseline level.

Table (9): Comparison between studied groups as regard heart rate in different times (b/min).

HR (b/min)	Placebo (N=18)	Ketamine (N=18)	Midazolam (N=18)	p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
0 min							
Mean±SD	103.72 ± 3.72	107.27 ± 3.61	103.61 ± 2.85	<0.001	0.019	0.999	0.006
Median	102.50	108	102.50	(HS)	(S)	(NS)	(S)
(Range)	(98 – 110)	(100 – 113)	(100 – 110)				
10 min							
Mean±SD	103.72 ± 3.72	115.33 ± 4.29†	102.61 ± 3.03	<0.001	<0.001	0.704	<0.001
Median	102.50	115	101	(HS)	(HS)	(NS)	(HS)
(Range)	(98 – 110)	(105 – 123)	(100 – 108)				
20 min							
Mean±SD	103.72 ± 3.72	121.38 ± 5.32†	102.38 ± 2.17	<0.001*	<0.001	0.489	<0.001
Median	102.50	121	102.50	(HS)	(HS)	(NS)	(HS)
(Range)	(98 – 110)	(110 – 129)	(98 – 106)				
p-value	1.000§	<0.001**	0.443§				
(Sig.)	(NS)	(HS)	(NS)				

Kraskall Wallis H test.
* One Way ANOVA test.
§ Friedman's test.
** Repeated measure ANOVA test.
p-value <0.05 is significant
Sig.: signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.
† significant difference when compared to baseline level

Table (10): Comparison between studied groups as regard respiratory rate at different times (/min).

RR (/min)	Placebo (N=18)	Ketamine (N=18)	Midazolam (N=18)	p-value (Sig.)	p1-value (Sig.)	p2-value (Sig.)	p3-value (Sig.)
0 min							
Mean±SD	21.11 ± 1.18	18.88 ± 1.18	22.27 ± 0.89	<0.001	<0.001	0.006	<0.001
Median (Range)	21 (20 – 23)	18.50 (17 – 21)	22 (21 – 24)	(HS)	(HS)	(S)	(HS)
10 min							
Mean±SD	21.11 ± 1.18	22.05 ± 1.34†	21.61 ± 1.19†	0.120	0.094	0.517	0.661
Median (Range)	21 (20 – 23)	22 (20 – 24)	22 (20 – 24)	(NS)	(NS)	(NS)	(NS)
20 min							
Mean±SD	21.11 ± 1.18	24.61 ± 1.64†	22 ± 1.18	<0.001	<0.001	0.090	<0.001
Median (Range)	21 (20 – 23)	24.50 (22 – 27)	22 (20 – 24)	(HS)	(HS)	(NS)	(HS)
p-value	1.000§	<0.001§	0.351§				
(Sig.)	(NS)	(HS)	(NS)				

Kraskall Wallis H test.
* One Way ANOVA test.
§ Friedman's test.
** Repeated measure ANOVA test.
p-value <0.05 is significant
Sig.: signficance.
p1-value: difference between Placebo and Ketamine.
p2-value: difference between Placebo and Midazolam.
p3-value: difference between Ketamine and Midazolam.
† significant difference when compared to baseline level.

Discussion

Preoperative anxiety in unpremedicated children was a challenging situation. First, they were very afraid of being separated from their parents and secondly they were worried about physical harm like needle puncture or intravenous line insertion. Children aged 5 to 8 years were especially vulnerable to this problem, since their understanding is limited. The fact that preoperative anxiety in children could lead to postoperative maladaptive behaviors in the form of eating problems, bad dreams, enuresis, increased fear of doctors and hospital was well known. Hence all pediatric patients were premedicated in order to decrease preoperative anxiety, allow smooth induction, and prevent postoperative psychological insult and behavioral changes (Kain *et al*., 1997a).

The route of administration for premedication in pediatric age group should also be considered carefully. Intra muscular injections were painful, oral premedication in gastro intestinal disturbance often rejected by small children. Children and their parents were very reluctant to allow rectal administration of drugs. The intra nasal route administration of pre medications had been used successfully and safely by different researchers (Danie*l et al.*, 2004).

Since the use of nose drops was widely known in general public, this route could be well accepted by children and their parents for premedication administration. Administration of s-ketamine and midazolam was an appropriate premedication in preschool children.

This study compared the effect of intranasal ketamine and intranasal midazolam as preoperative sedation drugs regarding the onset of sedation, hemodynamic changes, degree of sedation, venipuncture, acceptance of mask and intraoperative oral secretion grading.

Regarding the onset of sedation: the result of this study found that onset of sedation was earlier in the intranasal midazolam as The onset of sedation for ketamine group and midazolam group was respectively 14.96 ± 3.1 and 8.16 ±2.1. Most patients became sedated 6-10 minutes when compared to intranasal ketamine as most patients sedated after 16-20 minutes.

In agreement with this study: Wilton *et al*., 1988 found that significant sedation developed from 5 to 10 minutes with 0.02 mg midazolam.

Also, Khatavkar and Bakhshi 2014 found that the onset of sedation was earlier with midazolam than ketamine.

Also, Knoester et al. 2002 found that the onset of sedation was earlier in midazolam as compared with ketamine or fentanyl or other premedicants and these results were in accordance with the result of this study.

In disagreement with this study, Gracia *et al.*, 1998 found that there was no difference in the onset of sedation between ketamine and midazolam that occurred in 10 minutes but the mean onset time of sedation was not mentioned in their study.

On five point sedation scale, A total of 9 patients (50%) were asleep (score 4) in ketamine group while 10 patients (55.6%) were asleep in the midazolam group. However, number of patients with no response (score 6) were more in the ketamine group than in the midazolam (6 vs. 4, 33.3% vs. 22.2 %). This result found that no significant difference between intranasal ketamine and midazolam however ketamine was slightly better with significant no response patient.

Regarding the degree of sedation, Garcia *et al*., 1998 found no significant difference between intranasal midazolam and ketamine.

The result of Morioka *et al*., 1997 went hand in hand with the result of this study regarding sedation score in which it was higher with the use of ketamine than with midazolam.

According to the heart rate and blood pressure: Changes in blood pressure in the three groups showed that increase in blood pressure was highly significant in the ketamine group $P < 0.001$. Hypertension persisted in ketamine group. According to heart rate, showed that Tachycardia was highly significant in the ketamine group $P < 0.001$. Tachycardia persisted in ketamine group $P = 0.0220$.The heart rates for the ketamine and midazolam groups pulse rates were preoperatively 103.82 ± 8.4633 and 101.22 ± 10.2884, after premedication 112.84 ± 9.1397 and 101.88 ± 13.47, intra operatively 121.64 ± 12.8557 and 101.2 ± 7.5683 and postoperatively 114 ± 10.5917 and 110.2 ± 8.9397 respectively.

Significant tachycardia in ketamine group $P <0.001$. Tachycardia was statistically highly significant in the ketamine group after premedication ($P < 0.001$ $P = 0.0019$). Five patients in the midazolam group showed heart rate <70. This was not statistically significant $P = 0.718$.

These findings were in agreement with Bourgoin *et al*., 2003 who found that blood pressure and heart rate increased by 30 % even with deeper level of sedation.

This was in contrast with Christensen *et al*., 2007 who found that intranasal ketamine drops were associated with no changes in blood pressure or pulse rate.

According to changes in respiratory rate: there was no significant difference between ketamine and intranasal midazolam. However, respiratory rate was increased slightly with ketamine. This was in accordance with Green *et al*., 2011 who found that there was no depression of pulmonary gas exchange or relaxation of upper airway muscles and there was no effect on respiratory rate, tidal volume, minute ventilation or end tidal CO2.

In this study, as regard the venipuncture and acceptance of the mask: Not possible to insert IV line was observed in 12% in ketamine group and 6% in midazolam group. Overall there was no statistically significant difference in venipuncture score in both groups. According to acceptance of the mask, More number of patients in midazolam group accepted mask readily (12vs. 10, 66.7% vs. 55.6%). Less number of patients refused face mask in midazolam group (1 vs. 2, 5.6% vs. 11.2%). These differences were statistically insignificant ($P > 0.05$.).

This was in agreement with Garcia *et al*., 1998 who found that intranasal midazolam and intranasal ketamine produced sedative effect to the extent that anesthesiologist

could use the mask or cannulate the patient with no intervention.
Also, Kahreci *et al*., 1997 found that ketamine and intranasal midazolam produce sedative effects better than any drugs which allowed the anesthesiologist to deal with patient with comfort and these results were in agreement with the results of this study.

According to intraoperative secretion grading: Copious secretions were observed in 44% in ketamine group versus only 6% in the midazolam group 50% in midazolam group showed no secretions. These were statistically highly significant ($P < 0.001$). Copious secretions were observed in 44% in ketamine group versus 5.6% in the midazolam group. 50% in midazolam group showed no secretions. These were statistically highly significant ($P < 0.001$).
This was in accordance with the results of Filatov *et al*., 2000 who found that ketamine increased salivation and increased secretion in the upper airway that could lead to laryngospasm.
Also, Bell *et al*., 2005 found that Ketamine increased salivary secretions, which could produce potential problems in children by causing upper airway obstruction. Although swallowing, cough, sneeze, and gag reflexes were relatively intact with ketamine and silent aspiration could occur.
While, Weksler *et al*., 1993 found that no increase in intraoperative secretions recorded with intranasal ketamine and this was in contrast to the result of this study and this might be due to the use of atropine in Weksler"s study.

Conclusion

The use of intranasal ketamine or intranasal midazolam 30 minutes before induction of general anesthesia will decrease anxiety, facilitate introduction of intravenous access and application of intubating mask easily with hemodynamic stability. So, We recommend the use of intranasal ketamine and midazolam as preoperative pediatric sedatives to decrease anxiety of children before start of general anesthesia to overcome drawbacks of pediatric anxiety and fear postoperatively and Intranasal midazolam was better than ketamine according to onset of sedation which started earlier and intraoperative secretions were scanty with midazolam in comparison with ketamine**.**

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