Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Jan 19; 11(B):184-190.
https://doi.org/10.3889/oamjms.2023.11326
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Anesthesiology*

Intranasal Ketamine for Premedication in Children: A Comparative Study in Ghana

Audrey Anno[1], Robert Djagbletey[2], Pokua Sarpong[1], Ernest Aniteye[2], Eugenia Lamptey[2], George Aryee[2], Amanda Quarshie[1], Raymond Essuman[2], Ebenezer Owusu Darkwa[2]*, Amanda Quarshie[1],

[1]Department of Anaesthesia, Korle-Bu Teaching Hospital, Accra, Ghana; [2]Department of Anaesthesia, University of Ghana Medical School, College of Health Sciences, University of Ghana, Accra, Ghana

Edited by: Mirko Spiroski
Citation: Anno A, Djagbletey R, Sarpong P, Aniteye E, Lamptey E, Aryee G, Quarshie A, Essuman R, Darkwa EO. Intranasal Ketamine for Premedication in Children: A Comparative Study in Ghana. Open Access Maced J Med Sci. 2023 Jan 19; 11(B):184-190. https://doi.org/10.3889/oamjms.2023.11326
Keywords: Premedication; Ketamine; Paediatric; Intranasal; Sedation; Face mask
***Correspondence:** Ebenezer Owusu Darkwa, Department of Anaesthesia, University of Ghana Medical School, Korle-Bu, Accra.
E-mail: eoddarquah@yahoo.co.uk
Received: 29-Nov-2022
Revised: 06-Jan-2023
Accepted: 09-Jan-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Premedication is helpful especially in children in reducing the stress associated with anesthesia and surgery. Pediatric patients for surgery in Korle Bu Teaching Hospital are currently not sedated preoperatively due to unavailability of effective pediatric sedative preparations. Ketamine is readily available, inexpensive, and has been used for pediatric sedation through various routes with good outcomes in other geographical regions. Its intranasal use shows promise and avoids the anxiety and pain associated with establishing of an intravenous access and administration of drugs intravenously and intramuscularly.

AIM: The aim of this study was to assess the efficacy of intranasal ketamine as premedication for pre-operative sedation.

MATERIALS AND METHODS: A double-blind, randomized, and controlled trial was conducted on 76 pediatric elective surgical patients aged between 1 and 6 years at the Korle-Bu Teaching Hospital. Subjects were randomly assigned to receive 10 mg/kg intranasal ketamine (Treatment group) or 0.9% normal saline (Control group) 30 min before induction of anesthesia. Ease of separation from parents was assessed before (Pre-intervention) and 30 min after administration of intranasal solution (Postintervention). The level of sedation and acceptance of face mask were assessed 30 min after intranasal administration.

RESULTS: The mean separation score in the treatment group was significantly lower pre-intervention ($p = 0.026$) but significantly higher 30 min post-intervention compared to control group ($p < 0.0001$). There was a significantly higher mean sedation score (2.8 ± 0.8 vs. 1.7 ± 0.7; $p < 0.0001$) and face mask acceptance score (3.4 ± 0.8 vs. 1.9 ± 1.2; $p < 0.0001$) among the treatment group compared to the control group. The incidence of salivation was significantly higher among the treatment group compared to the control group (17.9% vs. 0%; $p = 0.007$).

CONCLUSION: The use of intranasal ketamine as premedication preoperatively in pediatric surgical patients is safe and results in improved sedation scores, better separation scores, and acceptance of face mask.

Introduction

The pre-operative period can be a stressful time for children. Children find themselves in unfamiliar settings with unfamiliar faces and sometimes sense their parents' anxiety which make them anxious and fearful. Anxiety in children undergoing surgery is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms [1]. Anxiety and separation from parents result in autonomic hyperactivity, dysrhythmias, breath holding, and laryngospasm under the initial effects of general anesthesia [2]. There could be negative behavioral manifestations for weeks to months following frightening induction room experiences [3] such as new onset enuresis, feeding difficulty, sleep disturbances, nightmares, apathy, and withdrawal [1], [4].

Pre-operative anxiety may activate the human stress response [5] with alterations of immune function leading to a high susceptibility to infection and sometimes neoplastic disease [6], [7], [8]. Children are particularly vulnerable to the global surgical stress response because of limited energy reserves, larger brain masses, and obligatory glucose requirements [9]. Due to the fact that acute psychological stress (such as pre-operative anxiety) is associated with immediate stress hormone release [5], the contribution of this psychological factor to the global perioperative stress response cannot be ignored.

Consensus is evident among anesthesiologists about the need to treat anxiety before surgery [10]. Pre-operative interventions that have been used to try to reduce anxiety in children include psychological and pharmacological methods. However, pharmacological means of reducing anxiety seems to be more effective and adequate when used alone [11], [12].

Intranasal administration of medication, which is a transmucosal route, is receiving a lot of attention as an alternative method of providing sedation in the pre-operative period due to the fact that the rich

vascular plexus of the nasal cavity provides a direct route to the blood stream once the medication crosses the mucous membrane. Absorption of intranasal drugs occurs directly into the central circulation, bypassing the enterohepatic circulation resulting in a higher bioavailability and shorter onset of action [13]. There is some growing evidence that molecules that come into contact with the nasal mucosa are absorbed not only into the blood, but also directly into the cerebrospinal fluid [14]. Medications that have been administered intranasally for sedoanalgesia in children in the perioperative period include midazolam, ketamine, fentanyl, sufentanil, and dexmedetomidine [11], [12].

Ketamine being a water-soluble drug has been used in the premedication of children using different dosages and routes of administration including the oral, rectal, and intranasal routes. Ketamine is one of the most commonly studied sedative drugs used intranasally [15]. Intranasal ketamine has been successfully used for sedation for computed tomography scan, brief dental procedures, and also for procedural sedation to suture lacerations in pediatric patients in the emergency room.

The use of intranasal ketamine in pediatric patients has been variously studied. Questions still remain on the optimal dose required, the technique of administration and there are concerns regarding its safety [16], [17], [18], [19], [20], [21], [22], [23].

Pediatric sedative premedication formulations are not readily available in Ghana; hence, most pediatric patients are not sedated preoperatively and therefore become uncooperative after separation from their parents. Uncooperative children struggle so much with anesthesia providers during induction predisposing them to life-threatening complications and psychological trauma. Ketamine is readily available, inexpensive and it is being used for pediatric sedation for procedures through the intravenous or intramuscular route in Ghana. Its intranasal use shows promise and avoids the anxiety and pain associated with establishing of an intravenous access and administration of drugs intravenously and intramuscularly. This study therefore aimed to assess efficacy of intranasal ketamine as premedication for pre-operative sedation and also to determine its effect on ease of separation of children from their parents as well as their acceptance of the face mask at induction of anesthesia at the Korle-Bu Teaching Hospital in Ghana.

Materials and Methods

Study design

The study was a prospective, randomized, double-blind, and controlled trial.

Study site

The study was conducted at the pediatric theaters of the Korle-Bu Teaching Hospital, which is the largest tertiary and referral hospital in Ghana, with a bed capacity of 2000 and has over 3000 members of staff. The pediatric surgery unit of the hospital undertakes various general and urological surgeries on pediatric patients up to the age of 12 years. The unit is managed by a team of consultant pediatric surgeons. Elective surgical procedures are performed twice in a week for which a consultant anesthetist is always in attendance.

Study population

American Society of Anaesthesiology (ASA) Class I and II children aged 1–6 years old, weighing 8–20 kg who were scheduled for elective surgical procedures were included in the study after obtaining an informed consent from the parents/guardian.

Children who were ASA III and above, those with a history of recent nasal discharge (<2 weeks), seizures, autism, or behavioural disorders, had any alteration in level of consciousness/suspicion of increased intracranial pressure, glaucoma, drug allergies, hypertension, and known diagnosis of hyperthyroidism or porphyria from medical records were excluded from the study.

Sample size determination

In conducting this study, a total number of 76 children were randomly recruited consisting of 39 cases and 37 controls using the formula by Edwardes [24] and adjusting for a 25% increase over the minimum sample size required.

Procedures

All the patients who participated in the study were assessed preoperatively at the anesthetic clinic. Parents/guardians were educated on the recommended standard pre-operative fasting guidelines to ensure that the children were appropriately fasted. All the children who met the eligibility criteria during the 3-month study period were consecutively recruited to the study. Children recruited into the study were randomized into the study groups by allowing their parents/guardians to pick a ballot from an envelope without replacement.

The intranasal solutions that were administered were prepared and given coded labels by an independent anesthetist who was not directly involved in the study. The anesthetist who administered the intranasal medication and the parents of the children were blinded to the treatment/intervention a child was receiving. The code to the labels and thus the intervention administered was only revealed to the investigators at the end of data analysis.

Parenteral ketamine (Rotexmedica, Germany, 50 mg/mL) was used. A dose of 10 mg/kg of intranasal ketamine was used for the study. All the participants in the study thus received 0.2 mL/kg of an intranasal solution (0.1 mL/kg/nostril). The treatment group received ketamine while the control group received 0.9% normal saline.

A two milliliter luer lock syringe (B-Braun, Germany) and a mucosal atomiser device (MAD Nasal 300 by Teleflex) was used to administer the intranasal solution into each nostril of the patients 30 min before induction of anesthesia.

Atomization was chosen as a mode of intranasal delivery because it is associated with higher acceptance, less aversive reaction, rapid onset, and recovery of sedation [25].

Baseline measurements of heart rate (HR), blood pressure (BP), respiratory rate, and oxygen saturation (SpO_2) were recorded before administration of the intranasal solution and then at 5-min intervals thereafter for 30 min using a Drager Vista 120 patient monitor (Dragger GmbH, Germany, 2012) with pediatric settings. The children were also monitored constantly for excessive salivation. Ease of separation from parents was assessed before and 30 min after administration of intranasal solution. Thirty minutes after administration of intranasal solution, the level of sedation was evaluated using the Modified Ramsay Sedation Score (Table 1), the ease of separation of children from their parents as well as degree of acceptance of the facemask for induction was assessed using a four-point scoring system (Tables 2 and 3).

Table 1: Scale for sedation score

Value	Level of sedation
1	Awake: Patient is anxious and agitated, restless, or both
2	Awake: Patient is cooperative, orientated, and tranquil
3	Awake: Patient responds to commands only
4	Asleep: Patient reacts with a brisk response to a light glabellar tap or a loud auditory stimulus
5	Asleep: Patient reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus
6	Asleep: Patient does not respond to pain

Data were entered using Microsoft Access 2016, cleaned and exported into Statistical Package for the Social Sciences version 25 for analysis. Continuous variables were summarized as mean ± standard deviation. Repeated measures analysis of variance (ANOVA) was used in analyzing HR, systolic BP (SBP), diastolic BP (DBP), and SpO_2. Chi-square test was used in determining the association between categorical variables while comparisons of means were done using the t-test. A statistically significant level was set at an alpha value <0.05.

Table 2: Scale for separation score

Value	Separation score
1	Poor (crying, clinging)
2	Fair (crying but not clinging)
3	Good (whimpers but easily reassured)
4	Excellent (easy separation)

Table 3: Scale for acceptance of face mask

Value	Acceptance of face mask
1	Poor (pushes face mask away/violently struggles)
2	Fair (pushes face mask away but gently)
3	Good (accepts face mask with a little reassurance)
4	Excellent (accepts face mask quietly)

Approval to conduct the study was sought from the Ethical and Protocol Review Committee of the University of Ghana Medical School (Protocol Identification Number: MS-Et/M.12 - P 4.3/2013-2014). Written and informed consent was obtained from parents/guardians before recruiting the participants in the study.

Results

There was no statistically significant difference between the two study groups ($p > 0.05$) with respect to age, sex, weight, and ASA physical status classification (Table 4).

Table 4: Background characteristics of participants

Variable	Group		p-value
	Treatment	Control	
Sex, n (%)	n=39	n=37	
Male	28 (71.8)	29 (78.4)	0.508
Female	11 (28.2)	8 (21.6)	
Age, mean (± SD)	2.6 (± 1.4)	2.7 (± 1.4)	0.717
Weight, mean (± SD)	12.9 (± 3.0)	13.1 (± 3.2)	0.780
ASA status, n (%)			
I	21 (53.8)	13 (35.1)	
II	18 (46.2)	24 (64.9)	0.101

A repeated measure ANOVA showed there was an overall non-significant change in HR over time ($p = 0.792$) between the two groups. The mean HR of the treatment group, however, was generally higher than the control group up to about 25-min post-intervention (Figure 1).

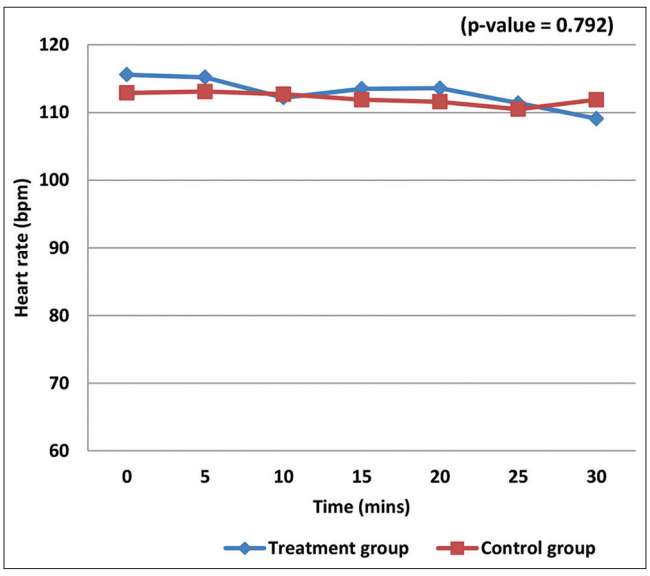

Figure 1: Variation in heart rate

The SBP and the DBP of the treatment group were consistently higher than that of the control group.

This was noted to be significant between 5 min and 20 min post-intervention. The elevated BPs of the treatment group gradually diminished by the 30th min post-intervention (Figures 2 and 3).

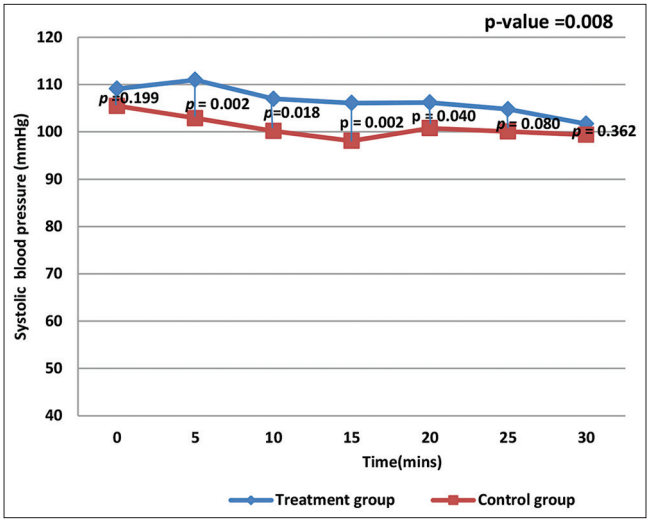

Figure 2: Variation in systolic blood pressure

The SpO_2 of patients in both groups remained fairly constant above 97% at all the measurement times during the study with non-significant variation between the two study groups (Figure 4).

The mean separation score within the treatment group pre-intervention compared to 30-min post-intervention was significant ($p < 0.0001$) (Table 5 and 6). The mean separation score within the control group pre-intervention compared to 30 min post-intervention was not significant ($p = 0.534$)

The mean separation scores in the treatment group were significantly lower pre-intervention ($p = 0.026$); however, it was significantly higher 30-min post-intervention compared to control group ($p < 0.0001$) (Tables 5 and 6).

The mean sedation score and face mask acceptance score were significantly higher in the treatment group compared to the control group.

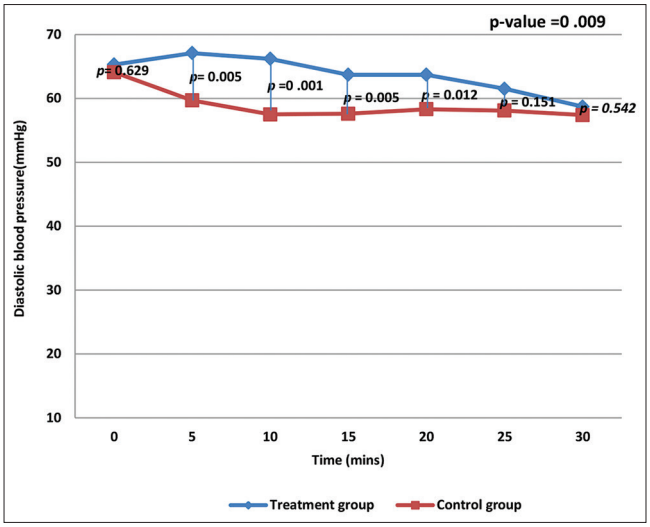

Figure 3: Variation in diastolic blood pressure

Incidence of excess salivation among the study participants was 17.9% in the treatment group and 0% in the control group ($p = 0.007$).

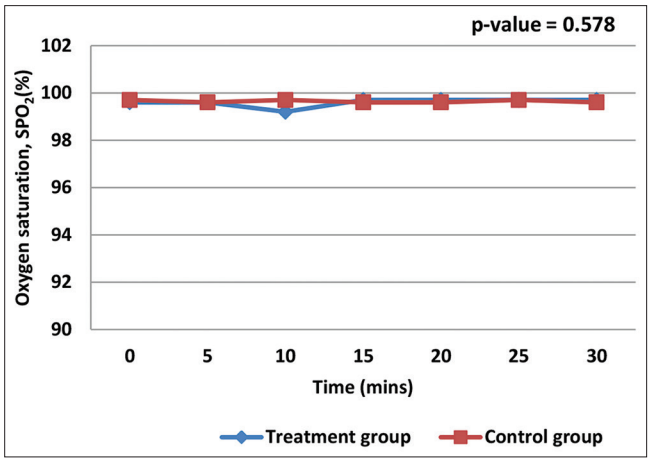

Figure 4: Variation in oxygen saturation

Discussion

The mean (±SD) age of children from this study was 2.7 (±1.4) years indicating that a vast majority of the children involved in this study were in the younger age group that is more likely to exhibit pre-operative anxiety [10]. Many children have been reported to refuse to accept the face mask for pre-oxygenation and induction of anesthesia, leading to a stormy induction period which can result in personality and behavioral changes [26]. Children under 5 years are especially vulnerable since they are too young to understand the reasons for the unpleasant experience [27]. This separation anxiety can be observed in children as young as 7–8 months of age [10].

Table 5: Separation, acceptance of facemask, and sedation scores of participants

Variable	Treatment mean ± SD	Control mean ± SD	p-value
Separation score			
Pre-intervention	2.0 ± 0.9	2.5 ± 1.3	0.026*
30-min Post-intervention	3.9 ± 0.3	2.6 ± 1.2	<0.0001*
Acceptance of face mask	3.4 ± 0.8	1.9 ± 1.2	<0.0001*
Modified Ramsay Sedation Score (after 30 min of drug administration)	2.8 ± 0.8	1.7 ± 0.7	<0.0001*

*Statistically significant ($p < 0.05$).

In this study, the Ramsey sedation score was significantly lower in the control group depicting a higher level of anxiety. This is not unusual as pre-operative anxiety among children have been estimated to be as high as 60% [28]. Pre-operative administration of intranasal ketamine was found to provide sedation, depicted by better sedation scores among children in the treatment group compared to controls.

Pre-operative administration of ketamine has been found to offer effective sedation in children. The intranasal route of administration has been found to be effective, usually painless with a fast onset similar to the intravenous route. Several studies have found

Table 6: Separation, acceptance of facemask, and sedation scores of participants

Variable	Groups; n (%)		p-value
	Treatment (n = 39)	Control (n = 37)	
Separation score before drug administration			
Poor	17 (43.6)	15 (40.5)	
Fair	9 (23.1)	2 (5.4)	0.007*
Good	12 (30.8)	10 (27.0)	
Excellent	1 (2.6)	10 (27.0)	
Separation score (30 min after drug administration)			
Poor	0 (0.0)	13 (35.1)	
Fair	0 (0.0)	4 (10.8)	<0.0001*
Good	3 (7.7)	10 (27.0)	
Excellent	36 (92.3)	10 (27.0)	
Acceptance of face mask (for induction of anesthesia)			
Poor	0 (0.0)	22 (59.5)	
Fair	8 (20.5)	5 (13.5)	<0.0001*
Good	9 (23.1)	4 (10.8)	
Excellent	22 (56.4)	6 (16.2)	
Modified Ramsay Sedation Score (after 30 min of drug administration)			
Awake: Patient is anxious	0 (0.0)	17 (45.9)	
Awake: Patient is cooperative	17 (43.6)	18 (48.6)	<0.0001*
Awake: Patient responds to commands	11 (28.2)	0 (0.0)	
Asleep: Patient responds to glabellar tap	11 (28.2)	2 (5.4)	
Side effects			
Salivation	7 (17.9)	0 (0.0)	0.012*
None	32 (82.1)	37 (100)	

*Statistically significant ($p < 0.05$).

intranasal ketamine to be effective for the provision of pre-operative sedation in children with no side effects [29], [30]. Most of these studies used ketamine at a dose of 5–6 mg/kg.

Tsze *et al.* [31] have proposed higher doses of intranasal ketamine (9 mg/kg) to achieve significant increase in the proportion of successful sedations. This informed our choice of a dose of 10 mg/kg in this study.

There was a statistically significant ($p < 0.0001$) better sedation scores among children in the treatment group compared to controls similar to findings by Weksler *et al*. [32] in their study recorded a sedation failure of 22% which is at variance with ours which did not record any sedation failure. They however used an intranasal ketamine dose of 6 mg/kg (compared to a dose of 10 mg/kg ketamine used in this study) and they did not state clearly how intranasal administration was performed (by drops or atomization). Therefore, a possible drug run off into the pharynx if drug was administrated by drops and the use of a lower dose may account for the failure rate they reported.

Table 7: Comparison of mean HR, SBP, DBP and SpO_2 between the treatment and the control groups

Variable	Group: mean (± SD)		p-value	Follow-up test (p-value)
	Ketamine (treatment) n = 39	Saline (control) n = 37		
HR			0.792	-
Baseline	115.6 (±13.5)	112.9 (±18.0)		
5 min	115.2 (±13.0)	113.1 (±17.4)		
10 min	112.2 (±14.7)	112.7 (±17.3)		
15 min	113.5 (±12.4)	111.9 (±18.1)		
20 min	113.6 (±10.8)	111.6 (±17.5)		
25 min	111.4 (±11.7)	110.5 (±17.7)		
30 min	109.1 (±12.1)	111.9 (±17.8)		
SBP				
Baseline	109.1 (±13.3)	105.5 (±10.2)	0.008*	0.199
5 min	111.0 (±11.8)	102.9 (±10.2)		0.002*
10 min	107.0 (±13.8)	100.2 (±10.5)		0.018*
15 min	106.1 (±12.0)	98.1 (±9.4)		0.002*
20 min	106.2 (±12.1)	100.8 (±10.7)		0.040*
25 min	104.8 (±11.9)	100.1 (±11.2)		0.080
30 min	101.7 (±11.4)	99.4 (±10.5)		0.362
DBP				
Baseline	65.3 (±9.7)	64.1 (±11.1)	0.009*	0.629
5 min	67.1 (±11.4)	59.7 (±10.1)		0.005*
10 min	66.2 (±12.4)	57.5 (±8.2)		0.001*
15 min	63.7 (±10.4)	57.6 (±8.3)		0.005*
20 min	63.7 (±10.4)	58.3 (±7.4)		0.012*
25 min	61.5 (±12.1)	58.1 (±7.7)		0.151
30 min	58.7 (±11.2)	57.4 (±7.3)		0.542
SPO_2				
Baseline	99.6 (±0.9)	99.7 (±0.5)	0.578	-
5 min	99.6 (±0.9)	99.6 (±0.6)		
10 min	99.2 (±2.2)	99.7 (±0.6)		
15 min	99.7 (±0.7)	99.6 (±0.7)		
20 min	99.7 (±0.6)	99.6 (±0.6)		
25 min	99.7 (±0.6)	99.7 (±0.6)		
30 min	99.7 (±0.6)	99.6 (±0.8)		

*Statistically significant ($p < 0.05$), SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SpO_2: Oxygen saturation.

Intranasal ketamine is reported to be a safe pre-operative sedative with preservation of respiratory activity [20]. It was, therefore, not surprising to find a non-significant change in SpO_2 between the treatment and control groups.

Comparing the pre- and post-intervention mean separation scores, our study found significant difference among the treatment group but failed to demonstrate such difference among the controls. This demonstrates the effectiveness of intranasal ketamine in improving separation scores in children when administered preoperatively.

The better separation scores in the control group, pre-intervention, could be attributed to the fact that the control group had a higher mean age compared to the treatment group and thus were more cooperative at the time of separation [10]. The separation score of the treatment group however improved significantly ($p < 0.0001$) 30 min after administration of intranasal ketamine with a mean separation score of 3.9 ± 0.3 representing a good to excellent separation score. This finding is supported by the work of Gharde *et al*. [27].

The remarkably improved separation scores noticed in this study were associated with significant ($p < 0.0001$) improvement in acceptance of facemask at induction of anesthesia among participants in the treatment group compared to the control group. This is similar to findings by Aldrete *et al*. [17].

The HR, SBP, and DBP were generally higher among the treatment compared to the control group during the study period. The elevated HR of the treatment group participants was not significant ($p = 0.792$) (Table 7). However, the systolic and DBP were significantly higher among the treatment group between 5 min and 20 min post-intervention compared to controls. This increase in the BPs reduced within 30 min (Figures 2 and 3). This is not surprising since ketamine is known to stimulate the sympathetic nervous system with resultant hypertension and tachycardia but preservation of cardiac output [33]. Although ketamine causes elevation of HR and BPs, it was noticed from this study that this increase appears to be transient as it reduces with time. This finding has also been noted in other studies [34] and may be attributable to the sedative effect of ketamine.

Although several studies using intranasal ketamine for pre-operative sedation in children have

reported good efficacy with no side effects [29], [30], the dose of ketamine used in these studies was lower (5–6 mg/kg) than that of the present study. Apart from salivation, we did not record any other side effects of ketamine including psychotomimetic/emergence phenomena.

In this study though none of the participants in the control group experienced salivation, nearly a fifth of the participants in the treatment group experienced salivation. A finding found to be significant and similar to that of Heinz *et al*. [23].

Conclusion

The use of intranasal ketamine as premedication preoperatively in pediatric surgical patients results in significantly improved sedation scores, separation scores, and acceptance of face mask with preservation of respiratory activity and a transient increase in BP and HR.

Acknowledgment

The authors express their sincere gratitude to the parents of the children who consented for their children to participate in the study.

References

1. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150(12):1238-45. https://doi.org/10.1001/archpedi.1996.02170370016002
   PMid:8953995
2. Malinovsky JM, Populaire C, Cozian A, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children. Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. Anaesthesia. 1995;50(4):351-4. https://doi.org/10.1111/j.1365-2044.1995.tb04616.x
   PMid:7747857
3. Politis GD. Preanesthetic sedation for pediatric patients lacking intravenous access. In: Pediatric Anesthesia Handbook. New York: McGraw-Hill; 2002. p. 41-55.
4. Kotiniemi LH, Ryhänen PT, Moilanen IK. Behavioural changes in children following day-case surgery: A 4-week follow-up of 551 children. Anaesthesia. 1997;52(10):970-6. https://doi.org/10.1111/j.1365-2044.1997.202-az0337.x
   PMid:9370839
5. Chrousos GP, Gold PW. The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. JAMA. 1992;267(9):1244-52.
   PMid:1538563
6. Ader R, Cohen N, Felten D. Psychoneuroimmunology: Interactions between the nervous system and the immune system. Lancet. 1995;345(8942):99-103. https://doi.org/10.1016/s0140-6736(95)90066-7
   PMid:7815892
7. Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, *et al*. Hormonal responses to graded surgical stress. Arch Intern Med. 1987;147(7):1273-8.
   PMid:3606284
8. Weissman C. The metabolic response to stress: An overview and update. Anesthesiology. 1990;73(2):308-27. https://doi.org/10.1097/00000542-199008000-00020
   PMid:2200312
9. Deshpande S, Platt MP, Aynsley-Green A. Patterns of the metabolic and endocrine stress response to surgery and medical illness in infancy and childhood. Crit Care Med. 1993;21(9 Suppl):S359-61. https://doi.org/10.1097/00003246-199309001-00036
   PMid:8365226
10. McCann ME, Kain ZN. The management of preoperative anxiety in children: An update. Anesth Analg. 2001;93(1):98-105. https://doi.org/10.1097/00000539-200107000-00022
    PMid:11429348
11. Hannallah RS, Rosales JK. Experience with parents' presence during anaesthesia induction in children. Can Anaesth Soc J. 1983;30(3 Pt 1):286-9. https://doi.org/10.1007/BF03013809
    PMid:6336550
12. Kain ZN, Mayes LC, Wang SM, Caramico LA, Hofstadter MB. Parental presence during induction of anesthesia versus sedative premedication: Which intervention is more effective? Anesthesiology. 1998;89(5):1147-56; discussion 9A-10A. https://doi.org/10.1097/00000542-199811000-00015
    PMid:9822003
13. Sarkar MA. Drug metabolism in the nasal mucosa. Pharm Res. 1992;9(1):1-9. https://doi.org/10.1023/a:1018911206646
    PMid:1589391
14. Westin UE, Boström E, Gråsjö J, Hammarlund-Udenaes M, Björk E. Direct nose-to-brain transfer of morphine after nasal administration to rats. Pharm Res. 2006;23(3):565-72. https://doi.org/10.1007/s11095-006-9534-z
    PMid:16489488
15. Papolos DF, Teicher MH, Faedda GL, Murphy P, Mattis S. Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype. J Affect Disord. 2013;147(1-3):431-6. https://doi.org/10.1016/j.jad.2012.08.040
    PMid:23200737
16. Reid C, Hatton R, Middleton P. Case report: Prehospital use of intranasal ketamine for paediatric burn injury. Emerg Med J. 2011;28(4):328-9. https://doi.org/10.1136/emj.2010.092825
    PMid:21292791
17. Aldrete JA, Jesus JC, Russell LJ, d'Cruz O. Intranasal ketamine as induction adjunct in children: Preliminary report. Anesthesiology. 1987;67:A514. https://doi.org/10.1097/00000542-198709001-00514
18. Louon A, Reddy VG. Nasal midazolam and ketamine for paediatric sedation during computerised tomography. Acta Anaesthesiol Scand. 1994;38(3):259-61. https://doi.org/10.1111/j.1399-6576.1994.tb03885.x
    PMid:8023666
19. Louon A, Lithander J, Reddy VG, Gupta A. Sedation with nasal ketamine and midazolam for cryotherapy in retinopathy of prematurity. Br J Ophthalmol. 1993;77(8):529-30. https://doi.org/10.1136/bjo.77.8.529

PMid:8025055

20. Diaz JH. Intranasal ketamine preinduction of paediatric outpatients. Paediatr Anaesth. 1997;7(4):273-8. https://doi.org/10.1046/j.1460-9592.1997.d01-93.x
PMid:9243683
21. Weber F, Wulf H, Gruber M, Biallas R. S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. Pediatr Anesth. 2004;14(12):983-8. https://doi.org/10.1111/j.1460-9592.2004.01358.x
PMid:15601346
22. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996;77(2):203-7. https://doi.org/10.1093/bja/77.2.203
PMid:8881626
23. Heinz P, Geelhoed GC, Wee C, Pascoe EM. Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. Emerg Med J. 2006;23(3):206-9. https://doi.org/10.1136/emj.2005.028969
PMid:16498158
24. Edwardes MD. Sample size requirements for case-control study designs. BMC Med Res Methodol. 2001;1:11. https://doi.org/10.1186/1471-2288-1-11
PMid:11747473
25. Pandey RK, Bahetwar SK, Saksena AK, Chandra G. A comparative evaluation of drops versus atomized administration of intranasal ketamine for the procedural sedation of young uncooperative pediatric dental patients: A prospective crossover trial. J Clin Pediatr Dent. 2011;36(1):79-84. https://doi.org/10.17796/jcpd.36.1.1774746504g28656.
PMid:22900449
26. Savage GH. Insanity following the use of anaesthetics in operations. Br Med J. 1887;2(1405):1199-200. https://doi.org/10.1136/bmj.2.1405.1199
27. Gharde P, Chauhan S, Kiran U. Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. Ann Card Anaesth. 2006;9(1):25-30.
PMid:17699904
28. Dreger VA, Tremback TF. Management of preoperative anxiety in children. AORN J. 2006;84(5):778-80, 782-6, 788-90 passim; quiz 805-8. https://doi.org/10.1016/s0001-2092(06)63965-3
PMid:17144057
29. García-Velasco P, Román J, de Heredia BB, Metje T, Villalonga A, Vilaplana J. Nasal ketamine compared with nasal midazolam in premedication in pediatrics. Rev Esp Anestesiol Reanim. 1998;45(4):122-5.
PMid:9646650
30. Weber F, Wulf H, El Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. Can J Anesth. 2003;50(5):470-5. https://doi.org/10.1007/BF03021058
PMid:12734155
31. Tsze DS, Steele DW, Machan JT, Akhlaghi F, Linakis JG. Intranasal ketamine for procedural sedation in pediatric laceration repair: A preliminary report. Pediatr Emerg Care. 2012;28(8):767-70. https://doi.org/10.1097/PEC.0b013e3182624935
PMid:22858745
32. Weksler N, Ovadia L, Muati G, Stav A. Nasal ketamine for paediatric premedication. Can J Anaesth. 1993;40(2):119-21. https://doi.org/10.1007/BF03011307
PMid:8443849
33. Liu J, Du M, Liu L, Cao F, Xu Y. Sedation effects of intranasal dexmedetomidine combined with ketamine and risk factors for sedation failure in young children during transthoracic echocardiography. Pediatr Anesth. 2019;29(1):77-84. https://doi.org/10.1111/pan.13529
PMid:30450703
34. Audenaert SM, Wagner Y, Montgomery CL, Lock RL, Colclough G, Kuhn RJ, *et al*. Cardiorespiratory effects of premedication for children. Anesth Analg. 1995;80(3):506-10. https://doi.org/10.1097/00000539-199503000-00012
PMid:7864415