Randomized Trial

Analgo-Sedative Effects of Oral or Nebulized Ketamine in Preschoolers Undergoing Elective Surgery: A Comparative, Randomized, Double-Blind Study

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Background: Premedication in children with ketamine is useful to produce mild sedation, decrease anxiety, help the child separation from parents, and provide postoperative pain relief with no or little adverse effects.

Objectives: The aims of this study were to compare the level of sedation, parental separation, successful venous cannulation, and postoperative analgesia of oral or nebulized ketamine in preschoolers undergoing elective surgery.

Study Design: A prospective, comparative, double-blind, randomized study.

Setting: Zagazig University Hospitals.

Methods: In the preparation room, 30 minutes before induction of anesthesia, 62 children were randomly divided into 2 groups: group O (n = 31) received oral ketamine 10 mg/kg in 2 mL apple juice, and group N (n = 31) received nebulized ketamine 3 mg/kg plus 2 mL isotonic saline solution by a standard hospital jet nebulizer via a mouth mask with a continuous 6 L/min flow of 100% oxygen.

Results: At 10 minutes after premedication, sedation score was 3 in group O (34.4%) compared with group N (0%), and at 20 minutes in group O (93.5%) compared with group N (9.6%) ($P < 0.001$). However, at 30 minutes, 51.6% of group O showed a sedation score of 1 versus 0% of group N ($P < 0.001$). There were 70.9% of group O versus 6.4% of group N who showed an Emotional State Score of 1 ($P < 0.0001$), and 29.03% of group O versus 19.3% of group N who showed an Emotional State Score of 2 ($P = 0.37$), with statistically nonsignificant adverse effects in both groups. Low mean modified Children's Hospital of Eastern Ontario Pain Scale score in group O compared with group N at 30, 60, 90 minutes ($P < 0.0001$).

Limitations: In this study, although the dose of nebulized ketamine was 3 mg/kg, which was more than the optimum dose investigated in previous studies, it was not adequate, so we recommend conducting more studies investigating higher doses.

Conclusions: Oral ketamine 10 mg/kg as premedication 30 minutes before induction of anesthesia is more effective than 3 mg/kg nebulized ketamine in producing more sedation, satisfactory separation from parents, successful venous cannulation, and effective postoperative analgesia, as it is more tolerable and accepted by preschoolers undergoing elective surgery.

Key words: Nebulized ketamine, oral ketamine, preschooler, elective surgery

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Preoperative communication, premedication interventions, and being accompanied by parents are useful methods in decreasing preoperative separation anxiety, postoperative psychological trauma, and ensuring smooth induction for preschoolers undergoing elective surgery (1). Procedural sedation and analgesia was defined by O'Donnell et al (2) as a drug-induced state of decreasing awareness, pain, and memory that allows the patient to continue his or her own protective reflexes and purposeful movements.

Ketamine is an anesthetic drug having analgo-sedative properties with different routes of administration in children (intravenous [IV], intramuscular [IM], subcutaneous, oral, rectal, sublingual, intranasal, and nebulized) (3). It produces its analgesic properties in acute pain management from reversible antagonizing of the N-methyl-D-aspartate (NMDA) receptors, reducing the levels of many proinflammatory mediators in the acute phase, and acting on other non-NMDA pathways that play important roles in pain and mood regulation, such as its effect on μ-opioid receptors, nicotinic, muscarinic cholinergic receptors, γ-aminobutyric acid receptors, activation of high-affinity D2 dopamine receptors, and L-type voltage-gated calcium channels (4). The oral route is most popular than other routes, as it is safe, efficient, acceptable, and familiar for pediatric patients (5).

Ketamine inhalation is safe with rapid absorption, and an affordable route of administration (6).

Table 1. *SS-5, ESS-4, and MAS (4-point Likert scale).*

SS-5	
1	Rarely awake, needs shaking or shouting to wake up
2	Asleep, eyes closed, wakes up when called softly or lightly touched
3	Sleepy, but eyes open spontaneously
4	Awake
5	Agitated
ESS-4	
1	Calm
2	Apprehensive, not smiling, tentative behavior, withdrawn
3	Crying
4	Thrashing, crying with movements of the arms and legs, resisting
MAS	
1	Excellent (unafraid, cooperative, accepts, mask readily)
2	Good (slight fear of mask, easy reassurance)
3	Fair (moderate fear of mask, not calmed with reassurance)
4	Poor (terrified, crying, or combative)

The aims of this study was to compare the analgo-sedative effects of oral or nebulized ketamine in premedication of preschoolers undergoing elective surgery. Our primary aims were to compare sedation level, separation state from parents, successful IV cannulation in the 2 groups, mask tolerability in the nebulized group, and recognizing the adverse effects. Our secondary aim was to compare postoperative analgesia and the changes in hemodynamics of the 2 groups.

Methods

This study was approved by the University's institutional review board (IRB #5296-17-3-2019), and written informed consent was obtained from all patients participating in the trial. The trial was registered prior to patient enrollment at clinicaltrial.gov (NCT03885427; date of registration March 27, 2019).

This was a prospective, comparative, double-blind, randomized, interventional study conducted on 62 children from March to May 2019. Written informed consent was obtained from all parents of the children included in this study.

The children included in this study were of either gender, aged between 3 and 6 years, with body mass index (BMI; 15-18kg/m²) belonging to American Society of Anesthesiologists (ASA) I, II physical status undergoing elective surgery of approximately 30 minutes to 1 hour duration under general anesthesia. Children with a history of recent respiratory tract infection, increased intracranial pressure, increased intraocular pressure, allergy or hypersensitivity to ketamine, cardiac dysrhythmia, and/or congenital heart disease, altered mental status, and epilepsy were excluded from this study.

In preparation room, 30 minutes before induction of anesthesia, 62 children were randomly divided into 2 groups by a computer-generated randomization table: group O (n = 31) premedicated with 10 mg/kg oral ketamine in 2 mL apple juice, and group N (n = 31) premedicated with 3 mg/kg nebulized ketamine plus 2 mL isotonic saline solution by a standard hospital jet nebulizer via mouth mask with a continuous 6 L/min flow of 100% oxygen, and the treatment was stopped when the nebulizer began to sputter.

The ketamine in both groups was given 30 minutes before induction of general anesthesia, based on the results of a previous clinical trial, which reported a sedation onset time of approximately 20 to 30 minutes (7).

Then standard monitoring was connected to the child (noninvasive blood pressure, pulse oximetry, and

electrocardiogram). This study was double-blinded, therefore the parents and the outcome assessor (the anesthesiologist not sharing in the study) who assessed the primary and secondary outcomes were unaware of the study groups that each child belonged to.

The heart rate, respiratory rate, peripheral oxygen saturation, and mean arterial blood pressure were recorded at baseline after admission in preparatory room, 10, 20, and 30 minutes after administration of ketamine.

The level of sedation was assessed by the Sedation Scale (SS-5; Table 1) (1) at 10, 20, and 30 minutes. When the SS-5 score reached 3 points and below, it was considered an acceptable sedation level.

The separation state was assessed at 30 minutes after premedication with ketamine and designated as satisfactory separation if the Emotional State Scale (ESS-4; Table 1) (1) score was no more than 2 points.

Assessing the mask acceptance in the nebulized ketamine group was done using the Mask Acceptance Scale (MAS; Table 1) (4-point Likert scale) (8). Children who had MAS of 1 or 2 were considered satisfactory acceptance of the nebulized mouth mask; scores of 3 or 4 were considered unsatisfactory.

Incidence of hallucination, nystagmus, hypersalivation, and abnormal movement were recorded. Successful venous cannulation was defined as an ESS-4 ≤ 2 at time of attempted cannulation, regardless of whether the vein was actually cannulated on the first attempt. Children whose vein was cannulated were transferred to the operating room, then preoxygenated with 5 L/min 100% O2 for 3 to 5 minutes, and remedication with atropine 0.02 mg/kg was given. Induction was done by fentanyl 1 ug/kg, and propofol 3 mg/kg, then endotracheal intubation was facilitated by atracurium 0.5 mg/kg, and intubation was done by soft seal cuffed sterile polyvinyl chloride tracheal tube according to the equation (child's age/4)+4, and the cuff was inflated with air. The children in whom IV cannulation was not possible on the first attempt, and those with an ESS-4 score ≥ 3 points, were induced with sevoflurane. Maintenance of anesthesia was done using sevoflurane 1 minimum alveolar concentration and atracurium 20% of the initial dose every 20 minutes. The last dose of atracurium was given 20 minutes before extubation.

At the end of the surgery, the inhalational anesthetic was turned off, and the muscle relaxant was reversed by a combination of neostigmine 0.5 mg/kg and atropine 0.02 mg/kg. The child was extubated and transferred to the recovery room. The intensity of pain was assessed in the recovery room using the modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (Table 2) (9) immediately after recovery, and every 30 minutes for 4 hours postoperatively. In postoperative ward, children were also monitored (mean arterial blood pressure, peripheral oxygen saturation, heart rate). CHEOPS pain score = sum (points for all 6 parameters). Interpretation: minimum score 6, maximum score 12. Postoperative pain management regimen was oral paracetamol 15 mg/kg per dose to a maximum of 1 g per dose every 4 hours. A child with modified CHEOPS score > 6 were given rescue analgesic with IV paracetamol 15 mg/kg to the maximum daily dose 60 mg/kg not exceeding 2 g. The sample size was assuming that the percent of successful IV cannulation in the oral ketamine group was 68% and in the nebulized group was 30% (1), therefore the total sample size was 62 children (31 in each group) using open Epi info with confidence interval 95% and power of test 80%.

Statistical Analyses

Data were analyzed with SPSS version 15.0 (SPSS Inc., Chicago, IL). Quantitative data were expressed as mean ± standard deviation and analyzed by an independent sample t test, whereas qualitative data were expressed as number and percentage and were analyzed by the chi-square test. *P* value was considered significant if < 0.05 and highly significant if < 0.001.

Table 2. *Modified CHEOPS*

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Composed	Grimace
Verbal	Positive	None or other complaints	Pain complaint
Torso	Neutral	Shifting, tense, upright	Restrained
Leg	Neutral	Kicks, squirms, drawn up	Restrained
Touch	No touching	Reach, touch, grab	Restrained

Results

All 62 patients in both groups of the study were comparable regarding age, gender, BMI, ASA physical status, and the duration of surgery (Table 3). Basal hemodynamics (heart rate, mean arterial pressure), respiratory rate, and peripheral oxygen saturation were comparable between the 2 groups with no statistically significant difference at 10, 20, and 30 minutes after premedication (Table 4). At 10 minutes, sedation score was 3 with highly statistically significant difference in group O 11 (34.4%) than in group N 0 (0%), also at 20 minutes there was highly statistically significant difference in group O 29 (93.5%) than in group N 3 (9.6%); $P < 0.001$. However, there were 16 (51.6%) and 13 (41.9%) children of group O versus no child of group N (0%) who showed sedation scores of 1 and 2, respectively, from rarely awake and need shaking to wake up at 30 minutes after premedication with statistically significant difference ($P < 0.001$; Table 5). Successful venous cannulation and satisfactory separation accepted at ESS-4 score ≤ 2, comparing the 2 groups. Regarding the ESS-4 at 30 minute after premedication, there were 22 children (70.9%) of group O versus 2 (6.4%) of group N who showed an ESS-4 score of 1 with $P < 0.0001$, and 9

Table 3. *Patients characteristics and duration of surgery.*

	Group O (n = 31)	Group N (n = 31)		*P*
Age (years)	4.69 ± 1.45	4.64 ± 1.21	f = 0.14	0.88
Sex Female Male	 13 18	 11 20	$x^2 = 0.26$	0.60
BMI (kg/m^2)	17.13 ± 2.24	18.02 ± 2.48	f = 1.48	0.14
ASA I II	 27 4	 28 3	$x^2 = 0.15$	0.69
Duration of surgery (min)	40.34 ± 7.13	41.29 ± 8.19	f = 0.48	0.62

Data were expressed as mean ± SD, or No (%). $P < 0.05$was significant. x^2 = chi square test. ASA = American Society of Anesthesiologist. f = one way analysis of varience.

Table 4. Heart rate, mean arterial blood pressure, respiratory rate, and peripheral oxygen saturation (SpO_2) at preset times preoperatively.

Variables	Group O (n = 31)	Group N (n = 31)	T test	*P* value
Heart rate(beat/min.)				
At baseline	112.7 ± 21.38	109.58 ± 20.5	0.53	0.5
At 10min.	102.88 ± 12.69	104.30 ± 13.11	0.43	0.66
At 20min.	93.8 ± 11.32	99.32 ± 12.63	-1.8	0.07
At 30min.	92.91 ± 13.79	98.36 ± 12.76	1.6	0.11
Mean arterial BP (mmHg)				
At Baseline	70.22 ± 6.31	72.43 ± 6.95	1.31	0.19
At 10min.	69.87 ± 7.11	72.13 ± 6.81	1.27	0.20
At 20min.	67.82 ± 6.42	69.93 ± 7.12	1,22	0.22
At 30min.	67.74 ± 6.84	69.85 ± 6.94	1,20	0.23
RR (breath/min)				
At baseline	28.43 ± 4.21	26.95 ± 3.87	-1.44	0.15
At 10min.	25.72 ± 3.62	27.31 ± 2.93	1.9	0.06
At 20min.	24.45 ± 3.11	25.53 ± 3.94	1.19	0.23
At 30min.	24.22 ± 3.72	25.71 ± 3.43	1.63	0.10
SpO_2(%)				
At Baseline	98.43 ± 0.67	98.34 ± 0.72	0.50	0.61
At 10min.	98.22 ± 0.71	98.11 ± 0.78	0.58	0.56
At 20min.	98.32 ± 0.63	98.29 ± 0.73	-0.17	0.86
At 30min.	98.34 ± 0.66	98.35 ± 0.62	0.06	0.95

Data were expressed as mean ± SD or percentage(%). $P < 0.05$ was significant. RR = Respiratory Rate. BP = blood pressure x^2 =chi square test

(29.03%) of group O versus 6 (19.3%) of group N who showed an ESS-4 score 2 with *P* value 0.37 (Table 6). Two (6.45%) children showed satisfactory MAS score of 1 in the nebulized ketamine group, and 6 (19.3%) children in the nebulized ketamine group showed satisfactory MAS score 2 versus 12 (38.7%), and 11 (35.4%) children showed unsatisfactory MAS scores (3 and 4), respectively. Two children had nystagmus in group O and one child in group N with no statistically significant difference and only one child in group O had abnormal movement (3.2%). There was hypersalivation in 3 patients in group O (9.6%) with 2 children in group N (6.4%). One child in group O (3.2%) versus no child in group N (0%) parents reported unusual behavior with hallucination (Table 7). Regarding postoperative pain, there were lower modified CHEOPS scores in group O than in group N at 30, 60, and 90 minutes with highly statistically significant difference ($P < 0.0001$) (Fig. 1).

Table 5. *Sedation scores after administration of the drug preoperatively.*

Time	Sedation score	Group O (n = 31)	Group N (n = 31)	x^2	*P*
At 10 min.	1	0 (0%)	0 (0%)	4.05	< 0.001
	2	0 (0%)	0 (0%)		
	3	11 (34.4%)	0 (0%)		
	4	20 (64.5%)	26 (83.8%)		
	5	0 (0%)	5 (16.1%)		
At 20 min.	1	0 (0%)	0 (0%)	6.89	< 0.001
	2	2 (6.4%)	0 (0%)		
	3	29 (93.5%)	3 (9.6%)		
	4	0 (0%)	25 (80.6%)		
	5	0 (0%)	3 (9.6%)		
At 30 min.	1	16 (51.6%)	0 (0%)	6.86	< 0.001
	2	13 (41.9%)	0 (0%)		
	3	2 (6.4%)	9 (29.03%)		
	4	0 (0%)	20 (64.5%)		
	5	0 (0%)	2 (6.4%)		

Data were expressed as No (%). $P < 0.05$ was significant. $P < 0.001$ was highly significant. x^2 = chi square test

Table 6. *Emotional State Score at 30 min of administration of the drug in the preoperative period.*

Score	Group O (n = 31)	Group N (n = 31)	x^2	*P*
1	22 (70.9%)	2 (6.4%)	26.75	< 0.0001
2	9 (29.03%)	6 (19.3%)	0.77	0.37
3	0 (0%)	8 (25.8%)	9.03	0.002
4	0 (0%)	15 (48.3%)	19.46	< 0.0001

Data were expressed as No (%), $P < 0.0001$ was highly significant. x^2 = chi square test

Table 7. *Preoperative side-effects.*

	Group O (n = 31)	Group N(n = 31)	x^2	*P*
Nystagmus	2 (6.4%)	1 (3.2%)	0.34	0.55
Abnormal movement	1 (3.2%)	0 (0%)	0.99	0.31
Hypersalivation	3 (9.6%)	2 (6.4%)	0.21	0.64
Hallucination	1 (3.2%)	0 (0%)	0.99	0.31

Data were expressed as No (%), $P < 0.0001$ was highly significant. x^2 = chi square test

Discussion

Preoperative anxiety is a great problem in children and their parents as it can be transmitted from parents to their children. Untreated preoperative anxiety produces poor outcome, delayed induction time, tachycardia, hypertension, large anesthetic consumption, and postoperative behavioral changes (10,11).

Ketamine is an effective sedative and analgesic drug for the prevention of separation anxiety and emergence agitation in children especially in developing countries (9,12).

Oral ketamine often requires higher and frequent doses as its bioavailability is lower (17%-24%) compared with IV (100%), IM (93%), sublingual/transbuccal (30%), intranasal (25%-50%), and inhaler (70%) due to extensive first pass metabolism in liver and intestine (13-15).

The perfect premedication should be of rapid onset, short duration, easy route of administration, acceptable by child, less side effects, and has adequate pain relief (16).

Therefore this study was done to compare the sedative and analgesic effects of oral or nebulized ketamine in preschoolers undergoing elective surgery.

A study by Adigun et al (3) used oral ketamine at a dose of 10 or 15 mg/kg for lumbar puncture in children undergoing intrathecal chemotherapy, and

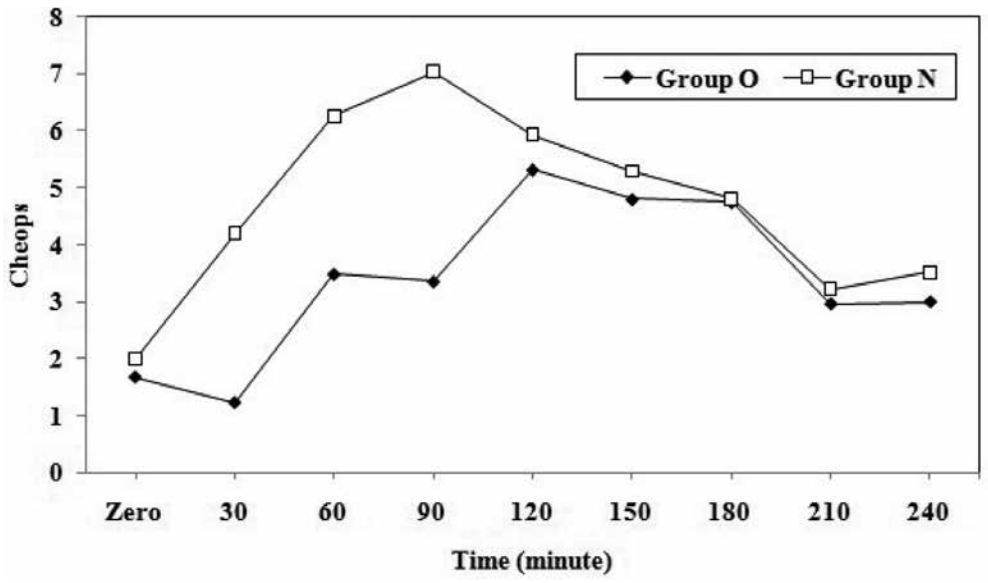

Fig. 1. *Modified CHEOPS in both groups. Mean ± SD.*

they found no cardiorespiratory compromise in both groups and no desaturation occurred. Also, Jain et al (17) revealed in their result that the patients in both nebulized ketamine and ketamine with clonidine groups remained hemodynamically stable. This agreed with our study.

Regarding sedation scores, our results revealed that 16 of 31 children in group O showed significant sedation scores (1 and 2) versus no children in group N at 30 minutes after administration of the drug. Also, successful venous cannulation and satisfactory separation accepted at ESS-4 score ≤ 2 were approved in group O than group N. This was explained by a study done by Jonkman et al (15) on bioavailability of inhaled ketamine, who concluded that a substantial reduction in bioavailability of inhaled ketamine was due to some quantity of liquid ketamine that remained in the container of the nebulizer, or aerosolized ketamine that adhered to the mouth piece, or the drug was swallowed, and/or large inhaled aerosol particles (>5 μm) are mainly trapped in the oropharynx and do not reach the bronchial tree, where small particles (<1 μm) are exhaled.

Also, we noticed in our study that oral ketamine sweetened in a juice drink was more tolerable and acceptable by children than a compressor nebulizer mouth mask, and this was in agreement with Ogboli-Nwasor et al (5). In Nigeria, ketamine is not available for oral administration, and syrup is made by mixing with soda (Fanta) to mask the bitter taste of the drug as reported by Ogboli-Nwasor et al (5). Also, in Egypt, and other developing countries, ketamine is not available in oral administration, so we used 2 mL of apple juice to sweeten it.

In the current study, there were no statistically significant differences between the 2 groups regarding side effects. Two patients had nystagmus in group O and one patient in group N, and one patient in group O had abnormal movement. This was in agreement with Ogboli-Nwasor et al (5) who explained that by small volume of the oral ketamine dose. There was hypersalivation in 3 patients in group O, and 2 patients in group N, which did not need interference during induction of anesthesia. This was in alliance with Adigun et al (3) who observed in their study increased secretion in both groups comparing 10 or 15 mg/kg oral ketamine without needing any intervention, and recommended using atropine as antisialagogue orally or IM with ketamine to prevent the increase in secretion. One patient in group O versus no patient in group N (0%) parents reported unusual behavior with hallucination.

In a study by Jain et al (17) comparing nebulized ketamine and ketamine with clonidine in postoperative sore throat found no side effects between both groups. This was in alignment with our results.

Regarding postoperative pain, there was less complaints with low modified CHEOPS score in group O than group N at 30, 60, and 90 minutes. Also, Matche et al (18) concluded in a case report study for pain management with IV and oral ketamine in a child with acute on chronic pancreatitis that oral ketamine can be used safely in managing pediatric pain.

Ahuja et al (19) found that nebulized ketamine in a dose of 50 mg (1 mL) (with 4 mL of the saline solution) before induction of anesthesia was better than saline solution to attenuate postoperative sore throat pain at 2 hours postoperative.

Limitations

In this study, although the dose of nebulized ketamine was 3 mg/kg, which was more than the optimum dose investigated in previous studies (20,21), it was not adequate, therefore we recommend conducting more studies investigating higher doses.

Conclusions

Oral ketamine 10mg/kg as premedication 30 minutes before induction of anesthesia is more effective than 3 mg/kg nebulized ketamine in producing good sedation, satisfactory separation from parents, successful venous cannulation, and effective postoperative analgesia with less adverse effects, as it is more tolerable and accepted by preschoolers undergoing elective surgery.

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References

1. Qiao H, Xie Z, Jia J. Pediatric premedication: A double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine. *BMC Anesthesiol* 2017; 17:158.
2. O'Donnell J, Bragg K, Sell S. Procedural sedation: Safely navigating the twilight zone. *Nursing* 2003; 33:36-44.
3. Adigun T, Brown B, Amanor BS. Oral ketamine use for lumbar puncture in children undergoing intrathecal chemotherapy in a developing country. *Int J Med Sci Clin Invent* 2018; 5:3921-3924.
4. Cohen S, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusion for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med* 2018; 43:521-546.
5. Ogboli-Nwasor E, Amaefule KE, Audu SS. Use of oral ketamine for analgesia during reduction/manipulation of fracture/dislocation in the emergency room: An initial experience in a low-resource setting. *Pain Stud Treat* 2014; 2:17-20.
6. Jonkman K, Duma A, Velzen M, Dahan A. Ketamine inhalation. *Br J Anesth* 2017; 118:268-269.
7. Yuen VM, Hui TW, Irwin MG, et al. A randomized comparison of two intranasal dexmedetomidine doses for premedication in children. *Anesthesia* 2012; 67:1210-1216.
8. Bahat R, Santhorsh M, Annigeri VM, Rao RP. Comparison of intranasal dexmedetomidine and dexmedetomidine-ketamine for premedication in pediatric patients: A randomized double-blind study. *Anesth Essays Res* 2016; 10:349-355.
9. Jeong JW, Kim YW, Moon GM, et al. The effect of ketamine on the separation anxiety and emergence agitation in children undergoing brief ophthalmic surgery under desflurane general anesthesia. *Korean J Anesthesiol* 2012; 63:203-208.
10. Das S, Kumar A. Preoperative anxiety in pediatric age group-a brief communication. *J Anesth Crit Care Open Access* 2017; 8:00317.
11. Fortier MA, Del Rosario AM, Martin SR, Kain ZN. Perioperative anxiety in children. *Paediatr Anaesth* 2010; 20:318-322.
12. World Health Organization. Ketamine (INN) update review report: 37th Expert Committee On Drug Dependence, Agenda item 6.1. 2015.
13. Nguyen L, Marshalek JP, Weaver BC, Cramer KJ, Pollard SE, Matsumoto RR. Off-label use of transmucosal ketamine as a rapid-acting antidepressant: A retrospective chart review. *Neuropsychiatr Dis Treat* 2015; 11:2667-2673.
14. Malinovsky JM, Servin F, Cozia A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after iv, nasal and rectal administration in children. *Br J Anaesth* 1996; 77:203-207.
15. Jonkman K, Duma A, Olofsen E, et al. Pharmacokinetics and bioavailability of inhaled esketamine in healthy volunteers. *Anesthesiology* 2017; 127:675-683.
16. Kain ZN, Hofstadter MB, Mayes LC, et al. Effects on amnesia and anxiety in children. *Anesthesiology* 2000; 93:676-684.
17. Jain S, Bendwal HP, Gohiya S, Alwani N, Pancholi S, Romday R. Comparison of nebulized ketamine and ketamine with clonidine in postoperative sore throat. *Int Surg J* 2017; 4:1579-1583.
18. Matche P, Kavya H, Gurudutt CL. Pain management with iv and oral ketamine in a child with acute on chronic pancreatitis: Old wine in new bottle-a case report. *J Recent Adv Pain* 2018; 4:66-68.
19. Ahuja V, Mitra S, Sarna R. Nebulized ketamine decrease incidence and severity of post-operative sore throat. *Indian J Anaesth* 2015; 59:37-42.

20. Zanaty O, El Metainy S. A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. *Anesth Analg* 2015; 121:167-171.
21. Abdel-Ghaffar HS, Kamal SM, El Sherif FA, Mohamed SA. Comparison of nebulised dexmedetomidine, ketamine, or midazolam for premedication in preschool children undergoing bone marrow biopsy. *Br J Anaesth* 2018; 121:445-452.