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Preanesthetic nebulized ketamine vs preanesthetic oral ketamine for sedation and postoperative pain management in children for elective surgery

A retrospective analysis for effectiveness and safety

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Abstract

Preoperative anxiety is a major problem in children leading to a poor outcome. Preanesthetic oral ketamine is generally used in children but has less bioavailability due to the first-pass effect. Even ketamine has an unpleasant taste. Preanesthetic inhaled ketamine is also reported effective and safe in children. The objectives of the study were to compare the effectiveness and safety of preanesthetic nebulized ketamine against preanesthetic oral ketamine for sedation and postoperative pain management in children.

Children received 10 mg/kg oral ketamine (children received preanesthetic oral ketamine [OK cohort], n = 142), or nebulized with 3 mg/kg ketamine (children were preanesthetic nebulized with ketamine [NK cohort], n = 115), or received apple juice (children suspectable to preoperative ketamine and received apple juice only [OA cohort], n = 126) before anesthesia for elective surgery. Data regarding preoperative hemodynamic parameters, sedation score measurements, postoperative pain management, postoperative nausea and vomiting management, and postoperative complications were collected and analyzed.

Preoperative hemodynamic parameters for oral and nebulized ketamine administration were stable. Nebulized ketamine was provided higher sedation than apple juice ($P = .002$, $q = 4.859$) and oral ketamine ($P = .002$, $q = 3.526$). Children of NK cohort had required fewer fentanyl consumption until discharge than those of OA (55.45 ± 7.19 μG/ child vs 65.15 ± 15.24 μG/ child, $P < .0001$, $q = 9.859$) and OK (55.45 ± 7.19 μG/child vs 60.19 ± 8.12 μG/child, $P < .0001$, $q = 4.953$) cohorts. Children of the NK cohort had consumed higher ondansetron syrup than those of the OA cohort but fewer than those of the OK cohort until discharge. Gastrointestinal side effects were reported in the OK cohort, and nose irritation and drowsiness were reported in the NK cohort.

Like preanesthetic oral ketamine, preanesthetic inhaled ketamine also has safety for children. Preanesthetic inhaled ketamine can provide effective sedation in low doses during operation than preanesthetic oral ketamine.

Level of evidence: III.

Abbreviation: VAS = visual analog scale.

Keywords: hemodynamic parameters, ketamine, pediatrics anesthesia, postoperative pain, preanesthetic medication, sedation

1. Introduction

Preoperative anxiety is a major problem in children leading to poor outcomes, delayed induction time, excess anesthetic consumption, hypertension, tachycardia, and postoperative behavioral changes.[1] Even, the behavior of children and personality has adverse effects if children failed to cooperate before the induction of anesthesia.[2] Preanesthetic medications are an effective strategy for sedation and postoperative pain and psychological trauma management in children.[3]

Ketamine is an effective sedative and analgesia in children to prevent preoperative anxiety but causes emergence agitation.[1,4] Ketamine provides analgesia effect by reversible antagonist action of N-methyl-D-aspartate receptors.[5] It has analgesic and sedative effects in different doses of administration.[6] The oral route of ketamine is generally used and is reported to be safe and effective in pediatrics[7] but requires a higher dose than inhaled ketamine[8] because of the oral route has a high first-pass effect.[9] Even ketamine has an unpleasant taste. Inhaled ketamine is also reported effective with manageable adverse effects in children.[10] Therefore, there is a need for the route of administration with rapid action, short duration of action, and with fewer side effects for preanesthetic medications.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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The objectives of the nonrandomized retrospective study were to compare the effectiveness and safety profile of preanesthetic nebulized ketamine against preanesthetic oral ketamine for sedation and postoperative pain management in children for elective surgery.

2. Materials and methods

2.1. Ethics approval and consent to participate

The designed protocol (CTGU/CL/09/20 dated March 28, 2020) was approved by the anesthesiology ethics committee of China Three Gorges University and the Chinese Society of Anesthesiology. The study reporting adheres to the law of China, the V2008 Declarations of Helsinki. An informed consent form was signed by parents (legally authorized persons) of children regarding anesthesia, surgery, and the publication of the study in the form of article irrespective of time and language before operations. As this was a retrospective study, the registration in the Chinese Clinical Trial registry was waived by the institutional review board.

2.2. Study population

Children who were admitted for elective surgery were included in the analysis. Children who did not receive any type of preanesthetic ketamine intervention were excluded from the analysis.

2.3. Cohorts

A total of 142 children received 10 mg/kg oral racemic mixture of S and R-ketamine injectable solution (Ketalar, Parke-Davis Pharmaceuticals Ltd, Vega Baja, PR) in 100 mL apple juice a 2 hours before anesthesia (children received preanesthetic oral ketamine [OK cohort]), a total of 115 children were nebulized with 3 mg/kg racemic mixture of S and R-ketamine solution in normal saline (Baxter Pharmaceuticals Pvt Ltd, Deerfield, IL) by jet nebulizer (Ningbo Five Continents Medical Instrument Co, Ltd, Yuyao, Zhejiang, China) via mouth mask a half an hour before anesthesia (children were preanesthetic nebulized with ketamine [NK cohort]),[11] and 126 children had drink 100 mL apple juice only (because clinicians reported suspectable to preoperative ketamine) a 2 hours (the current guidelines of the institute for preoperative fasting recommend 2 hours of fasting for clear liquids) before operation (children suspectable to preoperative ketamine and received apple juice only [OA cohort]). Children who have acceptance for nebulization, were nebulized for ketamine, and those who have acceptance for oral intake, they were received oral ketamine in apple juice. On operative day, only liquid diet including apple juice was given.

2.4. Preoperative hemodynamic parameters

Heart rate, mean arterial blood pressure, respiratory rate, and peripheral capillary oxygen saturation were recorded at baseline (on admission in the preoperative room), 5 minutes, and half an hour after administration of ketamine or apple juice in all cohorts.[11] The hemodynamic parameters were evaluated by anesthesiologists (at least 3-years of experience) of the institute.

2.5. Anesthesia method

Children were entered into the operation room, cannulated, preoxygenated with 100% oxygen for 5-minutes. A total of 0.02 mg/kg atropine (Atrisolon, Intas Pharmaceuticals, Ahmedabad, Gujarat, India), 1 μG/kg fentanyl (Durogesic, Johnson & Johnson, Pvt Ltd, IL) injection, 3 mg/kg propofol (Diprivan, AstraZeneca Pharmaceuticals, Cambridge, United Kingdom), and 0.5 mg/kg atracurium (Acubax, Baxter Pharmaceuticals Pvt Ltd, Deerfield, IL) were administered. Blood pressure, electrocardiogram, and pulse oximetry were monitored throughout surgery. At the end of surgery, 0.5 mg/kg neostigmine (Prostigmin, Nicholas Pharmaceuticals, USA) was administered and children were transferred to the postoperative care unit (neostigmine plus atropine was an option for antagonism). All anesthesia procedures were performed by anesthesiologists (at least 3-years of experience) of institute.[11]

2.6. Sedation score measurements

After the administration of drugs and immediately before the operation, sedation status was evaluated based on the score from 1 to 5.

1. agitated,
2. alert,
3. calm,
4. drowsy, and
5. sleep.[12]

The sedation score had been evaluated one time by anesthesiologists (at least 3-years of experience) of the institute.

2.7. Postoperative pain evaluation

Immediately after the consciousness of children, postoperative pain was accessed by visual analog scale (VAS) in the range of 10 to 0. 10 considered as maximum possible pain and 0 considered as absent pain.[13] VAS score was administered by operative nurses (at least 3-years of experience; unaware of preanesthetic medication) of institutes.

2.8. Postoperative pain management

After the operation, children had received 10 mg/mL paracetamol infusion (100 mL Perfalgan, Bristol Myers Squib, New York, NY, maximum 2 infusions per day and maximum for 3 days).[14] When VAS score increased more than 3, 25 μG fentanyl injection (0.5 mL, 50 μG fentanyl/mL injection) was administered by nursing staff (at least 3-years of experiences; unaware of preanesthetic medication) of institutes.

2.9. Postoperative nausea and vomiting management

On the occasion of nausea and/or vomiting, the nursing staff (at least 3-years experiences; unaware of preanesthetic medication) of institutes had given 5 mL of oral ondansetron syrup (Zofran 4 mg/ 5 mL syrup, Novartis Pharmaceuticals UK Ltd, London, UK) to children.[15]

2.10. Postoperative complications

The other postoperative complications during hospitalization and also after discharge in follow-up were collected from medical records of children of institutes and analyzed.

2.11. Statistical analyses

The sample size was calculated based on sedation status during surgery, at 80% power ($\beta = 0.1$), considering a 5% level of confidence, and a 2-sided type I error of 5% ($\alpha = 0.05$).[16] The

study was hypothesized that more than 80% ± 5% of children were received desired sedation status (sedation score >3) through preanesthetic oral/ nebulized ketamine. The minimum number of children in each cohort required (the sample size) was 110. Ordinal and constant data are presented as frequency (percentages) and continuous data are presented as mean ± standard deviation. SPSS V26, IBM Corporation, Armonk, NY was used for statistical analysis. One-way analysis of variance following the Tukey *post hoc* test (considering critical value [q] >3.327 as significant) for continuous data and the Fischer exact test for constant data[17] were performed for statistical analysis. All results were considered significant at a 95% confidence interval.

3. Results

3.1. Study population

From January 15, 2019 to December 13, 2019, a total of 387 children (age more than 3 years and less than 10 years) with weight 12 kg and more were admitted to the department of surgery for elective surgery at the Yichang Central People's Hospital and The First College of Clinical Medical Science, China Three Gorges University, Yichang, Hubei, China and referring hospitals and planned for general anesthesia. Among them 2 children had reported a history of epilepsy, 1 child had altered mental status, and 1 child had a respiratory tract infection. Therefore, these children were not subjected to any type of preoperative interventions. A total of 383 children were subjected to preanesthetic interventions (oral/nebulized ketamine or apple juice) before surgery. In the retrospective analysis, children were stratified on the basis of preanesthetic medication used as reported in Figure 1.

3.2. Preoperative and operative conditions of children

All included children had an age between 3 and 10 (4.15 ± 1.17) years. All included children have an American Society of Anesthesiologists status I or II. The other preoperative and operative clinical conditions of the enrolled children are reported in Table 1. There was no significant difference for the preoperative and operative clinical conditions of children among cohorts ($P > .05$ for all).

3.3. Preoperative hemodynamic parameters

There was no significant decrease in heart rate, arterial blood pressure, respiratory rate, and peripheral capillary oxygen saturation at baseline among cohorts. Also, 30 minutes after interventions, hemodynamic parameters had no significant changes as compared to baseline in all cohorts ($P > .05$ for all parameters). Oral ketamine or nebulized ketamine did not change heart rate, arterial blood pressure, respiratory rate, or

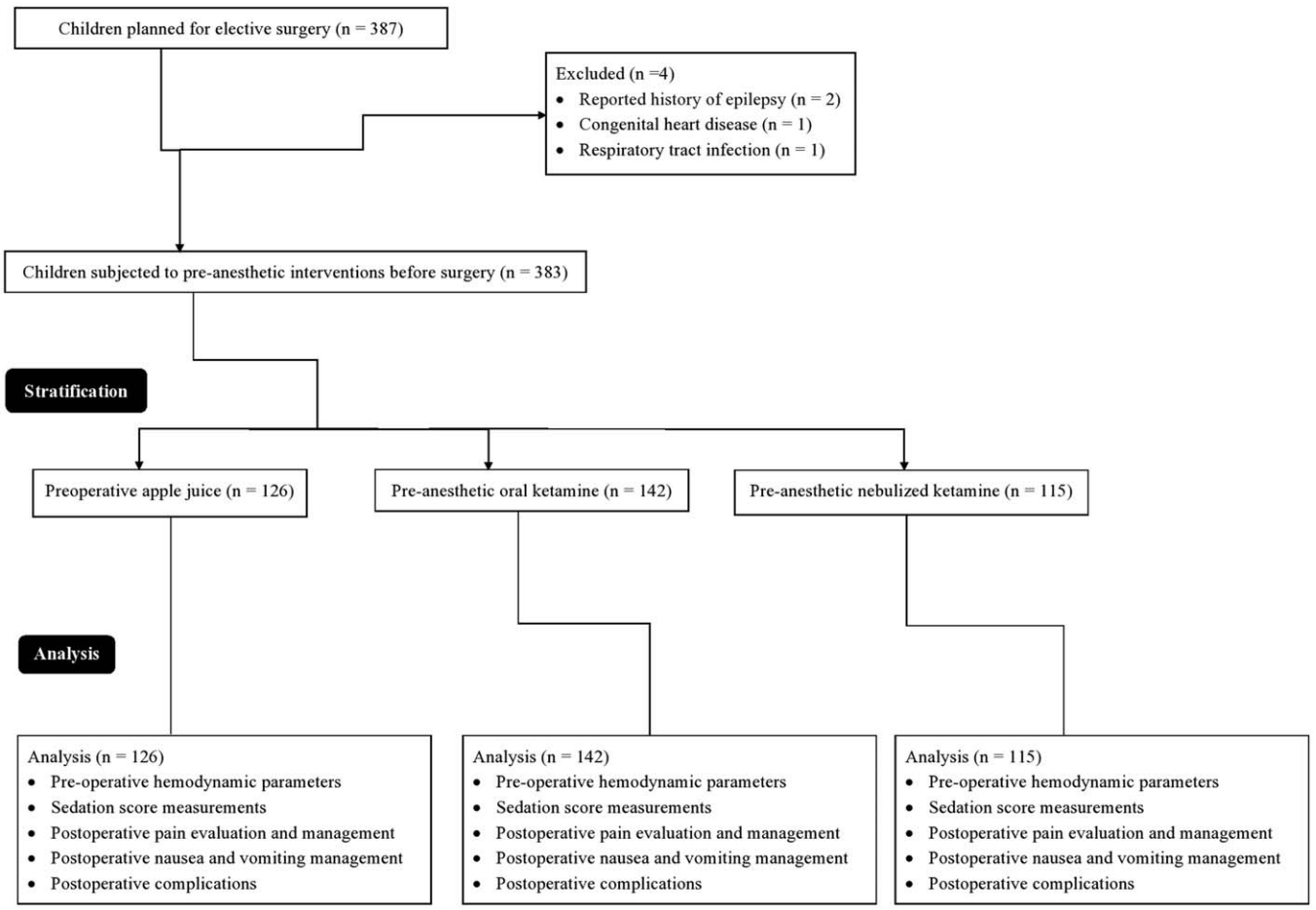

Figure 1. Flow diagram of the study.

Table 1

Preoperative and operative clinical conditions of children enrolled in the study.

Characteristics Preanesthetic interventions	Total	Cohorts OA Apple juice	 OK Oral ketamine	 NK Nebulized ketamine	Comparison between cohorts
Numbers of children	383	126	142	115	*P*-value
Age (yrs)					
Minimum	3	4	3	3	.061
Maximum	10	8	9	10	
Mean ± SD	4.15 ± 1.17	3.95 ± 1.61	4.21 ± 1.11	4.41 ± 1.79	
Body mass index (kg/m^2)					
Minimum	16.51	16.51	17.09	16.88	.055
Maximum	20.32	20.22	19.89	20.32	
Mean ± SD	17.18 ± 1.65	16.85 ± 2.01	17.39 ± 1.72	17.81 ± 1.82	
Gender					
Male	219 (57)	71 (56)	81 (57)	67 (58)	.955
Female	164 (43)	55 (44)	61 (43)	48 (42)	
American Society of Anesthesiologists status					
I	298 (78)	91 (72)	115 (81)	92 (80)	.181
II	85 (22)	35 (28)	27 (19)	23 (20)	
Ethnicity					
Han Chinese	353 (92)	116 (92)	131 (92)	106 (92)	.986
Mongolian	26 (7)	9 (7)	9 (7)	8 (7)	
Tibetan	4 (1)	1 (1)	2 (1)	1 (1)	
Elective Surgeries					
Correction of bone fractures	222 (58)	73 (58)	78 (55)	71 (62)	.074
Congenital cardiac defects	84 (22)	29 (23)	40 (28)	15 (13)	
Abdominal wall defects	61 (16)	21 (17)	19 (13)	21 (18)	
Appendicitis	16 (4)	3 (2)	5 (4)	8 (7)	
Duration of surgery (min)	76.22 ± 8.23	71.85 ± 15.16	75.21 ± 9.89	77.01 ± 25.12	.064

Constant data are demonstrated as frequency (percentages) and continuous data are demonstrated mean ± standard deviation.
One-way analysis of variance for continuous data and the Fischer exact test for constant data were performed for statistical analysis.
A $P < .05$ was considered as significant.

Table 2

Preoperative hemodynamic parameters.

Parameters Pre-anesthetic interventions	Cohorts OA Apple juice	 OK Oral ketamine	 NK Nebulized ketamine	Comparison between cohorts
Numbers of children	126	142	115	*P*-value
Heart rate				
Baseline	113.15 ± 15.14	111.21 ± 12.15	109.14 ± 16.18	.100
5 min after administration	106.85 ± 14.13	104.23 ± 9.42	102.92 ± 15.12	.055
30 min after administration	89.22 ± 14.12	87.15 ± 12.85	85.61 ± 11.14	.090
Mean arterial blood pressure				
Baseline	70.12 ± 5.21	71.21 ± 4.56	71.98 ± 7.99	.053
5 min after administration	69.15 ± 4.98	70.55 ± 4.12	70.51 ± 6.55	.053
30 min after administration	68.54 ± 4.55	68.52 ± 3.53	67.29 ± 5.53	.051
Respiratory rate (breath/min)				
Baseline	29.21 ± 3.98	29.01 ± 4.01	29.12 ± 3.95	.919
5 min after administration	28.22 ± 4.23	27.95 ± 3.53	28.12 ± 4.56	.861
30 min after administration	27.58 ± 3.52	26.52 ± 4.55	26.58 ± 3.55	.056
Peripheral capillary oxygen saturation				
Baseline	98.43 ± 1.42	98.53 ± 1.11	98.63 ± 1.52	.516
5 min after administration	98.08 ± 2.01	97.62 ± 1.69	97.59 ± 1.61	.051
30 min after administration	98.01 ± 0.90	97.61 ± 2.43	97.53 ± 1.98	.105

Data are demonstrated as mean ± standard deviation.
Baseline: On admission in the preoperative room.
One-way analysis of variance was performed for statistical analysis.
A $P < .05$ was considered as significant.
After administration: After administration of ketamine or apple juice.

Table 3

Preoperative sedation score measurements of children after intervention and before operation.

	Cohorts			Comparison between cohorts			
Sedation score	OA	OK	NK				
Preanesthetic interventions	Apple juice	Oral ketamine	Nebulized ketamine		*q*-value		
Numbers of children	126	142	115	*P*-value	Between OA and OK	Between OA and NK	Between OK and NK
3	28 (22)	29 (20)	5 (4)	.002	1.507	4.859	3.526
4	43 (34)	40 (28)	43 (37)				
5	55 (44)	73 (52)	67 (56)				
Mean ± SD	4.21 ± 0.79	4.31 ± 0.79	4.54 ± 0.58*				

Data are demonstrated as frequency (percentage).
One-way analysis of variance following Tukey *post hoc* test was performed for statistical analysis.
A $P < .05$ with $q > 3.327$ was considered as significant.
* Significantly higher than OA and OK cohorts.
1: agitated, 2: alert, 3: calm, 4: drowsy, and 5: sleep.
Sedation score had been evaluated one time by anesthesiologists.

peripheral capillary oxygen saturation ($P > .05$ for all evaluation points, Table 2) before surgery.

3.4. Sedation score measurements

Nebulized ketamine was provided higher sedation than apple juice only (4.54 ± 0.58/child vs 4.21 ± 0.79/child, $P = .002$, $q = 4.859$) and oral ketamine (4.54 ± 0.58/child vs 4.31 ± 0.79/child, $P = .002$, $q = 3.526$). Oral ketamine had no significant effects on sedation score (no statistical difference for sedation score with respect to children of OA cohort, 4.31 ± 0.79/child vs 4.21 ± 0.79/child, $P = .002$, $q = 1.507$). The detailed sedation score of children after administration of all drugs and before operation is reported in Table 3.

3.5. Postoperative pain

Ketamine oral or nebulized was successful in the reduction of postoperative pain. Postoperative pain of children of NK cohort was lesser than those of OA cohort ($P < .0001$, $q = 6.744$) and OK cohort ($P < .0001$, $q = 3.359$). Also, the postoperative pain of children was lesser in the OK cohort than those of the OA cohort ($P < .0001$, $q = 3.664$). The details of the postoperative pain of children are reported in Table 4.

3.6. Postoperative pain management

Children of NK cohort had required fewer paracetamol infusion until discharge than OA cohort (3.69 ± 0.45 g/child vs 4.15 ± 1.05 g/child, $P < .0001$, $q = 6.539$) and OK cohort (3.69 ± 0.45 g/child vs 3.95 ± 0.68 g/child, $P < .0001$, $q = 3.799$) but children of NK cohort and those of OK cohort had required the same amount of paracetamol infusion ($P < .0001$, $q = 2.996$) until discharge (Fig. 2).

Children of NK cohort had consumed fewer total fentanyl until discharge than those of OA cohort (55.45 ± 7.19 μG/child vs 65.15 ± 15.24 μG/child, $P < .0001$, $q = 9.859$) and OK cohort (55.45 ± 7.19 μG/child vs 60.19 ± 8.12 μG/child, $P < .0001$, $q = 4.953$). Also, children of the OK cohort had required fewer total fentanyl until discharge than those of the OA cohort ($P < .0001$, $q = 5.313$, Fig. 3).

3.7. Postoperative nausea and vomiting management

Children of NK cohort had consumed higher total ondansetron syrup until discharge than OA cohort (17.19 ± 2.15 mL/child vs 16.45 ± 2.11 mL/ child, $P < .0001$, $q = 3.797$) but fewer total ondansetron syrup until discharge than those of OK cohort (17.19 ± 2.15 mL/child vs 17.98 ± 2.15 mL/child, $P < .0001$, $q = 4.168$). Children of OK cohort had consumed higher total

Table 4

Postoperative pain measurements.

	Cohorts			Comparison between cohorts			
Visual analog scale score	OA	OK	NK				
Preanesthetic interventions	Apple juice	Oral ketamine	Nebulized ketamine		*q*-value		
Numbers of children	126	142	115	*P*-value	Between OA and OK	Between OA and NK	Between OK and NK
3	0 (0)	0 (0)	5 (4)	<.0001	3.664	6.744	3.359
4	42 (33)	51 (36)	49 (43)				
5	41 (33)	65 (46)	49 (43)				
6	29 (23)	22 (15)	11 (9)				
7	12 (10)	4 (3)	1 (1)				
8	2 (1)	0 (0)	0 (0)				
Mean ± SD	5.13 ± 1.04	4.86 ± 0.79	4.60 ± 0.76*				

Ordinal data are demonstrated as frequency (percentages).
One-way analysis of variance following Tukey *post hoc* test was performed for statistical analysis.
A $P < .05$ and $q > 3.327$ were considered as significant.
* Significantly fewer than OA and OK cohorts.
0: Absent pain, 10: Maximum possible pain.

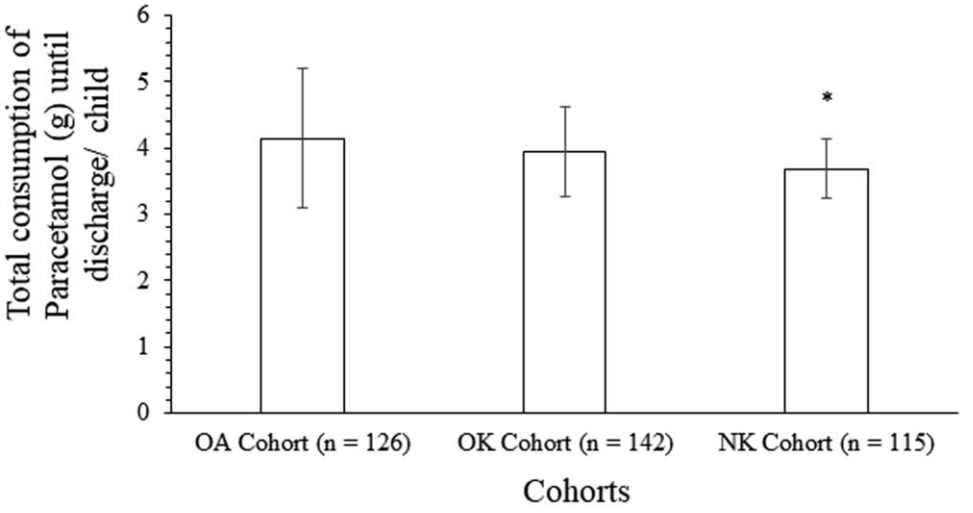

Figure 2. Paracetamol infusion consumption for postoperative pain management. Data are demonstrated as mean ± standard deviation. One-way analysis of variance following the Tukey *post hoc* test was performed for statistical analysis. A $P < .05$ and $q > 3.327$ were considered as significant. *Significantly fewer than OA and OK cohorts. 10 mg/mL, 100 mL paracetamol infusion administered for postoperative pain management (maximum 2 infusions per day, and maximum for 3 days). OA cohort = children suspectable to preoperative ketamine and received apple juice only, OK cohort = children received preanesthetic oral ketamine.

ondansetron syrup until discharge than those of OA cohort ($P < .0001$, $q = 8.273$, Fig. 4).

3.8. Postoperative complications

Besides common surgical problems like pain and inflammation of the skin or rash at the injection site, nausea, specific ketamine-related problems, for example, gastrointestinal side effects were reported in the OK cohort, and nose irritation and drowsiness were reported in the NK cohort. The detailed postoperative complications are reported in Table 5.

4. Discussion

The current study is reported stable preoperative hemodynamic parameters for oral ketamine administration and also for nebulized ketamine administration. The results of the hemodynamic parameters of the current study were agreed with those of randomized trials.[7,11,18] Like preanesthetic oral ketamine, preanesthetic inhaled ketamine also has safety for children.

Nebulized ketamine was provided higher sedation than apple juice only and oral ketamine. The results of the sedation of the current study were agreed with those of randomized trials.[3,7,11] Inhaled ketamine has 70% bioavailability and oral ketamine has 17% to 24% bioavailability[8] (high margin between 2 values). The intranasal route does not require intravenous cannulation or injection but has high bioavailability.[19] Preanesthetic inhaled ketamine can provide effective sedation in low doses during operation than preanesthetic oral ketamine.

The current study is reported less consumption of paracetamol infusion and total fentanyl until discharge for children of the NK

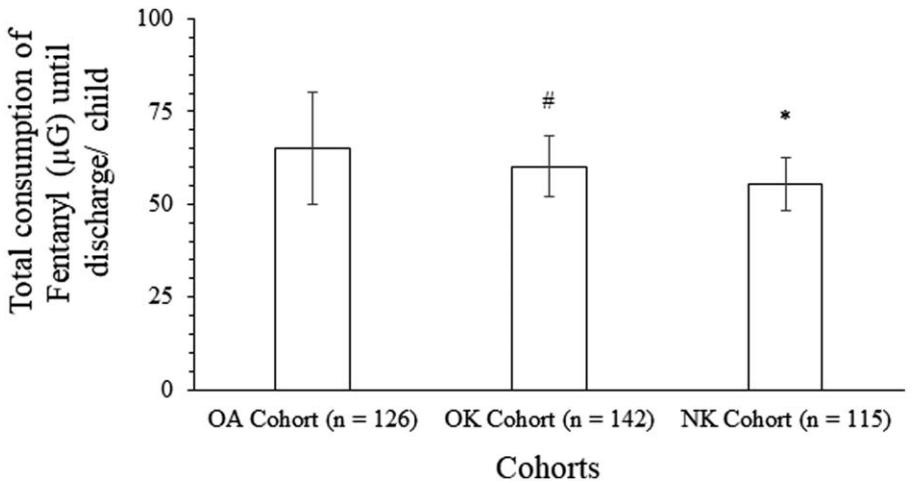

Figure 3. Total fentanyl consumption until discharge. Data are demonstrated as mean ± standard deviation. One-way analysis of variance following the Tukey *post hoc* test was performed for statistical analysis. A $P < .05$ and $q > 3.327$ were considered as significant. *Significantly fewer than OA and OK cohorts. #Significantly fewer than the OA cohort. When VAS score increased more than 3, 25 μG fentanyl injection was administered. OA cohort = children suspectable to preoperative ketamine and received apple juice only, OK cohort = children received preanesthetic oral ketamine.

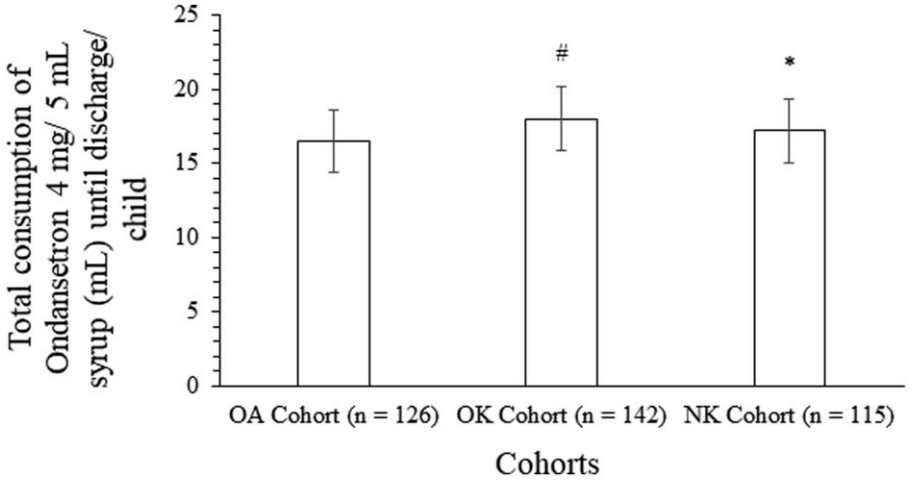

Figure 4. Postoperative nausea and vomiting management. Data are demonstrated as a mean ± standard deviation. One-way analysis of variance following the Tukey *post hoc* test was performed for statistical analysis. A $P < .05$ and $q > 3.327$ were considered as significant. #Significantly higher than OA and NK cohorts. *Significantly fewer than OK cohort. On the occasion of nausea and/or vomiting, 5 mL of oral ondansetron syrup (4 mg/ 5 mL) was given. NK cohort = children were preanesthetic nebulized with ketamine, OA cohort = children suspectable to preoperative ketamine and received apple juice only, OK cohort = children received preanesthetic oral ketamine.

cohort than those of OK and OA cohorts. The results of the postoperative pain management of the current study were agreed with those of a randomized trial.[11] Ketamine affects μ-opioid receptors and provides a fentanyl sparing effect.[5] Postoperative pain of children is significantly reduced by preanesthetic oral and nebulized ketamine.

Children of the NK cohort had consumed fewer total ondansetron syrup until discharge than those of the OK cohort. The results of postoperative nausea and vomiting management of the current study were agreed with those of randomized trials.[3,18] Fentanyl was used with propofol for anesthesia was responsible for vomiting.[15] Also, ketamine itself has emetic property in children.[20,21] In the NK cohort children had lesser consumption of fentanyl until discharge and preanesthetic ketamine than the OK cohort. Therefore, preanesthetic nebulized ketamine may have less postoperative nausea and vomiting than oral ketamine.

Gastrointestinal side effects were reported in the OK cohort and nose irritation and drowsiness were reported in the NK cohort. The results of the postoperative complications of the current study were agreed with those of randomized trials.[3,7,11,18,22] Preanesthetic inhaled and oral ketamine have manageable postoperative adverse effects.

There are several limitations of the study that have to be reported, for example, retrospective study, lack of randomized

Table 5

Postoperative complications.

	Cohorts				Comparison between cohorts		
Adverse effect	**OA**	**OK**	**NK**				
Preanesthetic interventions	**Apple juice**	**Oral ketamine**	**Nebulized ketamine**		***q*-value**		
Numbers of children	**126**	**142**	**115**	***P*-value**	**Between OA and OK**	**Between OA and NK**	**Between OK and NK**
Agitation	1 (1)	2 (1)	2 (2)	.806	N/A	N/A	N/A
Gastrointestinal side effects	1 (1)	11 (8)*	2 (2)	.004	4.326	0.558	3.647
Nose irritation	1 (1)	2 (1)	11 (10)*	.001	0.385	5.218	4.988
Drowsiness	1 (1)	2 (1)	7 (6)*	.019	0.448	3.664	3.329
Dry mouth	1 (1)	2 (1)	5 (4)	.122	N/A	N/A	N/A
Laryngospasm	1 (1)	1 (1)	2 (2)	.681	N/A	N/A	N/A
Cough	2 (2)	3 (2)	5 (4)	.366	N/A	N/A	N/A
Hoarseness	0 (0)	0 (0)	2 (2)	.096	N/A	N/A	N/A
Double vision	0 (0)	1 (1)	2 (2)	.309	N/A	N/A	N/A
Skin inflammation/rash	0 (0)	2 (1)	2 (2)	.361	N/A	N/A	N/A
Loss of appetite	0 (0)	0 (0)	1 (1)	.313	N/A	N/A	N/A
Increase in salivation	0 (0)	0 (0)	1 (1)	.313	N/A	N/A	N/A
Pain when urinating	0 (0)	0 (0)	1 (1)	.313	N/A	N/A	N/A

Data are demonstrated as frequency (percentages).

One-way analysis of variance following the Tukey *post hoc* test was performed for statistical analysis.

A $P < .05$ and $q > 3.327$ were considered as significant.

* Significant adverse effect.

N/A = not applicable.

trial. The negative control group of nebulized normal saline was absent in the study. The randomized trial provides exact results without bias but there is restriction bias of inclusion criteria in trial. While in clinical practice, there is wide scope for inclusion. Therefore, retrospective analysis of clinical practice provides more insight than a randomized trial. Data related to hospital stays did not evaluate. Different surgical procedures where preanesthetic medication was common and considered for analysis only. The hospital stays dependent upon surgical procedures. Therefore, such data did not use for analysis. The measurements of children's acceptance of nebulized ketamine did not evaluate. It is well-known that ketamine has an unpleasant taste. Therefore, children may have higher acceptance for nebulized ketamine than oral ketamine. The oral ketamine has less bioavailability but not what estimated bioavailability is. An oral dose of 10 mg/kg seems like an high dose. This would be important to estimate if equipotent doses of nebulized ketamine and oral ketamine is used in the future study. The intranasal ketamine dose administered is much lower (3 mg) than that suggested by the most recent literature (7 or 9 mg). Timing and context (caregiver separation, monitor application, painful procedure) of sedative efficacy assessment are primary and comparative data between studies. They lack the study. Given the mean age of the children [3–10 (4.15 ± 1.17) years], observational algometric scales are the validated tools but the study had used VAS. The possible justification for the same is that the VAS is reported as a continuous scale for self-report of pain intensity in children aged 6 years and older.[13] Moreover, it is not specified how often and at what time interval the pain was assessed. So, it becomes difficult to establish whether children had received an accurate evaluation and treatment as often as needed. The dosage of drugs in pediatric age must be related to the weight/body surface of the children. A total of 10 mg of paracetamol and 25 μG of fentanyl may not be a correct dosage for all children alike. Also, elective surgeries include correction of bone fractures, congenital cardiac defects, abdominal wall defects, and appendicitis, paracetamol is not sufficient in these surgeries. However, the surgeons have used fentanyl in severity.

5. Conclusions

Preanesthetic inhaled ketamine can provide effective sedation in low doses during operation than preanesthetic oral ketamine. Postoperative pain of children is significantly reduced by preanesthetic oral and nebulized ketamine. Like preanesthetic oral ketamine, preanesthetic inhaled ketamine also has safety for children. Preanesthetic nebulized ketamine may have less postoperative nausea and vomiting than preanesthetic oral ketamine. Preanesthetic inhaled and oral ketamine have manageable postoperative adverse effects.

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