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SCIENTIFIC ARTICLE

Preemptive nebulized ketamine for pain control after tonsillectomy in children: randomized controlled trial

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KEYWORDS
Children;
Tonsillectomy;
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IV ketamine;
Nebulized ketamine

Abstract
Objectives: The administration of ketamine as nebulized inhalation is relatively new and studies on nebulized ketamine are scarce. We aimed to investigate the analgesic efficacy of nebulized ketamine (1 and 2 mg.kg^{-1}) administered 30 min before general anesthesia in children undergoing elective tonsillectomy in comparison with intravenous ketamine (0.5 mg.kg^{-1}) and saline placebo.
Methods: One hundred children aged (7–12) years were randomly allocated in four groups ($n = 25$) receive; Saline Placebo (Group C), Intravenous Ketamine 0.5 mg.kg^{-1} (Group K-IV), Nebulized Ketamine 1 mg.kg^{-1} (Group K-N1) or 2 mg.kg^{-1} (Group K-N2). The primary endpoint was the total consumption of rescue analgesics in the first 24 h postoperative.
Results: The mean time to first request for rescue analgesics was prolonged in K-N1 (400.9 ± 60.5 min, 95% CI 375.9–425.87) and K-N2 (455.5 ± 44.6 min, 95% CI 437.1–473.9) groups compared with Group K-IV (318.5 ± 86.1 min, 95% CI 282.9–354.1) and Group C (68.3 ± 21.9 min, 95% CI 59.5–77.1; $p < 0.001$), with a significant difference between K-N1 and K-N2 Groups ($p < 0.001$). The total consumption of IV paracetamol in the first 24 h postoperative was reduced in Group K-IV (672.6 ± 272.8 mg, 95% CI 559.9–785.2), Group K-N1 (715.6 ± 103.2 mg, 95% CI 590.4–840.8) and Group K-N2 (696.6 ± 133.3 mg, 95% CI 558.8–834.4) compared with Control Group (1153.8 ± 312.4 mg, 95% CI 1024.8–1282.8; $p < 0.001$). With no difference between intravenous and Nebulized Ketamine Groups ($p = 0.312$). Patients in intravenous and Nebulized Ketamine Groups showed lower postoperative VRS scores compared with Group C ($p < 0.001$), no differences between K-IV, K-N1 or K-N2 group and without significant adverse effects.

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Conclusion: Preemptive nebulized ketamine was effective for post-tonsillectomy pain relief. It can be considered as an effective alternative route to IV ketamine.

PALAVRAS-CHAVE
Crianças;
Amigdalectomia;
Analgesia;
Cetamina IV;
Cetamina nebulizada

Uso preventivo de cetamina nebulizada para controle da dor após amigdalectomia em crianças: estudo randômico e controlado

Resumo
Objetivos: A administração de cetamina por via inalatória através de nebulizador é relativamente nova e os estudos sobre este assunto são escassos. Nosso objetivo foi investigar a eficácia analgésica da cetamina nebulizada (1 e 2 mg.kg^{-1}) administrada 30 minutos antes da anestesia geral em crianças submetidas à amigdalectomia eletiva, em comparação com cetamina intravenosa (0,5 mg.kg^{-1}) e placebo (soro fisiológico).
Métodos: Cem crianças com idades entre 7–12 anos foram randomicamente alocadas em quatro grupos (n = 25) e receberam: soro fisiológico para controle (Grupo C); 0,5 mg.kg^{-1} de cetamina intravenosa (Grupo C-IV); 1 mg.kg^{-1} de cetamina nebulizada (Grupo C-N1); 2 mg.kg^{-1} de cetamina nebulizada (Grupo C-N2). O desfecho primário foi o consumo total de analgésicos de resgate nas primeiras 24 horas de pós-operatório.
Resultados: O tempo médio para a primeira solicitação de analgésicos de resgate foi prolongado nos grupos C-N1 (400,9 ± 60,5 min, IC 95% 375,9–425,87) e C-N2 (455,5 ± 44,6 min, IC 95% 437,1–473,9) em comparação com o Grupo C-IV (318,5 ± 86,1 min, IC 95% 282,9–354,1) e o Grupo C (68,3 ± 21,9 min, IC 95% 59,5–77,1; $p < 0,001$), com uma diferença significativa entre os grupos C-N1 e C-N2 ($p < 0,001$). O consumo total de paracetamol IV nas primeiras 24 horas de pós-operatório foi reduzido no Grupo C-IV (672,6 ± 272,8 mg, IC 95% 559,9–785,2), Grupo C-N1 (715,6 ± 103,2 mg, IC 95% 590,4–840,8) e Grupo C-N2 (696,6 ± 133,3 mg, IC 95% 558,8–834,4) em comparação com o Grupo C (1153,8 ± 312,4 mg, IC 95% 1024,8–1282,8; $p < 0,001$). Não houve diferença entre os grupos de cetamina intravenosa e nebulizada ($p = 0,312$). Os pacientes dos grupos de cetamina intravenosa e nebulizada apresentaram escores VRS pós-operatórios menores, em comparação com o Grupo C ($p < 0,001$), sem diferenças entre os grupos C-IV, C-N1 ou C-N2 e sem efeitos adversos significativos.
Conclusão: A administração preventiva de cetamina nebulizada foi eficaz no alívio da dor pós-amigdalectomia. Cetamina nebulizada pode ser considerada como uma via alternativa eficaz à cetamina IV.

Introduction

Tonsillectomy continues to be the most common pediatric Otolaryngologic procedure worldwide.[1] Post-tonsillectomy pain is the most common complication of this procedure and if not properly managed it can lead to several complications such as poor oral intake, dehydration, the need for IV fluids and prolonged hospital stay.[2] Non-steroidal Anti-Inflammatory Agents (NSAIDs), systemic opioids, intravenous paracetamol, and local anesthetics have been commonly used for post-tonsillectomy pain control in children.[3–5] However, systemic opioids may cause respiratory depression, sedation, or nausea and vomiting[3,4] and NSAIDs might interfere with bleeding.[6]

Ketamine, a non-competitive N-Methyl-D-Aspartate antagonist (NMDA), blunts central hypersensitivity caused by pain at sub-anesthetic doses (0.3 mg.kg^{-1} or less).[7] Perioperative systemic and local ketamine improved postoperative analgesia and reduced postoperative opioid consumption in a wide range of surgical procedures including tonsillectomy.[1,7] Considering that ketamine has less effect on airway patency and respiratory drive, it could be an ideal choice in children with sleep apnea.[8]

Intravenous ketamine has been administered as an adjunct to fentanyl[9] or intravenous paracetamol[10] in tonsillectomy and significantly attenuated postoperative pain. Inhalation of nebulized ketamine is an alternative new route of administration that is relatively easy to set up, needle-free and is associated with high bioavailability.[11]

The aim of this study was to investigate the analgesic efficacy of two doses of nebulized ketamine (1 and 2 mg.kg^{-1}) administered 30 min before general anesthesia in children undergoing tonsillectomy in direct comparison with intravenous ketamine (0.5 mg.kg^{-1}) and placebo controls.

Patients and methods

Enrollment and eligibility

This randomized double-blind (for the patients and researchers) clinically controlled trial was approved by the medical ethics committee, faculty of medicine, Assiut University, Assiut, Egypt (IRB n° 17300154, date: December 27, 2015). The study followed the regulations and amendments of the Helsinki Declaration and written consent was taken from the patients' legal guardians participating in the trial. The trial was registered prior to patient enrollment at Clinical Trials.gov (NCT02720406). One hundred patients ASA I-II of both sexes, aged from 7–12 years old scheduled for elective tonsillectomy (with or without adenoidectomy) under general anesthesia were enrolled in this study. Excluded from the study any child with a cardiac, respiratory or neuropsychiatric disorder, increased intracranial or intraocular pressure and history of porphyria or known allergy to study drugs.

Randomization and blinding

Randomization was performed according to a computer-generated randomization table, with group allocation concealed in sealed opaque envelopes. One hundred patients were allocated in four groups (of 25 patients each) to receive; Saline Placebo (Control Group or Group C), Intravenous Ketamine 0.5 mg.kg^{-1} (Group K-IV), Nebulized Ketamine 1 mg.kg^{-1} (Group K-N1) or Nebulized Ketamine 2 mg.kg^{-1} (Group K-N2). A blinded physician prepared the study medications in color-coded syringes. All patients in the studied groups received study drugs by both the nebulization and intravenous routes as study protocol. Intravenous saline placebo was administered to all groups except Group K-IV who received intravenous ketamine. Nebulized saline placebo was administered to control and K-IV groups while nebulized ketamine was administered to patients in Group K-N1 and K-N2. Intravenous study medications were diluted with saline 0.9% up to 2 mL volume and administered after induction of anesthesia and before surgery. Nebulized medications were diluted with saline 0.9% up to 3 mL volume and administered 30 min before induction of general anesthesia.

Nebulization was done by standard hospital jet nebulizer via a mouthpiece (Mxineb Nebulizer with 010–631 T piece + tubing, Flexicare Medical Ltd, Cynon Valley Business Park, Mountain Ash. CF45 4ER. UK), with a continuous flow of 100% oxygen at 6 L min^{-1} for 10 min. The attending anesthesiologist, surgeon, data collecting personnel and the patient guardians were blinded to the patient group assignment.

The study protocol and assessments

Preoperatively, all patients received nebulized study drug according to patient group assignment. Patients were monitored during nebulizer administration and for 30 min after its end. Routine standard monitoring included non-invasive blood pressure, peripheral arterial oxygen saturation, electrocardiography and end-tidal carbon dioxide (Cardiocap II: Datex-Ohmeda, Helsinki, Finland). All children received EMLA cream (Eutectic Mixture of Local Anesthetics; Astra Zeneca, London, UK) for intravenous cannulation unless contraindicated. Upon arrival at the operating theater the patients' level of sedation was assessed using a five point sedation scale[12] as follows; 1 = agitated, 2 = alert, 3 = calm, 4 = drowsy, and 5 = asleep (A score $\geq$ 3 denoted acceptable sedation).

The anesthetic technique was standardized for all groups. Anesthesia was induced with propofol 2–3 mg.kg^{-1}, fentanyl 1 μg.kg^{-1} and atracurium 0.5 mg.kg^{-1} for muscle relaxation. The size of the cuffed endotracheal tube was selected according to the patients' age. Anesthesia and muscle relaxation were maintained with sevoflurane in a 50% oxygen/air mixture and 0.15 mg.kg^{-1} atracurium at fixed intervals. All patients received volume cycled mechanical ventilation in ventilator settings that maintained normocarbia. Before surgery, all patients received the intravenous study drug solution according to group assignment. Intraoperative, patients received IV paracetamol 15 mg.kg^{-1} and 10 mL.kg^{-1} normal saline infusion. At the end of the procedure, residual neuromuscular blockade was reversed with standard doses of neostigmine and atropine. Patients were extubated awake in the recovery position and transported to the Post Anesthesia Care Unit (PACU). The anesthesia time (time in minutes from induction of anesthesia till its discontinuation) and time to extubation (time in minutes from the discontinuation of anesthesia till extubation) were recorded. After fulfilling the criteria of full recovery, patients were transferred to the ward.

Verbal rating pain scale (Ranging from 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain and lastly 4 = excruciating pain) was recorded on admission to PACU (baseline), and at 30 min, 1, 2, 3, 4, 5, 6, 12 and 24 h postoperative. Patients received IV paracetamol 15 mg.kg^{-1} as rescue analgesia if requested and if VRS scores were $\geq$2. The time to first request for rescue analgesia and the total consumption of postoperative rescue analgesics were recorded. Any perioperative adverse events were treated and recorded such as hypotension, hypertension, bradycardia, tachycardia, desaturation (SpO_2% < 92%), postoperative vomiting, agitation, nystagmus, photophobia, excess salivation, and hallucination.

Statistical analysis

Power calculation

The primary endpoint was the total consumption of rescue analgesics in the first 24 h postoperative. Secondary outcomes were; postoperative verbal rating pain score, the time to first request for rescue analgesics, hemodynamics, time to extubation and perioperative adverse effects. Based on previous researches,[9,10,13] at a power of 80%, with 95% Confidence Interval and a 2 sided Type I error of 5%, 21 patients were required in each group to detect a significant difference between the four studied groups in the mean total consumption of rescue analgesics in the first 24 h postoperative. To account for patients dropouts, we recruited 100 patients who were equally distributed between study groups.

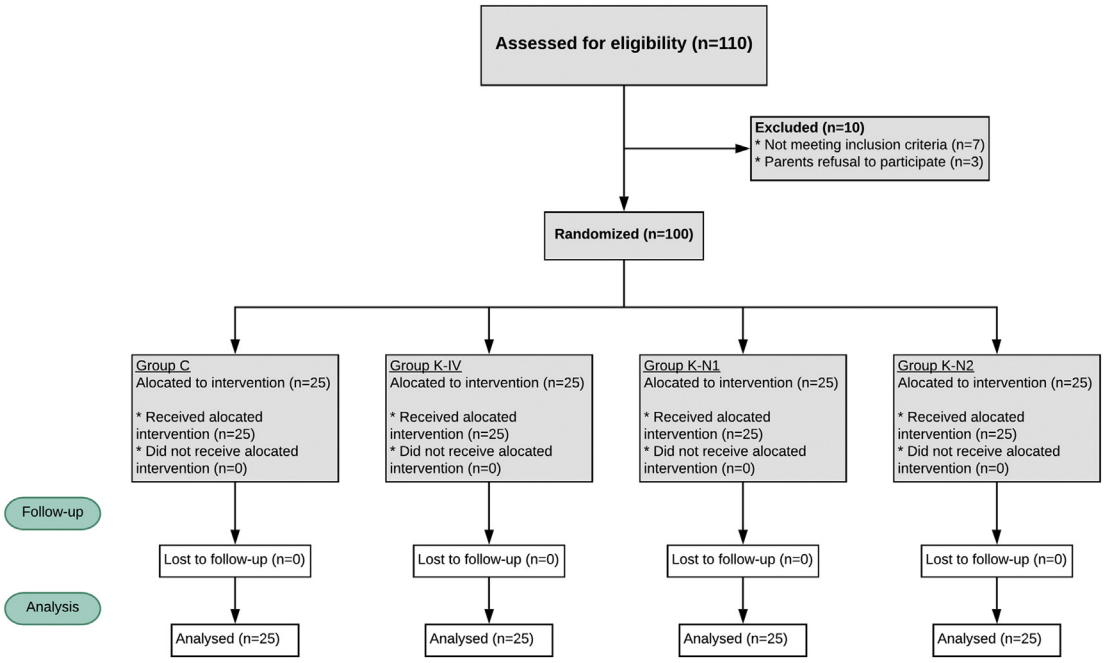

Figure 1 Participant flow diagram. Group C, Placebo Control; K-IV, Intravenous Ketamine 0.5 mg.kg^{-1}; K-N1, Nebulized Ketamine 1 mg.kg^{-1}; K-N2, Nebulized Ketamine 2 mg.kg^{-1}.

Statistical testing

SPSS (Statistical Package for Social Science) version 19 was used for data entry and analysis. Data were presented as mean ± SD with a 95% Confidence Interval, median (and range) and number or percentages for categorical data. One sample Kolmogorov–Smirnov test was used for testing the distribution of continuous data and, according to parametric or nonparametric statistical tests was selected. Normally distributed continuous variables were analyzed using the one-way analysis-of-variance test with post hoc for multiple comparisons. Kruskal Wallis test was used to compare non-parametric data while Mann-Whitney was used to compare between two groups. Categorical data were analyzed using the Chi-square test or Fisher exact test as appropriate; $p < 0.05$ was considered statistically significant.

Results

Among the 110 patients who were screened for eligibility, 100 were finally recruited and equally distributed in the four

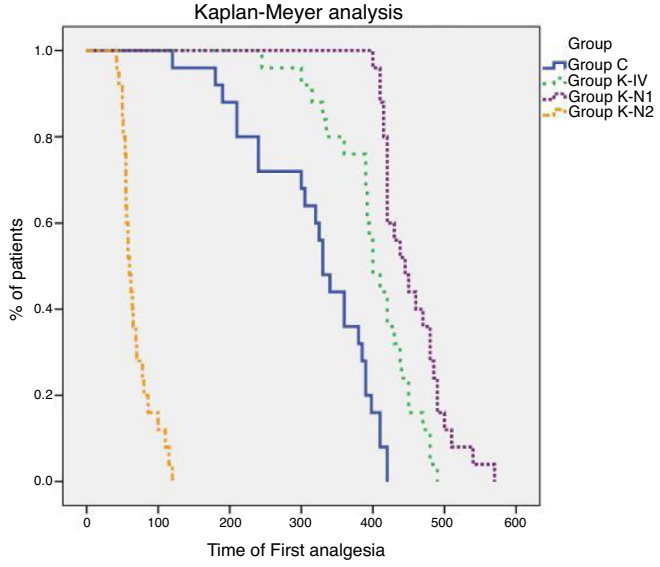

Figure 2 Kaplan–Meier curve for time to first request for rescue analgesia. Group C, Placebo Control; K-IV, Intravenous Ketamine 0.5 mg.kg^{-1}; K-N1, Nebulized Ketamine 1 mg.kg^{-1}; K-N2, Nebulized Ketamine 2 mg.kg^{-1}.

Table 1 Patients' Demographics, clinical data and postoperative adverse effects.

Variable	Group C n = 25	Group K-IV n = 25	Group K-N1 n = 25	Group K-N2 n = 25	P value
Age (years)	10.4 ± 1.6 (9.7-11.1)	10.2 ± 1.7 (9.5-10.9)	10.9 ± 1.3 (10.4-11.4)	10.4 ± 1.7 (9.7-11)	0.263
Sex: Male/Female	12/13	11/14	13/12	12/13	0.852
Weight (Kg)	32.3 ± 4.8 (31.9-40.9)	33.5 ± 9.8 (29.5-37.6)	36.4 ± 8.3 (33-39.9)	36.4 ± 10.95 (27.3-31.3)	0.362
ASA class I/II	25/0	25/0	25/0	25/0	–
Anesthesia time (min.)	27.1 ± 14.7 (21.2-32.9)	26.3 ± 10.1 (21.2-29.5)	27.6 ± 12.96 (22.2-32.9)	29.1 ± 11 (24.7-33.5)	0.584
Time to Extubation (min.)	7.6 ± 1.3 (7.1-8.2)	6.2 ± 1.50 (5.6-6.8)	6.3 ± 1.43 (5.7-6.9)	6.1 ± 1.50 (5.5-6.8)	**0.001**
Sedation score					0.041
Agitated	3	4	1	2	
Alert	22	21	21	18	
Calm	0	0	3	5	
Drowzy	0	0	0	0	
Asleep	0	0	0	0	
Median (range)	2 (1-3)	2 (1-2)	2 (1-3)	2 (1-3)	
Postoperative adverse effects: Vomiting (n)	2	3	5	9	0.099

Data are presented as mean ± SD with 95% Confidence Interval, median (range) and number. Group C, Placebo Control; K-IV, Intravenous Ketamine 0.5 mg.kg^{-1}; K-N1, Nebulized Ketamine 1 mg.kg^{-1}; K-N2, Nebulized Ketamine 2 mg.kg^{-1}; ASA; American Society of Anaesthesiologists. $p < 0.05$; significant difference vs. Group C.

study groups (Fig. 1). The demographic and clinical characteristics of enrolled patients are shown in Table 1. Upon arrival at the OR, patients in Nebulized Ketamine Groups showed higher sedation scores compared with patients in the K-IV Group and the Control Group ($p < 0.041$). With no significant difference between K-N1 and K-N2 Groups ($p = 0.763$). The mean time to extubation was 7.6 ± 1.32 min (95% CI 7.1–8.1) in Group C vs. 6.2 ± 1.50 (5.6–6.8), 6.3 ± 1.43 (5.7–6.9) and 6.1 ± 1.50 (5.5–6.7) in K-IV, K-N1 and K-N2 groups, respectively, ($p < 0.001$), with no significant difference between intravenous and nebulized ketamine groups ($p = 0.891$) (Table 1).

Kaplan–Meier survival analysis of analgesia free time demonstrated a significant advantage of ketamine groups over the Control Group (log-rank $p < 0.001$). The mean time to first request for rescue analgesics was significantly prolonged in K-N1 (400.9 ± 60.5 min, 95% CI 375.9–425.87) and K-N2 (455.5 ± 44.6 min 95% CI 437.1–473.9) groups compared with Group K-IV (318.5 ± 86.1 min, 95% CI 282.9–354.1) and Group C (68.3 ± 21.9 min, 95% CI 59.5–77.1; $p = 0.000$), with a significant difference between K-N1 and K-N2 groups ($p < 0.001$) (Fig. 2). The total consumption of iv paracetamol in the first 24 h postoperative was significantly reduced in Group K-IV (672.6 ± 272.8 mg, 95% CI 559.9–785.2), Group K-N1 (715.6 ± 103.2 mg, 95% CI 590.4–840.8) and Group K-N2 (696.6 ± 133.3 mg, 95% CI 558.8–834.4) compared with the Control Group (1153.8 ± 312.4 mg, 95% CI 1024.8–1282.8; $p < 0.001$). With no significant differences between intravenous and nebulized ketamine groups ($p = 0.312$). The number of patients' requests for rescue analgesia was significantly reduced in K-N1, K-N2, and K-IV groups compared with the Control Group ($p < 0.001$) (Table 2).

From 30 min after the admission to PACU till the first 24 h postoperative, patients in the intravenous and Nebulized Ketamine Groups showed a significantly lower postoperative VRS scores compared with the Control Group ($p < 0.001$). With no significant differences between K-IV, K-N1 or K-N2 at any time point (Table 3).No significant differences were recorded between groups in the intraoperative hemodynamic vitals including non-invasive blood pressure, heart rate or peripheral arterial oxygen saturation (data not presented).

Regarding the postoperative adverse effects, vomiting occurred in 2, 3, 5 and 9 patients in Group C, K-IV, K-N1 and K-N2, respectively ($p = 0.099$) (Table 1). No patient in this study showed hypertension, tachycardia, increased secretions, dizziness, hallucinations or emergence agitation.

Discussion

The main findings in this study were; compared to saline placebo, both intravenous ketamine (0.5 mg.kg^{-1}) and nebulized ketamine (1 and 2 mg.kg^{-1}) significantly prolonged the time to first request for rescue analgesia, reduced analgesic consumption and Pain scores in the first 24 h postoperative. Compared to intravenous ketamine, nebulized ketamine significantly prolonged the time to first request for rescue analgesia in a dose-dependent manner with comparable

Table 2 Postoperative pain profile.

Variable	Group C ($n=25$)	Group K-IV ($n=25$)	Group K-N1 ($n=25$)	Group K-N2 ($n=25$)	p-Value
Time to first request for rescue analgesia (min)	68.3 ± 21.9 (59.5–77.1)	318.5 ± 86.1 (282.9–354.1)	400.9 ± 60.5 (375.9–425.9)	455.5 ± 44.6 (437.1–473.9)	<0.001
Total dose of rescue analgesia (iv paracetamol) (mg)	1153.8 ± 312.4 (1024.8–1282.8)	672.6 ± 272.8 (559.9–785.2)	715.6 ± 103.2 (590.4–840.8)	696.6 ± 133.3 (558.8–834.4)	<0.001
Number of patients' requests for analgesics					<0.001
Once	0	14	18	18	
Twice	12	9	7	7	
Thrice	15	0	0	0	

Data are presented as mean ± SD with 95% Confidence Interval and number. Group C, Placebo Control; K-IV, intravenous ketamine 0.5 mg.kg^{-1}; K-N1, Nebulized Ketamine 1 mg.kg^{-1}; K-N2, Nebulized Ketamine 2 mg.kg^{-1}; $p<0.05$, significant difference vs. Group C.

Table 3 Postoperative Verbal Rating pain Scale (VRS) score.

	Group C ($n=25$)	Group K-IV ($n=25$)	Group K N1 ($n=25$)	Group K-N2 ($n=25$)	p-Value
VRS 0 min	0 (0–1)	00	00	00	NA
VRS 30 min	1 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)	<0.03
VRS 1 h	1 (0–3)	1 (0–2)	1 (0–2)	0 (0–2)	<0.03
VRS 2 h	2 (1–3)	1 (0–3)	1 (0–2)	1 (0–2)	<0.001
VRS 3 h	2 (1–4)	1 (0–4)	1 (0–2)	1 (0–2)	<0.001
VRS 4 h	2 (1–4)	1 (0–2)	1 (0–2)	1 (0–2)	<0.001
VRS 5 h	2 (1–3)	1 (0–3)	1 (1–3)	1 (1–3)	<0.001
VRS 6 h	2 (1–3)	1 (0–3)	1 (1–2)	1 (0–3)	<0.001
VRS 12 h	2 (1–3)	1 (0–3)	1 (0–2)	1 (0–2)	<0.001
VRS 24 h	2 (1–3)	1 (1–3)	1 (1–3)	1 (1–3)	<0.02

Data are presented as median and range. Group C, placebo control; K-IV, intravenous ketamine 0.5 mg.kg^{-1}; K-N1, nebulized ketamine 1 mg.kg^{-1}; K-N2, nebulized ketamine 2 mg.kg^{-1}; $p<0.05$, significant difference vs. Group C; NA, not applicable.

postoperative analgesic consumption and pain scores without significant adverse events.

These findings are in accordance with many studies that proved that ketamine can be a valuable pre-emptive analgesic adjunct to various analgesic drugs and techniques.[1,9,10] Cho et al. in their systemic meta-analysis found that both local and systemic ketamine efficiently reduced postoperative pain and analgesic consumption after tonsillectomy.[1] Elshammaa et al., in their study showed that intravenous ketamine 0.5 mg.kg^{-1} was an effective adjunct to fentanyl in children undergoing tonsillectomy that reduced postoperative pain without delaying home discharge.[9] Kimiaei et al., showed that the combination of intravenous paracetamol and low dose ketamine 0.25 mg.kg^{-1} reduced pain after tonsillectomy compared to paracetamol only analgesia.[10]

The administration of ketamine as nebulized inhalation is relatively new and studies on nebulized ketamine are scarce. However, these studies showed the efficacy of ketamine for reduction of postoperative sore throat in adults[14] and for sedative premedication in children.[15,16] Ketamine administered by nebulized inhalation results in rapid absorption into the systemic circulation from the nasal and pharyngeal mucosa.[11] Its uptake is faster than any route other than the intravenous administration as 70% of inhaled ketamine is absorbed directly by the alveoli into the circulation (fast path) and 30% of the drug is absorbed slowly either by the gastrointestinal or pulmonary mucosa.[11] In accordance, we found in this study that nebulized ketamine administration reduced postoperative IV paracetamol consumption and pain scores as much as IV ketamine. However, we found that ketamine inhalation significantly prolonged the time to the first request to postoperative analgesia than the IV administration and in a dose-dependent manner. Zanaty and Metainy and Abdel-Ghaffar et al., in their clinically randomized studies, have confirmed the analgesic efficacy of nebulized ketamine in the early postoperative period (1–2 h).[15,16] However, these two studies were powered to investigate the sedative premedication efficacy of nebulized ketamine, their age group was younger than ours and the operative procedures were other than tonsillectomy with shorter postoperative follow-up study periods. Further studies on the analgesic efficacy of ketamine inhalation for tonsillectomy are needed in both adult and pediatric population.

The two doses of nebulized ketamine used in this study were selected based on previous studies.[15,16] Further dose finding studied for inhaled ketamine analgesic dose are needed.

Psycho-mimetic adverse effects are the most annoying limitations for ketamine administration such as hallucination, dizziness and frightening dreams.[3] However, these adverse effects are not common with sub-anesthetic low doses.[3] Dahmani et al., in their systemic meta-analysis, found that the incidence of psycho-mimetic adverse events in Ketamine Group was low and the degree of sedation and the incidences of adverse effects, in general, were similar between the Control Group and Ketamine Group when low dose ketamine was used during anesthesia.[17] In accordance, in this study, we found no significant differences between groups in the incidence of adverse effects.

Swallowed blood and pharyngeal irritation in addition to the emetogenic effects of postoperative opioid analgesia are responsible for the high incidence of vomiting (40%–65%) after pediatric tonsillectomy.[18,19] Previous studies reported that ketamine has no emetogenic effect and patients received ketamine showed a low incidence of postoperative nausea and vomiting.[1,17] This positive effect of ketamine on emesis was attributed to its efficacy in reducing postoperative opioid consumption.[19,20] In contrast, in this study, we did not find a significant difference in the incidence of postoperative vomiting between Ketamine Groups and the Control Group. Our use of IV paracetamol for postoperative analgesia might be a contributing factor.

In this study, patients in the Control Group showed significantly prolonged mean time to extubation compared with those who received intravenous and nebulized ketamine. We can attribute this finding the intraoperative analgesic effect of ketamine that might be reduced the intraoperative anesthetic consumption yielding to a rapid recovery profile in Ketamine Groups.

A limitation of this study that was that we did not assess serum levels of ketamine to prove the local effect of nebulized ketamine analgesia in tonsillectomy. Further clinical and pharmacokinetic studies of nebulized ketamine (1 and 2 $mg.kg^{-1}$) in children are needed.

Conclusion

Nebulized ketamine (1 and 2 $mg.kg^{-1}$) administered before tonsillectomy significantly prolonged the time to first request for rescue analgesia in a dose-dependent manner, reduced pain scores and analgesic consumption in the first 24 h postoperative without significant adverse effects. Nebulized ketamine can be considered as an alternative route when IV ketamine is difficult or unsuitable.

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Conflicts of interest

The authors declare no conflicts of interest.

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