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The Effect of Administration of Ketamine and Paracetamol Versus Paracetamol Singly on Postoperative Pain, Nausea and Vomiting After Pediatric Adenotonsillectomy

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Abstract

Background: Tonsillectomy is one of the most common surgeries in children and posttonsillectomy pain and agitation management is a great challenge for anesthesiologists.
Objectives: The aim of this study was to compare the efficacy of a single dose of ketamine combined with paracetamol with paracetamol alone in the management of postoperative pain in tonsillectomy.
Materials and Methods: In this study, the subjects were randomly allocated into the two groups: the ketamine and control. Intravenous paracetamol infusion (15 mg/kg) was started 15 minutes before the end of surgery in both groups, continued with the IV injection of ketamine (0.25 mg/kg) in the ketamine group and an equal volume of saline in the control group. Using the children's hospital of eastern Ontario (CHEOPS) pain scale, pain and agitation score and also the incidence of nausea and vomiting after the surgery were recorded in 0.5, 6 and 12 hours after the operation. Data were analyzed using SPSS software version 16 and P value less than 0.05 was considered as statistically significant in all cases.
Results: There was no significant difference between the two groups considering demographic data (age, sex distribution, weight and height). The CHEOPS pain scales were significantly lower in the ketamine group compared to the control group at 0.5 and 6 hours after the surgery (P = 0.003 and P = 0.023, respectively). There was no significant difference in the CHEOPS scale at 12 hours after the surgery, dose of adjuvant analgesic and the incidence of nausea and vomiting after the surgery between the two groups.
Conclusions: According to the results of the current study, postoperative analgesia in children was improved in the ketamine group. Therefore, for better management of posttonsillectomy pain, low-dose ketamine administration with paracetamol is recommended.

Keywords: Paracetamol, Ketamine, Tonsillectomy, Pain

1. Introduction

Tonsillectomy with or without adenoidectomy is one of the most common surgeries in children. The tonsillectomy operation is associated with complications such as nausea, vomiting, hemorrhage and postoperative pain and the latest is the most common. If the postoperative pain is not well-controlled, especially in children, it can lead to a longer recovery period, delayed discharge, nutritional deficiencies, and resulting in dehydration of patients. These factors will increase the hospitalization period and the need for intravenous fluids (1-6). On the other hand, children are the patients who mostly undergo tonsillectomy (7). Postoperative pain has more undesirable effects on preschool patients than adults (8). In developing countries the incidence of pain is higher and in spite of availability of cost-effective methods for pain care, acute and chronic pain is still undertreated (9).

For this purpose, a large number of studies have been designed to evaluate the analgesic effects of various drugs before and after the surgical procedure. Nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, ketamine, dextromethorphan and topical analgesics are counted to prevent postoperative pain of adenotonsillectomy (10-12). Gabapentinoids including gabapentin and pregabalin are also effective in the treatment of postoperative pain (13). A few number of studies have confirmed the beneficial effects of low-dose ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism results in analgesia by preventing central sensitization in dorsal horn neurons, that is administrated intravenously or topical, and reduces the needed analgesia after tonsillectomy (2, 14-16). Most studies have shown that the ketamine administration has no side effects such as hemodynamic, respiratory complications and airway problems (17, 18). Ketamine in subcutaneous, intravenous and

spray routs has been found safe and effective for post-tonsillectomy pain control (8, 19). However, there are still controversies and further clinical trials are needed to confirm this effect.

We aimed to assess the effects of ketamine in association with acetaminophen on postoperative pain (according to the CHEOPS), nausea and vomiting after pediatric adenotonsillectomy in this study.

The children's hospital of eastern Ontario pain scale (CHEOPS) is a widespread used behavioral scale for rating postoperative pain in children (20).

3. Patients and Methods

Because the patients enrolled in this study were children, before entering the study, parents were given full information about the study and informed consent was prepared. All standards for the control of postoperative pain and vomiting were administered for both groups. The university research ethics committee approval was obtained and the proposal has been registered in the center of the clinical trial (IRCT code: 201402179014N25).

In this randomized, triple blinded clinical trial, 98 American society of anesthesiologists (ASA) class 1 children aged between 3 and 12 years candidate for tonsillectomy were randomly allocated into the two groups (control and intervention).

Inclusion criteria were: 3 - 12 years age, candidate for elective adenotonsillectomy surgery, and score 1 of ASA criterion. Exclusion criteria included history of psychiatric illness, using analgesic drugs 24 hours before surgery, sensitivity to ketamine or acetaminophen, history of liver and neurological diseases, and use of cautery for hemostasis.

Based on the results of Javid et al.'s clinical trial (8) and using 95% of the confidence level and 90% of power, the sample size was estimated to be 49 patients in each of the control and intervention groups.

The method of random blocks (block randomization) was used; two terms, "intervention" and "comparison" were written twice on four sheets of paper and the patients were randomly classified into two groups: intervention (ketamine and acetaminophen), comparison (acetaminophen). This procedure was continued again for the next four patients until the desired sample size was gained. In both groups the acetaminophen and ketamine were administered intravenously 15 minutes before the end of surgery. The patients did not have information about the prescribed medication. The medications were prepared by a technician and an anesthesia assistant who measured and recorded the findings, was unaware about the prescribed medicine. In addition, the analyzer did not know about the results of encoding of intervention and comparison groups so that the study was conducted in three blinded form.

All patients were premedicated with midazolam 0.5 mg/kg, (Aburaihan, Iran) and atropine 0.02 mg/kg (Alborz Darou, Iran) orally one hour before the induction of anesthesia.

Induction of anesthesia was similar in both groups including fentanyl 1.5 μg/kg (Aburaihan, Iran) propofol 2 mg/kg (Fresenius Kabi Austria GmbH) and atracurium 0.5 mg/kg (Iran Hormone, Iran) and then all patients were intubated and dexamethasone 0.15 mg/kg (Darou Pakhsh, Iran) was administered. Inhalational anesthesia was continued to the end of surgery by a mixture of 50% NO_2/50% O_2 combined with isoflurane with MAC of 1%.

Intravenous paracetamol (UNI-PHARMA, Greece) infusion (15 mg/kg) was started 15 minutes before the end of the surgery and every 6 hours thereafter for the first 24 hours after surgery in both groups.

Intervention group received intravenous ketamine 0.25 mg/kg (2 mL) (Rotexmedica, Germany) 15 minutes before the end of the surgery. Control group received 2 mL of intravenous saline 15 minutes before the end of the surgery.

The surgery technique was sharp dissection with snake and we did not use cautery for the hemostasis. After the surgery, neuromuscular block was reversed with 0.045 mg/kg neostigmine (Alborz Darou, Iran) and 0.02 mg/kg atropine and after regular and adequate ventilation, the endotracheal tube was removed and the patients were transferred to postoperative care unit (recovery period).

Pain intensity was measured by children's hospital eastern Ontario pain scale (CHEOPS) pain score 30 minutes, 6 and 12 hours after surgery. CHEOPS pain score is the earliest tools used to assess and document pain behaviors in young kids. It assesses the efficacy of interventions used in alleviating pain. It is a behavioral scale and includes six categories: cry, facial, child verbal, torso, touch, and legs. These items are scored separately (8, 21).

The frequency of nausea and vomiting were recorded at half, 6 and 12 hours after surgery too.

If the pain score was greater than 4 based on CHEOPS scale, meperidine 0.25 mg/kg (up to 0.5 mg/kg) was administered for analgesia. The times of analgesic request and the frequency of need for narcotics to control the postoperative pain was recorded in the check list. When nausea and vomiting were observed, metoclopramide was prescribed as an antiemetic intravenously. The recurrences of vomiting, abnormal bleeding from the surgical site or any drug side effects were recorded.

The collected data was analyzed using SPSS software version 16 and P value less than 0.05 was considered as statistically significant in all cases. For comparison of qualitative data like percentage of nausea and vomiting, chi-square test was used and independent sample t-test was used to compare the mean values.

4. Results

In this study, 98 patients (49 patients in each group) were studied. Considering demographic data (age, sex distribution, weight and height), there was no significant difference between the two groups (Table 1).

Table 1. Demographic Data in the Ketamine and Control Groups

Variable	Ketamine	Control	P Value
Age, y	6.29 ± 2.2	6.84 ± 2.4	0.2
Height	118.79 ± 15.4	114.51 ± 22.19	0.2
Weight	23.5 ± 7.4	22.5 ± 6.5	0.5
Gender			≥ 0.05
Male	22	27	
Female	27	22	

Table 2. Comparison of the CHEOPS Scale, Nausea and Vomiting and Adjuvant Narcotic Usage in the Two Groups

Variable	Ketamine	Control	P Value
CHEOPS, 0.5 h[a]	3.4 ± 1.2	4.04 ± 0.7	0.003
CHEOPS, 6 h[a]	2.98 ± 0.9	3.37 ± .73	0.02
CHEOPS, 12 h[a]	2.9 ± 0.8	2.9 ± 0.8	0.7
Nausea, %	18.4	22.5	0.6
Vomiting, %	10.2	12.2	0.07
Adjuvant narcotic, %	14.28	22.5	0.07

Abbreviation: CHEOPS, Children's hospital of eastern Ontario pain scale.
[a]0.5, 6 and 12 hours after surgery.

The CHEOPS pain scales in the ketamine group compared to the control group were significantly lower at 30 minutes and also at 6 hours after the surgery (P = 0.003 and P = 0.023, respectively) (Table 2).

There was no significant difference in the mean of CHEOPS scale between the two groups at 12 hours after the surgery (Table 2).

There was no significant difference in the dose of adjuvant analgesic and the incidence of nausea and vomiting after the surgery in the two groups (Table 2).

No statistically significant difference was observed between the two groups regarding the frequency of need for rescue narcotics to control the postoperative pain with chi-square test, (P = 0.297) (Table 2).

No complications such as agitation, hemodynamic instability, changes in heart rate, respiratory distress or airway spasms and bleeding were observed in both groups during the first 24 hours after tonsillectomy.

5. Discussion

Pediatric pain management is one of the most important health care challenges. Pre-school aged children are particularly badly affected by adverse effects of postoperative pain than adults. So, effective management of postoperative pain including multi-method approach (different medicines with various mechanisms) is needed (22).

Providing perioperative analgesia by extreme use of opioid analgesics leads to a variety of perioperative side effects like respiratory depression, drowsiness, postoperative nausea and vomiting and ileus that delayed discharge. Therefore, nonopioid analgesic techniques as adjuvants for managing acute perioperative pain are extensively used now to minimize the adverse effects of opioids (23).

Ketamine possesses broad clinical applications due to its unique pharmacological characteristics and physical properties, which are newly discovered. It prevents pain associated with wind-up, at nonanalgesic doses has been reported to potentiate opioid analgesia in rodents and reduced 24 hours patient-controlled analgesia (PCA) morphine consumption and postoperative nausea or vomiting (24).

In recent years, better understanding of the role of NMDA receptors in pain modulation and anti-inflammatory properties of ketamine makes it a new choice in acute pain management and perioperative analgesia (25). It has been mentioned in a recent review that adding ketamine to opioids for patient-controlled analgesia reduced pain scores, cumulative morphine consumption and postoperative desaturation after thoracic surgery (26).

There are some reports of clinical applications of low dose ketamine for perioperative pain management. Intravenous (IV) low-dose ketamine (0.5 mg/kg) as pre-emptive analgesia provides good analgesia without any adverse effects in laparoscopic cholecystectomy (27). Preemptive intranasal ketamine has been reported to be effective for pain control after endoscopic nasal surgery (28).

The analgesic effect of low-dose (0.1 - 0.5 mg/kg) IV, IM or subcutaneous ketamine administration at the end of surgery in providing effective and safe posttonsillectomy pain control has been mentioned before (23, 25).

In a published meta-analysis in 2014 by Cho et al. it has been demonstrated that the local or systemic preoperative administration of ketamine could reduce pain without side-effects in children undergoing tonsillectomy and also it has been mentioned that further clinical trials with clear methodologies is needed (29).

Although there is evidence for the use of preoperative low dose ketamine in ameliorating patient's morbidity, the efficacy of ketamine when coadministered with acetaminophen has not been studied before.

The results of the current study showed that although no significant difference was observed between the two groups for postoperative nausea and vomiting and need for excessive narcotics, a meaningful decrease in pain intensity at 30 minutes and 6 hours after the surgery based on the CHEOPS pain scale was observed in the ketamine group compared to the control group. Consequently, a single dose of ketamine in our study could effectively reduce pain after adenotonsillectomy.

Correspondingly, Eghbal et al. who studied the efficacy of ketamine on postoperative pain of adenotonsillectomy surgery concluded that the low-dose ketamine during induction of anesthesia improves emergence agitation and postoperative pain following adenotonsillectomy in children (30), which are consistent with our findings.

In Honarmand et al.'s study (2013) the positive effects of ketamine on pain control were confirmed and they showed also that ketamine was significantly more effective than either analgesic such as peritonsillar infiltration of tramadol or other local analgesic agents (31).

Consistent to our findings, Da Conceicao et al. (2006) and Taheri et al. (2011) did not report any association between the rate of nausea and vomiting and ketamine administration in their studies (2, 32). Even in Eghbal's study, the agitation rate in the ketamine group was significantly lower than the control group who received intraoperative analgesic medication (30).

Among the reported cases, Almajali et al. (2013) reported increased restlessness and a higher rate of agitation in the ketamine group compared to the cases who received propofol during tonsillectomy surgery (33); however, their results could not be generalized to the current findings because of a higher dose of ketamine in Almajali study.

We were not able to assess the pain score at 24 hours after surgery because of discharging before 24 hours of admission and this can be considered as one of the limitations of the current study.

5.1. Conclusions

The findings of the current study indicate that administration of intravenous low-dose ketamine (0.25 mg/kg) can effectively reduce the pain after adenotonsillectomy surgery, without an increased rate of side effects such as nausea, vomiting and agitation. So, it can be used in combination with paracetamol to get more efficiency than paracetamol, singly.

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Footnote

Authors' Contribution: Hosein Kimiaei Asadi: acquisition of data and study concept and design; Mahshid Nikooseresht: administrative, technical, and material support, and drafting of the manuscript; Lida Noori: analysis and interpretation of data, and statistical analysis; Fatholah Behnoud: critical revision of the manuscript for important intellectual content and study supervision.

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