Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Comparing Preemptive Ketamine Nebulization and Intravenous Ketamine for Post-Operative Analgesia in Children Undergoing Tonsillectomy

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Article Type

Research Paper

Received:
Jul 31st 2023
Revised:
Oct 8th 2023
Accepted:
Mar 2nd 2024

ABSTRACT

Background and Objective: Tonsillectomy is a common surgical procedure performed in children to remove enlarged or infected tonsils. Postoperative pain management is crucial to ensure the smooth recovery and to prevent complications in pediatric patients undergoing tonsillectomy. This study aims to compare the effectiveness of preemptive ketamine nebulization versus intravenous injection of ketamine for pain relief in 5-10-year-old children undergoing tonsillectomy.

Methods: In this randomized controlled trial, 64 children, after ethical and parental approvals, were split into two groups. Both groups received glycopyrrolate (5 mcg/kg). One group had ketamine nebulization (1 mg/kg) 20 minutes before surgery, and the other received intravenous ketamine (1 mg/kg) just before entering the operating room. Pain levels were assessed using a verbal rating scale after surgery and one hour later. The time for first rescue analgesia was noted for both the groups. Parental separation scores and sedation levels were evaluated using a 5-Point sedation scale before the operation.

Findings: Following the surgery, there were no notable differences in pain scores between the groups in the Post Intensive Care Unit (PICU). However, one-hour after surgery, the ketamine nebulization group exhibited significantly lower pain scores ($p<0.05$) compared to the intravenous ketamine group. Moreover, the ketamine nebulization group had a significantly longer duration until the first rescue analgesia was needed (300±26.396 minutes) compared to the intravenous ketamine group (237.187±34.382 minutes) ($p<0.05$). Parental Separation Score and Sedation Score were similar in the two groups.

Conclusion: According to results, administering ketamine nebulization significantly prolongs the duration of pain relief compared to intravenous ketamine for tonsillectomy. Therefore, nebulization can be considered as an alternative method for administering ketamine.

Keywords: *Ketamine Nebulization, Intravenous Ketamine, Post-Operative Analgesia, Tonsillectomy.*

Cite this article: Deshmukh P, Hanagandi M, Gadvi P, Kamat C, Kerur R. Comparing Preemptive Ketamine Nebulization and Intravenous Ketamine for Post-Operative Analgesia in Children Undergoing Tonsillectomy. *Journal of Babol University of Medical Sciences*. 2025; 27: e21.

[DOI: 10.22088/jbums.27.1.21]

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Introduction

Tonsillectomy is a common surgical procedure performed in children to alleviate various upper airway conditions, such as recurrent tonsillitis and obstructive sleep apnea. Although tonsillectomy is generally safe, post-operative pain management remains a crucial aspect of patient care to ensure a smooth recovery and overall patient satisfaction. Effective pain relief not only improves the child's comfort but also facilitates early mobilization and reduces the risk of potential complications (1). The most frequent complication following tonsillectomy is pain, which, if inadequately addressed, may result in various issues such as reduced oral intake, dehydration, the requirement for intravenous fluids, and extended hospital stay (2). Post-tonsillectomy pain management in children has often involved the usage of Non-steroidal Anti-Inflammatory Agents (NSAIDs), systemic opioids, intravenous paracetamol, and local anesthetics, as documented in various studies (3-5). Systemic opioids, on the other hand, can produce respiratory depression, drowsiness, nausea, and vomiting (3, 4) and NSAIDs can interfere with bleeding (6).

Ketamine, a dissociative anesthetic agent, has gained popularity for its analgesic properties and potential to reduce post-operative pain. Ketamine, when administered at sub-anesthetic doses (0.3 mg/kg^{-1} or lower), acts as a non-competitive antagonist of N-Methyl-D-Aspartate (NMDA) receptors. This inhibitory effect on NMDA receptors helps to alleviate central hypersensitivity induced by pain (7). In various surgical procedures, such as tonsillectomy, the perioperative use of both systemic and local ketamine has been found to enhance postoperative pain relief and decrease the need for opioids during the recovery period. This improvement in analgesia and reduced opioid consumption has been observed across a wide range of surgeries (1, 7). Due to its minimal impact on airway patency and respiratory drive, ketamine might be an excellent option for children suffering from sleep apnea (8). Traditionally administered via the intravenous (IV) route, ketamine has shown promise in pediatric pain management due to its ability to minimize opioid consumption and mitigate opioid-related side effects, such as respiratory depression. However, the IV route may present challenges in pediatric settings, such as needle-related anxiety, difficulties in establishing vascular access, and risk of inadvertent drug administration.

An alternative approach to ketamine administration involves nebulization, a non-invasive method that delivers the drug in aerosolized form, allowing direct absorption through the respiratory tract. Nebulized ketamine has shown favorable pharmacokinetic properties, rapid onset of action, and ease of use, making it an attractive option for premedication and post-operative analgesia.

In tonsillectomy procedures, intravenous ketamine has been used as an additional treatment alongside fentanyl (9) or intravenous paracetamol (10). This combined approach has proven to be effective in significantly reducing postoperative pain. Moreover, an innovative alternative method of administering ketamine is through inhalation using nebulization. This approach is relatively simple to set up, doesn't require needles, and has the added benefit of high bioavailability (11-14).

Despite the growing interest in ketamine nebulization, limited studies have directly compared its efficacy with intravenous ketamine in the context of pediatric tonsillectomy which is very necessary to address for future research. Nebulized ketamine is shown to have higher bioavailability and better post-operative pain relief. Therefore, this prospective comparative study aims to investigate and compare the analgesic efficacy of preemptive ketamine nebulization with intravenous ketamine in children aged 5-10 years undergoing tonsillectomy.

[DOI: 10.22088/jbums.27.1.21]

Materials and methods

This research was carried out in a prospective manner, employing a randomized clinical design that spanned six months from April 2020 to September 2020. Institutional ethical approval was obtained for the study (MDC/DOME/454). The primary criterion used to determine the necessary sample size for the study was the "time taken for the first rescue analgesia post-surgery." Before the anesthesia procedure, a comprehensive preanesthetic evaluation was conducted. Patients with cardiac, respiratory, or neuropsychiatric conditions, as well as those with elevated intracranial or intraocular pressure, and individuals allergic to the study drug were excluded from the study. Moreover, all children underwent various assessments, including hemoglobin concentration, blood cell count, and coagulation profile. Written informed consent was obtained from parents of the children. To eliminate any potential bias in participant selection, the random allocation of children into the two groups was carried out using computer-generated randomization tables.

64 children were randomly divided into two groups. All patients were kept NBM (Nil by Mouth) for a period of 6 hours before surgery. Both groups were administered with Glycopyrrolate injection at dosage of 5 mcg/kg intravenously. Under standard monitoring, Group A received ketamine nebulization at a dose of 1mg/kg, given 20 minutes before the surgery, while Group B received intravenous ketamine 1mg/kg just before entering the operating theater (OT).

During the anesthesia induction, the children were anesthetized using inj. fentanyl 1 mcg/kg, Inj. Propofol 2 mg/kg, Inj. Atracurium 0.5 mg/kg, and combination of Oxygen and Nitrous oxide with Sevoflurane. A throat pack was inserted to maintain a clear surgical field. Throughout the procedure, the vital signs of the children, such as pulse rate, respiratory rate, blood pressure, SpO2 (oxygen saturation), and EtCO2 (end-tidal carbon dioxide) were continuously monitored. After the surgery, the children were extubated once the throat pack was removed and adequate suctioning and reversal of muscle relaxants were performed.

Children undergoing tonsillectomy procedure aged between the specified range of 5-10 years and willingness of the legal guardians to provide informed consent for participation in the study were included. Children with known allergies or adverse reactions to ketamine or any of its components, patients with a history of psychiatric disorders, known cardiorespiratory conditions, hepatorenal impairment and significant neurological conditions were excluded from the study.

After the surgery, the pain level of the patients was evaluated using Verbal Rating Scale (VRS), which ranged from 0 to 4: 0 represented no pain, 1 indicated mild pain, 2 denoted moderate pain, 3 severe pain and 4 signified excruciating pain. This assessment was conducted immediately after the patients were moved to the Post-Anesthesia Care Unit (PACU) and again one hour after the surgery. The time at which the first rescue analgesia was required was recorded. Furthermore, parental separation scores were also assessed preoperatively. These scores were based on the following categories:

1. Patient being unafraid and cooperative.
2. Slight fear or crying but comforted with assurance.
3. Moderate fear, crying without complete assurance.
4. Crying and requiring restraint.

In addition, the levels of sedation in the children were evaluated using a 5-point sedation score:

1. Agitated.
2. Alert.
3. Calm.
4. Drowsy.
5. Asleep when brought to the operating table.

[DOI: 10.22088/jbums.27.1.21]

All data are presented as mean±standard deviation, and/or a number (score). Demographic data were analyzed by t-test and Chi-Square test. VRS scores, Parental separation and 5-point sedation score was analyzed by Chi-Square test. P<0.05 was considered statistically significant.

Results

Nebulized ketamine was administered to individuals in Group A, with an average age of 7.41±1.14 years and a weight of 25.09±2.97 kg. Intravenous ketamine, on the other hand, was given to subjects in Group B, who had an average age of 7.56±1.27 years and weighed around 25.34±1.17 kg (Table 1).

Table. 1 Demographic information of patients

Type	Gender		Group	Age (years)	Weight (kg)
	Male	Female		Mean±SD	Mean±SD
Nebulization ketamine	17	13	A	7.41±1.14	25.09±2.97
Intravenous ketamine	14	16	B	7.56±1.27	25.34±1.17

According to the results, both groups had similar median 5-point sedation scores, with a median score of 2. The parental separation scores were also comparable between the groups. Initially, there was no significant difference in VRS pain scores between the groups upon transitioning to the PACU. However, one hour after surgery, a significant difference in VRS pain scores was observed (p<0.05). Furthermore, patients who received ketamine nebulization experienced a longer duration until they needed rescue analgesia (300±26.396 minutes) compared to those who received intravenous ketamine (237.187±34.382 minutes). This difference was statistically significant (p<0.05).

Discussion and conclusion

In the present study, both intravenous ketamine (at a dosage of 0.5 mg/kg^{-1}) and nebulized ketamine (at dosages of 1 and 2 mg/kg^{-1}) significantly increased the duration before patients requested additional pain relief, decreased the need for analgesics, and reduced pain scores during the initial 24 hours following surgery. In addition, nebulized ketamine, when compared to intravenous ketamine, dose-dependently prolonged the time to the first request for rescue analgesia, while maintaining comparable postoperative analgesic consumption and pain scores without causing any significant adverse effects. These findings align with numerous studies that have demonstrated the potential of ketamine as a beneficial pre-emptive analgesic supplement to various analgesic drugs and techniques. Cho et al., in their comprehensive meta-analysis, demonstrated that both local and systemic administration of ketamine effectively reduced postoperative pain and analgesic consumption following tonsillectomy (1).

In another study by Elshammaa et al., it was revealed that intravenous administration of ketamine at a dosage of 0.5 mg/kg^{-1} was a successful addition to fentanyl in children undergoing tonsillectomy, resulting in reduced postoperative pain without causing any delays in home discharge (9). Additionally, Kimiaei Asadi et al., discovered that combining intravenous paracetamol with a low dose of ketamine (0.25 mg/kg^{-1}) led to reduced pain after tonsillectomy compared to using paracetamol alone for analgesia (10). Laskowski et al., proposed that intravenous ketamine effectively reduces the overall need for opioids and prolongs the time before the first analgesic dose is required in painful procedures such as upper abdominal, thoracic, and major orthopedic surgeries. However, when it came to patients undergoing

[DOI: 10.22088/jbums.27.1.21]

tonsillectomy, they did not find significant benefits (15). It's worth noting that only four studies out of the total 47 enrolled studies focused on pediatric tonsillectomy (15). Consequently, their results were not able to establish a definitive conclusion regarding the effectiveness of ketamine on post-tonsillectomy pain in children.

On the other hand, Dahmani et al., attempted to consolidate data from numerous studies specifically concerning pediatric tonsillectomy, which led to a more robust conclusion regarding the efficacy of ketamine for tonsillectomy in children (16). However, it should be acknowledged that there were several issues with the analysis method used in this review.

In the present study, immediately after transferring to the PACU, there was no discernible difference in the VRS pain scores between the two groups. However, one hour after the operation, a significant difference in VRS pain scores was observed between the groups. According to Dahmani et al., the average time until rescue analgesia was significantly longer in the ketamine nebulization group compared to the intravenous ketamine group, indicating a significant difference (16). Additionally, both ketamine nebulization and intravenous ketamine resulted in similar levels of sedation (score 2) and acceptable Parental Separation scores (Score 1, 2). Therefore, nebulization proves to be an effective alternative method for administering ketamine.

In another study by Abdel-Ghaffar et al., the average time until the first request for rescue analgesics was significantly prolonged in both K-N1 and K-N2 groups compared to Group K-IV and Group C. Moreover, there was a significant difference between the K-N1 and K-N2 groups in terms of the time to first request for rescue analgesics (12).

In their study, Hasnain et al. showed that psycho-mimetic side effects, such as hallucinations, dizziness, and disturbing dreams, pose the most bothersome restrictions on the use of ketamine (3). Nevertheless, these unwanted effects are infrequent when employing sub-anesthetic low dosages.

In a comprehensive meta-analysis conducted by Dahmani et al., it was revealed that the occurrence of psycho-mimetic adverse events in the Ketamine Group was minimal. Additionally, when low doses of ketamine were administered during anesthesia, the level of sedation and the overall incidence of adverse effects were comparable between the Control Group and Ketamine Group (16). Similarly, in our own study, we observed no significant differences between the groups regarding the frequency of adverse effects.

In previous studies by Kovac (17) and Wong et al., (18) the elevated occurrence of vomiting (40-65%) following pediatric tonsillectomy can be attributed to several factors, including the ingestion of blood, irritation in the throat (pharyngeal irritation), and the emetogenic effects caused by postoperative opioid analgesia.

The administration of Ketamine Nebulization before tonsillectomy resulted in a significantly prolonged analgesic effect compared to Intravenous Ketamine. Furthermore, both groups showed similar scores in terms of Parental Separation and Sedation. These findings suggest that Nebulization can be considered as an alternative method for delivering ketamine.

Acknowledgment

We would like to acknowledge study participants. We also acknowledge Dr Vinita, Dr Preethi, Otorhinolaryngologists for their constant guidance for the research.

[DOI: 10.22088/jbums.27.1.21]

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[DOI: 10.22088/jbums.27.1.21]