


The Impact of Local Ketamine Injection at the Tonsillectomy Site on Postoperative Pain Reduction in Patients Under 18: A Double-Blind Clinical Trial

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Abstract

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Background and Purpose: Tonsillectomy is a common procedure for treating tonsil-related conditions, but it can lead to significant postoperative pain and complications. Effective pain management and anxiety reduction are critical in pediatric care. Current standard treatments, including injectable acetaminophen and opioids, have limitations. Ketamine, known for its analgesic and antihyperalgesic effects, has demonstrated efficacy in reducing postoperative pain and minimizing opioid use in both adults and children. This study evaluates the effectiveness of a local ketamine injection at the tonsillectomy site in alleviating postoperative pain in patients under 18 years of age through a double-blind, randomized clinical trial. **Materials and Methods:** This randomized, double-blind, controlled trial was conducted at the Bo Ali Sina Sari Medical Training Center between 2022 and 2023. Sixty pediatric patients scheduled for tonsillectomy were randomly assigned to either the intervention or control group. The intervention group received a local injection of 1 mg/kg ketamine (Elixir Pharmaceutical Company, Iran), while the control group received a placebo. Results: Pain intensity was significantly lower in the ketamine group compared to the control group at multiple time points: baseline, 20 minutes, 60 minutes, 6 hours, and 12 hours post-surgery. At baseline and 20 minutes, pain intensity was reduced by a factor of 3.6 in the ketamine group. After 60 minutes, pain was 3.4 times lower, and at 12 hours, the difference reduced to 0.967, with all comparisons showing statistical significance. **Conclusion:** Local administration of 1 mg/kg ketamine at the peritonsillar site effectively reduces postoperative pain in pediatric patients undergoing tonsillectomy. This approach provides a promising alternative to traditional pain management methods.

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Introduction

Tonsillectomy refers to the surgical removal of the tonsils, and it is one of the most common surgical procedures performed in children. It is one of the main treatments for recurrent tonsillar infections, obstructive bleeding, and sleep disorders (1-5).

Since the first tonsillectomy performed by Schmidt Sarmiento in São Paulo in 1920 at the Santa Casa de São Paulo Hospital, this surgery has been used to address chronic infections and obstruction caused by the palatine tonsils and is becoming one of the most frequently performed surgeries. Tonsillectomy and adenoidectomy are among the most common major surgeries for children in the United States (6-10).

For several decades, tonsillectomy has been the elective surgical treatment for recurrent acute tonsillitis (10-13). The COVID-19 pandemic significantly impacted the scheduling of elective surgeries, including tonsillectomies, due to the need to limit exposure and prioritize urgent cases. Postoperative care and recovery were also affected, with heightened concerns about managing infections and complications in a COVID-19 environment. The advent of COVID-19 vaccines had provided a crucial solution, offering protection for both patients and healthcare providers, which helped reduce the risk of transmission during surgeries (9, 12, 14-17). This has allowed elective procedures like tonsillectomy to resume with improved safety measures, ensuring better outcomes for patients. Other reasons for tonsillectomy in adults include suspected or confirmed neoplasms and symptoms associated with the tonsils that cause chronic sore throat (14, 18-20). Tonsillectomy is one of the most common surgeries performed worldwide. Despite its relatively simple technique, it can lead to complications that pose a risk to the patient's life. The most common complications include pain, bleeding, fever, dehydration, nausea, and vomiting (21, 22). Managing post-tonsillectomy complications is of paramount importance (2, 23). One of the main and significant complications of this procedure is pain, which can range from moderate to severe (24-26). Most patients undergoing this surgery experience acute pain, with 80% of them describing it as moderate to severe (27-29). Although tonsillectomy in children is an accepted treatment for upper airway obstruction or recurrent tonsillar infections, the painful recovery process is an unintended consequence. Poor pain management after tonsillectomy can lead to reduced food intake, dysphagia, dehydration, weight loss, delayed recovery, and increased risk of infection (30-34).

Effective pain control after tonsillectomy is critical. If left unmanaged, it can predispose children to chronic

pain syndromes. Despite numerous studies comparing and combining analgesics to find the most effective postoperative regimen, no consensus has been reached regarding the best treatment strategy. Additionally, studies have shown that inadequate pain control in childhood can lead to impaired pain responses in adulthood and both short- and long-term adverse effects. The foundation of pain control after surgery in children relies on preventive methods, which, in addition to reducing postoperative pain, decrease the need for analgesics and other postoperative complications (35-38).

The standard treatment for pain control in patients undergoing tonsillectomy includes intravenous acetaminophen or opioids. However, these methods have their drawbacks. The use of opioid medications in children with obstructive sleep apnea syndrome (OSAS) can lead to respiratory issues. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and ketorolac after tonsillectomy can increase the risk of bleeding at the surgical site. Therefore, the pain management approach after tonsillectomy must not only be safe but also highly effective (39-42). Ketamine has been one of the most popular sedatives used in pediatric emergency departments for painful procedures in the last two decades (43-45).

Locally administered ketamine during tonsillectomy surgery reduces the initial pain intensity (6-24 hours) and the need for analgesics in the postoperative care unit (17, 46, 47). A common misconception is that infants and young children do not experience or remember pain; however, this view is highly incorrect. Research on postoperative pain in children in 2020 showed that, within the first 48 hours after surgery, 74.2% of children experienced mild to severe pain (48). Studies have shown that poor pain management in children after surgery can lead to serious negative effects, including changes in physiology, behavior, and cognition (17, 49-54). Therefore, prioritizing postoperative pain treatment in children and addressing the barriers to these methods is crucial. Multimodal analgesia has been shown to be effective in pediatric surgeries. For moderate to severe postoperative pain, in addition to non-pharmacological treatments and NSAIDs (or paracetamol), opioids should be used (55, 56).

As mentioned, no ideal method for postoperative pain relief in children exists. Ketamine, a compound with analgesic and anti-hyperalgesic properties, has been shown to reduce postoperative pain and opioid requirements in both adults and children (46, 57). Ketamine exerts strong analgesic effects by blocking central pain perception at sub-anesthetic doses.

Intramuscular administration of ketamine for preoperative sedation reduces swallowing pain after tonsillectomy, while its application around the incision provides long-lasting pain relief (20, 58, 59). Various studies have supported the analgesic efficacy of this drug when administered locally at the site of the surgery (60, 61).

Local ketamine injection during tonsillectomy surgery, given as a single dose and requiring less involvement from staff, has advantages over other methods. It avoids issues of patient non-cooperation due to agitation from pain and maintains high accuracy, as no personnel other than the surgeon is involved. The use of local ketamine as a pain reduction method has gained attention in recent years. However, its effectiveness in children undergoing tonsillectomy has not yet been confirmed. Therefore, we have designed a clinical trial to examine the efficacy of local ketamine in children undergoing tonsillectomy.

Materials and Methods

Study Type

This study is a randomized, double-blind, controlled clinical trial conducted to compare the effect of subcutaneous ketamine administration on postoperative pain management following tonsillectomy in patients under 18 years of age who visited the Bou Ali Sina Educational and Treatment Center in Sari during the years 2022-2023.

For conducting the research, after obtaining the necessary permits and receiving approval from the ethics committee (with ethics code...), the study was explained to the patients, and informed consent was obtained. A total of 60 patients under 18 years of age, classified as ASA Class 1 and 2, who were candidates for tonsillectomy, were selected by convenient sampling.

Sample Size Calculation

To calculate the sample size, the results from Shakiri et al.'s study (62) for pain control were used. The mean pain score in the two groups (subcutaneous ketamine group and control group) were 3 and 3.9, respectively. According to the formula, the sample size for each group was determined to be 25 patients. Considering the possibility of patient dropout, the sample size for each group was adjusted to 30 patients.

Sampling Method

The sample size was calculated based on the results mentioned above and the VAS score. To control confounding variables and balance the groups in terms of numbers, a random block method based on patient entry order was used. The first four patients were assigned to two groups using the Random Allocation software. This process continued until the sample size

was completed. For age control, randomization was also used to make the groups as similar as possible. To ensure age equivalence between the groups, a comparison was made between their ages, and if any significant difference was found, linear regression models were used to adjust for age differences. There was no need for age matching, as statistical modeling methods addressed the impact of age. Group 1 received 1mg/kg of ketamine (Exir Pharmaceutical Company, Iran) subcutaneously, and Group 2 served as the control group.

Procedure

General anesthesia (GA) was induced uniformly in all patients with intravenous fentanyl (2µg/kg) (Abu Rayhan Pharmaceutical Company, Iran, Feniject), intravenous thiopental sodium (5mg/kg) (Kavosh Gostar Pharmaceutical Company, Iran, Thiopental vuAB), and intravenous atracurium (0.5mg/kg) (Caspeen Pharmaceutical Company, Iran, Atracurium).

After GA induction, the patient was positioned appropriately, prepped, and draped. The patient's mouth was exposed using a Davis gag, and the tonsils were grasped by Alice forceps and moved toward the midline. The tonsils were exposed and separated from the bed using a finger dissection technique. The lower tonsillar pole was separated using scissors. Ketamine was injected into the upper constrictor muscle. If bleeding was not controlled by packing, 3/0 Vicryl sutures were used. To control bleeding, electrocautery was not used.

In the intervention group, ketamine was administered locally at a dose of 1mg/kg during the surgery for all patients by the treating physician in the operating room. Subcutaneous ketamine administration in the intervention group during tonsillectomy has been studied in pediatric hernia surgeries and tonsillectomies, and no life-threatening complications have been reported. Secondary outcomes, such as increased oral and respiratory secretions, nystagmus, bradycardia, bronchospasm, and laryngospasm, were monitored. To prevent bronchospasm, atropine was administered at a dose of 0.01mg/kg (Alborz Darou Pharmaceutical Company, Iran) during surgery. Patients with a history of heart problems or arrhythmias were excluded from the study. If pain was not controlled with local ketamine and postoperative analgesics were required, intravenous acetaminophen (Samacetamol, Saman Pharmaceutical Company, Iran) at a dose of 12mg/kg every 4 hours or 15mg/kg every 6 hours, with a maximum dose of 75mg over 24 hours, was used. Pethidine was not administered during the

surgery. The student observed the procedure in the operating room.

The drugs administered during general anesthesia are as follows: Premedication included Midazolam (0.1–0.2mg/kg), Ketamine (0.1–1.2mg/kg), while induction involved Atropine (0.2–0.5mg/kg), Propofol (1–3mg/kg), and Nesdonal (2–5mg/kg).

Pain reduction was compared between the intervention and control groups. Statistical analysis was performed using descriptive statistics, including

mean \pm standard deviation for quantitative data and frequency tables for qualitative data. Repeated-measures analysis of variance or its non-parametric equivalent and the Chi-square test were used for data analysis. Kaplan-Meier plots and the Log-rank test were used to describe and compare hospitalization duration between the two groups. Data were analyzed using SPSS software, version 16 (IBM Armonk, NY, USA). A significance level of 5% was considered for this study.

Table 1. Comparison of VAS Pain Scores Between Ketamine and Control Groups at Different Time Intervals

| Group | Mean | Standard Deviation | Number | P-value |
|-----------------------------|--------|--------------------|--------|---------|
| VAS Baseline | | | | |
| Ketamine Group | 1.1333 | 1.19578 | 30 | .000 |
| Control Group | 4.7333 | 1.76036 | 30 | |
| Total | 2.9333 | 2.34966 | 60 | |
| VAS After 20 Minutes | | | | |
| Ketamine Group | 1.0667 | 1.04826 | 30 | .000 |
| Control Group | 4.7000 | 1.72507 | 30 | |
| Total | 2.8833 | 2.31496 | 60 | |
| VAS After 60 Minutes | | | | |
| Ketamine Group | 1.0667 | 1.04826 | 30 | .000 |
| Control Group | 4.4667 | 1.59164 | 30 | |
| Total | 2.7667 | 2.17354 | 60 | |
| VAS After 6 Hours | | | | |
| Ketamine Group | 1.6667 | 0.60648 | 30 | .000 |
| Control Group | 3.3000 | 1.29055 | 30 | |
| VAS After 12 Hours | | | | |
| Ketamine Group | 1.7000 | 0.65126 | 30 | .000 |
| Control Group | 2.6667 | 0.95893 | 30 | |
| Total | 2.1833 | 0.94764 | 60 | |

VAS (Visual Analog Scale)

The Visual Analog Scale (VAS) is a psychometric scale commonly used for assessing pain. It consists of two parts: numeric and facial. The numeric part is for children over 7 years old, while the facial part is for children under 7 years old who may not understand numeric values. In the numeric part, the person rates their pain on a scale of 0 to 10, where 0 indicates no pain, 1–2 indicates mild pain, 3–4 indicates moderate pain that interferes with activity, 5–6 indicates moderate pain that interferes with concentration, 7–8 indicates severe pain that interferes with basic needs, and 9–10 indicates excruciating, unbearable pain.

Pain levels were assessed postoperatively (in recovery, at 6 and 12 hours after surgery) using the VAS during recovery and hospitalization under observation. The facial scale was used for children aged 5 to 7 years, while the numeric scale was used for patients older than 7 years. Parents assisted in assessing pain for younger children.

Data Analysis Method

Data were first summarized and described using descriptive statistical methods, including frequency tables for qualitative variables, mean \pm standard deviation for quantitative variables, or median with interquartile range, along with graphical representations. To compare the two groups in terms of gender, the Chi-square test was used, and for age and BMI, the t-test was applied. The Chi-square test was used to compare the two groups regarding pain occurrence before and after the intervention, and for pain intensity comparison between the groups, the t-test was used. For longitudinal measurements, repeated-measures analysis of variance was conducted if the data were normally distributed, after verification using the Kolmogorov-Smirnov test; if the data were not normal, generalized estimating equations (GEE) were applied. Data analysis was performed using SPSS version 25, with a significance level set at 5%.

Results

A total of 60 participants were enrolled in the study and

divided into two groups of 30 each. The ketamine group consisted of 30 participants, and the placebo group also had 30 participants. Group 1 received 1mg of ketamine, and Group 2 was the control group. Among the participants, 53.3% were female and 46.7% were male in the ketamine group, while 36.7% were female and 63.3% were male in the placebo group. No significant difference was found between the two groups in terms of gender distribution ($p = 0.194$), indicating proper randomization of the participants. The significance level for all statistical tests was 0.05.

Table 1 shows the number, mean, and standard deviation of pain intensity and the difference in pain intensity at baseline, after 20 minutes, after 60 minutes, after 6 hours, and after 12 hours in the two groups receiving ketamine and the control group.

According to this table, the difference between the ketamine and control groups in terms of pain intensity at baseline, after 20 minutes, after 60 minutes, after 6 hours, and after 12 hours showed a significant difference in both groups.

Table 2. Comparison of Pain Intensity Scores (VAS) Between Ketamine and Control Groups at Different Time Points

| Group | Number | Mean Score | Total Scores | P-value |
|-----------------------------|--------|------------|--------------|---------|
| VAS After 20 Minutes | | | | |
| Ketamine Group | 30 | 17.12 | 513.50 | 0.000 |
| Control Group | 30 | 43.88 | 1316.50 | |
| Total | 60 | | | |
| VAS After 60 Minutes | | | | |
| Ketamine Group | 30 | 17.12 | 513.50 | 0.000 |
| Control Group | 30 | 43.88 | 1316.50 | |
| Total | 60 | | | |
| VAS After 6 Hours | | | | |
| Ketamine Group | 30 | 19.53 | 586.00 | 0.000 |
| Control Group | 30 | 41.47 | 1244.00 | |
| Total | 60 | | | |
| VAS After 12 Hours | | | | |
| Ketamine Group | 30 | 22.20 | 666.00 | 0.000 |
| Control Group | 30 | 38.80 | 1164.00 | |
| Total | 60 | | | |

Table 3. Comparison of VAS Scores Between Ketamine and Control Groups at Different Time Points: Non-Parametric Test Results

| Parameter | B | Sig. |
|-----------------------------|--------|-------|
| Baseline VAS | | |
| Ketamine Group | -3.600 | 0.000 |
| Control Group | 0a | . |
| VAS After 20 Minutes | | |
| Ketamine Group | -3.633 | 0.000 |
| Control Group | 0a | . |
| VAS After 60 Minutes | | |
| Ketamine Group | -3.400 | 0.000 |
| Control Group | 0a | . |
| VAS After 12 Hours | | |
| Ketamine Group | -0.967 | 0.000 |
| Control Group | 0a | . |

Table 2 shows the number, mean scores, and total scores of pain intensity after 20 minutes, 60 minutes, 6 hours, and 12 hours. It presents the number, mean scores, and total scores of pain intensity after 20 minutes, 60 minutes, 6 hours, and 12 hours using the non-parametric test in the ketamine and control groups.

According to this table, the difference between the ketamine and control groups in terms of pain intensity after 20 minutes, 60 minutes, and 12 hours showed a significant difference in both groups.

Table 3 shows the ratio of pain intensities between the two groups. On average, the ketamine group had 3.6

times lower pain intensity compared to the control group at baseline and 20 minutes after, 3.4 times lower

after 60 minutes, and 0.967 times lower after 12 hours. This lower ratio was also statistically significant.

Table 4. Comparison of Pain Intensity at Different Times Relative to Each Other

| Group | Time (I) | Time (J) | Sig.b |
|----------------|----------|----------|-------|
| Ketamine group | 1 | 2 | .965 |
| | | 3 | .965 |
| | | 4 | .043 |
| | 2 | 1 | .965 |
| | | 3 | . |
| | | 4 | .007 |
| | 3 | 1 | .965 |
| | | 2 | . |
| | | 4 | .007 |
| | 4 | 1 | .043 |
| | | 2 | .007 |
| | | 3 | .007 |
| Control group | 1 | 2 | 1.000 |
| | | 3 | .053 |
| | | 4 | .000 |
| | 2 | 1 | 1.000 |
| | | 3 | .101 |
| | | 4 | .000 |
| | 3 | 1 | .053 |
| | | 2 | .101 |
| | | 4 | .000 |
| | 4 | 1 | .000 |
| | | 2 | .000 |
| | | 3 | .000 |

Table 4 shows the ratio of pain intensities between the ketamine and control groups at different times relative to each other. According to these results, in the ketamine group, the pain intensity at time 1 compared to time 4, time 3 compared to time 4, and time 4 compared to other times showed a significant difference. In the control group, the pain intensity at times 1, 2, and 3 individually compared to time 4, and time 4 compared to other times, showed a significant difference.

Discussion

The results of this study indicated that there were no significant differences in the mean age, BMI, type of suture used, grade of tonsils, and gender distribution between male and female participants, suggesting that the distribution of variables was correct.

Both the ketamine and control groups showed significant differences in pain intensity at baseline, 20 minutes, 60 minutes, 6 hours, and 12 hours post-surgery. The ketamine group exhibited significantly lower pain intensity, with this difference gradually decreasing over time.

On average, the ketamine group experienced 3.6 times lower pain intensity compared to the control group at baseline and 20 minutes post-surgery, 3.4 times lower at 60 minutes, and 0.967 times lower at 12 hours. These differences were statistically significant.

In the ketamine group, there were significant differences in pain intensity between timepoints 1, 3, and 4, with the lowest pain intensity observed at timepoint 4. In the control group, significant differences were also found between timepoints 1, 2, 3, and 4, with the lowest pain intensity observed at timepoint 4.

A systematic review conducted by N. Aldamluji and colleagues, aimed at evaluating existing studies and providing recommendations for optimal pain management after tonsillectomy until 2019, concluded that the pain management regimen for tonsillectomy should include acetaminophen, non-steroidal anti-inflammatory drugs, and intravenous dexamethasone, with opioids considered as rescue analgesics. Ketamine (only for children), dexmedetomidine, or gabapentinoids may be considered when certain first-line analgesics are contraindicated (63, 64).

Another study by Mohammad Ali Damghani and colleagues, examining the analgesic effects of ketamine,

ketorolac, and dexamethasone after adenotonsillectomy in children aged 4 to 18 years, found that patients who used ketamine, ketorolac, and dexamethasone during the recovery period had significantly lower pain scores at six hours post-surgery and at discharge, with the highest pain scores observed in the control group. The administration of ketamine and ketorolac was effective for pain control and reduction post-surgery in adenotonsillectomy patients (65, 66).

In this study, similar to ours, 1 mg of ketamine was administered to pediatric patients under 18 years of age, and the results regarding ketamine's impact on pain reduction were comparable. However, in our study, the pain difference between the two groups remained significant up to 12 hours post-surgery.

A further study by Seyed Alireza Bameshki and colleagues, investigating the effects of ketamine on sedation and pain relief post-surgery in 50 children aged 5 to 12 years undergoing tonsillectomy, demonstrated that adding ketamine to midazolam preoperatively resulted in reduced restlessness and pain in the first 30 minutes after surgery. This finding aligns with our study, which also demonstrated a difference in pain levels between the two groups at 20 minutes post-surgery (67).

In contrast, a study by Juliana Alves de Sousa Caixeta and colleagues, investigating the effect of peri-tonsillar infiltration of tramadol, ketamine, and placebo on post-surgery pain in adenotonsillectomy patients, found no superiority of peri-tonsillar ketamine or tramadol over placebo in reducing post-surgery pain. However, our study's results differed, showing that ketamine injection was effective in post-operative pain management. The difference in findings could be due to the lower ketamine dose (0.5 mg) used in their study compared to the 1 mg dose in ours. This suggests that a higher ketamine dose (1 mg) may provide a better therapeutic effect (68).

This study had several limitations. The sample size of patients was small, which may limit the generalizability of the findings. Although

randomization was performed, convenience sampling could have introduced selection bias. The study was conducted at a single center, which affects the external validity of the results. Additionally, long-term follow-up was not conducted to assess delayed side effects of ketamine. While age and gender were controlled, other factors like comorbidities were not, which could influence pain outcomes. Lastly, the study only included ASA Class 1 and 2 patients, limiting its applicability to those with higher surgical risks.

Conclusion

Based on these findings, it can be suggested that 1 mg of peri-tonsillar ketamine may be an effective treatment for reducing post-tonsillectomy pain in pediatric populations and should be considered for use. Since our study focused solely on the impact of ketamine on post-operative pain, further research is recommended to investigate its effects on other surgical complications.

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Conflict of Interest

The authors declare no conflict of interest related to the publication of this article.

Ethical Approval

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences. All participants provided written informed consent before enrollment in the study.

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