Comparison of the effects of oral vs. peritonsillar infiltration of ketamine in pain reduction after tonsillectomy: A randomized clinical trial

Afsaneh Norouzi*, Abolfazl Jafari**, Hamid Reza Khoddami Vishteh***, and Shahin Fateh****

Abstract

**Background:** Although oral ketamine has been used in some cases to reduce pain in children, the use of this drug to reduce pain after tonsillectomy has not been studied yet.

**Methods:** This double-blind clinical trial was conducted in 2009 in 92 children who were aged three to nine years old, met ASA I or II criteria, and were candidate for tonsillectomy. Patients were divided randomly into two groups. Half an hour before general anesthesia, 5 mg/kg ketamine mixed in 2 cc/kg apple juice was given to the children in oral ketamine group and 2 cc/kg of apple juice alone was given to the children in the peritonsillar group. After general anesthesia and three minutes before surgery 1 cc of 0.9% normal saline in the oral group and 1 cc of ketamine (0.5 mg/kg) in the peritonsillar group was injected to the tonsil bed of patients.

**Results:** There was no difference between the two groups in terms of sex, age, and weight. Duration of surgery was significantly shorter in the peritonsillar group (P <0.001) and the severity of postoperative bleeding was significantly higher in peritonsillar group (P = 0.022). However, postoperative bleeding recurred in 25 patients (27%) and there was no statistically significant difference between the two groups. The level of pain in children six hours after surgery according to CHEOPS criteria was significantly lower in the peritonsillar group (0.9 ± 0.8) than in the oral group (2.6 ± 1) (P <0.001).

**Conclusions:** The finding of this study showed that, compared with the peritonsillar infiltration of ketamine, the use of oral ketamine before general anesthesia was less effective in reducing postoperative pain of tonsillectomy in children.

**Keywords:** tonsillectomy, adenotonsillectomy, postoperative pain, ketamine.

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Introduction

Adenotonsillectomy is one of the most common ear, nose, and throat surgeries in children and postoperative pain is one of its important complications. Inadequate control of postoperative pain leads to different complications such as poor nutrition, dehydration, sleep disorders, behavioral changes, nausea, and vomiting; moreover, it can increase the length of hospitalization and consequently increase healthcare costs. Despite the high prevalence of pain after tonsillectomy and adenotonsillectomy and the presence of different analgesics and assessment tools for measuring age-related pain, the choice of appropriate analgesic to be used after tonsillectomy operation is still controversial.

To reduce pain after tonsillectomy in children, different groups of drugs (oral paracetamol, opioids, NSAIDs, and local anesthetics) have been studied. Although paracetamol is a safe and effective analgesic, when it is used alone it cannot achieve an appropriate analgesic effect after tonsillectomy. Opiates may reduce upper airway tone, suppress the cough reflex, cause sedation and respiratory depression (especially in unintended outpatient surgery), and also lead to postoperative nausea and vomiting. Although NSAIDs are an alternative to opioids, they may increase the risk of postoperative bleeding and reoperation. In addition, local anesthetics are associated with vasoconstriction.

N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord are involved in central sensitization to painful stimuli. Ketamine is a non-competitive antagonist of NMDA receptors which has analgesic effects at sub-anesthetic doses. Safari et al showed that the use of ketamine reduced the need for postoperative opioids and other analgesics in children undergoing tonsillectomy. Intravenous injection, peritonsillar infiltration, rectal, spray at the site of surgery, continuous infusion and subcutaneous injection of ketamine have been investigated for pain reduction after tonsillectomy. To our knowledge, no previous studies have evaluated the role of oral ketamine for pain reduction after tonsillectomy.

The aim of the current study is to compare oral ketamine to peritonsillar ketamine infiltration for pain relief after tonsillectomy.

Materials and Methods

This double-blind clinical trial was conducted in 2009 on 92 children aged three to nine years old who were referred to Amir Kabir hospital in Arak City. Inclusion criteria were: being aged three to nine years old, meeting ASA I or II criteria, and candidate for tonsillectomy surgery. Exclusion criteria were: the presence of an underlying disease, and the presence of contraindications to the use of ketamine including upper airway active infection, increased intracranial pressure, open eyes surgery, and seizures. The study was approved by the Ethics Committee of the Arak University of Medical Sciences.

After explaining the procedures of the study to parents and obtaining their informed consent, patients who met inclusion criteria were divided randomly into two groups. In order to double-blind study, injectable medications were tagged using similar labels and oral ketamine was also given to patients mixed in apple juice by a medical student. Anesthesiologist and ENT specialists were unaware of the patient group and used apple juices and injectable medications for patients, respectively. Anesthesia was started using fentanyl and atropine as premedication and then anesthesia was induced using sodium thiopental 6 mg/kg and atracurium 0.5-1 mg/kg and it was sustained with isoflurane 1%, NO2 and O2 with a ratio of 50%. All patients were intubated and to prevent entering blood to the throat, which is of the factors causing nausea, gauze was placed in the throat.

Half an hour before general anesthesia, 5 mg/kg ketamine mixed in 2 cc/kg apple juice was given to the children in oral ketamine group and 2 cc/kg of apple juice alone was given to the children in the peritonsillar group. After the induction of general anesthesia and three minutes before surgery 1 cc of normal saline or 1 cc of ketamine (0.5 mg/kg) in the peritonsillar group was injected to the each tonsil bed of patients (a total of 2 cc injections for each child). Injection was performed by an ENT specialist.

Age, sex, weight, duration of surgery, intraoperative blood loss, postoperative bleeding (in the recovery room), nausea, vomiting, and postoperative bleeding recurrence six hours after surgery were recorded by the medical student who was unaware of...
patient group. In order to measure the pain six hours after surgery, Modified Scoring CHEOPS criterion was used (Table 1). The range for this criterion is from 0 to 10 where a higher score indicates greater pain. Power calculations had indicated that 46 children would be required per group to detect a difference of 30% in facial CHEOPS pain scoring with a power of 85% and \( \alpha = 0.05 \). SPSS 13 software was used for data analysis. Qualitative variables were described using frequencies and percentages and quantitative variables were described using mean and standard deviation. In order to compare the two groups, chi-square test and Mann-Whitney U test were used. P-value less than 0.05 was considered as a significant level.

### Results

There were no differences between the two groups in terms of sex, age, and weight (Table 2). Table 3 shows the comparison of the characteristics of surgeries and postoperative complications between the two groups. Duration of surgery was \( \leq 20 \) minutes in

#### Table 1

**Modified CHEOPS scoring**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry</td>
<td>No cry</td>
<td>Crying, moaning</td>
<td>Scream</td>
</tr>
<tr>
<td>Facial</td>
<td>Smiling</td>
<td>Neutral</td>
<td>Grimace</td>
</tr>
<tr>
<td>Verbal</td>
<td>Positive statement</td>
<td>Negative statement</td>
<td>Suffering from pain, another complaint</td>
</tr>
<tr>
<td>Torso</td>
<td>Neutral</td>
<td>Variable, taut, upright</td>
<td>Stretched</td>
</tr>
<tr>
<td>Legs</td>
<td>Neutral</td>
<td>Kicking</td>
<td>Stretched, continuous move</td>
</tr>
</tbody>
</table>

#### Table 2

**Comparison of demographic characteristics between groups**

<table>
<thead>
<tr>
<th></th>
<th>Oral group (N = 46)</th>
<th>Peritonsillar group (N = 46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>37 (80%)</td>
<td>9 (20%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30 (65%)</td>
<td>16 (35%)</td>
</tr>
<tr>
<td>Age group</td>
<td>( \leq 5 ) yr</td>
<td>9 (20%)</td>
<td>12 (26%)</td>
</tr>
<tr>
<td></td>
<td>6-7 yr</td>
<td>18 (39%)</td>
<td>11 (24%)</td>
</tr>
<tr>
<td></td>
<td>( \geq 8 ) yr</td>
<td>19 (41%)</td>
<td>23 (50%)</td>
</tr>
<tr>
<td>Weight</td>
<td>( \leq 20 ) Kg</td>
<td>18 (39%)</td>
<td>18 (39%)</td>
</tr>
<tr>
<td></td>
<td>21-24 Kg</td>
<td>18 (39%)</td>
<td>12 (26%)</td>
</tr>
<tr>
<td></td>
<td>( \geq 25 ) Kg</td>
<td>10 (22%)</td>
<td>16 (35%)</td>
</tr>
</tbody>
</table>

#### Table 3

**Comparison of surgery time and side effects between groups**

<table>
<thead>
<tr>
<th></th>
<th>Oral group (N = 46)</th>
<th>Peritonsillar group (N = 46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery time</td>
<td>( \leq 20 ) min</td>
<td>0 (0%)</td>
<td>19 (41%)</td>
</tr>
<tr>
<td></td>
<td>21-29 min</td>
<td>18 (39%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td></td>
<td>( \geq 30 ) min</td>
<td>28 (61%)</td>
<td>20 (44%)</td>
</tr>
<tr>
<td>Post-op bleeding</td>
<td>Mild</td>
<td>9 (20%)</td>
<td>14 (30%)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>37 (80%)</td>
<td>27 (59%)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>0 (0%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Post-op bleeding recurrence</td>
<td>9 (20%)</td>
<td>16 (35%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>0.153</td>
</tr>
</tbody>
</table>
19 patients (21%), 21-29 minutes in 25 patients (27%), and ≥30 minutes in 48 patients (52%). The durations of surgeries were significantly shorter in the peritonsillar group than in the oral group (P < 0.001). The severity of postoperative bleeding was mild in 23 patients (25%), moderate in 64 patients (70%), and severe in five patients (5%); overall, the incidence of postoperative bleeding was significantly higher in peritonsillar group than in the oral group (P = 0.022). Postoperative bleeding recurred in 25 patients (27%) and there was no statistically significant difference between the two groups. Only two patients had postoperative nausea and vomiting, and there was no significant difference between the two groups.

The level of pain in children six hours after surgery according to CHEOPS criteria was significantly lower in the peritonsillar group (0.9 ± 0.8) than in the oral group (2.6 ± 1) (P < 0.001). Table 4 shows the characteristics of pain in each item. All the children in the peritonsillar group had neutral facial expression; however in the oral group only half the children had neutral facial expression (P < 0.001). In the peritonsillar group, 39% of children were suffering from pain, whereas 76% of patients in the oral group were suffering from pain (P < 0.001). The leg condition was neutral in all children in the peritonsillar group, while only 30% of children in the oral group had neutral condition (P < 0.001). There was no significant difference between the two groups in terms of children cry and their body shape (Torso).

**Discussion**

The findings of this study showed that, compared with oral ketamine, the peritonsillar infiltration of ketamine after general anesthesia and immediately before tonsillectomy shortened the duration of operation and reduced the severity of postoperative pain. Although postoperative bleeding was more in the ketamine peritonsillar group, the recurrent bleeding, nausea, and vomiting after surgery was not significantly different between the two groups. Thus, it seems that, compared to peritonsillar infiltration, the use of oral ketamine 5 mg/kg is less effective in reducing pain in children after tonsillectomy.

Ketamine is a noncompetitive antagonist of the NMDA receptor. These receptors are located in the dorsal horn of the spinal cord and play an important role in the development of central sensitization to painful peripheral stimuli. Seemingly, hyperexcitability of the central nervous system appears to be the cause of the

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Oral group (N = 46)</th>
<th>Peritonsillar group (N = 46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cry</td>
<td>28 (61%)</td>
<td>36 (78%)</td>
<td>0.070</td>
</tr>
<tr>
<td>Crying, moaning</td>
<td>18 (39%)</td>
<td>10 (22%)</td>
<td></td>
</tr>
<tr>
<td>Screw</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Facial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smiling</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutral</td>
<td>23 (50%)</td>
<td>46 (100%)</td>
<td></td>
</tr>
<tr>
<td>Grimace</td>
<td>23 (50%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Verbal</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive statement</td>
<td>0 (0%)</td>
<td>16 (35%)</td>
<td></td>
</tr>
<tr>
<td>Negative statement</td>
<td>11 (24%)</td>
<td>12 (26%)</td>
<td></td>
</tr>
<tr>
<td>Suffering from pain, another complaint</td>
<td>35 (76%)</td>
<td>18 (39%)</td>
<td></td>
</tr>
<tr>
<td><strong>Torso</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Neutral</td>
<td>46 (100%)</td>
<td>46 (100%)</td>
<td></td>
</tr>
<tr>
<td>Variable, taut, upright</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Stretched</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Legs</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutral</td>
<td>14 (30%)</td>
<td>46 (100%)</td>
<td></td>
</tr>
<tr>
<td>Kicking</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Stretched, continuous move</td>
<td>32 (70%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>
wind-up phenomenon and subsequent hyperalgesia in the place of injury. The goal of preemptive analgesia is to prevent the afferent impulses to the spinal cord that is causing such a phenomenon. Hence, preemptive analgesia may prevent pain memory in the central nervous system and reduce the need for analgesics in the postoperative period. It has been shown that ketamine’s effects on these receptors can reduce pain in humans.

Ketamine has been used in different ways, at different doses and different times as an analgesic after tonsillectomy surgery, but the reported results were not consistent have been various. Some studies failed to show the effect of ketamine on reducing pain after tonsillectomy. O’Flaherty et al’s study which compared the effects of the administration of intravenous ketamine with that of placebo and Van Elstraet et al’s study which examined the effect of ketamine on pain after tonsillectomy in adults did not show a positive effect in reducing pain after tonsillectomy. However, other studies reported that using ketamine was effective in reducing pain following tonsillectomy. Murray et al showed that a low-dose of intravenous ketamine may be effective in reducing pain after tonsillectomy. Marcus et al and Elhakim et al stated that the intramuscular ketamine can be used as an alternative analgesic for tonsillectomy. Erhan et al. reported that ketamine injection in the tonsillar area was more effective than placebo in reducing pain without inducing sedation or nausea. Dal et al. reported that intravenous or peritonsillar infiltration of ketamine before adenotonsillectomy surgery could reduce postoperative pain and reduce the need for analgesics without causing any adverse effects. More recent studies have also suggested the effect of ketamine on reducing pain after tonsillectomy. Sizer et al showed that intravenous ketamine was effective in reducing pain following tonsillectomy. According to a study by Siddiqui et al. peritonsillar infiltration of ketamine with doses of 0.5 or 1 mg/kg reduced pain after tonsillectomy, compared to control. Our study also showed that peritonsillar infiltration of ketamine could be a useful method for reducing pain following tonsillectomy in children.

Although ketamine has been used via different methods to reduce pain after tonsillectomy, oral method, however, has not been used yet for this purpose. Filatov et al. have compared oral ketamine as premedication with rectal diazepam/diclofenac in adenoidectomy surgery and reported that oral ketamine group had slightly higher pain scores than other group. However, they conclude that oral ketamine is not suitable for premedication in upper airway surgeries. Oral ketamine has been effective in children for controlling pain in different cases such as abdominal malignancy surgery, sickle cell crisis, and chronic pains. It has also been used for anesthetic premedication in children in surgeries such as dental, ophthalmic and minor surgeries. In addition, oral ketamine is effective in postoperative agitation in children. In the present study we examined the effects of oral ketamine in reducing pain after tonsillectomy and compared it with peritonsillar ketamine. Although Ketamine reduced postoperative bleeding, overall it was associated with more pain in children than peritonsillar infiltration. Thus, it seems that oral ketamine with a dose of 5 mg/kg is less effective in reducing pain in children after tonsillectomy compared to peritonsillar infiltration.

Conclusions

The finding of this study indicated that, compared with the use of oral ketamine before tonsillectomy, the peritonsillar infiltration of ketamine after general anesthesia and immediately before tonsillectomy was more effective in reducing postoperative pain in children.
References

The key to Lock-up Postoperative Pain

**STEP I**
Initial bolus
Inject 1 ampoule Tramal® 100 mg i.v. or i.m. slowly over 2-3 minutes

**STEP II**
Ways of administration after initial bolus
- **Infusion**
  - Inject 2 ampoules Tramal®, each 100 mg, in 500 ml of infusion solution.
  - Infusion rate 12-24 mg Tramal®/h (16-20 ml/h in pts of 30-60 kg).

- **PCA**
  - Subsequent increments of 26 mg with a lock-out time of 5 minutes.
  - Usual dose 50 mg or 100 mg 4-6 hourly up to a total daily dose of 400 mg except in special clinical circumstances which might necessitate daily doses up to 480 mg.

- **Injection**
  - If needed further doses of Tramal® 50 mg up to a total of 200 mg (excluding the initial bolus) within the first 60 min.

**STEP III**
Follow-up
- 50 mg 1-2 capsules every 4-6 hours
- 50 mg 20-40 drops every 4-6 hours
- 100 mg 1 suppository every 4-6 hours
- Slow release 100 mg, 150 mg, 200 mg 1 tablet every 12 hours

**Intra-Operative**
Loading Dose
- 2.5 - 3 mg/kg at wound closure

**Post-Anaesthesia Care Unit**
If intra-operative dose not given then:
- BOLUS i.v.*
  - 100 mg over 2-3 mins

An intra-operative loading dose of Tramal® will reduce PONV rates**

*if needed further doses of 50 mg up to a total of 200 mg (incl. the initial bolus) may be given within the first 60 min.

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BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.¹

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If neuromuscular blockade is required within 24 hours of BRIDION administration, a nonneostigmine neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or sucking on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In the few individuals, allergic-like reactions (ir, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (13%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION, however, clinical trials have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or concomitant condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

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- 98% of BRIDION patients recovered to a TOF⁶ ratio of 0.9 from reappearance of T₂ ⁷ within 5 minutes⁸
- 97% of BRIDION patients recovered to a TOF⁹ ratio of 0.9 from 1 to 2 PTCs ¹ within 5 minutes³

Rapid reversal
- BRIDION rapidly reversed patients from reappearance of T₂ ⁷ in 1.4 minutes³
- BRIDION rapidly reversed patients from 1 to 2 PTCs ¹ in 2.7 minutes³


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