The comparison of ketamine with tramadol for postoperative pain relief on children following adenotonsillectomy or tonsillectomy

A meta-analysis of randomized controlled trials

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Abstract

Introduction: The comparison of ketamine with tramadol for pain control remains controversial in pediatric adenotonsillectomy or tonsillectomy. We conduct a systematic review and meta-analysis to explore the efficacy of ketamine vs tramadol for pain relief in children following adenotonsillectomy.

Methods: We have searched PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through October 2019 for randomized controlled trials (RCTs) assessing the effect of ketamine vs tramadol for pediatric adenotonsillectomy or tonsillectomy. This meta-analysis is performed using the random-effects model.

Results: Six RCTs are included in the meta-analysis. Overall, compared to ketamine group for pediatric adenotonsillectomy or tonsillectomy, tramadol is associated with substantially lower CHEOPS at 1 h (SMD = 1.56; 95% CI = 0.20–2.92; P = .02; low quality) and longer first time of additional pain medication (SMD = –0.47; 95% CI = –0.74 to –0.19; P = .0008; low quality), but demonstrates no obvious effect on CHEOPS at 6 h (SMD = 0.51; 95% CI = –1.17 to 2.19; P = .55; low quality), sedation scale at 1 h (SMD = –0.80; 95% CI = –3.07 to 1.48; P = .49; low quality) or additional pain medication (RR = 1.31; 95% CI = 0.85–2.02; P = .23; moderate quality).

Conclusions: Tramadol may be better to alleviate the postoperative pain after pediatric adenotonsillectomy or tonsillectomy.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: adenotonsillectomy, children, ketamine, tonsillectomy, tramadol

1. Introduction

Adenotonsillectomy is a common procedure in children. The postoperative pain is often associated with nausea, vomiting, and agitation. Several studies have developed various methods to prevent postoperative pain, and administration of different drugs (e.g., opioids, non-opioids, nonsteroidal anti-inflammatory drugs, and steroids) is conducted by intravenous (IV), subcutaneous, intramuscular, rectal, and peritonsillar infiltration.

Among them, ketamine is an anesthetic agent in the phencyclidine group and ensures central sensitization and opioid resistance due to the effect as an N-methyl-D-aspartate receptor antagonist. Its analgesic effect is produced by binding to the receptor in the spinal cord and brain after the surgery. Tramadol is another analgesic and a synthetic opioid of the aminocyclohexanol group with little respiratory depression. Tramadol has both systemic and local anesthetic effect on peripheral nerves from human and animal studies.

Recently, several studies have documented the analgesic efficacy of ketamine and tramadol for children with adenotonsillectomy or tonsillectomy, but their comparison is conflicting. With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to compare the analgesic efficacy of ketamine vs tramadol for pediatric adenotonsillectomy or tonsillectomy.

2. Materials and methods

Ethical approval and patient consent were not required because this was a systematic review and meta-analysis of previously published studies. This meta-analysis was conducted and...
reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[18]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to October 2019): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: “ketamine,” “tramadol”, and “adenotonsillectomy” or “tonsillectomy” or “paediatric” or “children.” We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria were as follows:
1. population: adenotonsillectomy or tonsillectomy was performed in children patients;
2. intervention treatments were ketamine vs tramadol;
3. study design was RCT.

2.2. Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, female, weight, duration of surgery and detail methods in each group, etc. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain the data when necessary.

The primary outcome was Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS) at 1 h. Secondary outcomes included CHEOPS at 6 h, sedation scale at 1 h, additional pain medication and first time of additional pain medication.

2.3. Assessment for risk of bias

The risk of bias tool was used to assess the quality of individual studies in accordance with the Cochrane Handbook for Systematic Reviews of Interventions,[19] and the following sources of bias were considered: selection bias, performance bias, attrition bias, detection bias, reporting bias, and other potential sources of bias. The overall risk of bias for each study was evaluated and rated: low, unclear, or high.[20]

Based on the methodological quality and the confidence, the quality of evidence for each outcome was assessed according to the GRADE recommendations as high quality, moderate quality, low quality, or very low quality.[21]

2.4. Statistical analysis

We estimated the standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (CHEOPS at 1 and 6 h, sedation scale at 1 h, and first time of additional pain medication) and risk ratio (RR) with 95% CI for dichotomous outcomes (additional pain medication). The random-effects model or fixed-effects model was used according to the heterogeneity.[22] Heterogeneity was reported using the I² statistic, and I² > 50% indicated significant heterogeneity.[22,23] Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 318 potentially relevant articles are identified initially. Finally, six articles are included in the meta-analysis.[10,11,16,17,24,25]

The baseline characteristics of the six eligible RCTs are summarized in Table 1. The six studies are published between 2004 and 2015, and the total sample sizes is 324. Four studies involve tonsillectomy,[11,17,24,25] while other two studies involve adenotonsillectomy.[10,16]

Among the six studies included here, three studies report CHEOPS at 1 and 6 h,[11,24,25] two studies report sedation scale at 1 h,[11,16] three studies report additional pain medication,[10,16,17] and four studies report first time of additional pain medication.[10,16,24,25] Risk of bias analysis shows that these six included RCTs generally have high quality despite of some unclear risk of bias (Fig. 2). The quality of evidence for each outcome is presented in Table 2.

3.2. Primary outcome: CHEOPS at 1 h

This outcome data is analyzed with the random-effects model, and tramadol leads to lower CHEOPS at 1 h than ketamine group for pediatric adenotonsillectomy or tonsillectomy (SMD = 1.56; 95% CI = 0.20–2.92; P = .02; low quality) with significant heterogeneity among the studies (I² = 94%, heterogeneity P < .00001) (Fig. 3).

3.3. Sensitivity analysis

Significant heterogeneity is observed for the primary outcome, but when performing the sensitivity analysis by omitting one study in turn, there is still significant heterogeneity.

3.4. Secondary outcomes

In comparison with ketamine group for pediatric adenotonsillectomy or tonsillectomy, tramadol demonstrates the similar CHEOPS at 6 h (SMD = 0.51; 95% CI = –1.17 to 2.19; P = .55; low quality; Fig. 4), sedation scale at 1 h (SMD = –0.80; 95% CI = –3.07 to 1.48; P = .49; low quality; Fig. 5) and additional pain medication (RR = 1.31; 95% CI = 0.85–2.02; P = .23; moderate quality; Fig. 6), but results in longer first time of additional pain medication (SMD = –0.47; 95% CI = –0.74 to –0.19; P = .0008; low quality; Fig. 7).

4. Discussion

Postoperative analgesia provides a very important role in adenotonsillectomy or tonsillectomy, and insufficient analgesia may cause some complications including postoperative throat ache, swallowing difficulty, aspiration, delayed discharge, and spasm.[26–28] Rescue analgesic drugs such as morphine and opioids may lead to postoperative respiratory depression and desaturation.[29] As an N-methyl-D-aspartate receptor antagonist, ketamine has the ability to decrease the need for postanesthetic analgesia at subanesthetic dose.[30] A 0.5-mg IV ketamine was documented to substantially reduce postoperative pain and did not increase the frequency of adverse effects.[31]
Figure 1. Flow diagram of study searching and selection process.

| Table 1 | Characteristics of included studies. |
|---------|-------------------------------------|
|        | Ketamine group                       | Tramadol group                      |
| NO.    | Author | Number | Age (years) | Female (n) | Weight (kg) | Duration of operation (min) | Methods                        | Number | Age (years) | Female (n) | Weight (kg) | Duration of operation (min) | Methods                        |
| 1      | Yenigun | 30     | 7.67 (2.59) | –          | 26.62 (6.77) | 31.87 (5.15) | Intravenous (i.v.) ketamine (0.5 mg/kg) for tonsillectomy | 30     | 6.25 (1.96) | –          | 21.17 (4.37) | 28.42 (7.13) | Tramadol hydrochloride infiltration (2 mg/kg) |
| 2      | Ugur   | 25     | 5.4 (1.7)   | 16         | 20.9 (7.5)   | 46.0 (14.7)  | Injections in peritonsillar fossa of ketamine (0.5 mg/kg) to 2 mL for adenotonsillectomy | 25     | 5.2 (1.6)   | 6          | 21.2 (5.4)   | 44.7 (10.2)  | Injections in peritonsillar fossa of tramadol (2 mg/kg) to 2 mL |
| 3      | Tekeloglu | 20    | 5.6 (1.3)   | 10         | 24.05 (5.56) | 36.5 (5.9)   | Tonsillar fossae injection with 0.4 mL (20 mg) ketamine for tonsillectomy | 20     | 6.0 (1.4)   | 11         | 24.95 (5.81) | 34.7 (9.2)   | Tonsillar fossae injection with 0.8 mL tramadol |

(continued)
Table 1

(continued).

| NO. | Author       | Number | Age (years) | Female (n) | Weight (kg) | Duration of operation (min) | Methods                                      | Number | Age (years) | Female (n) | Weight (kg) | Duration of operation (min) | Methods                                      |
|-----|--------------|--------|-------------|------------|-------------|-----------------------------|----------------------------------------------|--------|-------------|------------|-------------|-----------------------------|----------------------------------------------|
| 4   | Honarmand 2013 | 30     | 7.33 (3.2)  | 13         | 24.7 (10.3) | 55.5 (4.4)                 | IV ketamine 0.5 mg/kg for tonsillectomy      | 30     | 8.3 (2.8)   | 12         | 23.5 (9.9)  | 55.6 (4)                   | Peritonsillar infiltration of tramadol 2 mg/kg for tonsillectomy |
| 5   | Ayatollahi 2012 | 42     | 8.05 (2.67) | 18         | 42.14 (10.43)|                            | Peritonsillar infiltration with 0.5 mg/kg ketamine for tonsillectomy | 42     | 7.06 (2.21) | 14         | 40.56 (9.35) | Peritonsillar infiltration with 2 mg/kg tramadol |
| 6   | Umuruglu 2004 | 15     | 6.9 (2.1)   | 5          | 24.33 (6.54) | 43 (13.33)                 | IV 0.5 mg/kg ketamine for adenotonsillectomy | 15     | 6.06 (2.51) | 7          | 23.3 (10.23) | 45.6 (12.08)               | IV 1.5 mg/kg tramadol                              |

Figure 2. Risk of bias assessment. (A) Authors’ judgments about each risk of bias item for each included study. (B) Authors’ judgments about each risk of bias item presented as percentages across all included studies.
Ketamine and tramadol were reported to alleviate postoperative pain in children adenotonsillectomy or tonsillectomy, and there was no differences of postoperative recovery on the basis of the Wilson sedation scoring and no obstructive sleep apnea was observed. Our meta-analysis suggests that tramadol is associated with substantially lower CHEOPS at 1 h and longer first time of additional pain medication than ketamine for pediatric adenotonsillectomy or tonsillectomy, but there is no statistical difference of CHEOPS at 6 h, sedation scale at 1 h or additional pain medication between two groups. Regarding the sensitivity analysis, there is significant heterogeneity. Several factors may account for it. First, children with tonsillectomy or adenotonsillectomy are included and these two kinds of surgeries produce different levels of pain intensity. Secondly, different doses of analgesic drugs may show some influence on the pooling results. Thirdly, ketamine and tramadol are administered in different methods including intravenous infusion and peritonsillar infiltration. For instance, peritonsillar ketamine infiltrated for postoperative analgesia has a better analgesic effect as compared with IV ketamine. A significant

| Outcomes                        | Assumed risk                                      | Corresponding risk                                      | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---------------------------------|---------------------------------------------------|--------------------------------------------------------|--------------------------|-----------------------------|--------------------------------|----------|
| CHEOPS at 1 h                   | The mean cheops at 1 h in the intervention groups was 1.56 standard deviations higher (0–2.92 higher) | 204 (3 studies) | ⊕⊕⊝⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕ | 1.31 (0.85–2.02)                | Low quality | Very low quality |
| CHEOPS at 6 h                   | The mean cheops at 6 h in the intervention groups was 0.51 standard deviations higher (0–2.19 higher) | 204 (3 studies) | ⊕⊕⊝⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕ | 1.31 (0.85–2.02)                | Low quality | Very low quality |
| Sedation scale at 1 h           | The mean sedation scale at 1 h in the intervention groups was 0.8 standard deviations lower (0–1.48 higher) | 110 (2 studies) | ⊕⊕⊝⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕ | RR1.31 (0.85–2.02) | Low quality | Very low quality |
| Additional pain medication      | 267 per 1000                                      | 349 per 1000 (227–559) | RR1.31 (0.85–2.02) | 120 (3 studies) | Moderate | Very low quality |
| First time of additional        | The mean first time of additional pain medication in the intervention groups was 0.47 standard deviations lower (0 higher to 0.19 lower) | 224 (4 studies) | ⊕⊕⊝⊕ ⊕⊕⊕⊕ ⊕⊕⊕⊕ | RR1.7 (0.85–2.02) | Low quality | Very low quality |
| pain medication                 |                                                   |                                                        |                          |                             |                                |          |

Table 2
Summary of findings table.
Comparison of ketamine with tramadol

Patient or population: patients with children undergoing adenotonsillectomy or tonsillectomy
Settings:
Intervention: ketamine
Comparison: tramadol

Figure 3. Forest plot for the meta-analysis of CHEOPS at 1 h.
difference was present at hours 6 and 24 between the peritonsillar ketamine and IV ketamine administrations after pediatric tonsillectomy.\textsuperscript{[11]} Two included studies confirmed the safety of ketamine and tramadol for children, and reported the similar and mild adverse events such as postoperative nausea and vomiting.\textsuperscript{[16,24]} There are several potential limitations. First, our analysis is based on six RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, different doses and administration of analgesic drugs may have some influence on the pooling results. Finally, some unpublished and missing data may lead to some bias for the pooled effect.

5. Conclusions
Tramadol may provide better analgesic efficacy than ketamine in children with tonsillectomy or adenotonsillectomy.
References

[1] Galvão CP, Tinano MM, Nader CMFF, et al. Evolution of obstructive sleep apnea syndrome, nasal flow and systolic pressure of the pulmonary artery in children with indication for adenotonsillectomy and/or tonsillectomy over 18 months. Int J Pediatr Otorhinolaryngol 2019;120:210–4.

[2] Savage JR, Hilton MP, Poirier JP. Curettage versus other methods of adenotonsillectomy in children. Cochrane Database Syst Rev 2018;2018: doi: null. 2018-01-11.

[3] Aksakal C, Müslehiddinoglu A. Comparison of routine histopathological examination results in children and adults after tonsillectomy and/or adenotonsillectomy. Turk Arch Otorhinolaryngol 2018;56:170.

[4] Muller R, Thimmappa V, Sheyn A. Post-operative pain control following pediatric otolaryngology surgery. Madridge J Otorhinolaryngol 2018;3:37–40.

[5] Mathur V, Trivedi PC, Garg DK, et al. Effect of intraoperative iv dexamethomidine on emergence agitation after sevoflurane anaesthesia in children undergoing tonsillectomy with or without adenotonsillectomy. Indian J Clin Anaesth 2018;5:496–500.

[6] Hawley K. Tonsillectomy and adenoidectomy in children. JAMA Otolaryng Head Neck Surg 2019;145:300–1300.

[7] Playne R, Anderson BJ, Frampton C, et al. Analgesic effectiveness, pharmacokinetics, and safety of a paracetamol/ibuprofen fixed-dose combination in children undergoing adenotonsillectomy: a randomized, single-blind, parallel group trial. Paediatr Anaesthesia 2018;28:1087–95.

[8] Ugur MB, Yılmaz M, Altunkaya H, et al. Effects of intramuscular and peritonsillar injection of tramadol before tonsillectomy: a double blind, randomized, placebo-controlled clinical trial. Int J Pediatr Otorhinolaryngol 2008;72:241–8.

[9] Dal D, Celebi N, Elvan EG, et al. The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy 1. Pediatr Anesth 2007;17:263–9.

[10] Umuroğlu T, Eti Z, Çifçi H, et al. Analgesia for adenotonsillectomy in children: a comparison of morphine, ketamine and tramadol. Pediatr Anesth 2004;14:568–73.

[11] Yenigun A, Et T, Aytaç S, et al. Comparison of different administration of ketamine and intravenous tramadol hydrochloride for postoperative pain relief and sedation after pediatric tonsillectomy. J Craniofac Surg 2015;26:e21–4.

[12] Aydin ON, Ugur B, Ozgun S, et al. Pain prevention with intraoperative ketamine in outpatient children undergoing tonsillectomy or tonsillectomy and adenotonsillectomy. J Clin Anesth 2007;19:115–9.

[13] Hullett BJ, Chambers NA, Pascoe EM, et al. Tramadol vs morphine during adenotonsillectomy for obstructive sleep apnea in children. Pediatr Anesth 2006;16:648–53.

[14] Akkaya T, Bedrîlî N, Ceylan T, et al. Comparison of intravenous and peritonsillar infiltration of tramadol for postoperative pain relief in children following adenotonsillectomy. Eur J Anaesthesiol 2009;26:333–7.

[15] Atef A, Fawaz AA. Peritonsillar infiltration with tramadol improves pediatric tonsillectomy pain. Eur Arch Otorhinolaryngol 2008;265:571–4.

[16] Ugur KS, Karabayırli S, Demircioğlu BI, et al. The comparison of preincisional peritonsillar infiltration of ketamine and tramadol for postoperative pain relief on children following adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2013;77:1825–9.

[17] Tekelioğlu UY, Apuhan T, Akkaya A, et al. Comparison of topical tramadol and ketamine in pain treatment after tonsillectomy. Pediatr Anesth 2013;23:496–501.

[18] Moher D. Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

[19] Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011], The Cochrane Collaboration; 2011. Available at: www.cochrane-handbook.org.

[20] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[21] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

[22] Zhao J, Huang W, Zhang S, et al. Efficacy of glutathione for patients with cystic fibrosis: a meta-analysis of randomized-controlled studies. Am J Rhinol Allergy 2019;19438924198738153.

[23] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[24] Honarmand A, Safavi M, Kashefi P, et al. Comparison of effect of intravenous ketamine, peritonsillar infiltration of tramadol and their combination on pediatric posttonsillectomy pain: a double-blinded randomized placebo-controlled clinical trial. Res Pharm Sci 2013;8:177.

[25] Ayatollahi V, Behdad S, Hatami M, et al. Comparison of peritonsillar infiltration effects of ketamine and tramadol on post tonsillectomy pain: a doubleblinded randomized placebo-controlled clinical trial. Croatian Med J 2012;53:155–61.

[26] Cohen-Levy J, Quintal M-C, Abela A, et al. Persistent sleep disordered breathing after adenotonsillectomy and/or tonsillectomy: a long-term survey in a tertiary pediatric hospital. Sleep Breath 2018;22:1197–205.

[27] De Luca Canto G, Pacheco-Pereira C, Aydinsoz S, et al. Adenotonsillectomy complications: a meta-analysis. Pediatrics 2015;136:702–18.

[28] Zhang YZ, Wang X, Wu JM, et al. Optimal dexmedetomidine dose to prevent emergence agitation under sevofoflurane and remifentanil anaesthesia during pediatric tonsillectomy and adenotonsillectomy. Front Ph-armaco 2019;10:1091.

[29] Warwick J, Mason D. Obstructive sleep apnoea syndrome in children. Anaesthesia 1998;53:571–9.

[30] Schnabel A, Zahn PK, Pogatzki-Zahn EM. Use of ketamine in children—what are the next steps? Pediatr Anesth 2011;21:1085–1.

[31] Aspinall R, Mayor A. A prospective randomized controlled study of the efficacy of ketamine for postoperative pain relief in children after adenotonsillectomy. Pediatr Anesth 2001;11:333–6.