

# 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 or tonsillectomy.

**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

Adenoidectomy and/or tonsillectomy are known as the frequent performed operations in children.<sup>[1–3]</sup> The postoperative pain is common after the adenoidectomy and/or tonsillectomy.<sup>[4,5]</sup> Postoperative satisfaction, recovery and discharge times are

negatively affected by the serious pain after surgery.<sup>[6,7]</sup> 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.<sup>[8–10]</sup>

Among them, ketamine is the 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.<sup>[11,12]</sup> Its analgesic effect is produced by binding to the  $\mu$  receptor in the spinal cord and brain after the surgery.<sup>[12]</sup> Tramadol is another analgesic and a synthetic opioid of the aminocyclohexanol group with little respiratory depression.<sup>[13]</sup> Tramadol has both systemic and local anesthetic effect on peripheral nerves from human and animal studies.<sup>[10,14,15]</sup>

Recently, several studies have documented the analgesic efficacy of ketamine and tramadol for children with adenoidectomy or tonsillectomy, but their comparison is conflicting.<sup>[11,16,17]</sup> 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 adenoidectomy 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

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reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).<sup>[18]</sup>

### 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” and “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*,<sup>[19]</sup> 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.<sup>[20]</sup>

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.<sup>[21]</sup>

### 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.<sup>[22]</sup> Heterogeneity was reported using the  $I^2$  statistic, and  $I^2 > 50\%$  indicated significant heterogeneity.<sup>[22,23]</sup> 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.<sup>[10,11,16,17,24,25]</sup>

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,<sup>[11,17,24,25]</sup> while other two studies involve adenotonsillectomy.<sup>[10,16]</sup>

Among the six studies included here, three studies report CHEOPS at 1 and 6 h,<sup>[11,24,25]</sup> two studies report sedation scale at 1 h,<sup>[11,16]</sup> three studies report additional pain medication,<sup>[10,16,17]</sup> and four studies report first time of additional pain medication.<sup>[10,16,24,25]</sup> 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 ( $I^2=94\%$ , 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.<sup>[26–28]</sup> Rescue analgesic drugs such as morphine and opioids may lead to postoperative respiratory depression and desaturation.<sup>[29]</sup> As an N-methyl-D-aspartate receptor antagonist, ketamine has the ability to decrease the need for post-anesthetic analgesia at subanesthetic dose.<sup>[30]</sup> A 0.5-mg IV ketamine was documented to substantially reduce postoperative pain and did not increase the frequency of adverse effects.<sup>[31]</sup>

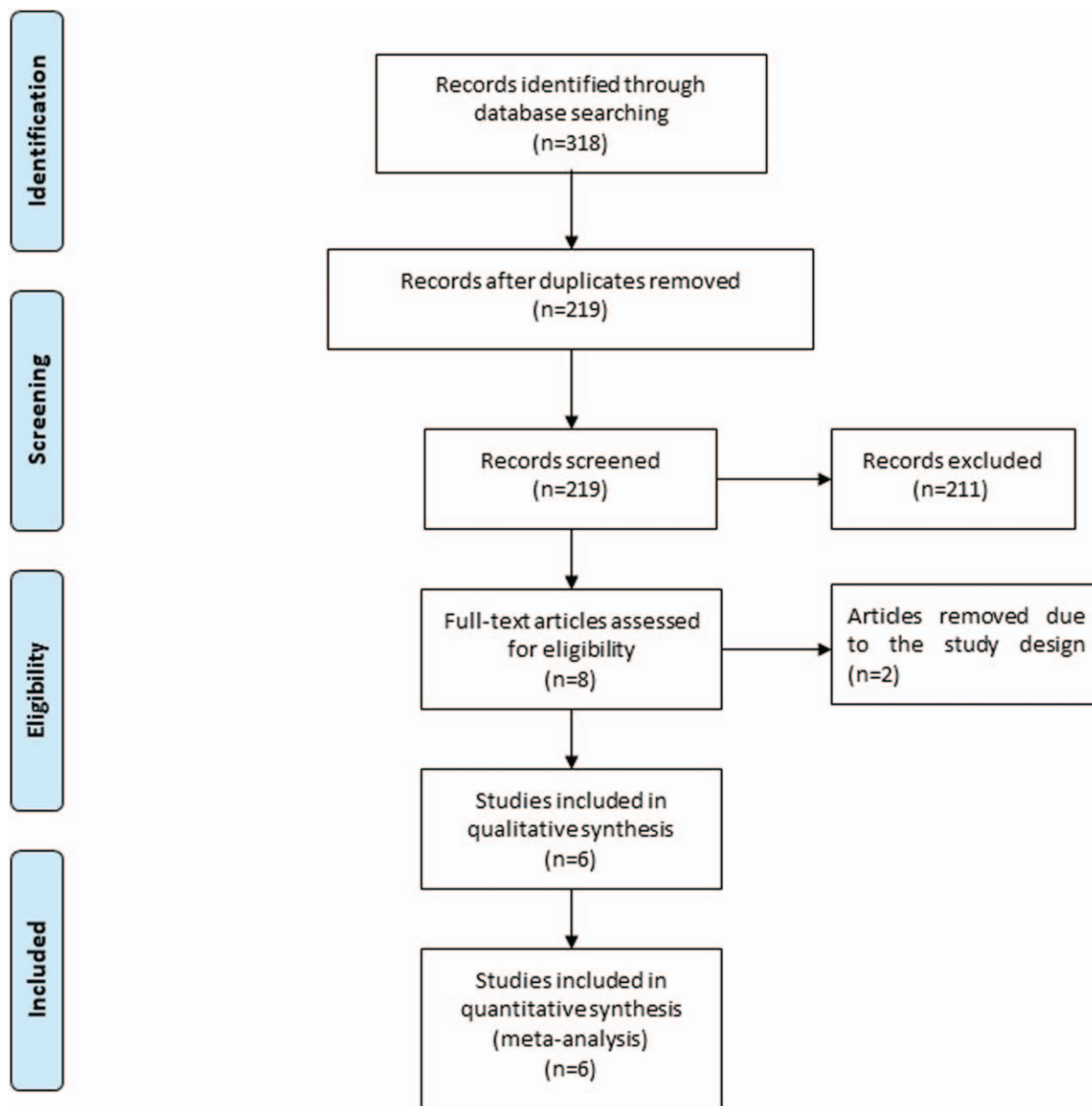


Figure 1. Flow diagram of study searching and selection process.

**Table 1**

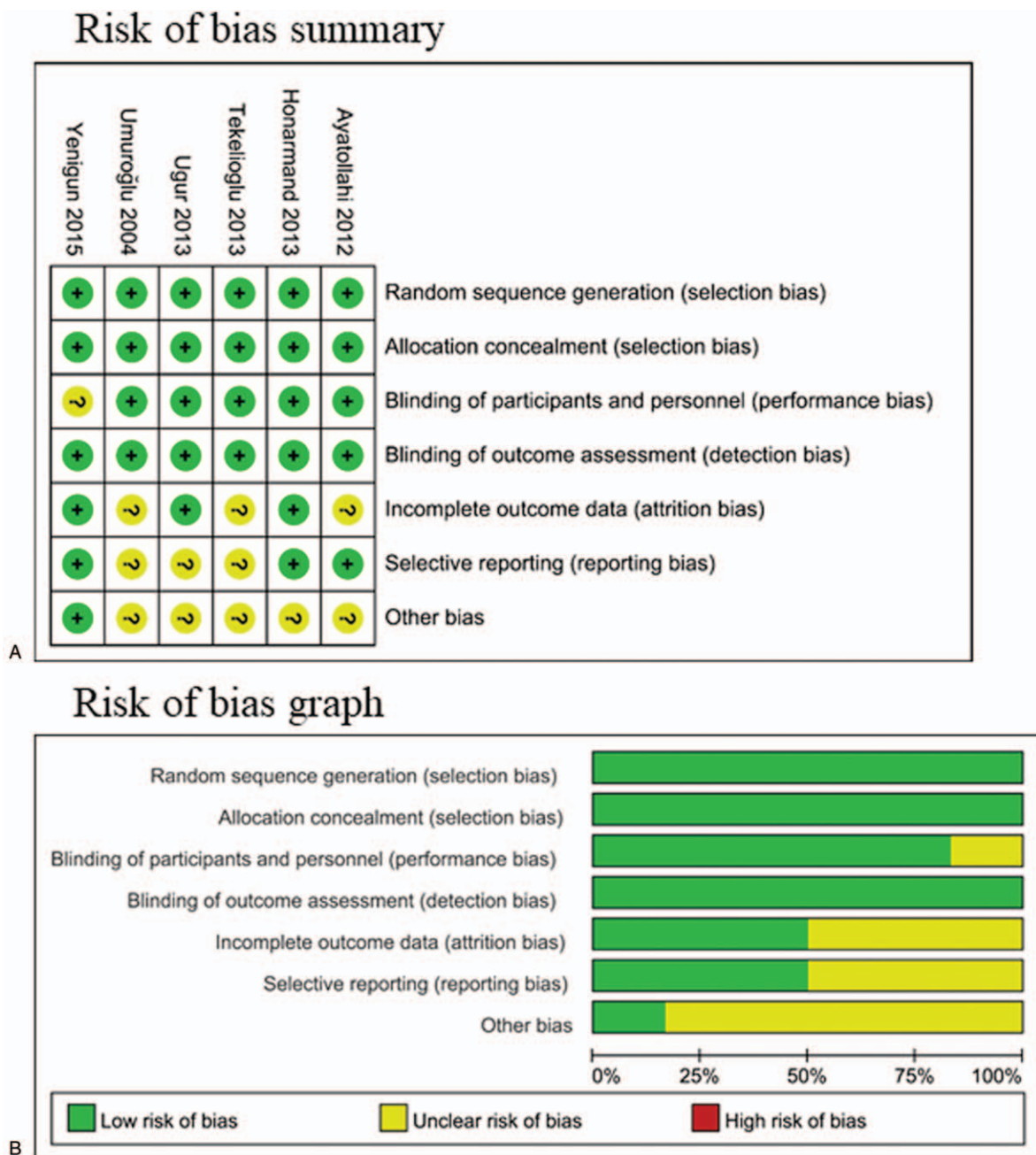
**Characteristics of included studies.**

NO.	Author	Number	Ketamine group					Methods	Tramadol group				
			Age (years)	Female (n)	Weight (kg)	Duration of operation (min)	Number		Age (years)	Female (n)	Weight (kg)	Duration of operation (min)	Methods
1	Yenigun 2015	30	7.67 (2.59)	–	26.62 (6.71)	31.67 (5.15)	Intravenous (IV) 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 2013	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	Tekelioglu 2013	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	Ketamine group						Tramadol group					
		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
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	Umuroglu 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.

**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**

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**Illustrative comparative risks\* (95% CI)**

Outcomes	Assumed risk		Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Tramadol	Ketamine					
CHEOPS at 1 h			The mean cheops at 1 h in the intervention groups was <b>1.56 standard deviations higher</b> (0–2.92 higher)		204 (3 studies)	⊕⊕⊕⊖ low <sup>†,‡</sup>	
CHEOPS at 6 h			The mean cheops at 6 h in the intervention groups was <b>0.51 standard deviations higher</b> (0–2.19 higher)		204 (3 studies)	⊕⊕⊕⊖ low <sup>†,‡</sup>	
Sedation scale at 1 h			The mean sedation scale at 1 h in the intervention groups was <b>0.8 standard deviations lower</b> (0–148 higher)		110 (2 studies)	⊕⊕⊕⊖ low <sup>†,‡</sup>	
Additional pain medication 267 per 1000			349 per 1000 (227–539)	RR1.31 (0.85–2.02)	120 (3 studies)	⊕⊕⊕⊖ moderate <sup>†</sup>	
First time of additional pain medication			The mean first time of additional pain medication in the intervention groups was <b>0.47 standard deviations lower</b> (0 higher to 0.19 lower)		224 (4 studies)	⊕⊕⊕⊖ low <sup>†,‡</sup>	

CI=confidence interval, RR=risk ratio.

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

\* The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes.

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% C).

<sup>†</sup>Unclear risk of bias.

<sup>‡</sup>*I*<sup>2</sup> > 50.

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.<sup>[11]</sup> Our meta-analysis suggests that tramadol is associated with substantially lower CHEOPS at 1h and longer first time of additional pain medication than ketamine for pediatric adenotonsillectomy or tonsillectomy, but there is no statistical difference of CHEOPS at 6h, sedation scale at 1h 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.<sup>[9]</sup> A significant

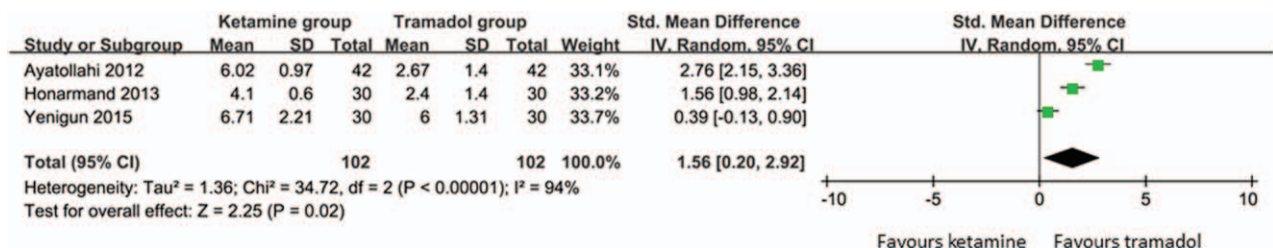


Figure 3. Forest plot for the meta-analysis of CHEOPS at 1 h.

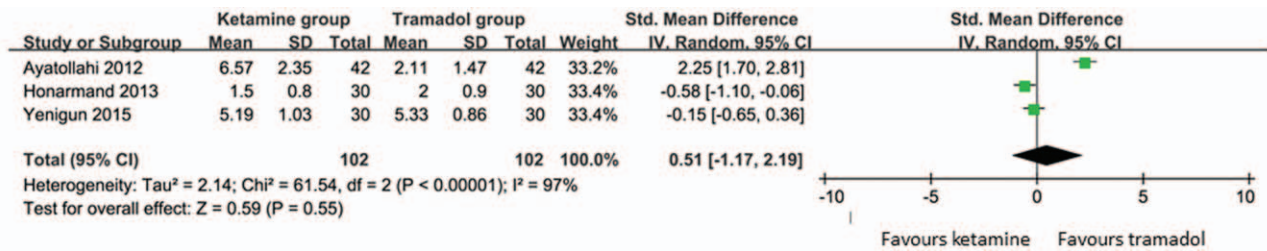


Figure 4. Forest plot for the meta-analysis of CHEOPS at 6h.

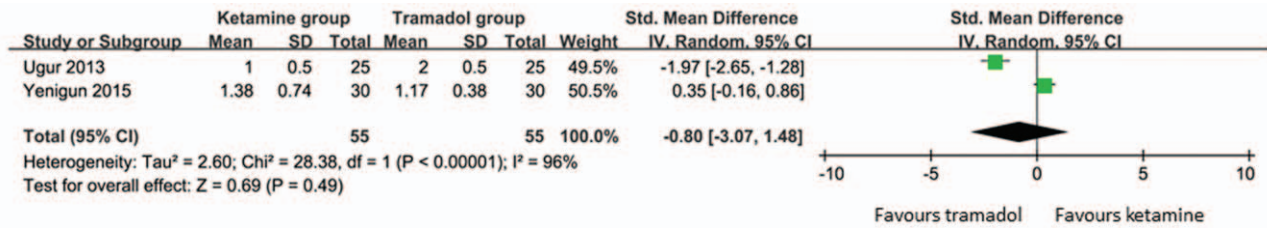


Figure 5. Forest plot for the meta-analysis of sedation scale at 1h.

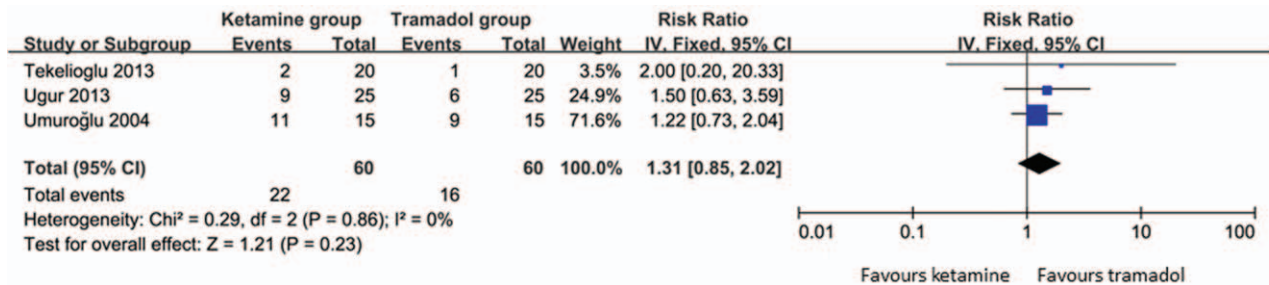


Figure 6. Forest plot for the meta-analysis of additional pain medication.

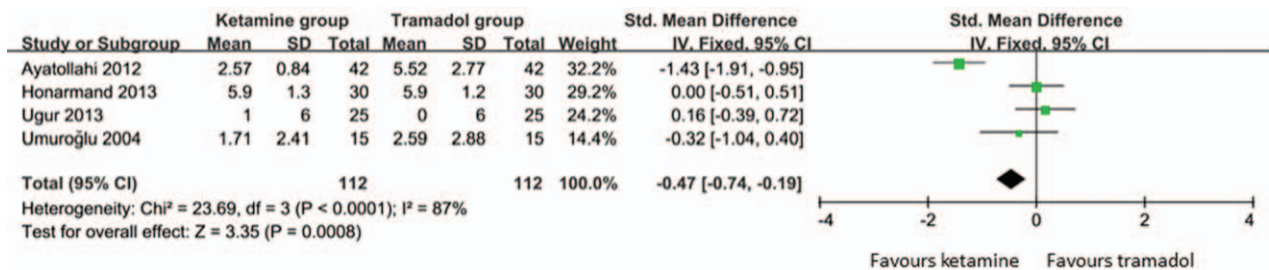


Figure 7. Forest plot for the meta-analysis of first time of additional pain medication.

difference was present at hours 6 and 24 between the peritonsillar ketamine and IV ketamine administrations after pediatric tonsillectomy.<sup>[11]</sup>

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.<sup>[16,24]</sup> 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.

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