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[Intervention Review]

Tramadol for postoperative pain treatment in children

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ABSTRACT

Background

According to current recommendations a multimodal approach is believed to be the gold standard for postoperative pain treatment in children. However, several surveys in the last few years demonstrated that postoperative pain in children is still a serious problem, mainly because opioids are avoided. One of the reasons for this is the fear of severe adverse events following opioid administration. Tramadol is a weak mu-opioid agonist and inhibits reuptake of noradrenaline and serotonin (5HT). Because of a relatively wide therapeutic window and a ceiling effect with a lower risk for severe adverse events (for example respiratory depression) tramadol is a widely used opioid in children. However, the exact efficacy and occurrence of adverse events following tramadol (in comparison with placebo or other opioids) for postoperative pain treatment in children and adolescents are currently not clear.

Objectives

To assess the effectiveness and side effect profile of tramadol for postoperative pain relief in children and adolescents undergoing different surgical procedures.

Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 6), MEDLINE via PubMed (January 1966 to July 2014) and EMBASE via Ovid (January 1947 to July 2014). There were no restrictions regarding language or date of publication. The reference lists of all included trials were checked for additional studies.

Selection criteria

All randomised controlled clinical trials investigating the perioperative administration of tramadol compared to placebo or other opioids for postoperative pain treatment in children and adolescents were included.

Data collection and analysis

Three review authors independently assessed the study eligibility, performed the data extraction and assessed the risk of bias of included trials.

Main results

Twenty randomised controlled trials involving 1170 patients were included in this systematic review. The overall risk of bias in included trials was assessed as unclear, because concealment of allocation processes and blinding of outcome assessors were poorly described. Due

to inconsistent outcome reporting, data from 17 included trials could be pooled for some endpoints only. Eight trials compared tramadol administration with placebo and five trials found that the need for rescue analgesia in the postoperative care unit (PACU) was reduced in children receiving tramadol (RR 0.40; 95% CI 0.20 to 0.78; low quality evidence). Only one trial investigated the number of patients with moderate to severe pain, but a non-validated pain scale was used (very low quality evidence). Four trials compared morphine with tramadol administration. There was no clear evidence of difference in the need for rescue analgesia in the PACU (RR 1.25; 95% CI 0.83 to 1.89; low quality evidence) with tramadol compared with morphine. No trials could be pooled for the outcome 'number of patients with moderate to severe pain'. Three trials were included for the comparison of tramadol with nalbuphine. There was no clear evidence for the need for rescue analgesia in the PACU (RR 0.63; 95% CI 0.16 to 2.45; low quality evidence). Only one trial reported the number of patients with moderate to severe pain, but used a non-validated pain scale (very low quality evidence). Two out of six included trials, which compared pethidine with tramadol, reported the number of children with a need for rescue analgesia within the PACU and showed no clear evidence (RR 0.93; 95% CI 0.43 to 2.02; very low quality evidence). Two trials reported the number of patients with moderate to severe pain and showed a lower RR in patients treated with tramadol (RR 0.64; 95% CI 0.36 to 1.16; low quality evidence). Only one trial was included, which compared tramadol with fentanyl, reporting the number of patients with the need for rescue analgesia (very low quality evidence). Generally, adverse events were poorly reported. Most data could be pooled for the comparison with placebo focusing on the RR for postoperative nausea and vomiting (PONV) in the postoperative care unit and 24 h postoperation. Children treated with tramadol, compared to placebo, did not show clear evidence of benefit for PONV in the postoperative care unit (RR 0.84; 95% CI 0.28 to 2.52; moderate quality evidence) and 24 h postoperation (RR 0.78; 95% CI 0.54 to 1.12; moderate quality evidence).

Authors' conclusions

The overall evidence regarding tramadol for postoperative pain in children is currently low or very low and should be interpreted with caution due to small studies and methodological problems (different validated and non-validated pain scales with different pain triggers, missing sample size calculations and missing intention-to-treat analysis). Nevertheless, we demonstrated that tramadol administration might provide appropriate analgesia when compared to placebo; this is based on results showing reduced rescue analgesia in children treated with tramadol compared to placebo. In contrast, the evidence regarding the comparison with other opioids (for example morphine) was uncertain. Adverse events were only poorly reported, so an accurate risk-benefit analysis was not possible.

PLAIN LANGUAGE SUMMARY

Does the perioperative administration of tramadol provide effective and safe postoperative analgesia in children?

Children experience pain after surgery ('postoperative pain') and according to recently published trials the management of this pain is of major concern. A combination of drugs may be the best way to treat postoperative pain, for example drugs called 'opioids', like morphine and codeine. However, there are concerns about severe side effects (adverse events) when using opioids. Tramadol is a weak opioid that is used worldwide to treat children with moderate to severe acute or chronic pain. Tramadol can be given to children before surgery to help reduce pain afterwards. It is believed that tramadol administration might be associated with a lower risk for respiratory or haemodynamic depression and might therefore be the ideal analgesic drug for children in the perioperative period. Our systematic review assessed the efficacy and adverse events of tramadol administration compared to placebo or other opioids. In July 2014 we found 20 small randomised controlled trials involving 1170 patients. These small trials had limited data but tramadol may be better than placebo. In five trials, mostly preschool children undergoing minor surgery (for example tonsillectomy) were treated with tramadol or placebo before the start of surgery. Children needed less rescue medication in the postoperative care unit when given tramadol, indicating better analgesia with tramadol. Due to the low amount of usable data, the evidence focusing on the comparison of tramadol with other opioids (for example morphine, nalbuphine, pethidine, fentanyl) is currently unclear. Adverse events were generally only poorly reported in the trials so that the side effects as a result of tramadol administration were not clear.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Tramadol compared with placebo

Tramadol compared with placebo for postoperative pain in children

Patient or population: children undergoing surgery

Settings: hospital

Intervention: 1 to 3 mg/kg tramadol intravenously

Comparison: placebo

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Number of patients requiring rescue analgesia (PACU)	RR 0.40 (0.20 to 0.78)	289 (5)	⊕⊕⊕⊖ low	double-downgraded due to unexplained heterogeneity and limitations in the study design (use of different pain scales and triggers for rescue analgesia)
Number of patients with moderate to severe pain (PACU)		44 (1)	⊕⊕⊕⊖ very low	triple-downgraded, due to high risk of publication bias, limitations in the study design (use of non-validated pain scale) and imprecision of results (wide CIs)
Number of patients with PONV (PACU)	RR 0.84 (0.28 to 2.52)	215 (3)	⊕⊕⊕⊖ moderate	downgraded due to imprecision of results (wide CIs)
Number of patients with PONV (24 hours postoperatively)	RR 0.78 (0.54 to 1.12)	150 (4)	⊕⊕⊕⊖ moderate	downgraded due to imprecision of results (wide CIs)

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 likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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.

RR = relative risk

CI = confidence interval

PONV = postoperative nausea and vomiting

PACU = postoperative care unit

Summary of findings 2. Tramadol compared with morphine

Tramadol compared with morphine for postoperative pain in children

Patient or population: children undergoing surgery

Settings: hospital

Intervention: 1 to 2 mg/kg tramadol intravenously

Comparison: 0.1 mg/kg morphine intravenously

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Number of patients requiring rescue analgesia (PACU)	RR 1.25 (0.83 to 1.89)	127 (3)	⊕⊕⊕⊕ low	double-downgraded due to unexplained heterogeneity and limitations in the study design (use of different pain scales and triggers for rescue analgesia)
Number of patients with moderate to severe pain (PACU)				no data available
Number of patients requiring rescue analgesia (24 hours postoperatively)	RR 1.62 (0.65 to 4.04)	151 (3)	⊕⊕⊕⊕ low	double-downgraded due to unexplained heterogeneity and limitations in the study design (use of different pain scales and triggers for rescue analgesia)

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 likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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.

RR = relative risk

CI = confidence interval

PONV = postoperative nausea and vomiting

PACU = postoperative care unit

Summary of findings 3. Tramadol compared with nalbuphine
Tramadol compared with nalbuphine for postoperative pain in children
Patient or population: children undergoing surgery

Settings: hospital

Intervention: 0.75 to 3 mg/kg tramadol intravenously or intramuscularly

Comparison: 0.1 to 0.3 mg/kg nalbuphine intravenously or intramuscularly

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Number of patients requiring rescue analgesia (24 hours postoperatively)	RR 0.63 (0.16 to 2.45)	110 (2)	⊕⊕⊕⊕ very low	triple-downgraded due to unexplained heterogeneity, limitations in the study design (use of different pain scales and triggers for rescue analgesia) and imprecision of results (wide CIs)

Number of patients with moderate to severe pain (PACU)	50 (1)	⊕⊕⊕⊕ very low	triple-downgraded, due to high risk of publication bias, limitations in the study design (use of non-validated pain scale) and imprecision of results (wide CIs)
Number of patients with PONV (PACU)	RR 1.00 (0.50 to 2.01) 137 (2)	⊕⊕⊕⊕ low	double-downgraded due to unexplained heterogeneity and imprecision of results (wide CIs)

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 likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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.

RR = relative risk

CI = confidence interval

PONV = postoperative nausea and vomiting

PACU = postoperative care unit

Summary of findings 4. Tramadol compared with pethidine

Tramadol compared with pethidine for postoperative pain in children

Patient or population: children undergoing surgery

Settings: hospital

Intervention: 1 to 3 mg/kg tramadol intravenously, per mouth or intramuscularly

Comparison: 1 to 1.5 mg/kg pethidine intravenously, per mouth or intramuscularly

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Number of patients requiring rescue analgesia (PACU)	RR 0.93 (0.43 to 2.02)	120 (2)	⊕⊕⊕⊕ very low	triple-downgraded due to unexplained heterogeneity, limitations in the study design (use of different pain scales and triggers for rescue analgesia) and imprecision of results (wide CIs)
Number of patients with moderate to severe pain (PACU)	RR 0.64 (0.36 to 1.16)	94 (2)	⊕⊕⊕⊕ low	double-downgraded due to unexplained heterogeneity and limitations in the study design (use of different pain scales and triggers for rescue analgesia)
Number of patients with PONV (PACU)	RR 0.75 (0.28 to 2.02)	156 (3)	⊕⊕⊕⊕ low	double-downgraded due to unexplained heterogeneity and imprecision of results (wide CIs)

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 likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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.

RR = relative risk

CI = confidence interval

PONV = postoperative nausea and vomiting

PACU = postoperative care unit

Summary of findings 5. Tramadol compared with fentanyl

Tramadol compared with fentanyl for postoperative pain in children

Patient or population: children undergoing surgery

Settings: hospital

Intervention: 0.5 mg/kg bolus followed by 150 µg/kg/h tramadol intravenously

Comparison: 2 µg/kg/h fentanyl intravenously

Outcomes	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Number of patients requiring rescue analgesia (24 hours postoperatively)		28 (1)	⊕⊕⊕⊕ very low	triple-downgraded, due to high risk of publication bias, limitations in the study design and imprecision of results (wide CIs)
Number of patients with moderate to severe pain (PACU)				no data available
Number of patients with PONV (24 hours postoperatively)		28 (1)	⊕⊕⊕⊕ very low	triple-downgraded, due to high risk of publication bias, limitations in the study design and imprecision of results (wide CIs)

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 likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

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.

RR = relative risk

CI = confidence interval

PONV = postoperative nausea and vomiting

PACU = postoperative care unit

BACKGROUND

Description of the condition

Results of several surveys in different European countries demonstrated that postoperative pain in children is still a relevant problem (Segerdahl 2008; Taylor 2008). In contrast, there is currently clear evidence that an adequate postoperative pain treatment may reduce the risk of subsequent morbidity (Kharasch 2003) and delayed wound healing (Glaser 1999). Furthermore, effective treatment of postoperative pain during infancy may be associated with a reduced incidence of persistent chronic postoperative pain (Page 2013) and a decreased sensitivity to subsequent painful stimuli in adulthood (Andrews 2002; Walker 2009; Weisman 1998). Finally, several studies have demonstrated that sufficient pain reduction or prevention is an important expectation of parents (Franck 2004; Romsing 1996). Improved postoperative pain management in children is therefore not only an ethical but also an essential healthcare issue in perioperative care.

Description of the intervention

In the last decade the number of outpatient procedures in children has increased in most western countries (Segerdahl 2008) because they are associated with a lower incidence of infection and reduced costs (Scaife 1988). Due to major advances in general and regional anaesthetic techniques a wide range of procedures can be performed as day-case surgery. However, unrelieved pain is one of the most common reasons for unanticipated hospital re-admission (Awad 2004). The success of day-case surgery is therefore dependent on effective postoperative pain management. Tramadol is a widely used weak opioid in the treatment of chronic and acute pain in children; it has one-tenth the potency of morphine and a ceiling effect with high doses (Bamigbade 1998; Dayer 1994). Its use (compared to other opioids) is believed to be associated with a lower incidence of side effects including respiratory or haemodynamic depression, nausea and vomiting, constipation and sedation (Bosenberg 1998; Scott 2000; Tarkkila 1998; Vickers 1992). However in the USA and the UK, tramadol has recently been placed in the drug abuse and dependence schedules, indicating a high risk for abuse. Like other opioids, tramadol does not inhibit prostaglandin synthesis so that patients with a high risk of postoperative bleeding or with renal impairment or asthma and undergoing surgery might benefit from pain therapy with tramadol.

How the intervention might work

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a central analgesic effect. It is available as a racemic mixture of (+) and (-) enantiomers. The following mechanisms have been described for its mode of action. The (+) enantiomer has only a weak affinity to μ -opioid receptors and inhibits serotonin reuptake, while the (-) enantiomer inhibits norepinephrine reuptake in the spinal cord (Bozkurt 2005; Scott 2000). Additionally, a local anaesthetic action has been described for tramadol. The latter different modes of action might explain, in part, the extended analgesic efficacy and the lower incidence of typical opioid related side effects (for example postoperative nausea and vomiting (PONV)). Nevertheless, almost 40% of the analgesic action is provided by O-desmethyl tramadol (M1) following the rapid metabolism of tramadol in the liver via the cytochrome P450 enzyme CYP2D6 (Bozkurt 2005; Hennies 1988; Lintz 1998). After oral administration tramadol is rapidly absorbed with an absolute

bioavailability of 65% to 70% due to extensive first-pass metabolism after absorption (Lintz 1998; Scott 2000). Generally, there are no significant differences in the pharmacokinetics (elimination half-life, distribution, serum clearance and concentration of metabolites) of tramadol between children and adults after oral application or intravenous injection (Murthy 2000; Payne 2002). However, recently published data suggest that the plasma time-concentration following tramadol administration might be different in infants due to immature metabolite elimination via the kidneys (Allegaert 2011). Therefore, higher adverse events rates might be possible within this age group following tramadol administration (Allegaert 2011). Apart from age, genetic variances might influence the analgesic efficacy, because around 8% of the Caucasian population has a cytochrome P450 enzyme (CYP2D6) deficiency, which impairs the analgesic properties of tramadol (see above). Furthermore, the important metabolism in the liver might be influenced by other drugs which are also metabolised by CYP2D6 enzymes, for example ondansetron.

Why it is important to do this review

Results from several clinical studies published in the last few years have suggested that tramadol might be an effective analgesic for moderate to severe pain in children. However, results from these studies seem inconsistent and a quantitative systematic review analysing the analgesic efficacy and adverse effects of tramadol in the treatment of postoperative pain in children and adolescents has not been available.

OBJECTIVES

To assess the efficacy and adverse events of tramadol for postoperative pain treatment in children and adolescents undergoing surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) investigating tramadol for postoperative pain in children.

Types of participants

We included all children and adolescents (0 to 18 years old) irrespective of sex or type of surgery.

Types of interventions

We included all RCTs investigating tramadol for postoperative pain in children and adolescents in comparison to placebo or any other opioid.

Types of outcome measures

We included studies when they reported any of the following outcome measures.

Primary outcomes

1. Number of patients requiring rescue analgesia (in postoperative care unit (PACU), 24 h postoperation)
2. Number of patients with moderate to severe pain (assessed with a postoperative pain scale) (in PACU, 24 h postoperation)

Secondary outcomes

1. Time to rescue analgesic (minutes) (in PACU, 24 h postoperation)
2. Total required dose of rescue analgesic (in PACU, 24 h postoperation)
3. Number of rescue analgesic doses (in PACU, 24 h postoperation)
4. Number of participants with adverse events (postoperative nausea and vomiting (PONV) (in PACU, 24 h postoperation), hypotension, bradycardia, respiratory depression, pruritus, sedation, obstipation)

Search methods for identification of studies

The general principle of the search strategy used for all databases consisted of a combination of indexed and free-text terms to reflect the concepts of 'tramadol', 'postoperative pain' and 'children'. We modified the search terms according to the constraints of each database ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#)).

Electronic searches

We searched the following data sources:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 7);
2. MEDLINE (PubMed) (January 1966 to July 2014);
3. EMBASE (Ovid) (January 1947 to July 2014).

Searching other resources

In addition, the reference lists of all included trials were checked for additional studies. If there were any data that were missing within included trials, the corresponding authors were contacted in order to receive additional information. Furthermore, we searched within the trials database ClinicalTrials.gov in order to identify additional studies.

Data collection and analysis

Two review authors (AS, SR) independently scanned the titles retrieved by the initial search to exclude irrelevant studies. The systematic search was not limited to any specific language. Two review authors (AS, SR) identified the studies which were included in this review by using a standardised study eligibility form developed by the review authors. If there were disagreements, we contacted a third review author (EPZ).

Selection of studies

Three review authors (AS, SR, CMF) independently performed the study quality assessment using the 'risk of bias' tables provided in The Cochrane Collaboration's Review Manager (RevMan 5) software ([RevMan 2014](#)). There were no restrictions concerning the language of the article or publication type. We resolved all differences by discussion among the review authors.

Data extraction and management

Three review authors (AS, SR, CMF) independently extracted the data using a standardised data extraction form developed by the review authors. We defined the number of participants with moderate to severe pain as participants with a pain score of > 3 ([Hirschfeld 2013](#)). If different pain scales (Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Faces Pain Scale - Revised (FPS-R)) were used in the included studies, we considered all pain

scales to be equivalent as long as they were based on a 0 to 10 scale ([Standing 2009](#)). Additionally, when postoperative pain intensity was assessed with non-validated scales (for example three point scales: low, moderate, severe pain), we extracted these results for the outcome 'number of patients with moderate to severe pain', but reported the results within the text. If multi-arm trials were included, data were extracted for each comparison (for example tramadol versus morphine). Furthermore, if different doses of tramadol were applied, we only extracted the results following the highest doses. If necessary, we retrieved additional data, missing in the published studies, by contacting the authors of the relevant articles. We resolved all differences in data extraction by discussion among the review authors at each step of the data extraction process.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies using the Cochrane Collaboration's tool for assessing risk of bias ([RevMan 2014](#)). The standard components of the domains included adequacy of allocation generation, allocation concealment, blinding, completeness of outcome data, possible selected outcome reporting and any other potential sources of bias. We judged each component as 'low risk' of bias, 'high risk' of bias or 'unclear'. We included a 'Risk of bias' table as part of the 'Characteristics of included studies' table and a 'Risk of bias' summary figure, which detailed all of the judgements made for all studies included in the review. Two review authors (AS, SR) independently carried out an assessment of the risk of bias. We resolved any disagreements by discussion between the review authors and with a further review author acting as arbiter (EPZ).

1. Allocation of intervention

We considered allocation of the intervention as adequate if it was generated by a random system (for example computer, random number table algorithm, tossing of a coin). We considered allocation inadequate if a non-random system was used (for example names, dates).

2. Concealment of allocation

We considered concealment adequate if an acceptable method, such as a central allocation system, sequentially-numbered sealed opaque envelopes or an on-site locked computer was used, ensuring that the group assignment was not revealed to participant recruiters, investigators or participants prior to the final allocation into the respective group. We considered concealment inadequate if it allowed the participant recruiters, investigators or participants to know the treatment allocation in advance, or if the concealment procedure was not reported.

3. Blinding of participants and personnel

We considered blinding adequate if participants and persons responsible for participants' care (for example nurses) were all blinded to the intervention. We considered blinding inadequate if participants or persons responsible for participants' care were not blinded to the intervention.

4. Blinding of outcome assessment

We considered blinding adequate if the outcome assessors were blinded to the intervention. We considered blinding inadequate if outcome assessors were not blinded to the intervention.

5. Incomplete outcome data reporting

We considered outcome data reporting adequate if all withdrawals and dropouts were described. We considered outcome data reporting inadequate if the numbers of dropouts and withdrawals were lacking, or if the reasons for withdrawals and dropouts were not given.

6. Selective reporting

We considered data reporting as adequate if all relevant pain outcomes (at least the validated pain scores) were reported. We considered outcome data reporting as inadequate if only selected pain outcomes or non-validated measurements were used.

Measures of treatment effect

For proportions (dichotomous outcomes) we calculated the risk ratio (RR) with 95% confidence interval (CI), while for continuous data we estimated the mean difference (MD) with 95% CI. To estimate the statistical significance of the results we calculated the 95% CI for each item. Furthermore, we calculated the number needed to treat to benefit (NNTB) for efficacy outcomes, and the number needed to treat to harm (NNTH) for adverse events if enough trials could be pooled (> four trials per outcome) and the result was significant.

Dealing with missing data

If there were doubts about missing data (patient dropouts, selective outcome reporting), we contacted the relevant authors to obtain further information. If the complete information could be obtained, we would perform intention-to-treat (ITT) analyses. If the complete information could not be obtained, we performed complete-case analyses. We planned to perform sensitivity analyses by imputing missing data (best case, worst case) in order to test the robustness of the retrieved results.

Assessment of heterogeneity

We assessed clinical and methodological differences in the included studies to decide if studies were sufficiently homogeneous to be combined. We analysed statistical heterogeneity using the I^2 statistic. We calculated this value for each of the outcomes listed above for the comparisons with sham interventions. We assumed relevant heterogeneity if the I^2 statistic was $\geq 30\%$.

Data synthesis

For dichotomous data we used the Mantel-Haenszel fixed-effect or random-effects models, while for continuous data the inverse variance fixed-effect or random-effects models were used, in RevMan 5.3. If the test for heterogeneity (I^2 statistic $\geq 30\%$) was positive, we carried out the analysis using the random-effects model. However, taking into account that random-effects models sometimes did not deliver more conservative results, especially in the presence of small-study effects, we reported the summary

statistics in conjunction with a sensitivity analysis (results obtained with a fixed-effect model). If random-effects model estimates demonstrated larger effect sizes, we discussed whether it is reasonable to conclude that the intervention was more effective in the smaller studies. We reported summary RRs and MDs with 95% CIs. We considered RRs with the range of the lower and upper bounds of the 95% CI not crossing one, and MDs with the range of the lower and upper bounds of the 95% CI not crossing zero, to be statistically significant. Where there were differences in methodological quality, we performed sensitivity analyses (high quality studies and /low quality studies).

Subgroup analysis and investigation of heterogeneity

We gave consideration to the magnitude of clinical and methodological heterogeneity. To evaluate the effects of clinical heterogeneity, we planned to perform subgroup analyses calculating the RR or MD in conjunction with the corresponding CI for each subgroup, if more than four trials were included for the outcome. We used a fixed-effect model Chi² test of heterogeneity to compare subgroups. Additionally, we considered non-overlapping subgroup CIs as consistent with a statistically significant difference.

We further analysed the data concerning the following subgroups, if available.

1. Type of surgery (head and neck, thoracic, abdominal, extremity).
2. Different doses of tramadol and routes of administration (oral, intravenous, intramuscular).

Summary of findings tables

We used the principles of the GRADE system ([Schunemann 2008](#)) to assess the quality of the body of evidence associated with specific outcomes (number of participants requiring rescue, number of patients with moderate to severe pain, PONV) in our review and constructed a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraised the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflected the item being assessed.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#)

Results of the search

The literature search identified 95 studies at the first stage. After exclusion by title and abstract 43 potentially relevant studies were identified. After reading the full texts 20 RCTs were finally included in the present systematic review ([Figure 1](#)). There were no significant disagreements between review authors during the extraction process.

Figure 1. Study flow diagram.

Included studies

Summary details of the 20 included studies are given in the [Characteristics of included studies](#) table.

Design

All 20 included studies were parallel group RCTs. Tramadol was administered intravenously (Ali 2008; Antila 2006; Bösenberg 1998; Chiaretti 2000; Cocelli 2012; Ekemen 2008; Engelhardt 2003; Hullett 2006; Moyado Garcia 2009; Ozalevli 2005; Ozer 2003; Ozköse 2000; Umuroglu 2004; van den Berg 1999; Viitanen 2001), orally (Payne 1999; Roelofse 1999) or by intramuscular injection (Barsoum 1995; Ertugrul 2006; Schäffer 1986). In four studies tramadol was applied before induction of general anaesthesia (Ali 2008; Chiaretti 2000; Payne 1999; Roelofse 1999), while in 12 trials tramadol was administered directly after induction (Antila 2006; Bösenberg 1998; Cocelli 2012; Ekemen 2008; Engelhardt 2003; Ertugrul 2006; Hullett 2006; Ozer 2003; Ozköse 2000; Umuroglu 2004; van den Berg 1999; Viitanen 2001). Four trials specifically mentioned that tramadol was given before (Moyado Garcia 2009) or after the end of surgery (Barsoum 1995; Ozalevli 2005; Schäffer 1986). Apart from two trials (Barsoum 1995; Ozalevli 2005) that applied tramadol specifically for postoperative pain treatment, in the other 18 trials tramadol was always applied as a prophylactic analgesic drug. Four trials applied tramadol as a bolus followed by a continuous infusion (Chiaretti 2000; Moyado Garcia 2009; Ozalevli 2005), while the remaining trials applied a bolus injection alone.

Sample sizes

The number of children and adolescents analysed in the 20 studies ranged from 24 to 152 (1170 in total). Sample size calculation and intention-to-treat analysis were not reported in any of the included studies.

Participants

Studies involved children aged from 1 to 18 years of age, with each study having a different age range. One trial reported that young adults (to 21 years) were also included; but a specific analysis of the demographic data of the different study groups showed that the mean age in all study groups was below 18 years (van den Berg 1999). Therefore, the review authors decided to include the data of this RCT. Another trial investigated the administration of tramadol only in neonates (up to 28 days old) that were undergoing surgery, as a postoperative continuous infusion (Alencar 2012). Due to this specific age, the authors decided to exclude this study because only this trial focused explicitly on neonates.

Common paediatric surgical procedures were performed within the included trials: ear-nose-throat (ENT) surgery (for example adenotonsillectomy, tonsillectomy) (Ali 2008; Antila 2006; Cocelli 2012; Engelhardt 2003; Ertugrul 2006; Hullett 2006; Ozalevli 2005; Ozer 2003; Ozköse 2000; Umuroglu 2004; van den Berg 1999; Viitanen 2001), lower abdominal surgery (Barsoum 1995; Bösenberg 1998; Ekemen 2008; Schäffer 1986) and dental extraction (Payne 1999; Roelofse 1999). In one study children underwent neurosurgical interventions for various disorders (Chiaretti 2000), while in another trial the surgical procedures were not explicitly described (Moyado Garcia 2009).

Interventions

Eleven trials were performed as multi-arm trials. The following interventions were compared in the included studies.

1. Tramadol versus placebo (Ali 2008; Antila 2006; Bösenberg 1998; Cocelli 2012; Ozköse 2000; Payne 1999; Roelofse 1999; Umuroglu 2004; van den Berg 1999; Viitanen 2001).
2. Tramadol versus morphine (Engelhardt 2003; Hullett 2006; Ozalevli 2005; Umuroglu 2004).
3. Tramadol versus nalbuphine (Barsoum 1995; Moyado Garcia 2009; Schäffer 1986; van den Berg 1999).
4. Tramadol versus pethidine (Barsoum 1995; Bösenberg 1998; Ekemen 2008; Ertugrul 2006; Ozer 2003; van den Berg 1999).
5. Tramadol versus fentanyl (Chiaretti 2000).

Outcomes

All trials investigated the efficacy and adverse effects following perioperative (before or after anaesthesia induction, before or after the end of surgery) administration of tramadol in comparison with placebo or other opioids (morphine, nalbuphine, pethidine, fentanyl). A validated pain scale (Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Faces Pain Scale (FPS), Toddler-Preschooler Postoperative Pain Scale (TPPPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)) was used in nine studies (Ali 2008; Chiaretti 2000; Ertugrul 2006; Moyado Garcia 2009; Ozalevli 2005; Ozköse 2000; Payne 1999; Schäffer 1986; Umuroglu 2004); however, the pain-trigger used for rescue analgesia differed significantly between the trials. The number of patients requiring rescue analgesia was recorded in 13 studies (Ali 2008; Barsoum 1995; Bösenberg 1998; Chiaretti 2000; Engelhardt 2003; Hullett 2006; Moyado Garcia 2009; Ozalevli 2005; Ozköse 2000; Schäffer 1986; Umuroglu 2004; van den Berg 1999; Viitanen 2001), while only three studies reported the time to rescue analgesic (Bösenberg 1998; Umuroglu 2004; Viitanen 2001). Outcome variables were either ordinal (for example severity of pain) or nominal in nature (for example presence of PONV). Methods used for statistical analysis included both nonparametric and parametric tests.

Excluded studies

Reasons for the exclusion of 23 studies are given in the [Characteristics of excluded studies](#) table. Five trials were excluded because they were not RCTs (Griessinger 1997; Mikhel'son 2002; Oliveira 2000; Ostreikov 1993; Sun 2010). Two trials were only available as conference abstracts, without including relevant outcome data (Bedirli 2011; Metodiev 2011). Three trials were retrospective studies (Apiliogullari 2011; Macarone 1998; Osifo 2008) and were excluded. Another trial tested different doses of tramadol and was therefore excluded (Finkel 2002). One trial explored only the pain from propofol injection and was therefore excluded (Borazan 2012). Two trials were excluded (Aguirre Córcoles 2003; Chu 2006) because they investigated tramadol delivered by a patient-controlled intravenous pain pump. Three trials investigated the caudal (Günes 2004), epidural (Demiraran 2005) or peritonsillar (Akkaya 2009) application of tramadol, while single trials compared tramadol with paracetamol (Pendeville 2000) and with ilioinguinal and iliohypogastric block (Khosravi 2006). Within the Courtney 2000 trial the adult and paediatric data were mixed, while in another trial no data from children

were reported (Altunkaya 2003). Finally, Alencar 2012 studied the continuous infusion of tramadol in 28 day old neonates as a sedating agent and was therefore excluded.

Risk of bias in included studies

See: [Figure 2](#); [Figure 3](#)

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2008	?	+	+	?	+	+	?
Antila 2006	+	?	+	?	+	+	?
Barsoum 1995	?	?	+	-	+	+	-
Bösenberg 1998	+	?	+	?	+	-	?
Chiaretti 2000	?	?	?	?	+	+	?
Cocelli 2012	+	?	?	?	+	+	?
Ekemen 2008	?	?	+	?	+	-	?
Engelhardt 2003	+	+	+	?	+	+	?
Ertugrul 2006	?	?	+	?	+	+	?
Hullett 2006	?	?	?	?	+	-	?
Moyado Garcia 2009	+	?	+	?	+	-	?
Ozalevli 2005	?	?	+	?	+	-	?
Ozer 2003	?	?	+	?	+	+	?
Ozköse 2000	?	?	+	?	+	+	?
Payne 1999	?	?	+	?	+	+	?
Roelofse 1999	?	?	+	?	+	+	?
Schäffer 1986	+	?	+	?	+	+	?
Umuroglu 2004	?	+	+	+	+	+	?
van den Berg 1999	+	?	-	+	+	+	?
Viitanen 2001	+	?	+	+	+	-	?

Figure 3. (Continued)

We assessed the methodological quality of included trials using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011).

Allocation

Sequence generation

Eight trials were rated as being at low risk of bias because a computer-generated random sequence (Antila 2006; Bösenberg 1998; Cocelli 2012; Engelhardt 2003; Viitanen 2001) or a predesigned table of random numbers (Moyado Garcia 2009; Ozköse 2000; van den Berg 1999) was used. The other included studies did not give clear information on how the randomisation sequence was generated; they were assessed as being at unclear risk of bias.

Concealment of allocation

In contrast, only three trials explicitly described the method of allocation concealment and were rated as being at low risk of bias (Ali 2008; Engelhardt 2003; Umuroglu 2004). The majority of included studies did not describe allocation concealment and thus were assessed as being at unclear risk of bias.

Blinding

Performance bias

Eight trials were performed as double-blinded studies, with the participant and provider of the intervention blinded to therapy (Bösenberg 1998; Ekemen 2008; Ertugrul 2006; Moyado Garcia 2009; Ozalevli 2005; Ozköse 2000; Roelofse 1999; Viitanen 2001). In three studies the participants and observers were blinded (Barsoum 1995; Ozer 2003; van den Berg 1999); the participants and investigators were blinded in six studies (Ali 2008; Antila 2006; Engelhardt 2003; Payne 1999; Schäffer 1986; Umuroglu 2004). Three studies were assessed as being at unclear risk of bias because the blinding was unclear (Chiaretti 2000; Cocelli 2012; Hullett 2006).

Detection bias

Only three studies explicitly noted that the observers were blinded to the investigation (Barsoum 1995; Ozer 2003; van den Berg 1999). One trial was rated as being at high risk for detection bias because the trialists stated that the drug doses were noted within the patients' records (Barsoum 1995). All other trials did not describe the blinding of outcome assessment and were rated as being at unclear risk of bias.

Incomplete outcome data

All trials reported that all participants were included in the analysis. Therefore, in all included trials this item was assessed as being at low risk of bias.

Selective reporting

Fourteen trials were rated as being at low risk of bias because all outcomes were measured and reported in full (Ali 2008; Antila 2006; Barsoum 1995; Chiaretti 2000; Cocelli 2012; Engelhardt 2003;

Ertugrul 2006; Ozer 2003; Ozköse 2000; Payne 1999; Roelofse 1999; Schäffer 1986; Umuroglu 2004; van den Berg 1999). In contrast, in three trials postoperative pain was measured but was only selectively reported (Bösenberg 1998; Ekemen 2008; Hullett 2006). In another three trials postoperative pain was not measured (Moyado Garcia 2009; Ozalevli 2005; Viitanen 2001).

Other potential sources of bias

There was only one trial that was rated as being at high risk of bias, because the trialists also used a self-reporting pain scale in the two year old children that was not validated for this age group (Barsoum 1995). We did not find any further potential sources of bias in all other trials.

Effects of interventions

See: [Summary of findings for the main comparison](#) Tramadol compared with placebo; [Summary of findings 2](#) Tramadol compared with morphine; [Summary of findings 3](#) Tramadol compared with nalbuphine; [Summary of findings 4](#) Tramadol compared with pethidine; [Summary of findings 5](#) Tramadol compared with fentanyl

Tramadol versus placebo (Comparison 1)

Ten studies investigated the comparison tramadol versus placebo (Ali 2008; Antila 2006; Bösenberg 1998; Cocelli 2012; Ozköse 2000; Payne 1999; Roelofse 1999; Umuroglu 2004; van den Berg 1999; Viitanen 2001) ([Summary of findings for the main comparison](#)).

Primary outcomes

Five studies including 289 patients investigated the number of children requiring rescue analgesia in the PACU (Ali 2008; Bösenberg 1998; Ozköse 2000; van den Berg 1999; Viitanen 2001). All the included trials for this outcome used different pain scales with different pain triggers. The RR for the need for rescue analgesia was significantly reduced in children treated with 1 to 3 mg/kg tramadol (administered during induction for adeno-tonsillectomy) compared to placebo (RR 0.40; 95% CI 0.20 to 0.78; $I^2 = 87\%$; [Analysis 1.1](#)). We explored the observed heterogeneity in subgroup analyses. The study quality was comparable and was therefore not further explored. There was only one trial which applied tramadol in children undergoing abdominal surgery (Bösenberg 1998), while the other trials investigated children undergoing ENT surgery (Ali 2008; Ozköse 2000; van den Berg 1999; Viitanen 2001). The subgroup analysis focusing on the influence of surgery revealed that following ENT surgery the RR for the need for rescue analgesia was lower (RR 0.39; 95% CI 0.3 to 0.52; [Analysis 1.2](#)) compared to abdominal surgery (RR 0.60; 95% CI 0.34 to 1.07; [Analysis 1.2](#)), but this result was influenced by heterogeneity ($I^2 = 38.8\%$) and the 95% CIs overlapped, which assumed a non-significant influence of surgery. The subgroup analysis ([Analysis 1.3](#)) focusing on the influence of tramadol dose revealed that the RR for the need for rescue analgesia was lower in children undergoing ENT surgery following 1 mg/kg tramadol (RR 0.07; 95% CI 0.02 to 0.21) (Ali 2008; Ozköse 2000) compared to 2 mg/kg (RR 0.63; 95% CI 0.48 to 0.83) (Bösenberg 1998; Viitanen 2001) or 3 mg/kg tramadol (RR 0.62;

95% CI 0.38 to 1.02) (van den Berg 1999). However, this subgroup analysis was influenced by heterogeneity ($I^2 = 86.2\%$) and the 95% CI overlapped, which indicated a non-significant influence of tramadol dose on this outcome. In contrast, the number of patients with moderate to severe pain was only reported in one trial, which used a non-validated five point verbal pain scale (none, mild, moderate, severe, very severe) (Bösenberg 1998). Fewer children undergoing adeno-tonsillectomy (9 out of 22) who received 2 mg/kg tramadol during induction, compared to placebo (15 out of 22), complained about moderate to severe pain in the PACU ($P > 0.05$).

Secondary outcomes

Three included trials (Bösenberg 1998; Umuroglu 2004; Viitanen 2001) investigated the outcome time to first rescue analgesic. Children treated with 1.5 (Umuroglu 2004) to 2 mg/kg tramadol (Bösenberg 1998; Viitanen 2001) for adeno-tonsillectomy did not show a significantly longer time to first rescue analgesic compared to placebo (MD 44.66; 95% CI -24.26 to 113.58; $I^2 = 71\%$; Analysis 1.4). Two included trials investigated the cumulative postoperative analgesic consumption of pethidine (relative potency compared to morphine 0.1) (Viitanen 2001) or fentanyl (relative potency compared to morphine 100) (Antila 2006) following administration of 1 to 2 mg/kg tramadol (during induction) or placebo in children undergoing adenoid-tonsillectomy. In the PACU, children treated with 2 mg/kg tramadol showed a significantly lower opioid consumption (calculated as morphine equivalents) (tramadol 0.4 mg/kg $\pm$ 0.5 versus placebo 0.7 mg/kg $\pm$ 0.39) (Viitanen 2001); however, 24 h postoperation, this difference was not confirmed in another trial following 1 mg/kg tramadol (tramadol 1.52 mg/kg $\pm$ 0.84 versus placebo 1.39 mg/kg $\pm$ 0.79) (Antila 2006). Adverse events were poorly reported. Six included trials reported data regarding the RR for PONV (Ali 2008; Antila 2006; Cocelli 2012; Ozköse 2000; Umuroglu 2004; van den Berg 1999). The pooled data analysis demonstrated that following tramadol administration the RR for PONV was not significantly higher in the PACU (RR 0.84; 95% CI 0.28 to 2.52; $I^2 = 15\%$; Analysis 1.5) or 24 h postoperation (RR 0.78; 95% CI 0.54 to 1.12; $I^2 = 0\%$; Analysis 1.6). In three included trials no children suffering from respiratory depression were noted following tramadol administration (Ali 2008; Umuroglu 2004; van den Berg 1999) (Analysis 1.7). Other adverse events were not reported.

Tramadol versus morphine (Comparison 2)

The comparison tramadol versus morphine was assessed by four included trials (Engelhardt 2003; Hullett 2006; Ozalevli 2005; Umuroglu 2004) (Summary of findings 2).

Primary outcomes

All trials reported data focusing on the outcome number of patients requiring rescue analgesia (Engelhardt 2003; Hullett 2006; Ozalevli 2005; Umuroglu 2004). All included trials used different pain scales with different pain triggers for this outcome. In the PACU and 24 h postoperation, children undergoing adeno-tonsillectomy who were treated with intraoperative tramadol 1 mg/kg to 2 mg/kg showed a non-significantly higher RR for the need for rescue analgesia compared to children treated with morphine 0.1 mg/kg (RR (PACU) 1.25; 95% CI 0.83 to 1.89; $I^2 = 0\%$; Analysis 2.1 (Engelhardt 2003; Hullett 2006; Umuroglu 2004); RR (24 h postoperation) 1.62; 95% CI 0.65 to 4.04; $I^2 = 0\%$; Analysis 2.2 (Engelhardt 2003; Hullett 2006; Ozalevli 2005)). Three

trials applied tramadol during induction (Engelhardt 2003; Hullett 2006; Umuroglu 2004) while only one specifically mentioned that tramadol was applied postoperation (Ozalevli 2005). Due to a lack of data the outcome number of patients with moderate to severe pain could not be assessed.

Secondary outcomes

Only one trial investigated the outcome time to first rescue analgesic and reported that 15 children undergoing adeno-tonsillectomy and treated with 1.5 mg/kg tramadol during induction (155.6 min $\pm$ 172.7) required the first rescue analgesic 112.4 min earlier than 15 children receiving 0.1 mg/kg morphine during induction (268 min $\pm$ 157.9) (Umuroglu 2004). All trials reported data on adverse events. Two trials investigated children with PONV in the PACU (Umuroglu 2004) and 24 h postoperation (Ozalevli 2005). In the PACU 3 out of 15 patients in each group complained about PONV following 1.5 mg tramadol compared to 0.1 mg/kg morphine during induction (Umuroglu 2004). In contrast, another study comparing 1 mg/kg tramadol versus 0.1 mg/kg morphine after surgery in children undergoing adeno-tonsillectomy reported that less children suffered from PONV following tramadol administration 24 h postoperation (3 out of 30 versus 11 out of 30) (Ozalevli 2005). Four trials reported the number of children with respiratory depression (Engelhardt 2003; Hullett 2006; Ozalevli 2005; Umuroglu 2004) but only one trial mentioned two children suffering from respiratory problems following 0.1 mg/kg morphine (Hullett 2006) (Analysis 2.3). Only one trial assessed the outcomes bradycardia, hypotension, pruritus and urinary retention following tramadol or morphine administration postoperation. Generally, either no children (in both groups) suffered from these adverse events (bradycardia, hypotension) or the results (pruritus: 0 in tramadol group versus 1 in morphine group, and urinary retention: 1 patient in each group) were comparably low (Ozalevli 2005).

Tramadol versus nalbuphine (Comparison 3)

Four trials were available for the comparison tramadol versus nalbuphine (Barsoum 1995; Moyado Garcia 2009; Schäffer 1986; van den Berg 1999) (Summary of findings 3).

Primary outcomes

The number of patients with a need for rescue analgesia was assessed in three included trials. All trials used different pain scales with different pain triggers. One trial reported that a higher number of patients treated with tramadol (3 mg/kg) compared to nalbuphine (0.3 mg/kg) required rescue analgesia in the PACU (14 out of 38 versus 11 out of 34) (van den Berg 1999); however, 24 h postoperation the latter result was not confirmed (RR 0.63; 95% CI 0.16 to 2.45; $I^2 = 54\%$; Analysis 3.1) (Barsoum 1995; Schäffer 1986). Only one included trial, which investigated drug administration for postoperative pain treatment following surgery, reported data on the outcome number of patients with moderate to severe pain (PACU) assessed on a four point verbal scale (no pain, mild, moderate, severe pain) following drug administration (Barsoum 1995); there was only one child in the nalbuphine group (0.1 mg/kg) that complained about moderate to severe pain 0.5 h after drug administration.

Secondary outcomes

In the PACU the RR for PONV was not significantly different in both groups (RR (PACU) 1.00; 95% CI 0.50 to 2.01; [Analysis 3.2](#)) ([Schäffer 1986](#); [van den Berg 1999](#)). Only one trial reported that at 24 h postoperation 1 child out of 25 children treated with tramadol suffered from PONV compared to no child treated with nalbuphine ([Barsoum 1995](#)). No patient with bradycardia ([Analysis 3.4](#)) or with respiratory depression ([Analysis 3.3](#)) was mentioned in two included trials ([Barsoum 1995](#); [Moyado Garcia 2009](#)). Only one trial reported patients with sedation or hypotension following 1 mg/kg tramadol compared to 0.1 mg/kg nalbuphine given at the end of surgery ([Moyado Garcia 2009](#)); whereas no patient suffered from hypotension, one patient in the tramadol group and two patients in the nalbuphine group complained about sedation postoperatively.

Tramadol versus pethidine (Comparison 4)

Six trials investigated the comparison tramadol versus pethidine ([Barsoum 1995](#); [Bösenberg 1998](#); [Ekemen 2008](#); [Ertugrul 2006](#); [Ozer 2003](#); [van den Berg 1999](#)). However, data could only be pooled for a low number of outcomes ([Summary of findings 4](#)).

Primary outcomes

Only two trials reported the number of patients requiring rescue analgesia and demonstrated that children treated with 2 to 3 mg/kg tramadol versus 1 to 1.5 mg/kg pethidine during induction showed a lower but non-significant RR for the need for rescue analgesia (RR 0.93; 95% CI 0.43 to 2.02; $I^2 = 66\%$; [Analysis 4.1](#)) ([Bösenberg 1998](#); [van den Berg 1999](#)). All included trials used different pain scales and pain triggers. At 24 h postoperation only one included trial reported that 3 out of 25 patients treated with tramadol required rescue analgesia compared to 8 out of 25 patients receiving pethidine; this trial compared the application of tramadol versus pethidine postoperation ([Barsoum 1995](#)). A similar result was seen in two trials regarding the number of patients with moderate to severe pain (RR 0.64; 95% CI 0.36 to 1.16; [Analysis 4.2](#)) ([Barsoum 1995](#); [Bösenberg 1998](#)).

Secondary outcomes

Only one trial investigated the time to first rescue analgesic and reported that 22 children treated with tramadol (251 min $\pm$ 143) instead of pethidine (223 min $\pm$ 123) during induction required their first rescue analgesic 28 minutes later ([Bösenberg 1998](#)). Adverse events were poorly reported. The most commonly reported outcome was PONV in the PACU. The results of three included trials could be pooled ([Ertugrul 2006](#); [Ozer 2003](#); [van den Berg 1999](#)) and revealed that the RR for PONV in the PACU was lower in children treated with tramadol compared to pethidine, but this result failed to reach significance (RR 0.75; 95% CI 0.28 to 2.02; $I^2 = 0\%$; [Analysis 4.3](#)). In one trial ([van den Berg 1999](#)) out of three included trials, two children treated with 1.5 mg/kg pethidine suffered from respiratory depression after surgery (RR 0.20; 95% CI 0.01 to 4.03; [Analysis 4.4](#)) ([Barsoum 1995](#); [Ekemen 2008](#); [van den Berg 1999](#)). Furthermore, no child with bradycardia ([Analysis 4.5](#)) ([Barsoum 1995](#); [Ekemen 2008](#)) or hypotension ([Ekemen 2008](#)) was noted in the included trials.

Tramadol versus fentanyl (Comparison 5)

Only one included trial investigated the comparison tramadol versus fentanyl in children for postoperative pain treatment ([Chiaretti 2000](#)) ([Summary of findings 5](#)).

Primary outcomes

The included trial reported data on the postoperative pain outcome in children treated with tramadol (bolus during induction followed by continuous infusion during surgery) or fentanyl (same regimen as in the tramadol group) for neurosurgical procedures ([Chiaretti 2000](#)). During the observation period (around 18 h) only 2 out of 14 children in the tramadol group compared to 0 out of 14 children in the fentanyl group required additional rescue analgesia.

Secondary outcomes

No other postoperative pain outcomes were reported. Adverse events were also poorly reported. More patients in the fentanyl group complained about PONV (6 out of 14 compared to 0 out of 14 in the tramadol group). No child suffering from respiratory depression or bradycardia was reported.

DISCUSSION

Summary of main results

The present quantitative systematic review included 20 randomised controlled trials (RCTs) including 1170 children undergoing surgery, which investigated the efficacy and adverse events following tramadol versus placebo or other opioids for postoperative pain treatment. The overall quality of the evidence is low and it should be interpreted with caution because all included trials used different validated and non-validated pain scales in children over a wide range of ages. Furthermore, different pain triggers were used for administration of rescue analgesia, which made it difficult to compare the results. Nevertheless, we performed a quantitative analysis on the need for rescue analgesia taking into account that, despite the use of different pain scales and triggers, children with significant postoperative pain were treated within all trials. In comparison with placebo, children receiving 1 to 2 mg/kg tramadol during induction for adeno-tonsillectomy showed a significantly lower RR for the need for rescue analgesia in the PACU. In addition, the number of children with moderate to severe pain in the PACU was lower following tramadol administration, but this result failed to reach significance. Further non-significant results were seen for the outcomes time to first rescue analgesic and cumulative postoperative analgesic consumption. The comparison of tramadol with other commonly used opioids is currently difficult to assess due to the lack of appropriate data for single opioids as comparators. Comparison with morphine suggested a similar or slightly lower analgesic efficacy of tramadol in the PACU and 24 h postoperation. Due to conflicting results and the lack of pooled outcome data the evidence for the comparisons with nalbuphine, pethidine and fentanyl is currently not clear. Generally, adverse events were only poorly and insufficiently reported. Most data could be pooled for PONV; and children treated with tramadol compared to placebo did not show a significantly higher RR for PONV in the PACU or 24 h postoperation. However, an appropriate risk-benefit analysis was not possible.

Overall completeness and applicability of evidence

Despite growing evidence in this field, postoperative pain in children is still a relevant health problem and cause for concern ([Groenewald 2012](#); [Stanko 2013](#)). This is problematic because there is evidence that untreated or insufficiently treated postoperative pain may increase suffering, complications, rehabilitation, cost

and, most recently addressed, lead to persistent postsurgical pain in children (Page 2013). A multimodal postoperative pain treatment including nonsteroidal analgesic drugs, regional anaesthesia and opioids is currently believed to be the gold standard in perioperative care (Michelet 2012; Russell 2013). However, opioids are still insufficiently administered in children, mainly due to the fear of side effects (Dadure 2009). The present review is significantly limited by the fact that different validated and non-validated pain scores with different pain triggers were used in children over a wide range of ages. This fact makes it difficult to compare the results of the included trials. Nevertheless, the review authors performed a quantitative analysis of 17 included trials taking into account that, despite different pain scores and pain triggers, children with significant postoperative pain were treated in all included trials. We demonstrated a significantly reduced RR for the need for rescue analgesia in children treated with 1 to 2 mg/kg tramadol compared to placebo. However, due to insufficient data, this could not be confirmed for the outcomes number of patients with moderate to severe pain and the time to first rescue analgesic. Additionally, evidence for the comparison with other opioids was sparse, due to limited data; we were only able to address one single outcome. The need for rescue analgesia was non-significantly increased in children treated with tramadol compared to morphine as well as compared to nalbuphine in the PACU and 24 h postoperation. Generally, adverse events for the comparison with placebo or other opioids were insufficiently addressed. The most commonly reported outcome parameter was PONV; tramadol, compared to placebo, did not significantly increase the RR for PONV in the PACU and 24 h postoperation. Furthermore, no children treated with tramadol suffered from respiratory depression. The latter result is important because respiratory depression might be the most feared adverse event following opioid administration in children (Niesters 2013). However, the total number of patients that was assessed was low and insufficient to address safety. Due to limited data, the comparison with other opioids regarding adverse events could not be sufficiently analysed; thus the risk-benefit profile of tramadol compared to placebo and to other common opioids remains unclear.

Quality of the evidence

Although the present review included 20 RCTs including 1170 participants, data could only be pooled for a low number of comparisons and relevant outcomes. Therefore, the presented results should be interpreted with caution due to the high risk for reporting bias. Furthermore, many trials included only a low number of participants, so that many results were imprecise and had wide confidence intervals. Another relevant problem was the use of different validated and non-validated pain scales, which might have particularly influenced the outcome number of patients with moderate to severe pain. Furthermore, different pain triggers were used for application of rescue analgesia, which might have influenced the outcomes number of patients requiring rescue analgesia, time to first rescue analgesic, total required dose of rescue analgesic and number of rescue analgesic doses. Additionally, the age range of included participants was wide and therefore different pain scores were used, but they were assessed as equivalent. Despite these limitations, data were analysed quantitatively in a similar way to another Cochrane Review focusing on postoperative pain in children (Standing 2009), but the evidence was downgraded due to heterogeneous methodology between the studies. Additionally, the impact of

subgroup and sensitivity analyses investigating the identified heterogeneity was limited due to the low number of included trials per outcome. Finally, the overall methodological quality of the included trials was assessed as moderate, because concealment of allocation processes and blinding of outcome assessors were poorly described. In conclusion, according to the GRADE approach (Schunemann 2008), the evidence for the comparisons with placebo (Summary of findings for the main comparison), morphine (Summary of findings 2), pethidine (Summary of findings 4), nalbuphine (Summary of findings 3) and fentanyl (Summary of findings 5) was double or triple downgraded due to the limited study design (use of different pain scales and triggers for rescue analgesia), imprecision of results and unexplained heterogeneity.

Potential biases in the review process

We planned to investigate the outcome postoperative pain scores, but this outcome could not be sufficiently analysed due to a lack of data and large heterogeneity in the pain scales used. Furthermore, these pain scales were mostly non-validated, and different pain triggers were used (even if the same pain scales were used). Because the outcome number of patients with the need for rescue analgesia was reported more widely within the included trials, the authors decided to analyse this outcome as the primary outcome. However, this variation to the initial protocol might have influenced the results, and the retrieved results should be interpreted with caution.

Agreements and disagreements with other studies or reviews

The current available evidence focusing on opioid treatment in children for postoperative pain is sparse. Our review group recently published another Cochrane review investigating nalbuphine for postoperative pain in children. The problems, which we addressed in the latter review, were almost the same as in the present review; limited evidence due to a low number of available trials and limited quality of the available evidence due to limitations in the study design (use of different pain scales and triggers for rescue analgesia), imprecision of results and unexplained heterogeneity (Schnabel 2014).

AUTHORS' CONCLUSIONS

Implications for practice

The overall quality of evidence regarding postoperative analgesia following tramadol use in children compared to placebo or other opioids is currently low or very low. Nevertheless, analysis of five included trials demonstrated that the prophylactic administration of tramadol (during induction of anaesthesia) might provide effective postoperative analgesia in children undergoing adeno-tonsillectomy, compared to placebo. The ideal tramadol dose is currently unclear. The latter finding might be important because adeno-tonsillectomies are one of the most painful surgical procedures during childhood (Groenewald 2012; Stanko 2013) and the use of other opioids (for example morphine) is feared due to an increased risk of postoperative respiratory problems (for example due to an underdiagnosed risk of sleep apnoea within this population) (Subramanyam 2014). One included trial specifically compared the risk of postoperative desaturation following tramadol or morphine administration in children with obstructive sleep apnoea who were undergoing adeno-

tonsillectomy. They reported 26% significantly fewer episodes of postoperative oxygen desaturation in the tramadol group (Hullett 2006). In contrast, a recently published case report revealed that a child with a ultrarapid CYP2D6 genotype and obstructive sleep apnoea syndrome suffered from severe postoperative respiratory depression following day-case tonsillectomy (Orliaguet 2015). The latter finding highlights the possible influence of genetic variations on the efficacy (8% to 10% possibility of a cytochrome P450 enzyme deficiency causing an inability to metabolize the prodrug tramadol into the active component (M1)) and the adverse effects of tramadol administration, which are currently unknown. To conclude, although tramadol administration might be an interesting option, for example for post-tonsillectomy pain, the current evidence is very limited and further research is urgently needed to further define a possible role of tramadol for postoperative pain treatment in children.

Implications for research

The following implications for research could be defined based on the results of this review.

- Because the evidence for tramadol use in children is currently sparse, due to incomplete and insufficient outcome reporting (including adverse events), additional randomised controlled trials comparing tramadol with other commonly used opioids are needed in order to enable an appropriate risk-benefit analysis. Postoperative pain should be assessed with validated pain scales and, accordingly, rescue analgesia should be given following clearly defined pain triggers (e.g. NRS > 3 based on a 0 to 10 point scale (Hirschfeld 2013)).

- Tramadol administration should be investigated in children undergoing different common paediatric surgical procedures in order to detect possible procedure specific differences.
- The possible influence of genetic variability on efficacy and adverse events should be assessed in children treated with tramadol for postoperative pain.
- Tramadol administration should be studied in patient groups with a high risk for opioid related adverse events (e.g. children with obstructive sleep apnoea undergoing adeno-tonsillectomy).
- Finally, tramadol administration should be studied in different age groups and dosages to further evaluate the clinical consequences of the reported pharmacokinetic findings (e.g. ceiling effect, higher risk for specific adverse events in younger age groups (Allegaert 2011)).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ali 2008

Methods	RCT Parallel design
Participants	Adeno-tonsillectomy, n = 90 (46 males, 44 females), children aged 4 to 10 years Group 1: 16 males, 14 females; mean age 7.46 years (SD 1.85) Group 2: 15 males, 15 females; mean age 7.53 years (SD 1.88) Group 3: 15 males, 15 females; mean age 7.61 years (SD 1.93)
Interventions	Group 1: placebo (saline) po + placebo (saline) iv (n = 30) Group 2: dextromethorphan 1 mg/kg po + placebo (saline) iv (n = 30) Group 3: placebo (saline) plus tramadol 1 mg/kg iv (n = 30) Administration time: 30 minutes before arrival in the operating room and during induction of anaesthesia
Outcomes	- Postoperative pain scales (FPS) (1, 2, 3, 4, 5, 6 h postoperation) - Analgesic and antiemetic requirements during 6-h observation period - Number of patients with adverse events (vomiting, respiratory parameters)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "Each patient was randomly assigned to one of three groups."
Allocation concealment (selection bias)	Low risk	Quote: "A sealed envelope method was used for randomization."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, prospective, doubleblind and placebo-controlled study design"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes are measured and fully reported.

Ali 2008 (Continued)

Other bias	Unclear risk	No apparent bias

Antila 2006

Methods	RCT Parallel design
Participants	Tonsillectomy, n = 45 (20 males, 25 females), children aged 5 to 15 years Group 1: 7 males, 8 females; mean age 12.5 years (SD 1.9) Group 2: 6 males, 9 females; mean age 12.5 years (SD 2.3) Group 3: 7 males, 8 females; mean age 11.9 years (SD 2.4)
Interventions	Group 1: placebo iv (n=15) Group 2: 2 mg/kg ketoprofen iv (n = 15) Group 3: 1 mg/kg tramadol iv (n = 15) Administration time: after the induction of anaesthesia and before surgical incision; after surgery the randomised study treatment was continued as a 6-h iv infusion in which the child received either another dose of saline control, ketoprofen (2 mg/kg) or tramadol (1 mg/kg)
Outcomes	- Postoperative pain scales (VAS) (30 min, 60 min, 90 min, 2 h, 6 h, and 24 h postoperation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization to treatment groups was performed by computer in blocks of nine patients."
Allocation concealment (selection bias)	Unclear risk	Quote: "Children were prospectively randomized to one of the three treatment groups"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The double-blind nature of the study was confirmed by having a nurse, not otherwise participating in the treatment of the patient, to prepare the coded study treatment syringes and infusions."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Tramadol for postoperative pain treatment in children (Review)

Barsoum 1995

Methods	Open trial Parallel design
Participants	Lower abdominal surgery (appendectomy, hernia repair, testicular or urethral surgery), n = 75 (61 males, 14 females), children aged 2 to 12 years Group 1: 22 males, 9 females; mean age 5.4 years (SD 2.6) Group 2: 20 males, 5 females; mean age 6.3 years (SD 1.9) Group 3: 19 males, 6 females; mean age 6.2 years (SD 2.8)
Interventions	Group 1: 0.1 mg/kg nalbuphine im (n = 25) Group 2: 2 mg/kg tramadol im (n = 25) Group 3: 1 mg/kg pethidine im (n = 25) Administration time: after the end of surgery (first expression of pain) an additional injection of the half initial dose was administrated 30 and 60 min, if inadequate analgesia
Outcomes	- Postoperative pain scales (VRS) (0.5, 1, 3, 6, 12, 24 h postoperation) - Number of patients with no or slight pain 1 h postoperation - Total analgesic consumption 24 h postoperation - Frequency of administration 24 h postoperation - Investigators' assessment of overall pain relief (excellent, very good, good, satisfactory, poor) at 24 h postoperation; number, nature, time of onset of adverse events (vomiting, haemodynamic, respiratory parameters); overall assessment of tolerability 24 h postoperation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "The children were randomised into 3 groups of 25,..."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was intended to be a double-blind (observer blinded),..."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "drug dosages were recorded in the patient records,..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data

Tramadol for postoperative pain treatment in children (Review)

Barsoum 1995 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	High risk	Verbal rating scale (VRS) was also used in the youngest children, which were 2 years old. However, at this age, this scale is not validated

Bösenberg 1998

Methods	RCT Parallel design
Participants	Inguinal surgery (orchidopexy, herniotomy), n = 88 (87 males, 1 female), children aged 2 to 10 years Group 1: 22 males, mean age 6 years (SD 3) Group 2: 22 males, mean age 5 years (SD 2) Group 3: 21 males, 1 female; mean age 5 years (SD 2) Group 4: 22 males, mean age 5 years (SD 2)
Interventions	Group 1: tramadol 1 mg/kg iv (n = 22) Group 2: tramadol 2 mg/kg iv (n = 22) Group 3: pethidine 1 mg/kg iv (n = 22) Group 4: placebo (n = 22) Administration time: after induction of anaesthesia
Outcomes	- Documentation of respiratory and haemodynamic parameters during anaesthesia - Postoperative pain scales (five-point verbal rating scale) (1, 2, 3, 4, 5, 6 h postoperation) - Recovery from anaesthesia - Number of patients with the need for rescue analgesia - Number of patients with moderate to severe pain

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...computer-generated randomisation."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "preserve blinding, the study medication was prepared in identical syringes by a designated third party" "Randomisation codes were masked to the patient, the investigator and nursing staff."

Bösenberg 1998 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	High risk	Postoperative pain was measured, but was only selectively reported. An overall pain intensity score was described, but no values at time points were specified
Other bias	Unclear risk	No apparent bias

Chiaretti 2000

Methods	RCT Parallel design
Participants	Major neurosurgical surgery, n = 42 (23 males, 20 female) Group 1: 10 males, 8 females; mean age 67.8 months (SD 66.5) Group 2: 6 males, 5 females; mean age 62 months (SD 50) Group 3: 7 males, 7 female; mean age 74 months (SD 47.5)
Interventions	Group 1: tramadol 1 mg/kg iv (n = 14) Group 2: tramadol 0.5 mg/kg iv followed by continuous infusion at the rate of 150 µg/kg/h (n = 14) Group 3: fentanyl by continuous infusion at the rate of 2 µg/kg/h (n = 14) Administration time: at the induction of general anaesthesia
Outcomes	- Postoperative pain scales (AFS scale and CHEOPS score) (every 4 h for 12 to 36 h postoperation) - Documentation of respiratory and haemodynamic parameters postoperation - Number of patients with adverse events (vomiting, nausea, apnoea, and bradycardia)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "Patients were allocated randomly to three intraoperative treatment groups"
Allocation concealment (selection bias)	Unclear risk	No detailed information

Chiaretti 2000 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Cocelli 2012

Methods	RCT Parallel design
Participants	Tonsillectomy, n = 90 (42 males, 48 female), children aged 2 to 9 years Group 1: 14 males, 16 females; mean age 6.3 years (SD 0.002) Group 2: 14 males, 16 females; mean age 6.17 years (SD 1.599) Group 3: 14 males, 16 female; mean age 6.1 years (SD 1.517)
Interventions	Group 1: placebo (saline) iv (n = 30) Group 2: 1.5 ml 0.75% ropivacaine to the tonsil lodge (n = 30) Group 3: tramadol 1 mg/kg iv (n = 30) Administration time: after induction of anaesthesia
Outcomes	- Documentation of haemodynamic parameters for 24 h postoperation - Postoperative pain scales at resting and swallowing (Maunuksela pain scores) (1, 2, 3, 6, 9, 12, 15, 18, 21, 24 h postoperation) - Number of patients with adverse events (hypotension, breathing difficulties and bleeding, vomiting, nausea)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... paediatric tonsillectomies: A randomized placebo controlled study", "Randomization was provided by the use of a random number generator"

Cocelli 2012 (Continued)

Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Ekemen 2008

Methods	RCT Parallel design
Participants	Lower abdominal surgery (e.g. hernia repair, appendectomy, testicular or ureteral surgery), n = 110, children aged 2 to 12 years Group 1: mean age 5.7 years (SD 0.39) Group 2: mean age 5.65 years (SD 0.56)
Interventions	Group 1: pethidine 1 mg/kg iv (n = 60) Group 2: tramadol 2 mg/kg iv (n = 50) Administration time: at the induction of anaesthesia
Outcomes	- Documentation of haemodynamic parameters and sedation score for 24 h postoperation - Postoperative pain scales (4-point restlessness-pain protocol) (5, 10, 20, 30 min, 6 and 24 h postoperation) - Number of patients with adverse events (episodes of vomiting, nausea, apnoea and bradycardia)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: " ... we designed prospective, randomized, controlled study."

Ekemen 2008 (Continued)

Allocation concealment (selection bias)	Unclear risk	No detailed information Quote: "Patients were allocated randomly to receive either.."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...were recorded by an assistant investigating anaesthetist, who was blind to test drug ..." "Physicians in recovery room, blind to the test drug...assessed residual analgesia..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	High risk	All outcomes were measured, but pain scores values were not specified
Other bias	Unclear risk	No apparent bias

Engelhardt 2003

Methods	RCT Parallel design
Participants	Tonsillectomy or adeno-tonsillectomy, n = 60, children aged 2 to 14 years Group 1: mean age 8.1 years (SD 4.2) Group 2: mean age 7.1 years (SD 3.6) Group 3: mean age 7 years (SD 4.2)
Interventions	Group 1: morphine 0.1 mg/kg iv (n = 20) Group 2: tramadol 1 mg/kg iv (n = 20) Group 3: tramadol 2 mg/kg iv (n = 20) Administration time: after induction of anaesthesia All patients received diclofenac (1 mg/kg) rectally prior to commencing surgery
Outcomes	- Postoperative pain scales (1 = pain free, 5 = worst possible pain) (every 4 hours for 24 h postoperation) - Sedation scores, analgesic requirements, respiratory rate, nausea and episodes of vomiting
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement

Engelhardt 2003 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "We conducted a prospective, double-blind, randomized controlled trial in children ..." "A computer-generated randomization table ..."
Allocation concealment (selection bias)	Low risk	Quote: "Each patient volunteer was given a subsequent study number, which determined the drug and dose to be given. The code was not broken during the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study drugs were diluted in water for injection to the total volume of 10 ml and given to the attending anaesthetist without disclosing the drug."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Ertugrul 2006

Methods	RCT Parallel design
Participants	Adeno-tonsillectomy, n = 45 (18 male, 27 female) children aged 1 to 7 years Group 1: 7 male, 8 female; median age 4.26 years (SD 1.57) Group 2: 6 male, 9 female; mean age 4.07 years (SD 1.54) Group 3: 5 male, 10 female; mean age 3.93 years (SD 1.66)
Interventions	Group 1: ketamine 0.5 mg/kg po (n = 15) Group 2: tramadol 1 mg/kg po (n = 15) Group 3: meperidine 1 mg/kg po (n = 15) Administration time: after induction of anaesthesia
Outcomes	- Postoperative pain scales (Toddler-Preschooler Postoperative Pain Scale) (30, 60, 120 and 240 min after extubation) - Postoperative agitation scores - Time to opening eyes upon command (min) - Number of patients with vomiting

Ertugrul 2006 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "After induction of anaesthesia and before tracheal intubation, children were randomly allocated to receive.."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Post-operative pain was scored blind ..."; "Post-operative pain was assessed in the recovery room 30, 60, 120 and 240 min after tracheal extubation by a blinded observer ..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Hullett 2006

Methods	RCT Parallel design
Participants	Adeno-tonsillectomy, n = 60, children aged 1 to 8 years Group 1: median age 5.0 years (P25 to P75 4.5 to 7.0) Group 2: mean age 5.0 years (P25 to P75 3.0 to 7.0)
Interventions	Group 1: morphine 0.1 mg/kg iv (n = 28) Group 2: tramadol 1 mg/kg iv (n = 32) Administration time: at induction of anaesthesia
Outcomes	- Postoperative pain scales (PMH Pain Assessment Tool) (0, 15, 30 min; 1, 2, 3, 4, 5, 6 h postoperation) - Sedation score - Time to first analgesic requirement and total numbers of doses - Number of patients with respiratory depression

Hullett 2006 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "... in this double blinded, prospective, controlled trial."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No detailed information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six other patients were excluded because of protocol violations or inadequate data collection"
Selective reporting (reporting bias)	High risk	All outcomes were measured, but pain scores values were only incompletely specified: - only description of number of patient with pain score > 6 at the first three study time points - no pain score values
Other bias	Unclear risk	No apparent bias

Moyado Garcia 2009

Methods	RCT Parallel design
Participants	Surgical procedures with expected moderate to severe postoperative pain (e.g. perineal fistula and bladder neck closure, bilateral oblique pelvic osteotomy, exploratory laparotomy, bilateral elongation of Achilles tendon, etc), n = 24 (14 males, 10 females; children aged 1 to 10 years) Group 1: 7 males, 5 females; mean age 6.2 years (2.5 to 10) Group 2: 7 males, 5 females; mean age 4.4 years (1.6 to 10)
Interventions	Group 1: nalbuphine iv (bolus 100 µg/kg, 0.2 µg/kg/min for 72 h) (n = 12) Group 2: tramadol iv (bolus 1 mg/kg, 2.0 µg/kg/min for 72 h) (n = 12) Administration time: before the end of surgery
Outcomes	- Postoperative pain scales (FPS, VAS) (every 1 h for the first 24 h, then every 4 h until the end of the 72 h study period)

Tramadol for postoperative pain treatment in children (Review)

Moyado Garcia 2009 (Continued)

- Documentation of haemodynamic and respiratory parameters during 72 h study period
- Sedation scores, episodes of vomiting

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "By means of a predesigned table of random numbers, children were allocated to receive..."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to preserve the double-blind design of the study, drugs were prepared on a case-by-case basis, according to the predesigned table of random numbers, by one of the investigators of the study (JCR-M) who did not participate in the evaluation of patients' eligibility or study outcomes. Evaluation of patients' eligibility, pain score in younger children, application of the visual analogue scale (VAS) in older children, and evaluation of adverse events during the study period were performed by an investigator (JCH-P) who was unaware of the patients' allocation group. Adherence to the protocol was also monitored by another investigator (DM-G)."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	High risk	All outcomes were measured, pain intensities were not mentioned within the text
Other bias	Unclear risk	No apparent bias

Ozalevli 2005

Methods	RCT Parallel design
Participants	Adeno-tonsillectomy, n = 60 (37 males, 23 females), children aged 6 to 12 years Group 1: 18 males, 12 females; mean age 7 years (6 to 11) Group 2: 19 males, 11 females; mean age 6 years (6 to 12)
Interventions	Group 1: tramadol iv (loading dose 1 mg/kg, bolus 0.2 mg/kg/10min) (n = 30) Group 2: morphine iv (loading dose 0.1 mg/kg, bolus 0.02 mg/kg/10min) (n = 30) Administration time: after surgery
Outcomes	- Documentation of haemodynamic and respiratory parameters during and after anaesthesia

Tramadol for postoperative pain treatment in children (Review)

Ozalevli 2005 (Continued)

- Postoperative pain scales (CHEOPS) (0, 15, 30, 60 min; 2, 4, 6, 24 h postoperation)
- Documentation of sedation score
- Cumulative opioid consumption
- Number of patients with adverse events (urinary retention, nausea)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "This prospective, randomized, double-blind study was designed..." "Randomization was performed consecutively."
Allocation concealment (selection bias)	Unclear risk	No detailed information Quote: "The patients were then randomly allocated to receive..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Thus both observers and patients were blinded to the drug used."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	High risk	All outcomes were measured. Pain intensity score (CHEOPS) was described, but no values were reported
Other bias	Unclear risk	No apparent bias

Ozer 2003

Methods	RCT Parallel design
Participants	Tonsillectomy with or without adenoidectomy, n = 50 (23 males, 27 females), children aged 4 to 7 years Group 1: 10 males, 15 females; mean age 5.7 years (SD 1.5) Group 2: 13 males, 12 females; mean age 6.8 years (SD 1.6)
Interventions	Group 1: tramadol 1 mg/kg iv (n = 25) Group 2: meperidine 1 mg/kg iv (n = 25)

Ozer 2003 (Continued)

Administration time: after induction of anaesthesia

Outcomes	- Documentation of MAP perioperatively - Postoperative pain score (FPS) at 0 min, 10 min, 20 min, 45 min postoperation) - Opioid related adverse events like nausea and vomiting
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "Fifty children ... were randomly assigned... "
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: " The nurse in the PACU who was unaware of the nature of the test drug assessed the agitation score. The same nurse evaluated analgesia..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Ozköse 2000

Methods	RCT Parallel design
Participants	Tonsillectomy with or without adenoidectomy, n = 45 (27 males, 18 females), children aged 2 to 11 years) Group 1: 8 males, 7 females; mean age 5.1 years (SD 2.8) Group 2: 10 males, 5 females; mean age 5.3 years (SD 2.9) Group 3: 9 males, 6 females; mean age 5.6 years (SD 3.2)
Interventions	Group 1: tramadol 0.5 mg/kg iv (n = 15) Group 2: tramadol 1 mg/kg iv (n = 15)

Ozköse 2000 (Continued)

Group 3: placebo iv (n = 15)

Administration time: after induction of anaesthesia

Outcomes	- Postoperative pain score (FPS ≤ 6 years, VAS > 7 years; 15 min, 30 min, 60 min postoperation) - Number of patients with need for additional analgesia - Opioid related adverse events - Documentation of HR and MAP perioperatively
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "... a randomized, double-blind and placebo-controlled protocol."
Allocation concealment (selection bias)	Unclear risk	No detailed information Quote: "...these syringes were consecutively used."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The syringes were marked only with a coded label ... ." "...the author who was unaware of group assignment... assessed pain ... ."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Payne 1999

Methods	RCT Parallel design
Participants	Dental extraction, n = 50 (26 males, 24 females), children aged 4 to 7 years Group 1: 21 males, 19 females; mean age 5.3 years (SD 1.1) Group 2: 5 males, 5 females; mean age 4.8 years (SD 1.2)
Interventions	Group 1: tramadol 3 mg/kg + 0.5 mg/kg midazolam po (n = 40) Group 2: placebo + 0.5 mg/kg midazolam po (n = 10)

Tramadol for postoperative pain treatment in children (Review)

Payne 1999 (Continued)

Administration time: after induction of anaesthesia

All children received midazolam

Outcomes	- Postoperative pain score (Oucher face pain scale) (15, 30, 60, and 120 min postoperation)
	- Documentation of oxygen saturation
	- Opioid related adverse events (respiratory, cardiovascular, or emetic incidents)
	- Documentation of HR and MAP perioperatively

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "...were included in a double-blind, randomized, placebo-controlled trial..."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The anaesthetist who did the anaesthetic assessments and the research sister who did the postanaesthetic recovery and pain assessments were not informed which study medication was administered."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Roelofse 1999

Methods	RCT
	Parallel design
Participants	Dental extraction, n = 60 (31 males, 29 females), children aged 4 to 7 years Group 1: 18 males, 14 females, mean age 5.3 years (SD 1.1) Group 2: 13 males, 15 females, mean age 5.1 years (SD 1.2)
Interventions	Group 1: tramadol 1.5 mg/kg + midazolam po (n = 31)

Roelofse 1999 (Continued)

Group 2: placebo + midazolam po (n = 29)

Administration time: after induction of anaesthesia

All children received midazolam

Outcomes	- Postoperative pain score (Oucher face pain scale) (15, 30, 60, and 120 min postoperation) - Opioid related adverse events (emesis) - Documentation of postoperative recovery - Number of patients with the need for rescue analgesia

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "... were included in a double-blind, randomized, placebo-controlled trial.."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither, anaesthetist, ..., nor research sister who did the post-anaesthetic recovery and pain assessments, were informed which study medication ..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Schäffer 1986

Methods	RCT Parallel design
Participants	Herniotomy, orchidopexy, circumcision, hydrocelectomy, n = 60, children aged 1 to 9 years Group 1: 25 males, 5 females; mean age 4.5 years (SD 1.9) Group 2: 26 males, 4 females; mean age 4.87 years (SD 2.4)

Schäffer 1986 (Continued)

Interventions	Group 1: 0.15 to 0.2 mg/kg nalbuphine im Group 2: 0.75 to 1 mg/kg tramadol im Administration time: after surgery (at the arrival in the recovery area)
Outcomes	- VAS pain scale (0 to 10 cm) (1, 2, 3, 4, 6, 8, 24 h postoperation) - Number of adverse events (vomiting, headache, singultus, hallucination, dry mouth)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...each group received in a randomized and double-blind manner ..."; "... received by an randomization plan..."
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...each group received in a randomized and double-blind manner ..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No detailed information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Umuroglu 2004

Methods	RCT Parallel design
Participants	Adeno-tonsillectomy, n = 60 (32 males, 28 females), children aged 5 to 12 years Group 1: 5 males, 10 females; mean age 6.9 (SD 2.1) Group 2: 9 males, 6 females; mean age 7.13 (SD 2.51) Group 3: 7 males, 8 females; mean age 6.06 (SD 2.51) Group 4: 7 males, 8 females; mean age 6.96 (SD 2.08)
Interventions	Group 1: ketamine 0.5 mg/kg iv (n = 15)

Tramadol for postoperative pain treatment in children (Review)

Umuroglu 2004 (Continued)

Group 2: morphine 0.1 mg/kg iv (n = 15)

Group 3: tramadol 1.5 mg/kg iv (n = 15)

Group 4: saline iv (n = 15)

Administration time: during induction of anaesthesia

Outcomes

- Postoperative pain score (5-P-NRS, CHEOPS); 1 min, 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min, 120 min, 240 min, 360 min postoperation
- Number of patients with need for additional analgesia
- Duration of postoperative analgesia, time to first rescue analgesia
- Opioid related adverse events (nausea, vomiting, sedation)
- Documentation of heart rate and oxygen saturation

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detailed information Quote: "A randomized, prospective, double-blind and placebo-controlled study design was used."
Allocation concealment (selection bias)	Low risk	Quote: "A sealed envelope method was used for randomization."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A randomized, prospective, double-blind and placebo-controlled study design was used." "pain scores... were assessed by an independent observer."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "pain scores... were assessed by an independent observer."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

van den Berg 1999

Methods	RCT Parallel design
Participants	Tonsillectomy with and without adenoidectomy; n = 152 (99 males, 53 females), children and young adults aged 8 to 21 years

Tramadol for postoperative pain treatment in children (Review)

van den Berg 1999 (Continued)

Group 1: 25 males, 12 females; mean age 13 (SD 15)

Group 2: 25 males, 13 females; mean age 14 (SD 15)

Group 3: 26 males, 12 females; mean age 16 (SD 14)

Group 4: 23 males, 16 females; mean age 15 (SD 14)

Interventions	Group 1: saline (n = 37) Group 2: tramadol 3 mg/kg iv (n = 38) Group 3: pethidine 1.5 mg/kg iv (n = 38) Group 4: nalbuphine 0.3 mg/kg iv (n = 39) Administration time: 30 sec before induction of anaesthesia
Outcomes	- Postoperative pain score (restlessness-pain score in PACU) - Number of patients with need for postoperative additional analgesia - Time to extubation - Documentation of heart rate, blood pressure - Opioid related adverse events (emesis, sedation)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A prospective, double-blind, randomized, controlled study ... "; "Each patient was block randomized ... "
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The test drugs were injected by the investigating anaesthetist, who was not blind to the test drug injected."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Nurses in the PACU, blind to the test drug administered ..., assessed residual analgesia ... "
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	Low risk	All outcomes were measured and completely reported
Other bias	Unclear risk	No apparent bias

Viitanen 2001

Methods	RCT Parallel design
Participants	Adenoidectomy, n = 80, children aged 1 to 3 years
Interventions	Group 1: tramadol 2 mg/kg iv (n = 40) Group 2: saline iv (n = 40) Administration time: after induction of anaesthesia All children received rectal ibuprofen (10 mg/kg) before start of surgery
Outcomes	- Postoperative cumulative pethidine consumption - Number of patients with the need for rescue analgesia - Duration of postoperative analgesia, time to first rescue analgesia - Opioid related adverse events (nausea, vomiting)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eighty children were allocated randomly... ", "According to a computer-generated table of random numbers... "
Allocation concealment (selection bias)	Unclear risk	No detailed information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both study drugs were prepared and administered by a nurse who did not otherwise participate in the care of the child."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "... assessed by a trained nurse who was blinded... "
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were evaluated. There were no missing data
Selective reporting (reporting bias)	High risk	All outcomes were measured, but pain score values were not reported
Other bias	Unclear risk	No apparent bias

iv = intravenously

po = per mouth

im = intramuscularly

SD = standard deviation

PONV = postoperative nausea and vomiting

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aguirre Córcoles 2003	Intravenous patient-controlled analgesia
Akkaya 2009	Peritonsillar infiltration of tramadol
Alencar 2012	Only neonates were studied, continuous application of tramadol on an intensive care unit
Altunkaya 2003	No children included
Apiliogullari 2011	Retrospective study
Bedirli 2011	Conference abstract
Borazan 2012	Propofol injection pain was assessed
Chu 2006	Intravenous patient-controlled analgesia
Courtney 2000	Children and adult included, no differentiation possible
Demiraran 2005	Epidural injection
Finkel 2002	Tested different dosages of tramadol (1 mg/kg versus 2 mg/kg)
Griessinger 1997	No RCT
Günes 2004	Caudal application
Khosravi 2006	Comparison with ilioinguinal and iliohypogastric block
Macarone 1998	Retrospective study
Metodiev 2011	Conference abstract
Mikhel'son 2002	No RCT
Oliveira 2000	No RCT
Osifo 2008	Retrospective study
Ostreikov 1993	No RCT
Pendeville 2000	Versus paracetamol
Sun 2010	No RCT

RCT = randomized controlled trial

iv = intravenous

DATA AND ANALYSES

Comparison 1. Tramadol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia (PACU)	5	289	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.20, 0.78]
2 Number of patients requiring rescue analgesia (PACU) (Subgroup: Surgery)	5	289	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.33, 0.54]
2.1 Abdominal surgery	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.34, 1.07]
2.2 ENT Surgery	4	245	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.30, 0.52]
3 Number of patients requiring rescue analgesia (PACU) (Subgroup: Dose)	5	289	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.33, 0.54]
3.1 Tramadol 1mg iv.	2	90	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.02, 0.21]
3.2 Tramadol 2mg iv.	2	124	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.48, 0.83]
3.3 Tramadol 3mg iv.	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 1.02]
4 Time to first rescue analgesic (min)	3	154	Mean Difference (IV, Random, 95% CI)	44.66 [-24.26, 113.58]
5 Number of patients with PONV (PACU)	3	215	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.28, 2.52]
6 Number of patients with PONV (24h postop)	4	150	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.12]
7 Number of patients with respiratory depression	3	165	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Tramadol versus placebo, Outcome 1 Number of patients requiring rescue analgesia (PACU).

Analysis 1.2. Comparison 1 Tramadol versus placebo, Outcome 2 Number of patients requiring rescue analgesia (PACU) (Subgroup: Surgery).

Analysis 1.3. Comparison 1 Tramadol versus placebo, Outcome 3 Number of patients requiring rescue analgesia (PACU) (Subgroup: Dose).

Analysis 1.4. Comparison 1 Tramadol versus placebo, Outcome 4 Time to first rescue analgesic (min).

Analysis 1.5. Comparison 1 Tramadol versus placebo, Outcome 5 Number of patients with PONV (PACU).

Analysis 1.6. Comparison 1 Tramadol versus placebo, Outcome 6 Number of patients with PONV (24h postop).

Analysis 1.7. Comparison 1 Tramadol versus placebo, Outcome 7 Number of patients with respiratory depression.

Comparison 2. Tramadol versus morphine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia (PACU)	3	127	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.83, 1.89]
2 Number of patients requiring rescue analgesia (24h postop)	3	151	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.65, 4.04]
3 Number of patients with respiratory depression	4	190	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.51]

Analysis 2.1. Comparison 2 Tramadol versus morphine, Outcome 1 Number of patients requiring rescue analgesia (PACU).

Analysis 2.2. Comparison 2 Tramadol versus morphine, Outcome 2 Number of patients requiring rescue analgesia (24h postop).

Analysis 2.3. Comparison 2 Tramadol versus morphine, Outcome 3 Number of patients with respiratory depression.

Comparison 3. Tramadol versus nalbuphine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia (24h postop)	2	110	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.16, 2.45]
2 Number of patients with PONV (PACU)	2	137	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 2.01]
3 Number of patients with respiratory depression	2	74	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of patients with bradycardia	2	74	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Tramadol versus nalbuphine, Outcome 1 Number of patients requiring rescue analgesia (24h postop).

Analysis 3.2. Comparison 3 Tramadol versus nalbuphine, Outcome 2 Number of patients with PONV (PACU).

Analysis 3.3. Comparison 3 Tramadol versus nalbuphine, Outcome 3 Number of patients with respiratory depression.

Study or subgroup	Tramadol n/N	Nalbuphine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsoum 1995	0/25	0/25			Not estimable
Moyado Garcia 2009	0/12	0/12			Not estimable
Total (95% CI)	37	37			Not estimable
Total events: 0 (Tramadol), 0 (Nalbuphine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 3.4. Comparison 3 Tramadol versus nalbuphine, Outcome 4 Number of patients with bradycardia.

Study or subgroup	Tramadol n/N	Nalbuphine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsoum 1995	0/25	0/25			Not estimable
Moyado Garcia 2009	0/12	0/12			Not estimable
Total (95% CI)	37	37			Not estimable
Total events: 0 (Tramadol), 0 (Nalbuphine)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Comparison 4. Tramadol versus pethidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia (PACU)	2	120	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.43, 2.02]
2 Number of patients with moderate/severe pain (PACU)	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.16]
3 Number of patients with PONV (PACU)	3	156	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.02]
4 Number of patients with respiratory depression	3	236	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.03]
5 Number of patients with bradycardia	2	160	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Tramadol versus pethidine, Outcome 1 Number of patients requiring rescue analgesia (PACU).

Analysis 4.2. Comparison 4 Tramadol versus pethidine, Outcome 2 Number of patients with moderate/severe pain (PACU).

Analysis 4.3. Comparison 4 Tramadol versus pethidine, Outcome 3 Number of patients with PONV (PACU).

Analysis 4.4. Comparison 4 Tramadol versus pethidine, Outcome 4 Number of patients with respiratory depression.

Analysis 4.5. Comparison 4 Tramadol versus pethidine, Outcome 5 Number of patients with bradycardia.

APPENDICES

Appendix 1. MEDLINE search strategy

1. Tramadol/
2. tramadol.mp.
3. k-315.mp.
4. ralivia er.mp.
5. rybix.mp.
6. ryzolt.mp.
7. tramahexal.mp.
8. tramake.mp.
9. tramalgin.mp.
10. tramedo.mp.
11. ultram.mp.
12. zamadol.mp.
13. zydol.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Pain, Postoperative/
16. (pain* and (postoperative or post operative or surg*)).mp.
17. 15 or 16
18. exp infant/
19. exp child/
20. adolescent/
21. (infant* or child* or adoles*).mp.

22.18 or 19 or 20 or 21
 23.randomized controlled trial.pt.
 24.controlled clinical trial.pt.
 25.randomized.ab.
 26.placebo.ab.
 27.drug therapy.fs.
 28.randomly.ab.
 29.trial.ab.
 30.groups.ab.
 31.23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
 32.14 and 17 and 22 and 31

key:

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

pt = publication type

ab = abstract

fs = floating subheading

Appendix 2. CENTRAL search strategy

#1	MeSH descriptor: [Tramadol] this term only
#2	tramadol
#3	k-315
#4	ralivia
#5	rybix
#6	ryzolt
#7	tramahexal
#8	tramake
#9	tramalgin
#10	tramedo
#11	ultram
#12	zamadol
#13	zydol
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15	MeSH descriptor: [Pain, Postoperative] this term only
#16	(pain* and (postoperative or post operative or surg*))
#17	#15 or #16
#18	MeSH descriptor: [Infant] explode all trees
#19	MeSH descriptor: [Child] explode all trees
#20	MeSH descriptor: [Adolescent] explode all trees
#21	(infant* or child* or adoles*)

#22 #18 or #19 or #20 or #21

#23 #14 and #17 and #22

Appendix 3. EMBASE search strategy

EMBASE (Ovid)

- 1 Tramadol/
- 2 tramadol.mp.
- 3 k-315.mp.
- 4 ralivia er.mp.
- 5 rybix.mp.
- 6 ryzolt.mp.
- 7 tramahexal.mp.
- 8 tramake.mp.
- 9 tramalgin.mp.
- 10 tramedo.mp.
- 11 ultram.mp.
- 12 zamadol.mp.
- 13 zydol.mp.
- 14 or/1-13
- 15 Pain, Postoperative/
- 16 (pain* and (postoperative or post operative or surg*)).mp.
- 17 15 or 16
- 18 exp infant/
- 19 exp child/
- 20 adolescent/
- 21 (infant* or child* or adoles*).mp.
- 22 or/18-21
- 23 random\$.tw.
- 24 factorial\$.tw.
- 25 crossover\$.tw.
- 26 cross over\$.tw.
- 27 cross-over\$.tw.
- 28 placebo\$.tw.
- 29 (doubl\$ adj blind\$).tw.
- 30 (singl\$ adj blind\$).tw.
- 31 assign\$.tw.

- 32   allocat\$.tw.
33   volunteer\$.tw.
34   Crossover Procedure/
35   double-blind procedure.tw.
36   Randomized Controlled Trial/
37   Single Blind Procedure/
38   or/23-37
39   (animal/ or nonhuman/) not human/
40   38 not 39
41   14 and 17 and 22 and 40

WHAT'S NEW

Date	Event	Description
26 June 2019	Review declared as stable	See Published notes

HISTORY

Protocol first published: Issue 1, 2012
Review first published: Issue 3, 2015

Date	Event	Description
27 January 2017	Review declared as stable	See Published notes .

CONTRIBUTIONS OF AUTHORS

Draft the protocol	AS,SR, PZ
Develop a search strategy	AS
Search for studies (usually 2 authors)	AS, SR, CMF
Obtain copies of studies	AS, SR, CMF
Select which studies to include (2 + 1 arbiter)	AS, SR, CMF, EPZ
Extract data from studies (2 authors)	AS, SR, CMF
Enter data into RevMan 5	AS, SR, CMF
Carry out the analysis	AS, SR
Interpret the analysis	AS, PZ

Draft the final write-up of the review	AS, PZ, EPZ
Update the review	AS, SR, EPZ
Content expert name	AS, EPZ
Methodologist name	AS

DECLARATIONS OF INTEREST

AS has no relevant conflicts of interests.

SR has no relevant conflicts of interests.

CMF has no relevant conflicts of interests.

PZ has no relevant conflicts of interests.

EPZ has no relevant conflicts of interests.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Postoperative pain scores could not be sufficiently analysed, because there was a large heterogeneity and mainly non validated pain scales were used. Accordingly, other outcomes were included in the summary of findings tables. The definition for moderate to severe pain has been changed from $NRS \geq 3$ to > 3 . Therefore, the authors decided to assess the outcome 'number of patients with the need for rescue analgesia' as the primary outcome. The systematic search also included the trial database ClinicalTrials.gov, but no other studies were identified. The authors calculated dichotomous data by using the Mantel-Haenszel method instead of the inverse-variance method as initially proposed. Within the risk of bias section the selective reporting domain has been clarified and we added criteria for the calculation of NNT/NNH (at least four studies). Finally, we reduced the number of planned subgroup analysis (no subgroup analysis focusing on the age of included children, duration of postoperative care (PACU/24h/48h))

NOTES

2017

A restricted search in January 2017 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

2019

A full updated search in March 2019 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be reassessed for updating in five years. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Readers should be aware that the Food and Drug Administration (FDA) issued an alert on 20 April 2017 restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*therapeutic use]; Fentanyl [therapeutic use]; Meperidine [therapeutic use]; Morphine [therapeutic use]; Nalbuphine [therapeutic use]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Tramadol [*therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Infant; Male