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Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy (Review)

Lewis SR, Nicholson A, Cardwell ME, Siviter G, Smith AF

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[Intervention Review]

Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy

Sharon R Lewis[1], Amanda Nicholson[2], Mary E Cardwell[3], Gretchen Siviter[4], Andrew F Smith[4]

[1]Patient Safety Research, Royal Lancaster Infirmary, Lancaster, UK. [2]Faculty of Health and Medicine, Furness Building, Lancaster University, Lancaster, UK. [3]Department of Anaesthetics, North Manchester General Hospital, Manchester, UK. [4]Department of Anaesthetics, Royal Lancaster Infirmary, Lancaster, UK

Contact address: Sharon R Lewis, Patient Safety Research, Royal Lancaster Infirmary, Pointer Court 1, Ashton Road, Lancaster, LA1 1RP, UK. Sharon.Lewis@mbht.nhs.uk, sharonrlewis@googlemail.com.

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ABSTRACT

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain relief following tonsillectomy in children. However, as they inhibit platelet aggregation and prolong bleeding time they could cause increased perioperative bleeding. The overall risk remains unclear. This review was originally published in 2005 and was updated in 2010 and in 2012.

Objectives

The primary objective of this review was to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. Our secondary outcome was to establish whether NSAIDs affect the incidence of other postoperative complications when compared to other forms of analgesia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 10); MEDLINE (inception until October 2012); EMBASE (inception until October 2012); *Current Problems* (produced by the UK Medicines Control Agency), *MedWatch* (produced by the US Food and Drug Administration) and the *Australian Adverse Drug Reactions Bulletins* (to May 2010). The original search was performed in August 2004. We also contacted manufacturers and researchers in the field.

Selection criteria

We included randomized controlled trials assessing NSAIDs in children, up to and including 16 years of age, undergoing elective tonsillectomy or adenotonsillectomy.

Data collection and analysis

Two authors independently assessed trial quality and extracted the data. We contacted study authors for additional information, where necessary.

Main results

We included 15 studies that involved 1101 children in this updated review. One study was added as a result of our 2012 search, another previously included study was removed due to lack of randomization. Fourteen included studies compared NSAIDs with other analgesics or placebo and reported on bleeding requiring surgical intervention. The use of NSAIDs was associated with a non-significant increase in the risk of bleeding requiring surgical intervention: Peto odds ratio (OR) 1.69 (95% confidence interval (CI) 0.71 to 4.01). Ten studies

involving 365 children reported perioperative bleeding requiring non-surgical intervention. NSAIDs did not significantly alter the number of perioperative bleeding events requiring non-surgical intervention: Peto OR 0.99 (95% CI 0.41 to 2.40) but the confidence intervals did not exclude an increased risk. Thirteen studies involving 1021 children reported postoperative vomiting. There was less vomiting when NSAIDs were used as part of the analgesic regime than when NSAIDs were not used: Mantel Haenszel (M-H) risk ratio (RR) 0.72 (95% CI 0.61 to 0.85).

Authors' conclusions

There is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatric tonsillectomy. They do however confer the benefit of a reduction in vomiting.

PLAIN LANGUAGE SUMMARY

Do nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of bleeding in children having their tonsils out?

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for pain relief following tonsillectomy in children. Bleeding is a recognized complication of this procedure and NSAIDs can interfere with blood clotting, so there has been concern that these drugs will increase the risk of bleeding. If bleeding is severe this may result in the child being re-admitted to hospital, having a blood transfusion or returning to theatre. It was therefore important to establish whether these drugs are safe to use in children having their tonsils out. The review focused on clinically significant bleeding that results in the child requiring additional treatment rather than the measured blood loss. We also wanted to establish whether NSAIDs affect the incidence of other postoperative complications such as nausea and vomiting when compared to other forms of analgesia. Additionally we aimed to investigate whether different types of NSAIDs were more likely to lead to bleeding.

The main limitation of our updated review was that bleeding following tonsillectomy is an uncommon event (occurring in 3% to 5% of children). We found all the data from randomized controlled trials that are currently available (15 trials studying approximately 1000 children). Our results were consistent with both an increased and decreased risk of bleeding. There were insufficient data to compare the risk of bleeding with each individual type of NSAID. However, we were able to compare ketorolac, which has been perceived as having a greater risk of bleeding, with the other NSAIDs and found no increased risk of bleeding. There was less nausea and vomiting when NSAIDs were used as part of the pain relief regime than when NSAIDs were not used.

There is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatric tonsillectomy. They do, however, confer the benefit of a reduction in vomiting.

Summary of findings for the main comparison. Nonsteroidal anti-inflammatory drugs for paediatric tonsillectomy

Nonsteroidal anti-inflammatory drugs for paediatric tonsillectomy

Patient or population: patients with paediatric tonsillectomy
Settings:
Intervention: nonsteroidal anti-inflammatory drugs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Nonsteroidal anti-inflammatory drugs				
Perioperative bleeding requiring surgical intervention	**Moderate**[1]		**OR 1.69** (0.71 to 4.01)	1044 (14 studies)	⊕⊕⊕⊖ **moderate** [2]	
	20 per 1000	**33 per 1000** (14 to 76)				
Perioperative bleeding requiring non-surgical intervention	**Moderate**[1]		**OR 0.99** (0.41 to 2.4)	745 (10 studies)	⊕⊕⊕⊖ **moderate** [2]	
	50 per 1000	**50 per 1000** (21 to 112)				
Vomiting	**Moderate**[3]		**RR 0.72** (0.61 to 0.85)	1021 (13 studies)	⊕⊕⊕⊕ **high**	
	357 per 1000	**257 per 1000** (218 to 303)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is 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.

[1] Based on Marret 2003.

2 Confidence interval crosses no effect and is inconsistent with an increased risk of bleeding.
3 Median control group risk from included studies.

BACKGROUND

Description of the condition

Tonsillectomy is one of the most common surgical procedures for children, both in the UK and globally. The most recent figures are set at over 45,000 tonsillectomies per year in the UK (www.hesonline.nhs.uk). Indications for tonsillectomy are recurrent throat infections, recurrent tonsillitis, peritonsillar abscess or obstructive sleep apnoea.

Description of the intervention

Effective pain relief is important for the management of the paediatric tonsillectomy patient and opioid analgesics are often selected for this purpose. However, opioids may increase the occurrence of nausea and vomiting, respiratory depression and excessive sedation, and urinary retention.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are also used for pain relief following tonsillectomy in children. They are proven analgesics (Langford 2006) and reviews (Kokki 2003; Romsing 1997) have shown that they are effective in the management of mild to moderate postoperative pain in children. NSAIDs may also reduce postoperative nausea and vomiting (Öztekin 2002) as well as the time to adequate oral intake and time to discharge (Tawalbeh 2001).

How the intervention might work

NSAIDs work by interfering with cyclo-oxygenase, which reduces the production of prostaglandins leading to a reduction in swelling and pain. Used as an alternative to opioids for pain relief they can avoid side effects such as nausea and vomiting, which could make NSAIDs a more suitable choice of analgesic for the paediatric tonsillectomy patient.

However, NSAIDs also inhibit platelet aggregation and may prolong bleeding time. This potential increased risk of bleeding has been a concern in the postoperative use of NSAIDs.

Why it is important to do this review

Bleeding after tonsillectomy is a well recognized and potentially serious complication. Estimates of the incidence of bleeding requiring treatment vary from 2% to 10%, and bleeding requiring re-operation from 1% to 5.5% (Marret 2003). This has raised concerns that NSAID use may lead to increased perioperative bleeding following tonsillectomy and concerns about increased rates of primary haemorrhage (bleeding within 24 hours of surgery) that may require operative intervention.

Two meta-analyses (Marret 2003; Moiniche 2003) reviewed the use of NSAIDs and the risk of bleeding after tonsillectomy in both adult and paediatric patients. Marret et al concluded that NSAIDs increased the risk of re-operation for haemostasis after tonsillectomy but Moiniche et al concluded that NSAIDs should be used cautiously until further data were available.

Our original review (Cardwell 2005) concluded that there is currently no evidence that using NSAIDs caused any statistically significant increase in bleeding requiring further clinical intervention. However, as bleeding requiring further surgical intervention following tonsillectomy is an uncommon event (Collison 2000), a large number of participants are required to provide an adequate number of events to give a significant result. The numbers required are increased further because this is a non-inferiority research question, with the aim being to show that the NSAIDs are not worse than other analgesic methods. It remains unknown whether the various NSAIDs may have different tendencies to cause bleeding following tonsillectomy in children.

OBJECTIVES

The primary objective of this review was to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. Our secondary outcome was to establish whether NSAIDs affect the incidence of other postoperative complications when compared to other forms of analgesia.

As discussed in the background, there is good evidence (Kokki 2003; Romsing 1997) to show that NSAIDs are effective analgesics in children. It was not the remit of our review to question this but rather to assess the risk of bleeding when using NSAIDs for pain relief following paediatric tonsillectomy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs). We only included those studies which reported results for the bleeding outcomes as below (Types of outcome measures).

Types of participants

We included children, aged up to and including 16 years of age, who underwent elective tonsillectomy or adenotonsillectomy. We included all indications for tonsillectomy and all surgical techniques. We excluded studies that were for adenoidectomy only.

We excluded patients with a bleeding tendency and those with contraindications to the use of NSAIDs (asthma, renal disease).

Types of interventions

We included studies in which patients had been given NSAIDs compared to either a placebo or other analgesics. NSAIDS could have been given pre-, intra- or postoperatively and by any route. Doses prescribed were on a mg/kg basis, as recommended by the British National Formulary (BNF 2010). We excluded any trials that included aspirin as aspirin is no longer recommended for use in children. We did not include the cyclo-oxygenase-2 (COX-2) inhibitors because these are known to have no effect on platelets (Meade 1993). Also, none of the COX-2 inhibitors are approved for use in children. We excluded trials for lozenges and local (intratonsillar) injections.

Types of outcome measures

Our original review outcomes were the following.

1. Bleeding requiring further surgical intervention.
2. Need for blood transfusion.
3. Nausea or vomiting, or both.
4. Prolonged hospital stay.
5. Postoperative pain scores in the first 24 hours.
6. Other side effects of NSAIDs.

We had to adjust our outcome measures from those in the protocol as some were not specifically mentioned in the included trials. We had wanted to look at the need for blood transfusion but as this was not specifically reported we altered our second outcome measure to 'bleeding requiring non-surgical intervention'. This included intravenous fluid therapy, prolonged observation and non-surgical haemostasis.

Our third outcome measure was nausea or vomiting, or both. In the majority of papers postoperative nausea and vomiting were measured as the number of patients having at least one emetic episode, although vomiting is unlikely to occur without nausea. Some papers (Kokki 2002; Öztekin 2002; Rawlinson 2011; St Charles 1997) attempted to separate nausea and vomiting, with nausea being measured by nurse questioning or observation, or discussion with the primary care giver. In the interests of clarity we changed our third outcome measure to 'vomiting'.

The outcome measure of increased hospital stay was not specifically reported, although it is implied by the need for further intervention. Our pain data were not fully comprehensive as we only included those papers that had bleeding as an outcome. Also, pain was measured in a variety of different ways making direct comparisons impossible. There is already good evidence (Kokki 2003; Romsing 1997) to show that NSAIDs provide good postoperative analgesia. After discussion with the Cochrane Anaesthesia Review Group we decided to exclude pain from our results and focus this meta-analysis on the risk of bleeding associated with the use of NSAIDs in paediatric tonsillectomy. Other side effects of NSAIDs were not mentioned in any of the included trials.

Therefore, our revised outcome measures were the following.

Primary outcomes

1. Perioperative bleeding requiring surgical intervention

Secondary outcomes

2. Perioperative bleeding requiring non-surgical intervention

3. Vomiting

Search methods for identification of studies

Electronic searches

We searched MEDLINE (from inception to October 2012) and EMBASE (from inception until October 2012) on all fields using the search strategies found in Appendix 1 and Appendix 2.

In the 2012 update, we searched www.clinicaltrials.gov and www.controlled-trials.com for relevant ongoing studies using the search term 'tonsillectomy'. We also did forward citation searches using Web of Science®; for this search we used the review's included studies published from 2000 onwards (Antila 2006; Keidan 2004; Kokki 2002; Pickering 2002; Rawlinson 2011; Öztekin 2002).

We did not impose language restrictions on any of our searches.

Searching other resources

We performed an advanced search of the Cochrane Central Register of Controlled Trials (CENTRAL) using the search strategy found in Appendix 3 and looked at all trials under the term 'tonsil*' (*The Cochrane Library* 2012, Issue 10). The Cochrane Anaesthesia Review Group Trials Search Co-ordinator performed handsearching as required. Our original search was performed in August 2004 and the search was repeated in 2012.

We also searched *Current Problems* (produced by the UK Medicines Control Agency), *MedWatch* (produced by the US Food and Drug Administration) and the *Australian Adverse Drug Reactions Bulletins* (to May 2010). This search was not done in the 2012 update.

We contacted all the pharmaceutical companies that manufacture NSAIDs and sought conference proceedings and sources of ongoing and unpublished studies. We also checked references of all identified RCTs to identify potentially relevant citations. This was not done in the 2012 update.

Data collection and analysis

Selection of studies

Two authors independently screened titles and abstracts identified from the electronic searches and handsearches (Dr M Cardwell and Dr G Siviter in the original review and 2010 update; Professor A Smith and Mrs S Lewis (AS and SL) in the 2012 update), following the eligibility criteria. The full papers were sourced for all those studies identified at this stage. Two authors, Dr A Nicholson (AN) and SL, then independently assessed all the full papers for eligibility and recorded their decisions on study eligibility forms. Descriptions of these decisions are included in the Characteristics of included studies and Characteristics of excluded studies. We resolved disagreements by discussion between the authors.

Data extraction and management

Two authors (AN and SL) independently extracted the data from all eligible studies including those from the original review. Any disagreement was resolved by consensus. If agreement was not obtained we sought independent expert advice (Professor A Smith). We contacted the study authors for clarification, when necessary.

A copy of the data extraction form used in the 2012 update is included in Appendix 4.

Assessment of risk of bias in included studies

Due to changes to the 'Risk of bias' tool in RevMan 5.2 since the previous update, we reconsidered the risk of bias for all included studies. These changes included separation of blinding of participants and personnel from blinding of outcome assessors. We considered each individual outcome for performance and detection bias (see the data extraction form in Appendix 4). Each included study was appraised according to the criteria described below.

For each of the following criteria, judgments were made as to 'Low' or 'High' risk of bias and 'Unclear', meaning that insufficient information was available to make a judgment.

1. Random sequence generation

Low: adequate sequence generation was reported using computer-generated random numbers, codes or sealed envelopes.

High: a system was used which was generated by a non-random approach, e.g. odd or even date of birth.

Unclear: the trial report did not describe one of the adequate methods but mentioned randomization.

2. Allocation concealment

Low: a randomization method was described that would not allow an investigator or participant to know or influence allocation to an intervention group before an eligible participant entered the study, such as masked drug prepared by a pharmacist not otherwise involved in the study.

High: an inadequate method of allocation was used, such as alternate medical record numbers or unsealed envelopes; or there was information in the study report indicating that investigators or participants were aware of group allocation.

Unclear: the trial report mentioned randomization but there was no information on the method used, or a method was reported that was not clearly adequate.

3. Blinding of participants and personnel

This item was graded as 'Low' if participants and personnel were blinded, 'High' for unblinded participants and personnel and 'Unclear' if the relevant information was not stated in the trial report.

4. Blinding of outcome assessors

This item was graded as 'Low' for blinded outcome assessment, 'High' for unblinded outcome assessment and 'Unclear' if the relevant information was not stated in the trial report.

5. Incomplete outcome data

Low: numbers of withdrawals or exclusions per group, with reasons, were provided; or it was clear from the report that there were no withdrawals or exclusions; or sufficiently low numbers of withdrawals and exclusions to not have a clinically relevant impact on the results.

High: some withdrawal was evident but the numbers per group and reasons were not provided.

Unclear: unclear from trial report whether there were any withdrawals.

We defined an intention-to-treat (ITT) analysis as having been conducted when all trial participants were analysed in the group to which they were randomized, regardless of which (or how much) of the treatment they actually received and regardless of other protocol irregularities, such as ineligibility. Where necessary, and possible, we contacted authors to establish the outcomes of withdrawn or excluded participants in order to include them in the ITT analysis. Participants were only included for the ITT analysis if outcome data were available.

6. Selective reporting bias

This item was graded 'Low' if all outcomes were reported, 'High' if outcomes were measured but not reported and 'Unclear' if there was insufficient information to permit judgement of high or low reporting bias.

7. Free of other sources of bias

In this section we considered, in particular, whether:

- the trial had been stopped early;
- the allocation groups were similar at baseline, and whether the type of surgery (tonsillectomy or adenotonsillectomy) performed in the two groups was similar;
- rescue analgesia was available, whether it included opioids, and if the use of rescue analgesia differed between the two groups.

Low: the trial appeared to be free of other components that could put it at risk of bias.

High: there were other factors in the trial that could put it at risk of bias.

Unclear: it was unclear whether the trial was or was not free of other components that could put it at risk of bias.

Measures of treatment effect

All our outcomes were dichotomous and we entered total and numbers of events, respectively, into Revman 5.2 (RevMan 5.2). Where studies presented combined results for nausea and vomiting it was assumed that these events could all be categorized under the 'vomiting' outcome. Vomiting was measured at various time points in each study. We took the data as the number of patients having at least one vomiting event within the first 24 hours. Where hours were not specified, data were taken from vomiting events in the ward or during the hospital stay, which could be assumed to be no more than 24 hours from the information within the texts of all but one paper (Thiagarajan 1993). For bleeding outcomes we used Peto odds ratios with 95% confidence intervals (CI) as a measure of effect as the outcome was rare and there were zero counts in some cells. For the more frequent vomiting outcome we used Mantel-Haenzsel (M-H) risk ratios.

If data had been presented in other forms such as hazard ratios and we had been unable to obtain the required tabular data from the study authors, we would have recorded effect estimates and used these in the analyses.

Unit of analysis issues

We included studies that reported more than one comparison. Antila (Antila 2006) compared the intervention drug against both placebo and another analgesic (tramadol). In other studies (Kokki 2002; Romsing 1998) the intervention drug was administered both pre- and postoperatively. We chose to include all of these results in the update, which allowed for subgroup analysis by timing of administration. Where these results needed to be presented in one comparison we divided the control group or combined the groups into a single pair-wise comparison (Section 16.5.4, Higgins 2011).

Dealing with missing data

We contacted the authors for clarification where data were missing or unclear. Some participants that were enrolled were excluded for a variety of reasons. In these cases we attempted to include them in our figures in order to follow the ITT principle and only if outcome data could be obtained from the authors.

Assessment of heterogeneity

We assessed heterogeneity between studies using the Chi^2 test and I^2 statistic. Important heterogeneity (Chi^2 $P < 0.1$ or $I^2 > 50\%$) was investigated using subgroup analyses. This heterogeneity may be due to:

- type of NSAID used;
- timing of administration;
- placebo or other treatment.

Assessment of reporting biases

If 10 or more studies were included in any one meta-analysis, funnel plots were examined to visually assess the presence of publication bias and the Egger's test was used to test for asymmetry.

Data synthesis

We attempted meta-analysis of the outcomes for which we had comparable effect measures and where measures of heterogeneity indicated that pooling of results was appropriate. The extent of the heterogeneity was considered before any meta-analysis was attempted. The presence of any I^2 values in excess of 80% for any group of studies argued against an overall estimate being presented. For studies similar enough to support meta-analysis, we performed the analyses in RevMan 5.2 (RevMan 5.2) using fixed-effect models.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis on the:

1. type of NSAID;
2. timing of administration;
3. surgical technique.

In the papers we identified with respect to the different NSAIDs, we were unable to perform subgroup analysis on all the individual NSAIDs as there were insufficient trials to do this. We were particularly interested in ketorolac as it is perceived to have a greater risk of bleeding and is not recommended for intraoperative use. Therefore, a subgroup analysis was performed on this drug alone, as there were sufficient papers to do so. All doses of drugs that fell within the recommended limits were included.

In the 2012 update we performed a subgroup analysis based on whether the intervention was administered pre- or postoperatively. We looked at the data both between studies and within studies, where possible. Our definition of preoperative was if the intervention was given after induction of anaesthesia and before surgery. Our definition of postoperative was if the intervention was given after surgery and before extubation.

We were unable to look at the surgical technique or underlying indication for tonsillectomy and the effects on bleeding outcomes as there were insufficient papers assessing these variables.

In the 2012 update we also chose to consider subgroup analysis on whether the intervention was compared against another analgesic treatment or against placebo.

Our subgroup analysis was therefore presented for each outcome as:

1. type of NSAID;
2. timing of administration;
3. type of control.

Clinical heterogeneity was assessed through careful evaluation of the populations, interventions and outcomes within each study. The Chi^2 test and I^2 statistic were used to estimate the extent of statistical heterogeneity.

Sensitivity analysis

A sensitivity analysis was performed by removing studies that had a high or unclear risk of bias in each domain. We compared these results with studies that had a low risk of bias (including baseline imbalances) for each outcome.

We also considered the use of different effect measures, for example M-H risk ratio versus Peto odds ratio, in sensitivity analysis.

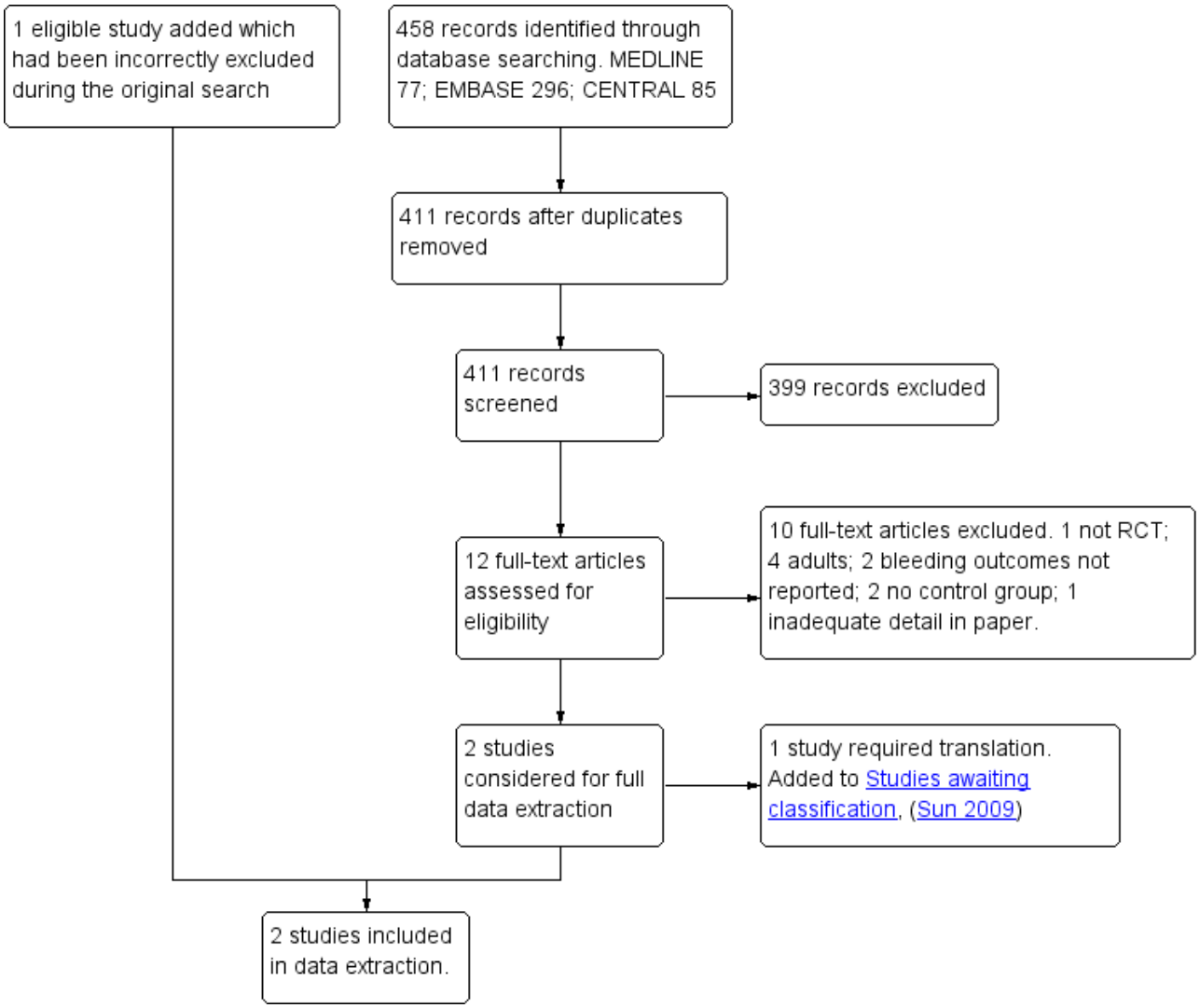
RESULTS

Description of studies

Results of the search

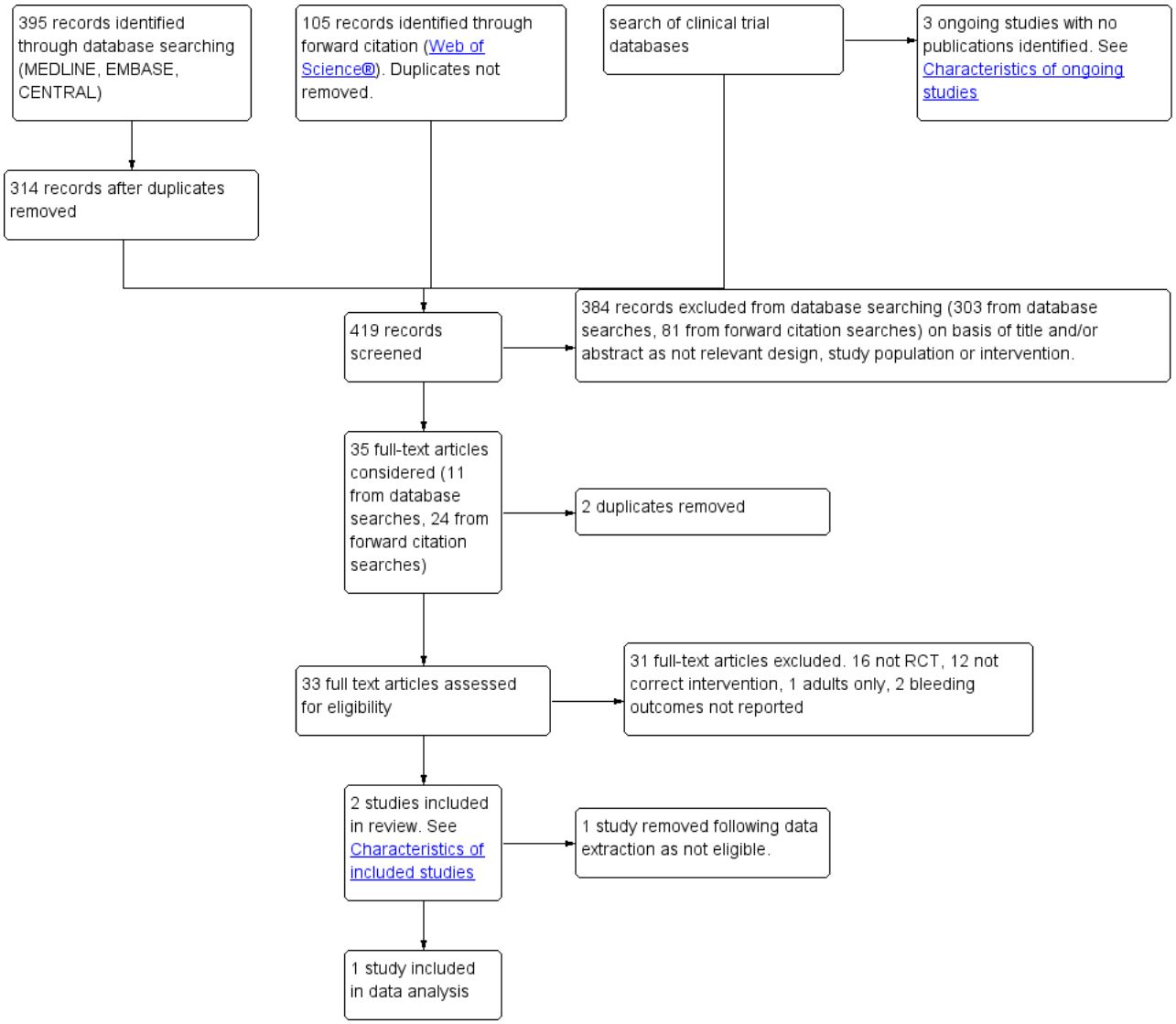
The original search resulted in 13 studies being eligible for inclusion (Cardwell 2005). A further two studies were added in the 2010 update (Cardwell 2010). One was from the repeated search (2004 to 2010) (Antila 2006) and one had been incorrectly excluded from the original review (Pickering 2002). Therefore, 15 studies were included in the 2010 published update; see the study flow diagram (Figure 1).

Figure 1. Study flow diagram for the results of the 2010 update database search.



During an updated search (2010 to 2012) we identified 395 references through searches of electronic databases, 105 from the forward citation search and 185 from searching ongoing trial databases. We identified three possible eligible studies from the ongoing trial databases, which have been included in Characteristics of ongoing studies. Of these, one is completed but as yet it is not published. We removed duplicates from our electronic database and forward citation searches, which resulted in 419 unique references. We excluded 384 studies on the basis of the titles and abstracts and then considered eligibility for 35 studies, from which two studies were added (Platzer 2011; Rawlinson 2011). Platzer 2011 (Platzer 2011) was later excluded during the data extraction process as no bleeding outcomes were reported. See the study flow diagram for the 2012 update (Figure 2).

Figure 2. Study flow diagram of May 2010 to October 2012 update search.



During data extraction one previously eligible study was excluded (Tawalbeh 2001) as there was no evidence of randomization. One study which had been awaiting classification (Sun 2009) was also excluded as it did not measure relevant outcomes. We therefore added one study but removed one study, so we included 15 studies in this update.

Included studies

There were 15 studies with 1101 patients, aged 1 to 16 years, that met our inclusion criteria. All children were scheduled for tonsillectomy, with some studies also including patients scheduled for additional surgery, for example adenoidectomy (Antila 2006; Harley 1998; Keidan 2004; Pickering 2002; Rawlinson 2011; Romsing 1998; Rusy 1995; Splinter 1996) or other procedures, or both (Öztekin 2002; St Charles 1997; Sutherland 1998). All patients were ASA I or I-II, with the exception of St Charles 1997 which did not provide this information.

Ketorolac was the intervention drug in six studies (Gunter 1995; Keidan 2004; Romsing 1998; Rusy 1995; Splinter 1996; Sutters 1995), administered at a dose of 1 mg/kg. There were three studies that had ibuprofen as the intervention drug (Harley 1998; Pickering 2002; St Charles 1997) at a dose of 5 mg/kg. There were three studies that had diclofenac as the intervention drug (Öztekin 2002; Rawlinson 2011; Thiagarajan 1993) at a dose of 1 mg/kg. There were two studies that had ketoprofen as the intervention drug, Antila 2006 at a dose of 2 mg/kg and Kokki 2002 at a dose of 0.5 mg/kg followed by a 3 mg/kg infusion. Tenoxicam at a dose of 0.75 mg/kg was the intervention drug for Sutherland 1998.

There were 10 studies in which the intervention drug was given preoperatively (Antila 2006; Keidan 2004; Kokki 2002; Öztekin 2002; Pickering 2002; Romsing 1998; Rusy 1995; Splinter 1996; Sutherland 1998; Thiagarajan 1993). Of these, all but one study (Pickering 2002) gave the intervention drug after induction of anaesthesia and before surgery. In Pickering 2002 the intervention drug was given one hour before surgery. There were seven studies in which the intervention drug was given postoperatively (Antila 2006; Harley 1998; Kokki 2002; Romsing 1998; St Charles 1997; Sutters 1995). For these, the intervention drug was given immediately following

surgery and before the end of anaesthesia (Antila 2006; Gunter 1995; Romsing 1998; Sutters 1995) or whilst in the postanaesthesia care unit (PACU), the ward or at home. For both Kokki 2002 and Romsing 1998 there were two comparison arms of pre- and postoperative administration of the intervention drug. In Antila 2006 the intervention drug was given both pre- and postoperatively to all patients in the intervention group. In Rawlinson 2011 the intervention drug was described as being given perioperatively.

There were 14 studies that reported perioperative bleeding requiring surgical intervention. Of these, some studies did not have perioperative bleeding requiring surgical intervention as a primary outcome (Antila 2006; Rawlinson 2011; Sutherland 1998) however they did report on this outcome and were therefore included. Keidan 2004 did not report the primary outcome but was included in the review as it reported data for the outcome perioperative bleeding requiring non-surgical intervention.

The 15 eligible studies are summarized in the Characteristics of included studies table.

Excluded studies

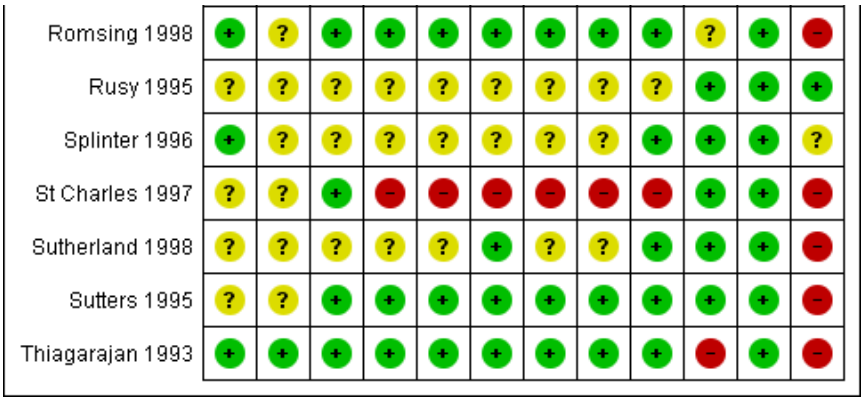
We excluded studies which had an incorrect design, population, intervention or did not include bleeding as an outcome (see Characteristics of excluded studies for more information). Many studies were retrospective; some looked at adults only, or a mixture of adults and children where the data from the children could not be extracted despite contacting the authors (Courtney 2001; Dommerby 1984; Petrusen 1991; Schmidt 2001); in other studies the intervention was either not an NSAID or was a COX-2 inhibitor. The references for the excluded studies contain those excluded in the original review and the earlier update.

Risk of bias in included studies

A summary of the 'Risk of bias' results can be found in Figure 3.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 3. (Continued)



Allocation

All studies were described as randomized however for several papers it was not clear how randomization was performed (Keidan 2004; Öztekin 2002; Rusy 1995; St Charles 1997; Sutherland 1998; Sutters 1995). Only one study (Thiagarajan 1993) had a low risk of bias for allocation concealment. Methods for allocation concealment were not reported in the other studies.

Blinding

Only one study (St Charles 1997) was assessed as having a high risk of blinding for performance and detection bias. All other studies were either described as single- or double-blinded in the abstract or within the text of the journal report. There were, however, few studies that provided a full or adequate description of blinding of either participants and personnel or outcome assessment (Gunter 1995; Kokki 2002; Romsing 1998; Sutters 1995; Thiagarajan 1993).

Incomplete outcome data

There was potential for attrition bias in some of the papers (Gunter 1995; Keidan 2004; Kokki 2002; Pickering 2002; Rawlinson 2011; Romsing 1998; Sutters 1995; Thiagarajan 1993) as some participants that were enrolled were excluded for a variety of reasons. Details of the reasons for these exclusions are given in the 'Risk of bias' tables in the Characteristics of included studies. We successfully contacted some authors (Kokki 2002; Sutters 1995) to obtain our required additional information regarding patient outcomes and we therefore included the data in an ITT analysis. We were unable to obtain further information on the remaining exclusions, despite attempts to contact the authors, and we therefore did not include these missing patients in the analysis.

Selective reporting

There was no risk of bias identified in any of the studies. All studies reported the expected outcome data.

Other potential sources of bias

Two studies (Gunter 1995; Splinter 1996) were terminated early due to risks of excessive bleeding, indicating a high risk for early stopping bias. Pickering (Pickering 2002) had an early stop to recruitment in the placebo group due to an increased demand for analgesics. One paper stopped the study prematurely because of excessive bleeding (Romsing 1998), which was found to be caused by one particular surgeon. This surgeon was then excluded from the trial and the trial continued. In the previous update it was decided that the data were taken only after the trial resumed. However, in this update we decided to include data from this surgeon to provide the most conservative results.

Another risk of bias considered was that of surgery type. Along with baseline imbalances we considered whether the authors reported a balance between tonsillectomies and other additional, related surgeries. Antila 2006, Harley 1998, Rusy 1995, Splinter 1996 and Sutherland 1998 had not provided sufficient detail to judge this domain as at a low risk of bias.

The use of additional opioid analgesics in the majority of studies, in both the intervention and control groups, had the potential to bias the results of the vomiting outcome. Only Harley (Harley 1998) did not describe any rescue analgesics and it was assumed that none were given. Gunter (Gunter 1995) reported that more patients in the intervention group received additional morphine as a rescue analgesic. However, in this paper the investigators stated that there was no difference in emesis rates for those patients who received more morphine. No other studies reported on whether the use of rescue analgesics had effected the vomiting data. The effect of this risk of bias was considered further in a Sensitivity analysis.

Summary of risk of bias

There were no studies that were judged as low risk of bias in all domains. This was often due to an unclear risk assessment, reflecting omission of detail in the paper, rather than an assessment of high risk of bias.

Effects of interventions

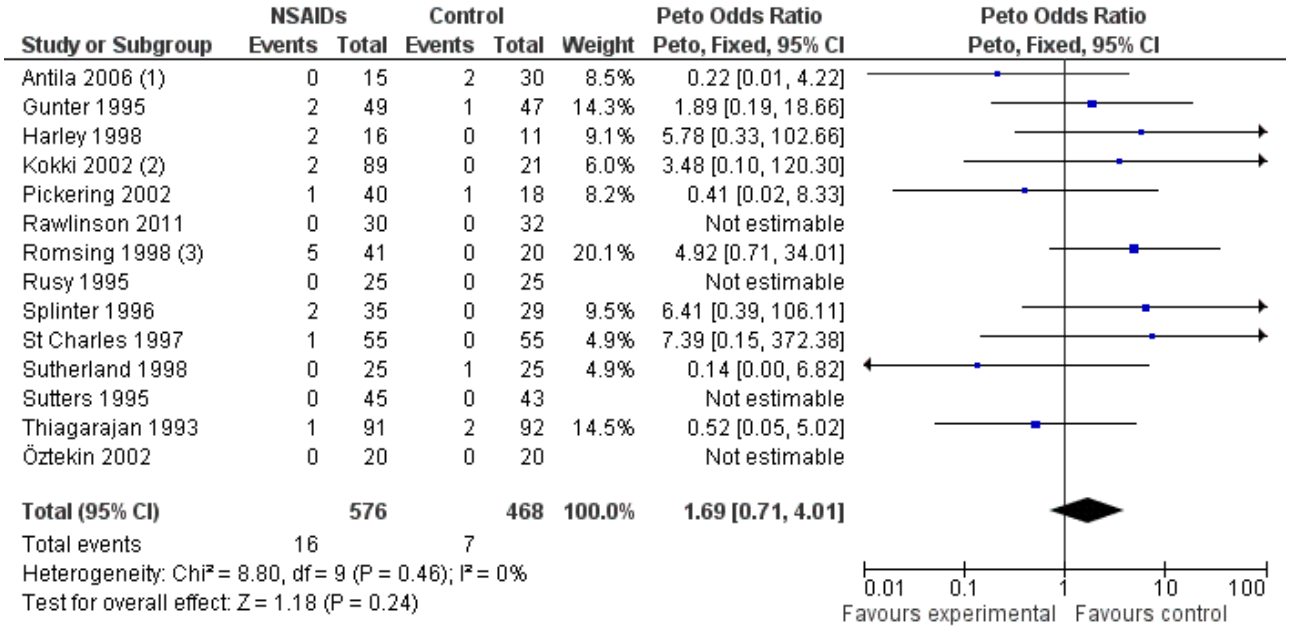
See: **Summary of findings for the main comparison** Nonsteroidal anti-inflammatory drugs for paediatric tonsillectomy

Outcome 1: perioperative bleeding requiring surgical intervention

Fourteen studies involving 1044 children compared NSAIDs with either another analgesic or placebo and assessed perioperative bleeding requiring surgical intervention. The incidence of bleeding was higher in the intervention group (16/576, 2.8%) than in the control group (7/468, 1.3%). Although the confidence interval of the effect estimate (Peto OR 1.69, 95% CI 0.71 to 4.01, P = 0.24) crossed

no effect it did not exclude an increased risk of bleeding requiring surgical intervention of up to four times in the group treated with NSAIDs (see Figure 4).

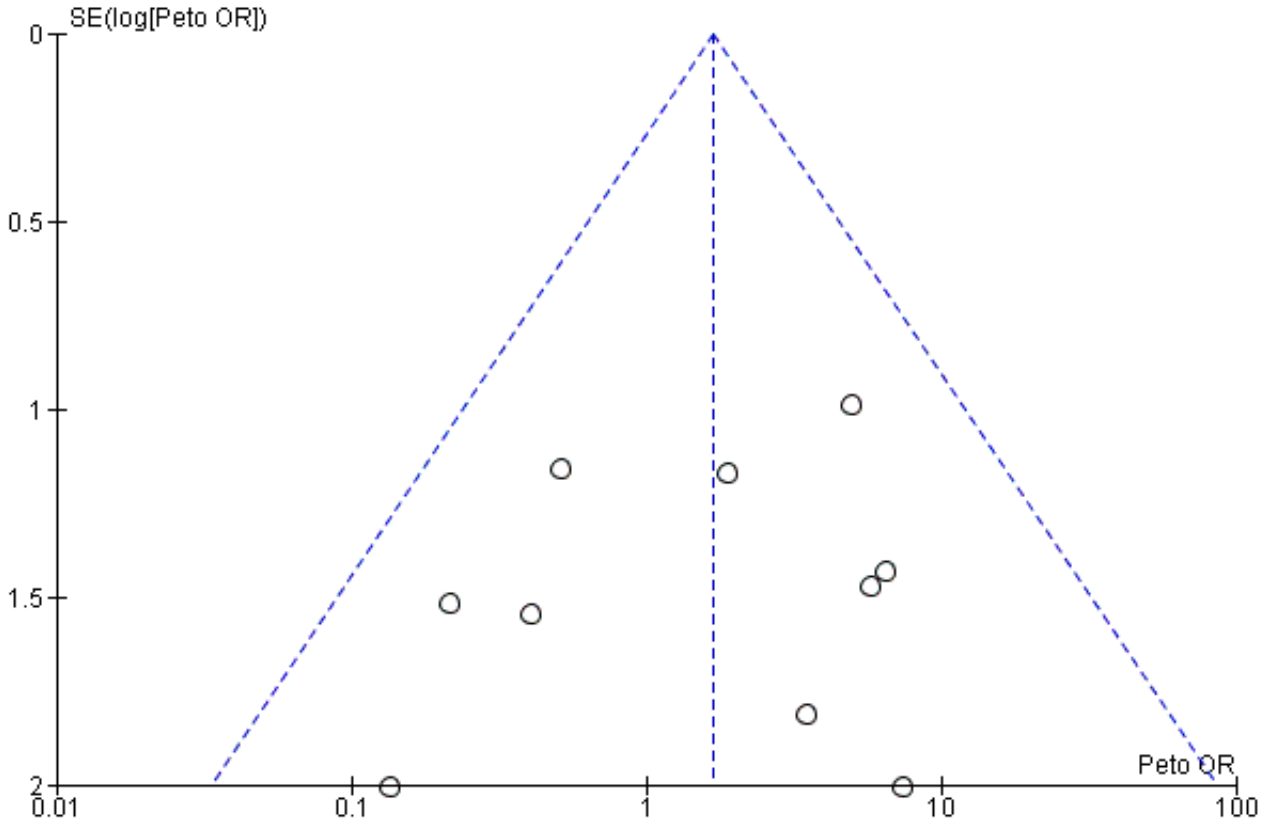
Figure 4. Forest plot of comparison: 1 Nonsteroidal versus control (analgesics or placebo), outcome: 1.1 Perioperative bleeding requiring surgical intervention.



(1) Antilla (2006): control group data used from combined tramadol and placebo events
(2) Kokki (2002): combined study data for pre- and post-op admin of intervention
(3) Romsing (1998): combined study data for pre- and post-op admin of intervention

A funnel plot of 10 studies contributing data showed no evidence of asymmetry. This suggests that publication bias did not affect the results (see Figure 5). There was no evidence of heterogeneity between these studies ($I^2 = 0\%$, $P = 0.46$).

Figure 5. Funnel plot of comparison: 1 Nonsteroidal versus control (analgesics or placebo), outcome: 1.1 Perioperative bleeding requiring surgical intervention.



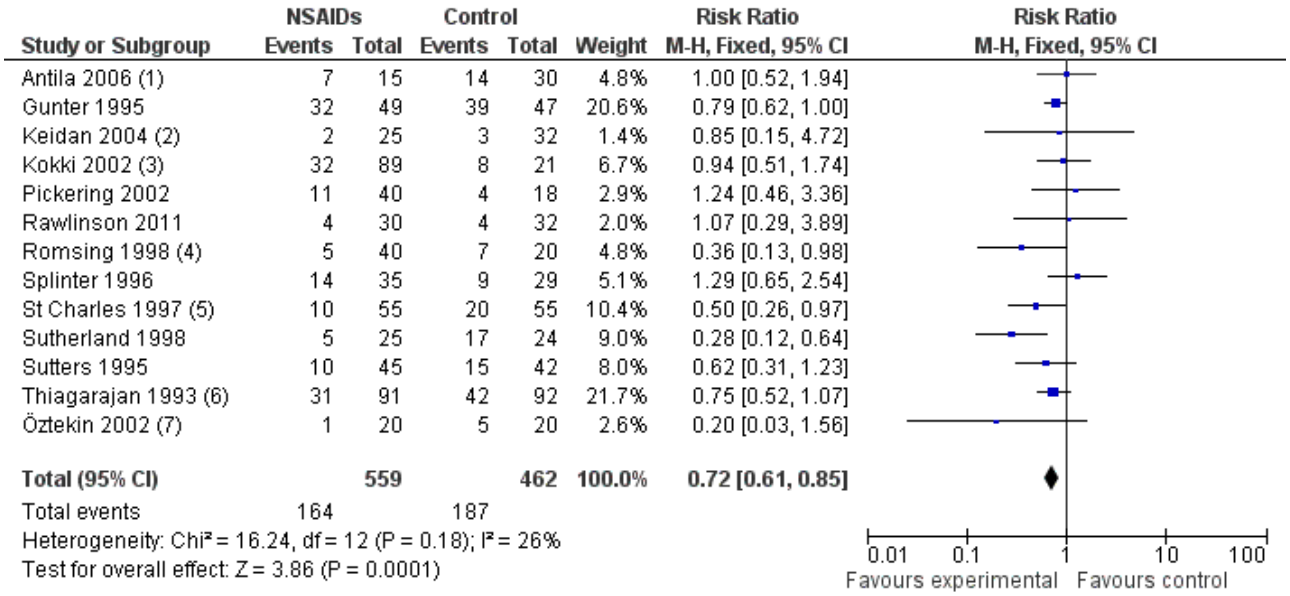
Outcome 2: perioperative bleeding requiring non-surgical intervention

Ten studies involving 745 children compared NSAIDs with either another analgesic or placebo and assessed perioperative bleeding requiring non-surgical intervention (see Analysis 1.2). NSAIDs did not significantly alter bleeding requiring non-surgical intervention (Peto OR 0.99, 95% CI 0.41 to 2.40) but again this finding did not exclude an increased risk of bleeding. However, there was evidence of moderate heterogeneity between studies for this outcome (I^2 = 61%, P = 0.05).

Outcome 3: vomiting

Thirteen studies involving 1021 children compared NSAIDs with either another analgesic or placebo and assessed vomiting. NSAIDs were shown to significantly reduce the risk of vomiting (M-H risk ratio (RR) 0.72, 95% CI 0.61 to 0.85, P = 0.0001) (see Figure 6). Heterogeneity was low between these studies (I^2 = 26%, P = 0.18).

Figure 6. Forest plot of comparison: 1 Nonsteroidal versus control (analgesics or placebo), outcome: 1.3 Vomiting.



(1) Antila (2006): control group data used from combined tramadol and placebo events
(2) Keidan (2004): data taken as number of events on first day
(3) Kokki (2002): combined study data for pre- and post-op admin of intervention. Data taken as total number of events
(4) Romsing (1998): combined study data for pre- and post-op admin of intervention
(5) St Charles (1997): data taken as number of events during hospital stay
(6) Thiagarajan (1993): data taken as number of events on ward
(7) Öztekin (2002): data taken as number of events on ward

Subgroup analyses

Type of NSAID

In our protocol we stated that if there were enough data we would create subgroups for individual drugs. After our search we found that we had inadequate numbers of papers to create subgroups for all the NSAIDs. However, we were able to do this for ketorolac. Five studies involving 359 children compared ketorolac against another analgesic or placebo and assessed Outcome 1, perioperative bleeding requiring surgical intervention (see Analysis 2.1). The children in the intervention group had an increased risk of bleeding with a Peto OR of 3.82 (95% CI 1.03 to 14.10). The nine studies using other NSAIDs had a lower risk of bleeding with a Peto OR of 0.89 (95% CI 0.28 to 2.83). The statistical test for differences between subgroups was not significant (P = 0.1)

For Outcome 2, perioperative bleeding requiring non-surgical intervention, the difference in the effect estimates between ketorolac and other NSAIDs was smaller (see Analysis 2.2) and again there was no statistical evidence of a difference between subgroups (P = 0.36). Analysis 2.3shows that the effect on vomiting was almost identical for ketorolac and the other NSAIDs.

Timing of administration

The subgroup analysis by timing of administration for Outcome 1, risk of bleeding requiring surgical intervention, showed a non-significant increased risk when NSAIDs were given postoperatively (Peto OR 3.18, 95% CI 0.65 to 15.58) (see Analysis 3.1) but differences between the timing subgroups were not significant for this outcome (P = 0.27); similarly for Outcomes 2 and 3 (P = 0.62 and P = 0.60, respectively) (Analysis 3.2; Analysis 3.3).

We excluded four studies from these subgroup analyses. One study (Pickering 2002) gave the drug preoperatively at one hour before surgery and three studies (Harley 1998; Kokki 2002; St Charles 1997) administered the intervention drug in the PACU or later. The time of administration was unclear in Rawlinson (Rawlinson 2011). We included this in the preoperative group but removing it made no difference to the results.

Type of control

The subgroup analysis by type of control, that is placebo or other analgesic treatment, for Outcome 1, risk of bleeding requiring surgical intervention, showed no difference between groups (P = 0.83, I^2 = 0%) (see Analysis 4.1). Similarly, there was no difference between placebo and other treatments for Outcome 3 (P = 0.88, I^2 = 0%) (see Analysis 4.3). For Outcome 2 there was evidence of heterogeneity between groups (P = 0.02, I^2 = 81.2%), with a higher odds ratio for bleeding in the other treatment control group compared with placebo, but even in this group the results were consistent with the possibility of both an increased and decreased risk of bleeding (OR 3.16, 95% CI 0.88 to 11.33).

Sensitivity analyses

Risk of bias

Sensitivity analysis was performed based on selection bias, by removing those six studies with an unclear method of

randomization. The results remained the same for the bleeding outcomes: Outcome 1 Peto OR 1.78 (95% CI 0.72 to 4.44); Outcome 2 Peto OR 0.99 (95% CI 0.41 to 2.40). The smaller sample size affected the results for the vomiting outcome in this sensitivity analysis: M-H RR 0.84 (95% CI 0.70 to 1.01).

We carried out similar sensitivity analyses for performance and detection bias and baseline imbalances by removing studies with an unclear or high risk of bias. The results were unchanged: six studies for performance bias from Analysis 1.1, Peto OR 1.51 (95% CI 0.51 to 4.47); eight studies for detection bias from Analysis 1.1, Peto OR 2.04 (95% CI 0.63 to 6.56); and five studies for baseline imbalances from Analysis 1.1, Peto OR 1.84 (95% CI 0.64 to 5.26).

Effect measures

A sensitivity analysis was also performed on the different effect measures used. The Peto OR was used for bleeding outcomes, which was deemed appropriate for rare events. Using a M-H RR as an alternative gave the result as 1.42 (95% CI 0.64 to 3.15) for Outcome 1, still showing a non-significant risk of perioperative bleeding with the use of NSAIDs. Using a M-H RR as an alternative for Outcome 2 did not affect the results, M-H RR of 0.99 (95% CI 0.47 to 2.07), still showing that NSAIDs did not affect bleeding requiring non-surgical intervention. For the vomiting outcome we looked at using Peto OR and again found that this did not alter the interpretation of the results (Peto OR 0.57, 95% CI 0.43 to 0.75) suggesting that NSAIDs reduced the risk of vomiting.

Early stopping

Our process of meta-analysis could not take account of the early stopping of some of the trials. We noted that the decision was made to stop two of the trials (Gunter 1995; Splinter 1996) before completion due to the higher number of bleeding events in the intervention group. Recruitment to the placebo group was stopped early in Pickering 2002 due to an increased need for analgesics in this group. These studies potentially introduced bias to the review, which may have increased the adverse effect of NSAIDs. Removing these studies did not, however, affect the results for Outcome 1 (Peto OR 1.62, 95% CI 0.57 to 6.64) nor Outcome 3 (M-H RR 0.64, 95% CI 0.51 to 0.79). Meta-analysis was not possible for Outcome 3 as removing these studies left only one remaining study (Romsing 1998).

Surgery type

A sensitivity analysis was performed by removing those studies with an unclear risk of bias for surgery type (Antila 2006; Harley 1998; Rusy 1995; Splinter 1996; Sutherland 1998), that is where there was no detail in the papers to demonstrate if the different surgeries performed were balanced between the intervention and control groups. This did not affect the results for any of the outcomes: Outcome 1 Peto OR 1.84 (95% CI 0.64 to 5.26); Outcome 2 Peto OR 0.54 (95% CI 0.20 to 1.49); Outcome 3 M-H RR 0.72 (95% CI 0.60 to 0.86).

Opioid rescue analgesic

To address the potential bias introduced by the use of rescue analgesics in both groups, we removed those studies in which patients in the control group were given more rescue analgesic than in the intervention group (Antila 2006; Kokki 2002; and the preoperative group for Romsing 1998). These three studies used opioid rescue analgesics (morphine, oxycodone and fentanyl, respectively). This sensitivity analysis did not affect the results for the vomiting outcome: M-H RR 0.70 (95% CI 0.58 to 0.84).

DISCUSSION

Summary of main results

The focus of our review was clinically relevant outcomes that affect patients, and to investigate whether there was an increased risk of bleeding associated with the use of NSAIDS at the time of paediatric tonsillectomy. Our first outcome was bleeding requiring surgical intervention and our results are consistent with both a decreased and an increased risk of bleeding in the intervention group. Our second outcome was bleeding requiring non-surgical intervention. This included methods of non- surgical haemostasis, intravenous fluid therapy and increased hospital stay.

As for bleeding requiring further surgical intervention, our results do not exclude an increased risk of bleeding associated with NSAID use. We therefore cannot draw any conclusions about the effect of NSAIDs on bleeding. Our subgroup analyses suggested an increased risk of bleeding requiring surgical intervention with ketorolac but the statistical test for differences between subgroups was not significant and this pattern was not seen with Outcome 2, bleeding requiring non-surgical intervention. There was some evidence of a difference in Outcome 2 with an increased risk of bleeding for those studies comparing NSAIDs against a placebo, rather than another analgesic treatment, but again this difference was not significant.

Our third outcome measure was vomiting. Our results suggest that children who receive NSAIDs are 25% less likely to vomit postoperatively than children who did not receive NSAIDs. The difference was statistically significant ($P \leq 0.001$). There are two possible mechanisms for this observed effect, both related to better pain control in the NSAIDs group. Many of the included studies had opioids available as a rescue analgesic. If children on NSAIDs received less opioid analgesic due to better pain control, this might explain the reduction in vomiting since opioids are known to lead to nausea and vomiting. If an opioid-sparing effect is assumed then in those studies in which less rescue analgesic was given to the intervention group the results would show a larger reduction in vomiting. Our sensitivity analysis showed no difference in the results when studies were removed in which less rescue analgesic was given.

Apart from an opioid-sparing mechanism, it is also possible that the reduction in vomiting seen in the NSAID group could be explained by a reduction in pain for those patients in the intervention group, since pain can lead to vomiting and nausea. We did not consider pain in this review due to the differences in reporting between studies, and therefore we were unable to consider a possible correlation between vomiting and pain.

Overall completeness and applicability of evidence

The objective of our review was to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. We were able to identify 15 studies with 1101 patients undergoing tonsillectomy surgery from our searches. All of these studies compared the use of NSAIDs with either another analgesic or a placebo. Bleeding, either requiring surgical or non-surgical intervention, was considered as an outcome in all the studies.

Bleeding requiring further surgical intervention is an uncommon event following tonsillectomy. Assessing the pooled numerical values for the number of events, we have approximately 500 patients in each group and only a very small number of bleeding events. The results of the pooled data, shown on the forest plot in Figure 4, showed no statistically significant increase in bleeding. However, power calculations indicated that 1469 patients in each group would be needed to detect a risk ratio of 1.5, a 5% assumed risk of bleeding in the control group and a 7.5% assumed risk in the NSAID group, with 80% power (α 0.05, two-tailed). Since this a non-inferiority research question, perhaps the more relevant power calculation is to exclude a 2.5% difference in bleeding with a one-sided α 0.025 and this would require 1194 patients in each group. This review, therefore, had insufficient numbers to be able to exclude an increased risk of bleeding associated with the use of NSAIDs in paediatric tonsillectomy.

We considered whether NSAIDs affect the incidence of postoperative vomiting, and 13 of our included studies reported on this outcome. Postoperative nausea and vomiting is a much more common event and this was reflected in our results. Again we had approximately 500 patients in each group and our results demonstrated a significant reduction in the risk of vomiting for the NSAIDs group. Power calculations for this outcome indicated that 354 patients in each group would be needed to detect a risk ratio of 0.75, a 40% assumed risk of vomiting in the control group and a 30% risk of bleeding in the NSAIDs group, with a power of 80% (α 0.05, two-tailed). This review, therefore, had sufficient numbers to potentially demonstrate that the use of NSAIDs for paediatric tonsillectomy reduces the risk of vomiting.

Quality of the evidence

We considered the quality of the studies using the 'Risk of bias' assessment tools. There were no studies that had a low risk of bias in all the domains, however our sensitivity analysis suggested that these biases did not affect the overall result. A funnel plot (see Figure 5) suggests an absence of bias across 10 included studies for our first comparison (Analysis 1.1). No outcome was graded down for quality in the 'Summary of findings' table.

The included studies date back to 1995 and we considered the directness of evidence and whether the interventions tested were still clinically relevant. Three papers studied ibuprofen (Harley 1998; Pickering 2002; St Charles 1997) but used doses of 5 mg/kg. However, ibuprofen is now prescribed to children in a dose of 10 mg/kg so the doses studied are half that now given, which may have an effect on the potential to cause bleeding.

Another study (Thiagarajan 1993) used papaveretum as the comparison drug, which is no longer commonly used for children. Five studies (Rawlinson 2011; Splinter 1996; Sutherland 1998; Sutters 1995; Thiagarajan 1993) administered either the intervention or comparison drug, or both, intramuscularly, which is also no longer commonly used for children. However, these are not variables that are likely to affect the results and we did not downgrade the evidence for indirectness.

Potential biases in the review process

This review considered studies of paediatric tonsillectomy patients. Although we attempted to account for different surgery types and to aim for balance, it must be acknowledged that some patients also underwent additional surgeries (commonly adenoidectomy) and this could have potentially affected the bleeding outcomes. We attempted to address this in the sensitivity analysis. There were also different surgical techniques used between studies, as well as different anaesthetics, which we did not consider in our subgroup analysis. These differing techniques and drugs could affect bleeding outcomes.

We also did not consider age or gender in our review, for which there may be risks associated with postoperative haemorrhage (Tomkinson 2011).

For our analysis we combined studies comparing different NSAIDs (ketorolac, ibuprofen, diclofenac, ketoprofen and tenoxicam) against different controls (placebo, morphine, fentanyl, codeine, acetominophen, tramadol and papaveretum). We considered subgroup analysis according to the intervention drug but we were only able to consider ketorolac for subgroup analysis. Within this subgroup ketorolac was considered against a variety of controls. The intervention and control drugs were also given by different routes (intravenously, intramuscularly or orally).

Our second subgroup analysis considered the timing of administration of the intervention drug. We were unable to perform this meta-analysis using data within study populations as there were only two studies for which this would have been possible. We chose to combine the data between those studies in which the intervention drug was given preoperatively and those studies in which it was given postoperatively. The differences between estimates may therefore be due to differences in the study populations or trial design, unrelated to timing of NSAID administration. However, we did not find any differences between the timing subgroups.

We limited our included study eligibility criteria to those studies which reported on perioperative bleeding requiring surgical or non-surgical interventions, as justified by our main objective to consider the effect of NSAIDs on bleeding. However, this meant that some studies were excluded from our review which could have potentially been included in our meta-analysis of the effect of NSAIDs on the incidence of vomiting. We did not include a measure of millilitres of blood as this was less relevant in paediatric cases. However, there were studies that measured such intraoperative blood loss and our definitions of perioperative bleeding requiring surgical or non-surgical bleeding did not allow for this. Our review did not, therefore, consider whether there may be a difference in the amount of bleeding that is subclinical.

Agreements and disagreements with other studies or reviews

Two meta-analyses (Marret 2003; Moiniche 2003) reviewed the use of NSAIDs and the risk of bleeding after tonsillectomy in both adult and paediatric patients. Marret et al concluded that NSAIDs increase the risk of re-operation for haemostasis after tonsillectomy. Moiniche et al concluded that NSAIDs should be used cautiously until further data are available.

The first review (Marret 2003) studied paediatric and adult data but only included trials published in English. The paper has not been updated. Our review includes a further two papers which have been published since that review. The outcome measures in that review were the need for surgical electrocautery to stop

the bleeding and postoperative bleeding requiring a change in postoperative management. The primary outcome, which required a return to theatre, was different from ours; and the need for surgical electrocautery probably overestimated the bleeding as this can be part of the primary surgical procedure. The papers included in the review were not exactly the same as ours as the review included two that only studied adult participants and the review did not include eight papers which we included. It is unclear from the review why these were not included but three papers (Kokki 2002; Öztekin 2002; Pickering 2002) do not appear to have been reviewed at all as they are not mentioned or referenced. We considered all three of these studies to be of sufficient quality to include in our review.

In the second review (Moiniche 2003) the papers reviewed were similar to ours except adult studies were also included and no papers published after December 2001 were included. The significance of their results was dependent on the method used. They found that re-operation because of bleeding occurred more often with NSAIDs. The Peto OR was statistically significant (Peto OR 2.33, 95% CI 1.12 to 4.83) and was of borderline significance using the method described by Shadish and Haddock (Sadish 1994) (OR 1.92, 95% CI 1.00 to 3.71); the NNT was 60 (95% CI 34 to 277). However, they did not find interoperative blood loss, postoperative blood loss or hospital admission to be more common with NSAIDs and therefore concluded that NSAIDs could be used cautiously until further data became available.

A Cochrane systematic review (Standing 2009) considered diclofenac for acute pain in children (perioperative pain, migraine, renal colic and soft tissue injury and fractures). This paper included two studies from our review (Öztekin 2002; Thiagarajan 1993) and included outcomes of bleeding requiring surgical intervention and nausea or vomiting, or both. The authors concluded that diclofenac did not appear to increase the incidence of perioperative bleeding (Mantel-Haenzel RR 1.25, 95% CI 0.31 to 4.97). They also conclude that there is a reduction in nausea and vomiting (Mantel-Haenzel RR 0.58, 95% CI 0.47 to 0.73).

AUTHORS' CONCLUSIONS

Implications for practice

The objective of this review was to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. From the data available to date, there is no evidence that using NSAIDs caused any statistically significant increase in bleeding that required further clinical intervention. Bleeding requiring further surgical intervention is an uncommon event following tonsillectomy. Although not statistically significant, our results showed an increased risk of bleeding requiring surgical intervention with a large confidence interval (95% CI 0.71 to 4.01). This indicates that the total number of participants studied is inadequate and further studies need to be performed. This is also shown in our power calculations. This limitation of our original review remains as only one paper was added to this updated review. There was less vomiting when NSAIDs were used as part of the analgesic regime compared to when NSAIDs were not used.

We therefore conclude that there is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatric tonsillectomy. They do, however, confer the benefit of a reduction in vomiting.

Implications for research

Further studies are required assessing the impact of NSAIDs on bleeding in paediatric tonsillectomy. Future studies should be sufficiently powered to consider the relatively uncommon risk of bleeding. They should be sufficiently blinded and avoid the bias introduced by opioid rescue analgesics, different surgical techniques and surgeries in addition to tonsillectomy. Stratifying by age and gender would also be considered for this potential difference in bleeding outcomes.

Currently none of the selective COX-2 inhibitors are approved for use in children and there remains limited information to support their use in treating pain following paediatric tonsillectomy. This would be a further potential topic for research in this field.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Antila 2006

Methods	Randomized, parallel group trial
Participants	• 45 children undergoing inpatient tonsillectomy with or without adenoidectomy • ASA I • Age: 9-15 years (mean 12.5±2.3, 11.9±2.4) • Sex distribution: M/F (6/9, 7/8) • Country: Finland
Interventions	1. Saline 10ml at induction followed by 100ml over 6 hours 2. Ketoprofen 2mg/kg at induction followed by 2mg/kg postoperation over six hours 3. Tramadol 1mg/kg at induction followed by 1mg/kg postoperation over six hours
Outcomes	1. Pain assessed by VAS scores 2. Number of fentanyl PCA requests in the first 24 hours 3. Measured blood loss in theatre 4. Bleeding requiring a return to theatre 5. Nausea and vomiting
Notes	The study had three groups (placebo, ketoprofen and tramadol). Placebo and tramadol group were combined and compared with ketoprofen group for data analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Baseline Imbalances All outcomes	Unclear risk	Although baseline imbalances appear comparable in Table 1, there are no details on types of surgery and whether this is balanced between groups
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Nurse, not otherwise participating in treatment of patient prepared the coded study treatment syringes and infusions. Assumed coded means not labelled with contents, i.e. double blind. Assumed surgeon unaware of group allocation
Blinding of participants and personnel (performance bias)	Unclear risk	N/a

Antila 2006 *(Continued)*

2.Perioperative bleeding requiring non-surgical intervention		
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	Nurse, not otherwise participating in treatment of patient prepared the coded study treatment syringes and infusions. Assumed coded means not labelled with contents, i.e. double blind. Assumed surgeon unaware of group allocation
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Assumed surgeon unaware of allocation but assessment of bleeding may have been made on the ward by nurses - unclear if ward nurses are blinded. Not clear who decided return to theatre is required
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	N/a
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	Unclear who measured this and whether they were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Ketoprofen group had less fentanyl than tramadol group which could affect vomiting results

Gunter 1995

Methods	Randomized, parallel group trial
Participants	• 97 children 1-12 years undergoing tonsillectomy • ASA I-II • Sex distribution not stated • Country: USA
Interventions	1. Ketorolac 1 mg/kg intravenously at end of surgery 2. Morphine 0.1 mg/kg intravenously at end of surgery
Outcomes	1. Bleeding requiring surgical intervention at less than 24 hours 2. Bleeding requiring surgery at more than 24 hours 3. Bleeding requiring non-surgical intervention at less than 24 hours 4. Bleeding requiring non-surgical intervention at more than 24 hours 5. Increased hospital stay 6. Emetic episodes
Notes	No analgesia given in theatre. Paracetamol 20 mg/kg given in recovery to all patients.

Gunter 1995 *(Continued)*

Morphine 0.05 mg/kg twice in recovery as rescue analgesia. One withdrawal from the morphine group due to an intraoperative arterial bleed. ITT analysis not performed as no details available on patient outcome. Study terminated early due to an increased incidence of major bleeding in ketorolac group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Baseline Imbalances All outcomes	Low risk	Type of surgery similar in both groups
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Subjects, families, anaesthesiologists, nurses and investigators were blinded to study drug assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study terminated at 97 patients after interim analysis revealed excessive bleeding in the study group. One exclusion not included in the data as no outcome details available
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Gunter 1995 *(Continued)*

Other bias All outcomes	Low risk	Some patients received extra morphine - but two doses more common in ketorolac group. Investigators state that no difference in emesis rates for those who received more

Harley 1998

Methods	Randomized, parallel group trial
Participants	• 27 children undergoing tonsillectomy or adenotonsillectomy • ASA I-II • Age 6-16 years, distribution in each group not stated • Sex distribution: M/F 17/10 (distribution of the two groups not stated) • Country: USA
Interventions	1. Ibuprofen 5 mg/kg six hourly as required postoperatively 2. Paracetamol 10 mg/kg and codeine 0.4 mg/kg mixture as required postoperatively
Outcomes	1. Bleeding requiring surgical intervention 2. Postoperative pain scores
Notes	Dose of paracetamol was low

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization code
Allocation concealment (selection bias)	Unclear risk	Not described
Baseline Imbalances All outcomes	Unclear risk	No breakdown of how many surgical interventions per group. Also no details of demographic data available
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Otolaryngology, operating-room and recovery room staff members all blinded to randomization codes. Not clear if parents were blinded. Intervention occurred after discharge, variable lengths of drug administration, reliability of parents recording data
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	N/a
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	N/a

Harley 1998 *(Continued)*

Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Not clear who assessed need for return to OR or presentation to hospital. Not clear if parents were blinded - their knowledge of intervention may have influenced return to hospital
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	N/a
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	N/a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up on three patients (10%) - not clear if these were lost before or after randomization. Also no statistical data for some patients - "As a result of factors such as follow-up compliance not all patients were available for each statistical comparison"
Selective reporting (reporting bias)	Low risk	Nausea and vomiting data probably not collected
Other bias All outcomes	Low risk	No rescue analgesics described, assumed not given

Keidan 2004

Methods	Randomized, parallel group trial
Participants	• 60 children undergoing adenotonsillectomy • ASA I -II • Age: 1.7-10 years (mean 4.3±2.6, 5.6±2.6) • Sex distribution: M/F (19/9, 18/4) • Country: Israel
Interventions	1. Ketorolac 1 mg/kg at induction 2. Fentanyl 2 µg/kg at induction
Outcomes	1. Emetic episodes 2. Pain assessed by the PACU nurse using The Objective Pain Scale 3. Agitation 4. Bleeding
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Received by random assignment. No further details given

Keidan 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details given
Baseline Imbalances All outcomes	Low risk	All had same surgical procedures. More boys in Ketorolac group and more history of motion sickness
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Unknown if surgeon or anaesthetist blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	Unknown if surgeon or anaesthetist blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	Unknown if surgeon or anaesthetist blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Unclear who is assessing this outcome
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	Unknown if surgeon or anaesthetist blinded
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	Unknown if surgeon or anaesthetist blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three patients excluded from analysis due to lack of data (no further explanation given)
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Extra fentanyl given as rescue analgesic, levels not given, could affect results for vomiting

Kokki 2002

Methods	Randomized, parallel group trial
Participants	• 110 children for elective tonsillectomy

Kokki 2002 *(Continued)*

- ASA I
- Age 3-16 years (mean 10, 11)
- Sex distribution: M/F (23/24, 7/13)
- Country: Finland

Interventions	1. Ketoprofen 0.5 mg/kg at induction followed by placebo postoperatively and ketoprofen infusion 3 mg/kg over 24 hours postop 2. Saline at induction followed by ketoprofen 0.5 mg/kg postoperatively and ketoprofen infusion 3mg/kg over 24hrs postop 3. Placebo. Saline bolus 10mls at induction and postoperatively then saline infusion over 24hrs postop
Outcomes	1. Bleeding requiring surgical intervention 2. Postoperative pain 3. Postoperative nausea and vomiting
Notes	Study had two ketoprofen groups. Have included both the pre- and post-ketoprofen groups to the analysis against the divided control group. Placebo control group is small, not explained by study authors, could be due to poor randomization or allocation concealment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Prescription in an envelope but no further details given
Baseline Imbalances All outcomes	Low risk	Demographic data all similar. All tonsillectomies. However, small placebo group
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Drug syringes prepared by nurses not otherwise involved in study
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Low risk	Drug syringes prepared by nurses not otherwise involved in study
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	Drug syringes prepared by nurses not otherwise involved in study
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Assume nurses assessing outcomes were blinded

Kokki 2002 *(Continued)*

Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Low risk	Assume nurses assessing outcomes were blinded
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Assume nurses assessing outcomes were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient excluded but e-mail contact with authors confirm outcomes and so included in order to follow ITT principle
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Oxycodone higher in placebo group and this not allowed for in analyses

Pickering 2002

Methods	Randomized, parallel group trial
Participants	• 103 children for elective tonsillectomy or adenotonsillectomy • ASA I-II • Age 3-15 years (mean 7.0, 7.0) • Sex distribution: M/F (21/19, 7/11) • Country: UK
Interventions	1. Rofecixib 0.625 mg/kg preoperatively 2. Ibuprofen 5 mg/kg preoperatively 3. Placebo preoperatively
Outcomes	1. Need for early postoperative analgesia 2. Interoperative blood loss 3. Time to first postoperative analgesia 4. Pain scores 5. Analgesic consumption in the first 24hrs 6. Vomiting and antiemetic use 7. Incidence of primary and secondary haemorrhage
Notes	Study had three groups. Data from the ibuprofen and placebo groups used in the review. Recruitment to placebo group finished early due to increased need for analgesics in this group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number table

Pickering 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Hospital pharmacist allocated children randomly to groups. But no further details on this
Baseline Imbalances All outcomes	Low risk	Demographic details comparable and no large differences in surgery types between groups. However, recruitment to placebo group finished early
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Patients and investigators blinded to group assignment. No mention of whether surgeon, anaesthetist or nurses blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	Patients and investigators blinded to group assignment. No mention of whether surgeon, anaesthetist or nurses blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	Patients and investigators blinded to group assignment. No mention of whether surgeon, anaesthetist or nurses blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Not clear who "investigators" are and whether they are assessing outcomes or not
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	Not clear who "investigators" are and whether they are assessing outcomes or not
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	Not clear who "investigators" are and whether they are assessing outcomes or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three exclusions: one patient from placebo group given diclofenac during surgery; two patients from ibuprofen group - one given diclofenac during surgery and one was too young. Small number of missing patients (5%) unlikely to affect results
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Rescue analgesics used in both groups is same as intervention drug

Rawlinson 2011

Methods	Randomized, parallel group trial

Rawlinson 2011 *(Continued)*

Participants	• 65 children for elective tonsillectomy or adentonsillectomy • ASA I - II • Age: 4 - 16 years (mean 7.4 ± 3.2, 7.3 ± 3.3) • Sex distribution: M/F (15/15, 15/17) • Country: UK
Interventions	1. Fentanyl 1–2 µg/kg intravenously, Diclofenac 1–2 mg/kg rectally during surgery. 2. Codeine 1.5mg/kg intramuscularly during surgery.
Outcomes	1. Incidence of postoperative vomiting and nausea 2. Time to first postoperative analgesia 3. Maximum pain scores 4. Fitness for discharge at 4 hrs 5. Primary or secondary haemorrhage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random list
Allocation concealment (selection bias)	Unclear risk	Numbered envelopes. Does not give further details
Baseline Imbalances All outcomes	Low risk	Similar number of tonsillectomies and adenotonsillectomies
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Not clear if surgical team/nursing staff were blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	Not clear if surgical team/nursing staff were blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	Not clear if surgical team/nursing staff were blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Investigator blinded to allocation made all postoperative observations
Blinding of outcome assessment (detection bias)	Low risk	Investigator blinded to allocation made all postoperative observations

Rawlinson 2011 *(Continued)*

2. Perioperative bleeding requiring non-surgical intervention		
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Investigator blinded to allocation made all postoperative observations
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three missing patients: two due to protocol violations and one due to cancellation of surgery. Not clear if randomized. Small number of missing patients (<10%) unlikely to affect results
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias All outcomes	High risk	Codeine group received ibuprofen postoperatively, Ibuprofen group received fentanyl

Romsing 1998

Methods	Randomized, parallel group trial
Participants	• 60 children undergoing tonsillectomy or adenotonsillectomy • ASA I-II • Age: 5-15 years (mean 9.4±3.2, 8.8±3.2) • Sex distribution: M/F (5/15, 6/14) • Country: Denmark
Interventions	1. Ketorolac 1 mg/kg intravenously preoperatively and saline postoperation 2. Saline preoperatively and ketorolac 1 mg/kg intravenously postoperation 3. Saline pre and postoperation
Outcomes	1. Intra-operative blood loss 2. Pain 3. Vomiting
Notes	Pain was primary outcome. Study stopped after first 15 children because of worries about a surgeon causing excess bleeding. Data used in 2012 update includes this surgeon. Also, included data from patient who had been excluded from the authors' results due to bleeding requiring immediate reoperation. Have included both the pre- and post-ketoprofen groups to the analysis against the divided control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	No details given as to how allocation was concealed
Baseline Imbalances All outcomes	Low risk	Distribution of tonsillectomies and adenotonsillectomies appear equivalent. Other demographic data also comparable

Romsing 1998 *(Continued)*

Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	All patients, parents, personnel involved in patient management and data collection were unaware of drug group assignment
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Low risk	All patients, parents, personnel involved in patient management and data collection were unaware of drug group assignment
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	All patients, parents, personnel involved in patient management and data collection were unaware of drug group assignment
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	All patients, parents, personnel involved in patient management and data collection were unaware of drug group assignment
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Low risk	All patients, parents, personnel involved in patient management and data collection were unaware of drug group assignment
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One patient excluded from Pre- group as given a different anaesthetic. Two patients excluded from Post- group: one given diclofenac; one needed re-operation due to bleeding. We included the patient who required bleeding in the results
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Distribution groups of excluded surgeon not given. More fentanyl given in post-ketaprofen and placebo group

Rusy 1995

Methods	Randomized, parallel group trial
Participants	• 50 children undergoing tonsillectomy and or adenoidectomy • ASA I-II • Age 2-15 years (means for each group not given but said to be the same for both groups) • Sex distribution not given • Country: USA

Rusy 1995 *(Continued)*

Interventions	1. Ketorolac 1 mg/kg at induction 2. Paracetamol 35 mg/kg at induction
Outcomes	1. Bleeding requiring surgical intervention 2. Measured blood loss 3. Extra haemostatic measures required during surgery and measured blood loss 4. Amount of rescue analgesia required
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear how randomization was performed
Allocation concealment (selection bias)	Unclear risk	Not enough detail in paper
Baseline Imbalances All outcomes	Unclear risk	No distribution given for tonsillectomies and adenotonsillectomies. Not data for other demographics
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Assume that patients is blinded but no details of whether surgeon and other personnel blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	Assume that patients is blinded but no details of whether surgeon and other personnel blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	N/a
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Only reports that investigator responsible for bleeding times is blinded. Unclear if other personnel are blinded
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	Only reports that investigator responsible for bleeding times is blinded. Unclear if other personnel are blinded
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	N/a

Rusy 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All data complete
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	Low risk	More acetaminophen used in comparison group, however vomiting not measured in this study, so not likely to affect results

Splinter 1996

Methods	Randomized, parallel group trial
Participants	• 64 undergoing elective tonsillectomy or adenotonsillectomy • ASA I-II • Age 2-12 years (7.1±3.1, 6.8±2.7) • Sex distribution not stated • Country: Canada
Interventions	1. Ketorolac 1 mg/kg intravenously at induction 2. Codeine 1.5 mg/kg intramuscularly at induction
Outcomes	1. Bleeding requiring surgical intervention 2. Increased hospital stay 3. Measured blood loss 4. Postoperative nausea and vomiting
Notes	Study designed to look at nausea and vomiting. Study terminated early at 64 patients because of excessive bleeding during interim analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	No details given
Baseline Imbalances All outcomes	Unclear risk	No demographic data given, nor balance of surgical groups
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Assumed anaesthetist not blinded. No details whether surgeon blinded
Blinding of participants and personnel (performance bias)	Unclear risk	Assumed anaesthetist not blinded. No details whether surgeon blinded

Splinter 1996 *(Continued)*

2.Perioperative bleeding requiring non-surgical intervention		
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	Assumed anaesthetist not blinded. No details whether surgeon blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Not clear who assessed bleeding
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	Not clear who assessed bleeding
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Assumed nurses and parents assessing vomiting were blind to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	Unclear risk	Distribution of rescue analgesics and anti-emetics between groups not described - these were given during observation period and would affect vomiting

St Charles 1997

Methods	Randomized, parallel group trial
Participants	• 110 children undergoing tonsillectomy with or without other procedures • ASA status not stated • Age 16-168 months (mean 77, 67) • Sex distribution: M/F (3.2, 3.2) • Country: USA
Interventions	1. Ibuprofen 5 mg/kg orally postoperation 2. Paracetamol up to 15 mg/kg and codeine 1 mg/kg orally postoperation
Outcomes	1. Bleeding requiring surgical intervention 2. Bleeding requiring nonsurgical treatment 3. Mild postoperative bleeding 4. Pain (mild or moderate or severe) 5. Nausea and emesis

St Charles 1997 *(Continued)*

Notes	Surgical technique included electro-dissection or cold dissection and snare techniques.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to one of two groups. No details given
Allocation concealment (selection bias)	Unclear risk	No details given.
Baseline Imbalances All outcomes	Low risk	Lots of surgical techniques but balanced. Demographic data clearly reported and largely equivalent
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	High risk	Assumed no-one blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	High risk	Assumed no-one blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	High risk	Assumed no-one blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	High risk	Inconsistencies in how data collected (some retrospectively from charts). No blinding. Not clear how bleeding detected. Parents in intervention group given free samples to take home
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	High risk	Inconsistencies in how data collected (some retrospectively from charts). No blinding. Not clear how bleeding detected. Parents in intervention group given free samples to take home
Blinding of outcome assessment (detection bias) 3. Vomiting	High risk	Nurses and parents not blinded - responsible for reporting and recording any signs of PONV
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data
Selective reporting (reporting bias)	Low risk	All expected outcome measures reported

St Charles 1997 *(Continued)*

Other bias All outcomes	High risk	Extra analgesics given in OR and during observation period. May affect vomiting outcomes. Inconsistencies mean that treatment was barely standardized

Sutherland 1998

Methods	Randomized, parallel group trial
Participants	• 50 children undergoing elective tonsillectomy and/or adenoidectomy, myringotomy or submucous diathermy of inferior turbinates (SMIT) • ASA I-II • Age 3-10 years (mean 6.2, 5.8) • Sex distribution: M/F (12/13, 13/11) • Country: UK
Interventions	1. Tenoxicam 0.75 mg/kg intramuscularly at induction 2. Morphine 0.2 mg/kg intramuscularly at induction
Outcomes	1. Blood loss requiring surgical intervention 2. Pain (measured rescue analgesia) 3. Vomiting
Notes	Study originally designed to look at pain. One withdrawal from morphine group included in our analysis so an ITT analysis could be performed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no further details given
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used but no further details given
Baseline Imbalances All outcomes	Unclear risk	Demographic data comparable. But no details given of surgery type
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Unclear if surgeon blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	N/a
Blinding of participants and personnel (performance bias)	Low risk	Nursing staff blinded

Sutherland 1998 *(Continued)*
3. Vomiting

Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Unclear who is assessing patients
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	N/a
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Nurses assessing patients were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for excluded child included in order to follow ITT principle
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Tenoxicam group required more morphine. Could affect vomiting results

Sutters 1995

Methods	Randomized, parallel group trial
Participants	• 87 children having tonsillectomy • ASA I-II • Age 7-16 years (mean 84.7 months±28.9, 85.0±26.7) • Sex distribution: M/F (26/19, 22/20) • Country: USA
Interventions	1. Ketorolac 1 mg/kg intramuscularly at completion of surgery 2. Saline intramuscularly at completion of surgery
Outcomes	1. Bleeding requiring surgical intervention 2. Bleeding requiring nonsurgical intervention 3. Mild bleeding that stops spontaneously 4. Measured blood loss
Notes	Fentanyl iv given in repeated doses 0.5 µ/kg in recovery. Child from control group excluded by authors due to postoperative oedema but included so an ITT analysis could be performed following e-mail confirmation from authors of no bleeding outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement

Sutters 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Group assignment was sealed in a manila envelope. No further details
Baseline Imbalances All outcomes	Low risk	Well documented and no differences in demographic or surgery type
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Anaesthetist aware of group allocation. But drug given after surgery. Not clear whether surgeon knew allocation but operations similar between groups
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Low risk	Anaesthetist aware of group allocation. But drug given after surgery. Not clear whether surgeon knew allocation but operations similar between groups
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	Anaesthetist aware of group allocation. But drug given after surgery. Not clear whether surgeon knew allocation but operations similar between groups
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Identity of injection not revealed to PACU nurse, the parents, or to investigator who performed clinical assessments. Not clear who did assessment of bleeding in PACU/DSA - but probably nurses or investigator
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Low risk	Identity of injection not revealed to PACU nurse, the parents, or to investigator who performed clinical assessments. Not clear who did assessment of bleeding in PACU/DSA - but probably nurses or investigator
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Identity of injection not revealed to PACU nurse, the parents, or to investigator who performed clinical assessments. Not clear who did assessment of bleeding in PACU/DSA - but probably nurses or investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	One exclusion because child had severe postop oedema. This patient was included in order to follow the ITT principle following e-mail contact with study author
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Higher use of fentanyl in ketorolac group. Could affect vomiting results

Thiagarajan 1993

Methods	Randomized, parallel group trial
Participants	• 198 children undergoing tonsillectomy • ASA I-II • Age 1-12 years (mean 5.6±2.2, 5.7±2.5) • Sex distribution not stated • Country: UK
Interventions	1. Diclofenac 1 mg/kg intramuscularly at induction 2. Papaveretum 0.2 mg/kg intramuscularly at induction
Outcomes	1. Bleeding requiring surgical intervention 2. Measured blood loss (subjective) 3. Postoperative pain scores 4. Postoperative nausea and vomiting
Notes	Papaveretum now not commonly used for children. Intramuscular analgesia now considered inappropriate for children. 15 withdrawals mentioned in paper, unable to get in touch with author to account for these.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial numbers were randomized in blocks
Allocation concealment (selection bias)	Low risk	Randomization code was held by the hospital pharmacy
Baseline Imbalances All outcomes	Low risk	Report on different surgical techniques but do not give information on male/female ratios
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Low risk	Syringes, identified only by the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Low risk	Syringes, identified only by the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Low risk	Syringes, identified only by the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Syringes, identified only by the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded

Thiagarajan 1993 *(Continued)*

1. Perioperative bleeding requiring surgical intervention		
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Low risk	Syringes, identified only be the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded
Blinding of outcome assessment (detection bias) 3. Vomiting	Low risk	Syringes, identified only be the patient's name were prepared by the pharmacy on day of operation. Therefore assumed all personnel blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Fifteen exclusions; five from diclofenac group and four from papaveretum group not given drugs because anaesthetist unaware of their participation in trial; one patient had obstructive sleep apnoea; five records lost or incomplete. Unable to account for withdrawals as unable to get in touch with the author
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Papaveretum given to more patients in intervention group. May affect vomiting results

Öztekin 2002

Methods	Randomized, parallel group trial
Participants	• 40 children for elective tonsillectomy and/or adenoidectomy or myringotomy • ASA I-II • Age: 5-14 years (mean 8.4±0.53, 8.9±0.45) • Sex distribution: M/F (6/14, 8/12) • Country: Turkey
Interventions	1. Diclofenac suppository (approximately 1mg/kg) prior to surgical incision 2. Nothing given
Outcomes	1. Pain assessed by VAS scores 2. Total morphine consumption at one hour and at discharge 3. Incidence of nausea and vomiting 4. Bleeding episodes requiring nasopharyngeal packing or re-operation
Notes	No placebo suppository given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear how randomization was performed

Öztekin 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details given
Baseline Imbalances All outcomes	Low risk	All demographic details given
Blinding of participants and personnel (performance bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Not clear if surgeons and staff on wards were blinded
Blinding of participants and personnel (performance bias) 2.Perioperative bleeding requiring non-surgical intervention	Unclear risk	Not clear if surgeons and staff on wards were blinded
Blinding of participants and personnel (performance bias) 3. Vomiting	Unclear risk	Not clear if surgeons and staff on wards were blinded
Blinding of outcome assessment (detection bias) 1. Perioperative bleeding requiring surgical intervention	Unclear risk	Parents and patients blinded. Aware that nurse measuring pain is blinded but no mention of other nurses being blinded
Blinding of outcome assessment (detection bias) 2. Perioperative bleeding requiring non-surgical intervention	Unclear risk	Parents and patients blinded. Aware that nurse measuring pain is blinded but no mention of other nurses being blinded
Blinding of outcome assessment (detection bias) 3. Vomiting	Unclear risk	Parents and patients blinded. Aware that nurse measuring pain is blinded but no mention of other nurses being blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data complete
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias All outcomes	High risk	Placebo group used more rescue morphine, both in PACU and ward, could affect vomiting results

ASA = American Society of Anesthesiologists; DSA = Day surgery area; ITT = Intention-to-treat; iv = Intravenously; M/F = Male/female; N/a = Not applicable; OR = Operating room; PACU = Postanaesthesia care unit; PCA - Patient-controlled analgesia; PONV = Postoperative nausea and vomiting; VAS = Visual analogue scale

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

Study	Reason for exclusion
Agrawal 1999	Retrospective study
Aho 2003	Adult participants
Azuma 1982	Not a randomized controlled study
Bailey 1997	Adult participants
Bhattacharya 2005	Does not look at bleeding
Bhattacharya 2009	No control group
Bone 1988	Does not look at bleeding
Calvet 1969	An uncontrolled study
Courtney 2001	A mixture of adult and paediatric participants. We obtained the original data from the authors to separate the two types of participants but it was not possible to determine exactly who had experienced bleeding.
De Lima Pontes 1985	Bleeding not assessed
Dommerby 1984	A mixture of adult and paediatric data. We wrote to the authors to try to separate the data but did not receive a reply
Elshammaa 2011	NSAIDs not studied
Fassolt 1974	Adult participants
Francois 1994	Bleeding not assessed
Gallagher 1995	Retrospective study
Geva 2011	NSAIDs not studied
Gonchar 1974	Not a randomized controlled trial
Hardy 2010	Bleeding not studied
Heaney 2007	No control group
Hiller 2004	Adult participants
Ismail 2010	Adult participants
Jeyakumar 2008	Retrospective study
Judkins 1996	Retrospective study
Kedek 2005	No detail on bleeding in paper. We emailed the author but did not receive a reply
Knudsen 1995	Adult participants
Kristensen 1986	Adult participants. No control group

Study	Reason for exclusion
Lacomme 1978	Bleeding not assessed
Lee 1996	Postoperative survey
Lindgren 1985	A second drug was included with trial drug, therefore no proper control
Louizos 2006	Adult participants
Mahadevan 1995	Audit
Martinez-Gallardo 1997	Adult participants
Mather 1995	Blood loss not studied
McKean 2008	Adult participants
Mendham 1996	No control group
Nakayama 1982	Only one study group
Nikanne 2005	Adult participants
Nordbladh 1991	Adult participants
Parker 1986	Adult participants
Pestieau 2011	NSAIDs not studied
Petrusen 1991	Mainly adult participants with a few older children. We were unable to separate out the paediatric and adult data
Platzer 2011	Majority of adenoidectomy patients. Bleeding not assessed
Purday 1995	Re-analysis of a retrospective study
Robb 1995	Re-analysis of a retrospective study
Robinson 1994	Retrospective study
Romsing 2000	All participants received diclofenac during the surgery. Randomization to either paracetamol or diclofenac occurred on the first day postoperatively
Rorarius 1993	Adult participants
Salonen 2001	Adult participants
Salonen 2002	All patients received ketoprofen. No control group
Schmidt 2001	Unable to separate adult and paediatric data
Smith 1999	Retrospective study
Stage 1988	Studied aspirin, which is no longer used in children
Stewart 2012	Not an RCT

Study	Reason for exclusion
Sun 2009	Bleeding not assessed
Swanepoel 1999	Did not compare a nonsteroidal anti-inflammatory drug with a control. Both groups took diclofenac: one orally and one rectally
Tamura 1972	Bleeding not assessed
Tawalbeh 2001	Not an RCT
Virtaniemi 1999	Adult patients
Watters 1988	Bleeding not assessed
Yaman 2011	Retrospective study
Zhang - AFT	Ongoing trial. Not tonsillectomy
Özkiris 2012	Not an RCT

NSAIDs = Nonsteroidal anti-inflammatory drugs; RCT = Randomized controlled trial.

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

Hartnick

Trial name or title	Postoperative Ibuprofen and the Risk of Bleeding After Tonsillectomy with or without Adenoidectomy
Methods	Randomized, double-blinded interventional study
Participants	Children aged 2 -18 yrs undergoing tonsillectomy with or without adenoidectomy
Interventions	Ibuprofen vs acetaminophen
Outcomes	Primary outcome level 3 postoperative haemorrhage
Starting date	May 2012
Contact information	Christopher Hartnick, Massachusetts Eye and Ear Infirmary. NCT01605903
Notes	Estimated enrolment of 1066 patients

KITS Study

Trial name or title	KITS Study - Ketorolac in Tonsillectomy Surgery: a Double Blinded, Randomized Clinical Trial
Methods	Double-blinded, randomized clinical trial
Participants	Children aged 3 - 15 yrs scheduled for tonsillectomy for sleep disordered breathing
Interventions	Ketorolac vs saline

KITS Study *(Continued)*

Outcomes	Primary outcome: pain
Starting date	December 2011
Contact information	Ban Tsui, University of Alberta. NCT01498796
Notes	

Wheeler

Trial name or title	Safety and Efficacy of Intravenous Ibuprofen for Treatment of Pain in Pediatric Patients undergoing Tonsillectomy
Methods	Multi-centre, randomized, double-blind, placebo controlled
Participants	Children 6 - 17 yrs old scheduled to undergo tonsillectomy
Interventions	Intravenous ibuprofen versus saline
Outcomes	1. number of fentanyl doses required postoperatively 2. postoperative pain as measured on VAS 3. time to discharge 4. time to swallow postoperatively 5. parent satisfaction 6. treatment-emergent adverse events, and changes in blood loss during surgery
Starting date	April 2011
Contact information	Art P Wheeler, Cumberland Pharmaceuticals Inc. NCT01332253
Notes	Study has been completed as of September 2012. Not yet published

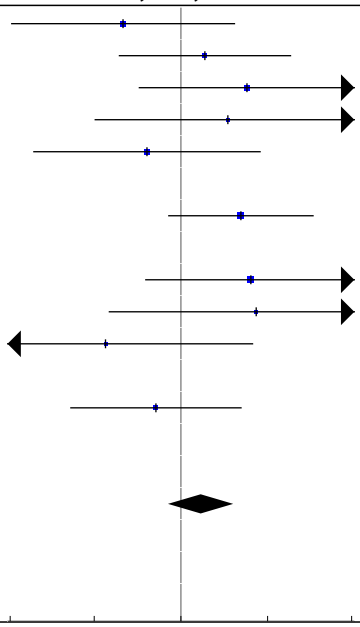
DATA AND ANALYSES

Comparison 1. Nonsteroidal versus control (analgesics or placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perioperative bleeding requiring surgical intervention	14	1044	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [0.71, 4.01]
2 Perioperative bleeding requiring non-surgical intervention	10	745	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.41, 2.40]
3 Vomiting	13	1021	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.61, 0.85]

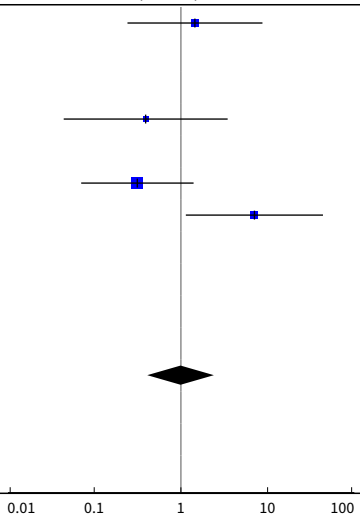
Analysis 1.1. Comparison 1 Nonsteroidal versus control (analgesics or placebo), Outcome 1 Perioperative bleeding requiring surgical intervention.

Study or subgroup	NSAIDs n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Antila 2006	0/15	2/30		8.49%	0.22[0.01,4.22]
Gunter 1995	2/49	1/47		14.34%	1.89[0.19,18.66]
Harley 1998	2/16	0/11		9.07%	5.78[0.33,102.66]
Kokki 2002	2/89	0/21		5.98%	3.48[0.1,120.3]
Pickering 2002	1/40	1/18		8.22%	0.41[0.02,8.33]
Rawlinson 2011	0/30	0/32			Not estimable
Romsing 1998	5/41	0/20		20.1%	4.92[0.71,34.01]
Rusy 1995	0/25	0/25			Not estimable
Splinter 1996	2/35	0/29		9.53%	6.41[0.39,106.11]
St Charles 1997	1/55	0/55		4.89%	7.39[0.15,372.38]
Sutherland 1998	0/25	1/25		4.89%	0.14[0,6.82]
Sutters 1995	0/45	0/43			Not estimable
Thiagarajan 1993	1/91	2/92		14.5%	0.52[0.05,5.02]
Öztekin 2002	0/20	0/20			Not estimable
Total (95% CI)	**576**	**468**		**100%**	**1.69[0.71,4.01]**
Total events: 16 (NSAIDs), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.8, df=9(P=0.46); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					



Analysis 1.2. Comparison 1 Nonsteroidal versus control (analgesics or placebo), Outcome 2 Perioperative bleeding requiring non-surgical intervention.

Study or subgroup	NSAIDs n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gunter 1995	3/49	2/47		24.44%	1.45[0.24,8.72]
Keidan 2004	0/25	0/32			Not estimable
Kokki 2002	0/89	0/21			Not estimable
Pickering 2002	2/40	2/18		16.56%	0.39[0.04,3.46]
Rawlinson 2011	0/30	0/32			Not estimable
Romsing 1998	4/40	5/20		35.3%	0.31[0.07,1.4]
Splinter 1996	5/35	0/29		23.69%	7.05[1.14,43.47]
St Charles 1997	0/55	0/55			Not estimable
Sutters 1995	0/45	0/43			Not estimable
Öztekin 2002	0/20	0/20			Not estimable
Total (95% CI)	**428**	**317**		**100%**	**0.99[0.41,2.4]**
Total events: 14 (NSAIDs), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.61, df=3(P=0.05); I^2=60.6%					
Test for overall effect: Z=0.02(P=0.98)					



Analysis 1.3. Comparison 1 Nonsteroidal versus control (analgesics or placebo), Outcome 3 Vomiting.

Study or subgroup	NSAIDs n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Antila 2006	7/15	14/30		4.84%	1[0.52,1.94]
Gunter 1995	32/49	39/47		20.64%	0.79[0.62,1]
Keidan 2004	2/25	3/32		1.36%	0.85[0.15,4.72]
Kokki 2002	32/89	8/21		6.71%	0.94[0.51,1.74]
Pickering 2002	11/40	4/18		2.86%	1.24[0.46,3.36]
Rawlinson 2011	4/30	4/32		2.01%	1.07[0.29,3.89]
Romsing 1998	5/40	7/20		4.84%	0.36[0.13,0.98]
Splinter 1996	14/35	9/29		5.1%	1.29[0.65,2.54]
St Charles 1997	10/55	20/55		10.37%	0.5[0.26,0.97]
Sutherland 1998	5/25	17/24		8.99%	0.28[0.12,0.64]
Sutters 1995	10/45	15/42		8.04%	0.62[0.31,1.23]
Thiagarajan 1993	31/91	42/92		21.65%	0.75[0.52,1.07]
Öztekin 2002	1/20	5/20		2.59%	0.2[0.03,1.56]
Total (95% CI)	**559**	**462**		**100%**	**0.72[0.61,0.85]**
Total events: 164 (NSAIDs), 187 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.24, df=12(P=0.18); I^2=26.11%					
Test for overall effect: Z=3.86(P=0)					

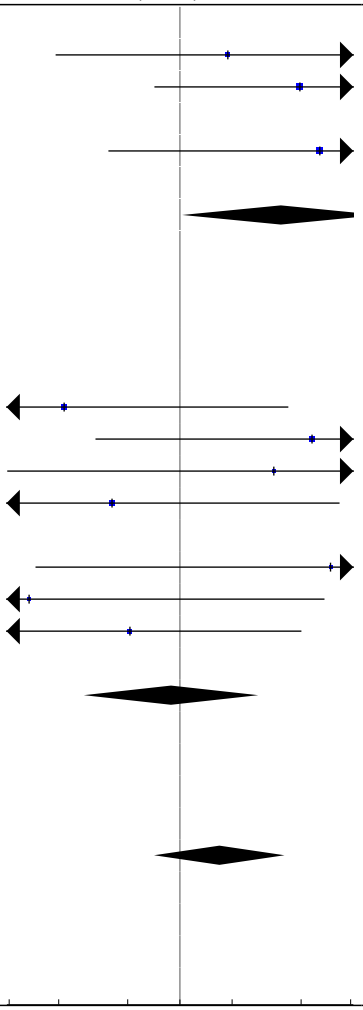
Favours experimental — Favours control

Comparison 2. Subgroup by NSAID type

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perioperative bleeding requiring surgical intervention	14	1044	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [0.71, 4.01]
1.1 Ketorolac	5	359	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.82 [1.03, 14.10]
1.2 NSAID other than ketorolac	9	685	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.28, 2.83]
2 Perioperative bleeding requiring non-surgical intervention	10	745	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.41, 2.40]
2.1 Ketorolac	5	365	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.45, 3.14]
2.2 NSAIDs other than ketorolac	5	380	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.04, 3.46]
3 Vomiting	13	1021	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.43, 0.76]
3.1 Ketorolac	5	364	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.35, 0.94]
3.2 NSAID other than ketorolac	8	657	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.40, 0.80]

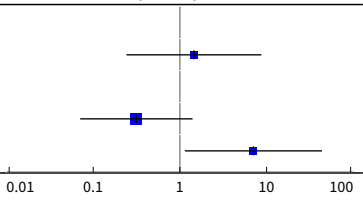
Analysis 2.1. Comparison 2 Subgroup by NSAID type, Outcome 1 Perioperative bleeding requiring surgical intervention.

Study or subgroup	Ketorolac n/N	NSAID other than Ketorola n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.1.1 Ketorolac					
Gunter 1995	2/49	1/47		14.34%	1.89[0.19,18.66]
Romsing 1998	5/41	0/20		20.1%	4.92[0.71,34.01]
Rusy 1995	0/25	0/25			Not estimable
Splinter 1996	2/35	0/29		9.53%	6.41[0.39,106.11]
Sutters 1995	0/45	0/43			Not estimable
Subtotal (95% CI)	**195**	**164**		**43.97%**	**3.82[1.03,14.1]**
Total events: 9 (Ketorolac), 1 (NSAID other than Ketorola)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
2.1.2 NSAID other than ketorolac					
Antila 2006	0/15	2/30		8.49%	0.22[0.01,4.22]
Harley 1998	2/16	0/11		9.07%	5.78[0.33,102.66]
Kokki 2002	2/89	0/21		5.98%	3.48[0.1,120.3]
Pickering 2002	1/40	1/18		8.22%	0.41[0.02,8.33]
Rawlinson 2011	0/30	0/32			Not estimable
St Charles 1997	1/55	0/55		4.89%	7.39[0.15,372.38]
Sutherland 1998	0/25	1/25		4.89%	0.14[0,6.82]
Thiagarajan 1993	1/91	2/92		14.5%	0.52[0.05,5.02]
Öztekin 2002	0/20	0/20			Not estimable
Subtotal (95% CI)	**381**	**304**		**56.03%**	**0.89[0.28,2.83]**
Total events: 7 (Ketorolac), 6 (NSAID other than Ketorola)					
Heterogeneity: Tau^2=0; Chi^2=5.56, df=6(P=0.47); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
Total (95% CI)	**576**	**468**		**100%**	**1.69[0.71,4.01]**
Total events: 16 (Ketorolac), 7 (NSAID other than Ketorola)					
Heterogeneity: Tau^2=0; Chi^2=8.8, df=9(P=0.46); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					
Test for subgroup differences: Chi^2=2.68, df=1 (P=0.1), I^2=62.72%					



Analysis 2.2. Comparison 2 Subgroup by NSAID type, Outcome 2 Perioperative bleeding requiring non-surgical intervention.

Study or subgroup	Ketorolac n/N	NSAID other than Ketorola n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.2.1 Ketorolac					
Gunter 1995	3/49	2/47		24.44%	1.45[0.24,8.72]
Keidan 2004	0/25	0/32			Not estimable
Romsing 1998	4/40	5/20		35.3%	0.31[0.07,1.4]
Splinter 1996	5/35	0/29		23.69%	7.05[1.14,43.47]



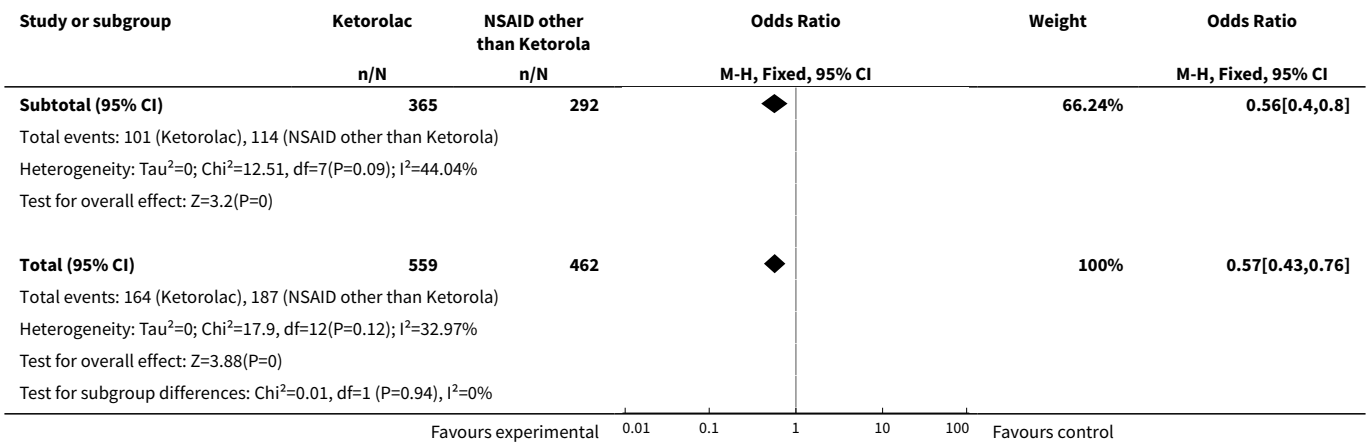
Study or subgroup	Ketorolac n/N	NSAID other than Ketorola n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Sutters 1995	0/45	0/43			Not estimable
Subtotal (95% CI)	**194**	**171**		**83.44%**	**1.19[0.45,3.14]**
Total events: 12 (Ketorolac), 7 (NSAID other than Ketorola)					
Heterogeneity: Tau²=0; Chi²=6.78, df=2(P=0.03); I²=70.5%					
Test for overall effect: Z=0.35(P=0.72)					
2.2.2 NSAIDs other than ketorolac					
Kokki 2002	0/89	0/21			Not estimable
Pickering 2002	2/40	2/18		16.56%	0.39[0.04,3.46]
Rawlinson 2011	0/30	0/32			Not estimable
St Charles 1997	0/55	0/55			Not estimable
Öztekin 2002	0/20	0/20			Not estimable
Subtotal (95% CI)	**234**	**146**		**16.56%**	**0.39[0.04,3.46]**
Total events: 2 (Ketorolac), 2 (NSAID other than Ketorola)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					
Total (95% CI)	**428**	**317**		**100%**	**0.99[0.41,2.4]**
Total events: 14 (Ketorolac), 9 (NSAID other than Ketorola)					
Heterogeneity: Tau²=0; Chi²=7.61, df=3(P=0.05); I²=60.6%					
Test for overall effect: Z=0.02(P=0.98)					
Test for subgroup differences: Chi²=0.83, df=1 (P=0.36), I²=0%					

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 2.3. Comparison 2 Subgroup by NSAID type, Outcome 3 Vomiting.

Study or subgroup	Ketorolac n/N	NSAID other than Ketorola n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Ketorolac					
Gunter 1995	32/49	39/47		11%	0.39[0.15,1.01]
Keidan 2004	2/25	3/32		1.93%	0.84[0.13,5.46]
Romsing 1998	5/40	7/20		6.51%	0.27[0.07,0.99]
Splinter 1996	14/35	9/29		4.71%	1.48[0.52,4.18]
Sutters 1995	10/45	15/42		9.61%	0.51[0.2,1.32]
Subtotal (95% CI)	**194**	**170**		**33.76%**	**0.58[0.35,0.94]**
Total events: 63 (Ketorolac), 73 (NSAID other than Ketorola)					
Heterogeneity: Tau²=0; Chi²=5.4, df=4(P=0.25); I²=25.97%					
Test for overall effect: Z=2.2(P=0.03)					
2.3.2 NSAID other than ketorolac					
Antila 2006	7/15	14/30		3.97%	1[0.29,3.46]
Kokki 2002	32/89	8/21		6.6%	0.91[0.34,2.43]
Pickering 2002	11/40	4/18		3.19%	1.33[0.36,4.92]
Rawlinson 2011	4/30	4/32		2.67%	1.08[0.24,4.76]
St Charles 1997	10/55	20/55		13.04%	0.39[0.16,0.94]
Sutherland 1998	5/25	17/24		11.06%	0.1[0.03,0.38]
Thiagarajan 1993	31/91	42/92		21.94%	0.62[0.34,1.12]
Öztekin 2002	1/20	5/20		3.78%	0.16[0.02,1.5]

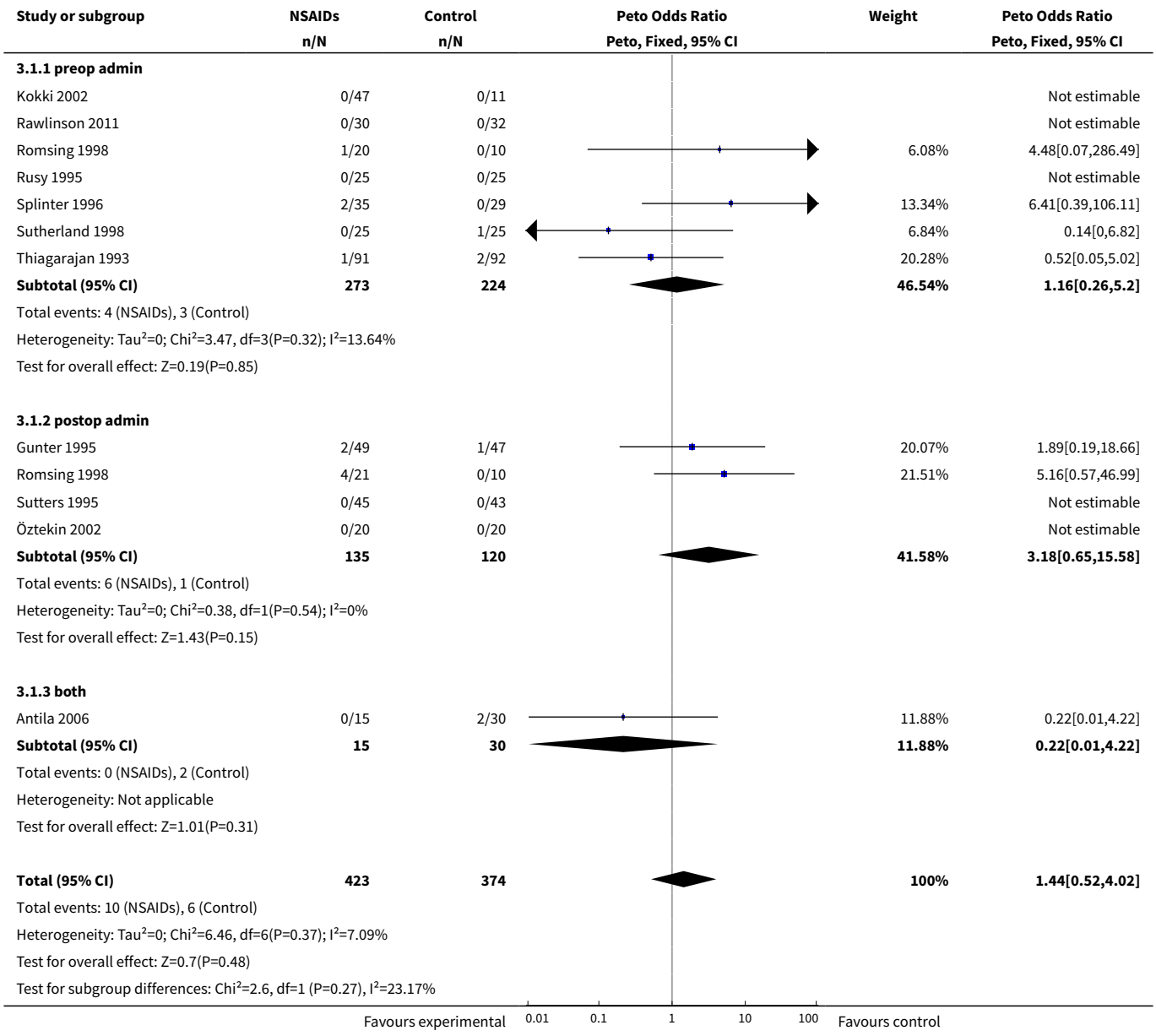
Favours experimental 0.01 0.1 1 10 100 Favours control



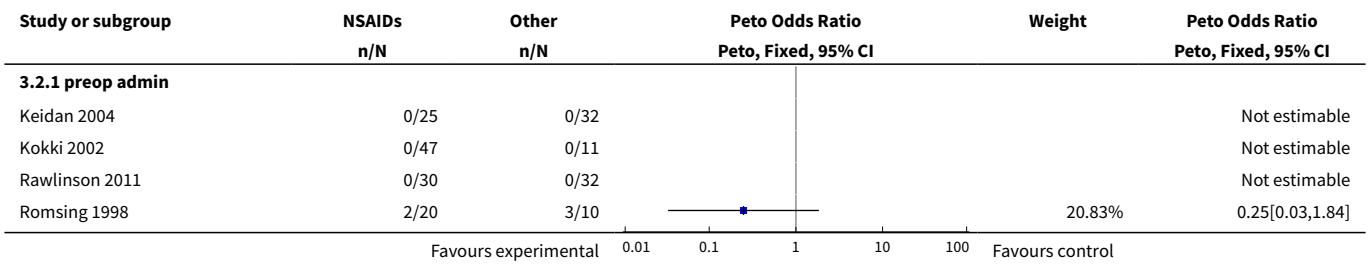
Comparison 3. Subgroup by timing of administration

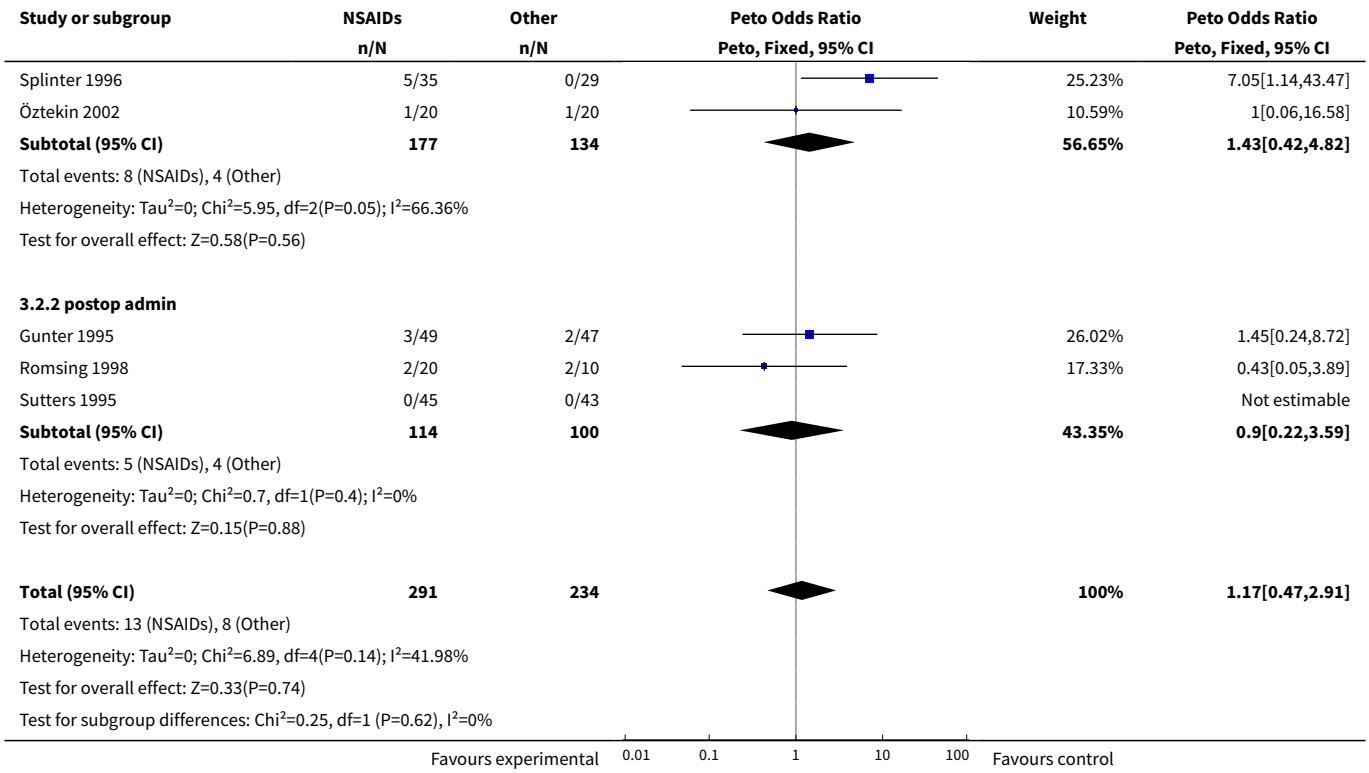
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perioperative bleeding requiring surgical intervention	11	797	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.52, 4.02]
1.1 preop admin	7	497	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.26, 5.20]
1.2 postop admin	4	255	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.18 [0.65, 15.58]
1.3 both	1	45	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.01, 4.22]
2 Perioperative bleeding requiring non-surgical intervention	8	525	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.47, 2.91]
2.1 preop admin	6	311	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.42, 4.82]
2.2 postop admin	3	214	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.22, 3.59]
3 Vomiting	11	801	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.86]
3.1 preop admin	8	543	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.54, 0.90]
3.2 postop admin	3	213	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.92]
3.3 both	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.52, 1.94]

Analysis 3.1. Comparison 3 Subgroup by timing of administration, Outcome 1 Perioperative bleeding requiring surgical intervention.

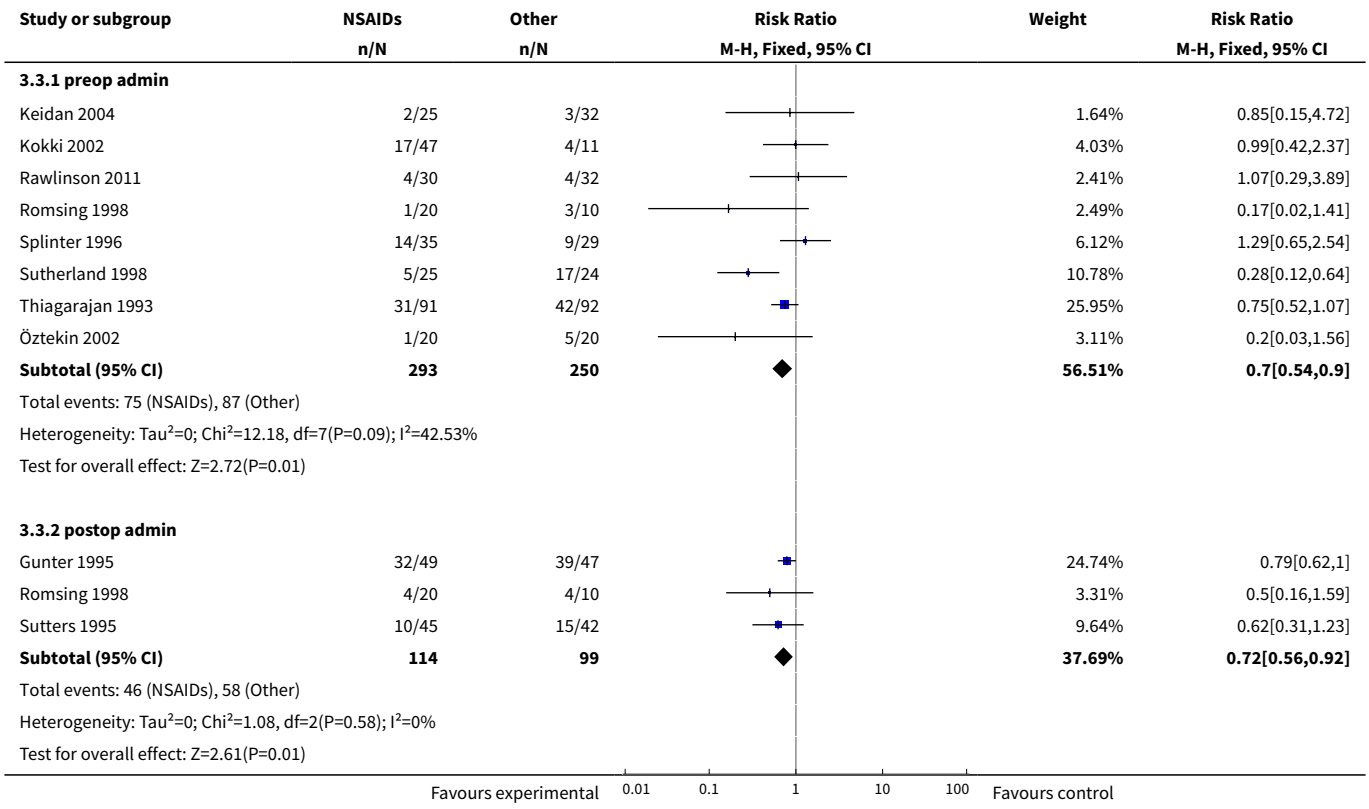


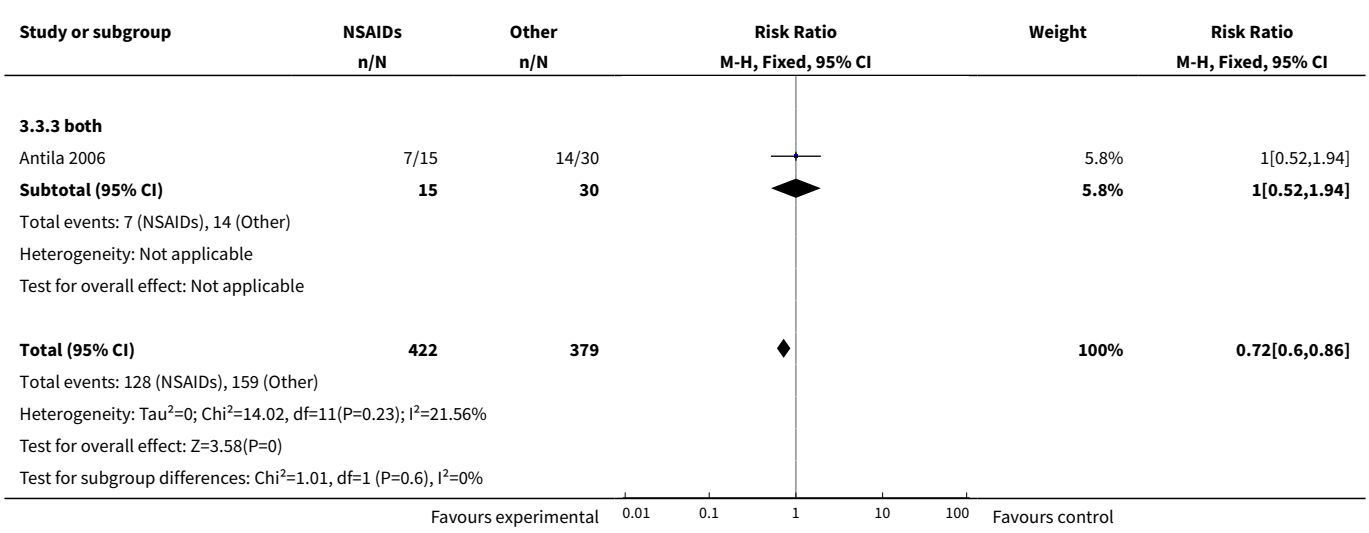
Analysis 3.2. Comparison 3 Subgroup by timing of administration, Outcome 2 Perioperative bleeding requiring non-surgical intervention.





Analysis 3.3. Comparison 3 Subgroup by timing of administration, Outcome 3 Vomiting.

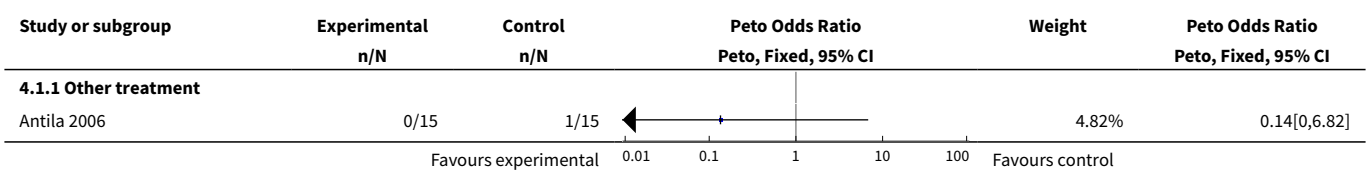


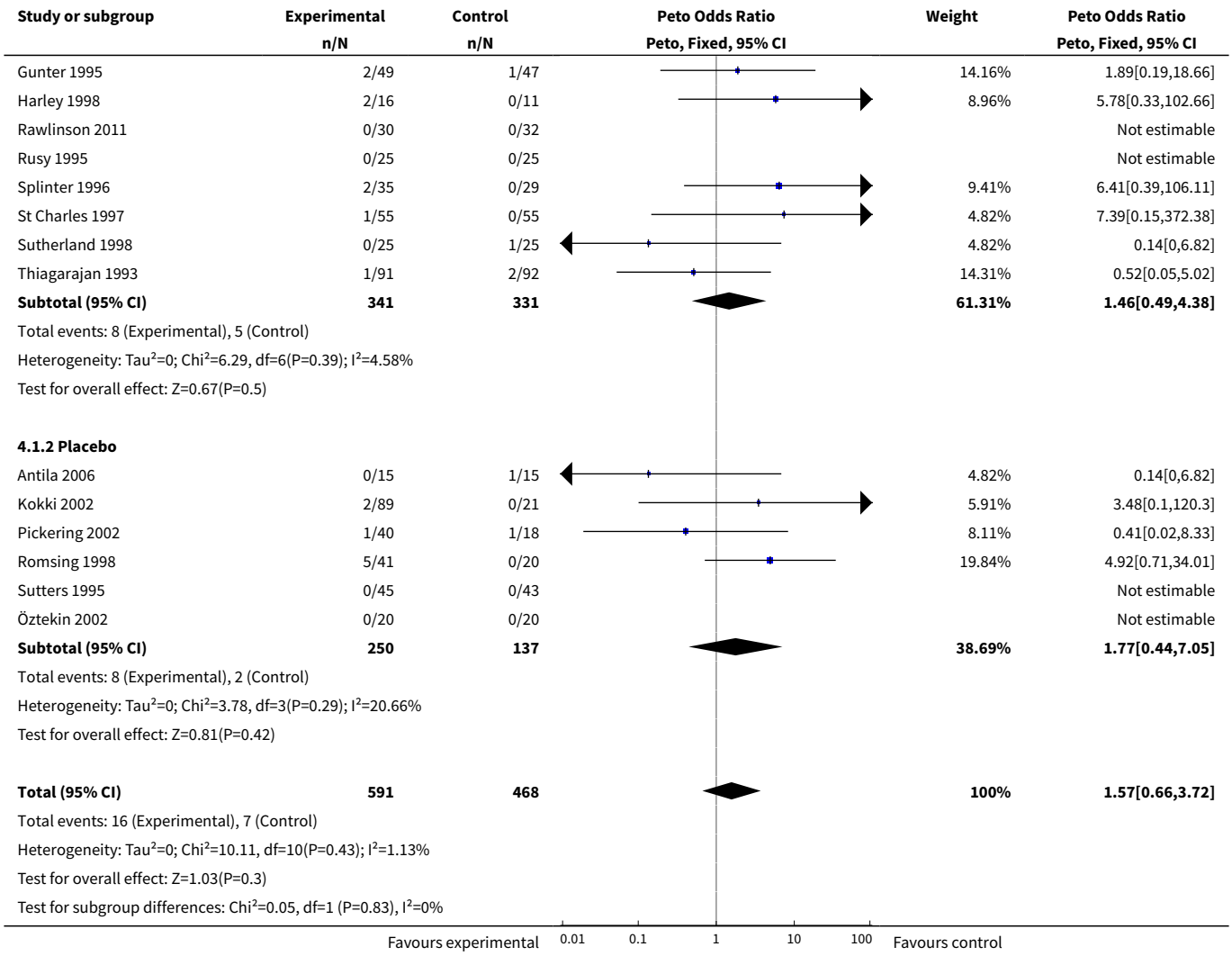


Comparison 4. Subgroup by control (placebo or other treatment)

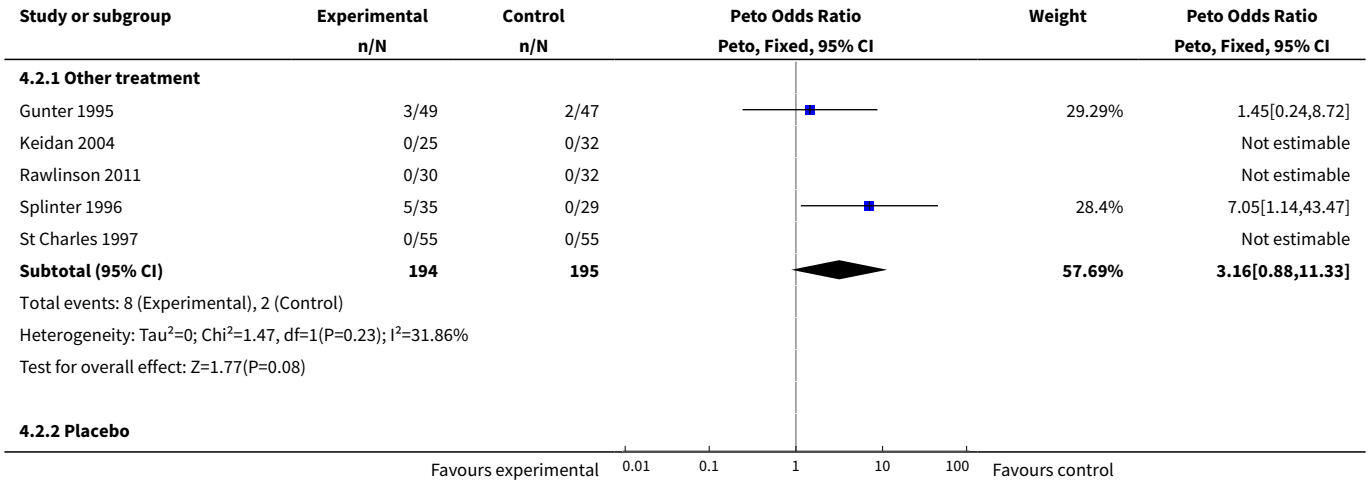
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perioperative bleeding requiring surgical intervention	14	1059	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.66, 3.72]
1.1 Other treatment	9	672	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.49, 4.38]
1.2 Placebo	6	387	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.44, 7.05]
2 Perioperative bleeding requiring non-surgical intervention	9	687	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.45, 3.14]
2.1 Other treatment	5	389	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.16 [0.88, 11.33]
2.2 Placebo	4	298	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.07, 1.40]
3 Vomiting	13	1036	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.62, 0.86]
3.1 Other treatment	8	651	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.88]
3.2 Placebo	6	385	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.51, 0.99]

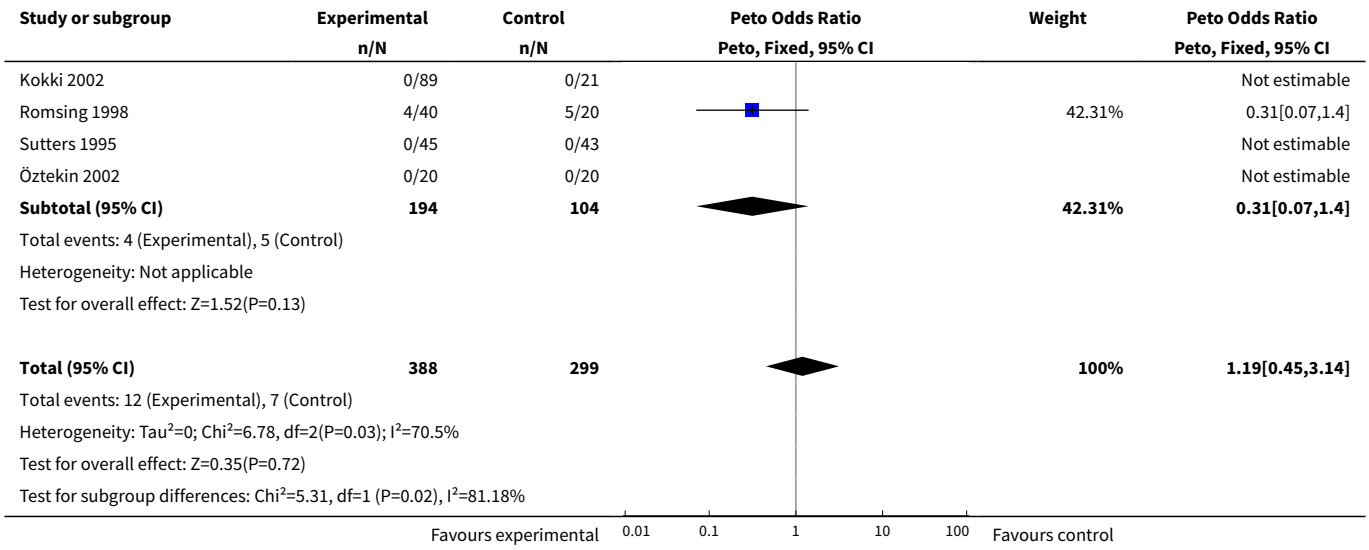
Analysis 4.1. Comparison 4 Subgroup by control (placebo or other treatment), Outcome 1 Perioperative bleeding requiring surgical intervention.



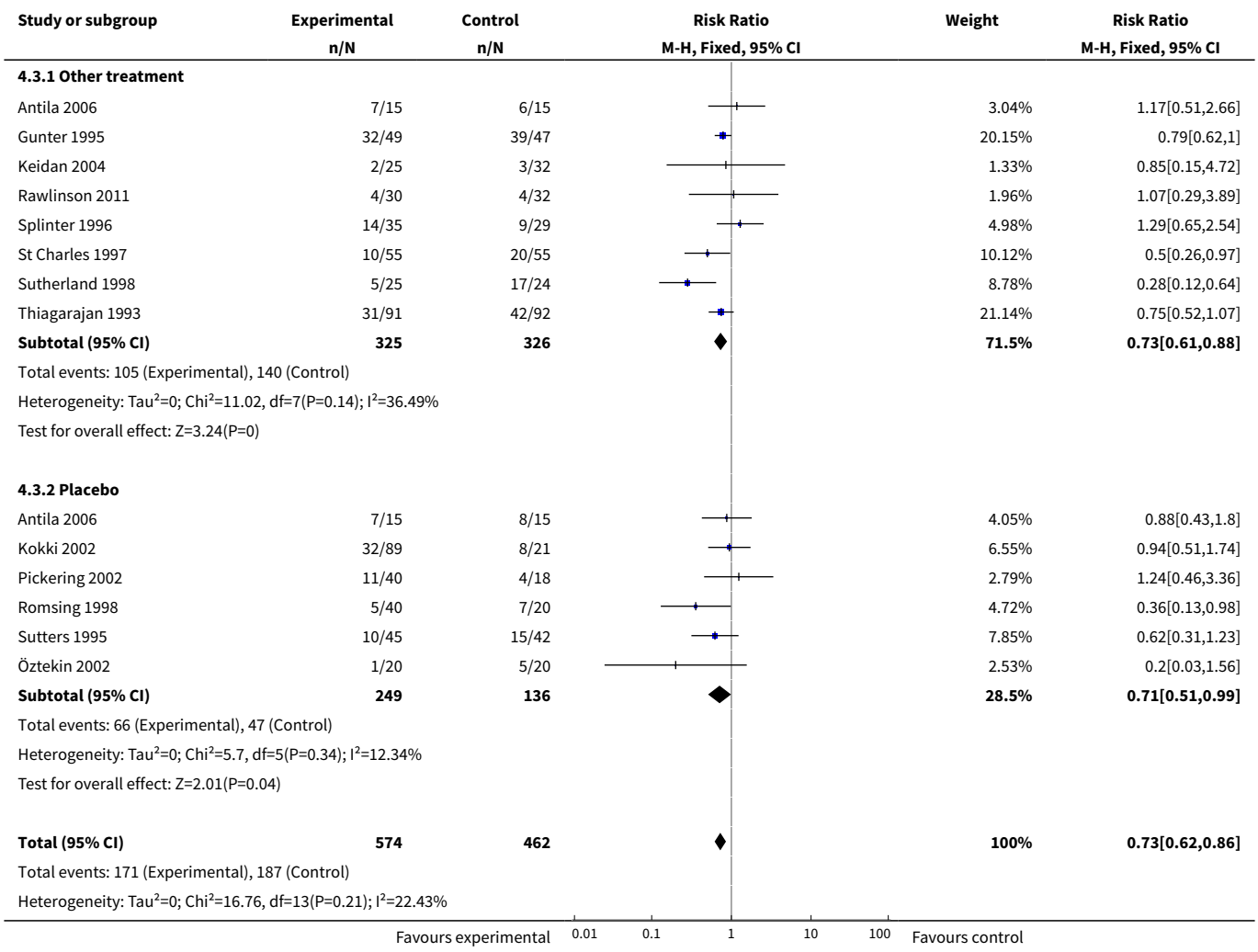


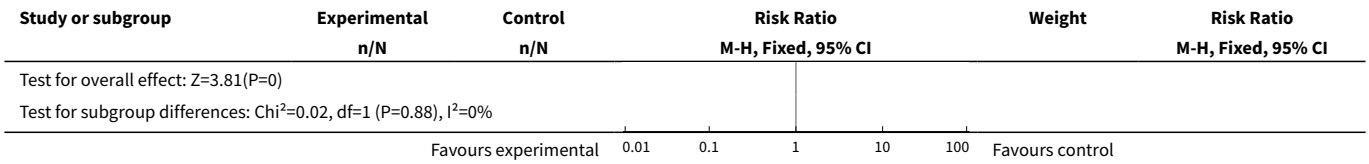
Analysis 4.2. Comparison 4 Subgroup by control (placebo or other treatment), Outcome 2 Perioperative bleeding requiring non-surgical intervention.





Analysis 4.3. Comparison 4 Subgroup by control (placebo or other treatment), Outcome 3 Vomiting.





APPENDICES

Appendix 1. Search strategy for MEDLINE (OvidSP)

1. exp tonsillectomy/ or tonsil*.ti,ab.
2. exp Anti-inflammatory agents/ or exp Analgesics-non-narcotic/ or exp cyclooxygenase-inhibitors/ or (Ketorolac or Ibuprofen or Diclofenac or Naproxen or Piroxicam or ketoprofen or indomethacin).mp. or exp Postoperative-Hemorrhage/ or (postoperative adj3 h?emorrhage).mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 2. Search strategy for EMBASE (OvidSP)

1 exp tonsillectomy/ or tonsil*.ti,ab.
2 exp antiinflammatory agent/ or exp analgesic-agent/ or exp postoperative-hemorrhage/ or (Ketorolac or Ibuprofen or Diclofenac or Naproxen or Piroxicam or ketoprofen or indomethacin).mp.
3 1 and 2
4 (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or factorial* or placebo* or volunteer* or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.
5 3 and 4

Appendix 3. Search strategy for CENTRAL (The Cochrane Library)

#1 MeSH descriptor Tonsillectomy explode all trees
#2 tonsil*
#3 (#1 OR #2)
#4 MeSH descriptor Anti-Inflammatory Agents explode all trees
#5 MeSH descriptor Analgesics, Non-Narcotic explode all trees
#6 Ketorolac or Ibuprofen or Diclofenac or Naproxen or Piroxicam or ketoprofen or indomethacin
#7 MeSH descriptor Cyclooxygenase Inhibitors explode all trees
#8 (#4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Postoperative Hemorrhage explode all trees
#10 (#3 AND (#8 OR #9))

Appendix 4. Data extraction form 2012 update

Data Collection Form

Review title or ID

Study ID *(surname of first author and year first full report of study published e.g. Smith 2001)*

(Continued)

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

1. General Information

Date form completed (dd/mm/yyyy)
Name/ID of person extracting data
Report title (title of paper/ abstract/ report that data extracted from)
Reference details
Report author contact details
Publication type (e.g. full report, abstract, letter)
Study funding sources (including role of funders)
Possible conflicts of interest (for study authors)

2. Study Eligibility

Study Characteristics	**Eligibility criteria**	**Yes No Unclear**	**Location in text** *(pg & ¶ /fig / table)*
Type of study	Randomized Controlled Trials		
Participants	Children <16yrs, who underwent elective tonsillectomy or adenotonsillectomy		
Types of intervention	NSAIDs. Any route of administration.		

(Continued)

Drug exclusions	Does trial include aspirin?
	Does trial include COX-2 inhibitors?
Types of outcome measures	Bleeding requiring further surgical intervention
	Bleeding not requiring further surgical intervention
	Nausea or vomiting, or both

INCLUDE	**EXCLUDE**

Reason for exclusion

DO NOT PROCEED IF EXCLUDED FROM REVIEW

3. Population and setting

	Description *(include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶ /fig / table)*
Population and description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		

(Continued)

Informed consent obtained	**Yes/No/Unclear**

4. Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Aim of study		
Design *(e.g. parallel, crossover, cluster)*		
Unit of allocation *(by individuals, cluster /groups or body parts)*		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study	**Yes/No/Unclear**	

5. Risk of Bias assessment

Domain	**Risk of bias**	**Support for judgement**	**Location in text** *(pg & ¶ /fig / table*

(Continued)

	Low/ High/ Unclear	
Random sequence generation *(selection bias)*		
Allocation concealment *(selection bias)*		
Baseline Imbalances		
Blinding of participants and personnel *(performance bias)*		**Outcome: Bleeding requiring surgical intervention**
		Outcome: Bleeding not requiring surgical intervention
		Outcome: Nausea or vomiting, or both
Blinding of outcome assessment *(detection bias)*		**Outcome: Bleeding requiring surgical intervention**
		Outcome: Bleeding not requiring surgical intervention
		Outcome: Nausea or vomiting, or both
Incomplete outcome data *(attrition bias)*		**Outcome: Bleeding requiring surgical intervention**
		Outcome: Bleeding not requiring surgical intervention
		Outcome: Nausea or vomiting, or both
Selective outcome reporting *(reporting bias)*		
Other bias		

(Continued)

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text *(pg & ¶ / fig / table*
Total no. randomized		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age *age range (mean)*	**Intervention** / **Comparison**	
Sex *Male/Female*	**Intervention** / **Comparison**	
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Anaesthetics used		

(Continued)

Rescue analgesics given *(and at what stage)*	
Rescue anti-emetics given *(and at what stage)*	
Other drugs given *(and at what stage)*	
Other relevant sociodemographics	
Subgroups measured	
Subgroups reported	

7.1 Intervention group

	Description as stated in report/paper	Location in text *(pg & ¶ /fig / table*
Intervention	NSAID	
Type of surgical procedure and method *(e.g. tonsillectomy by electrocautery)*		
No. randomized to group *(specify whether no. people or clusters)*		
Description *(type, dose)*		
Duration of treatment period		
Timing		

(Continued)

(e.g. pre-operatively, intra-operatively, post-operatively)

Delivery

(e.g. mechanism, medium, intensity)

Providers

(e.g. no., profession, training, ethnicity etc. if relevant)

Co-interventions

7.2 Comparison groups – *repeated as required*

	Description as stated in report/paper	Location in text (pg & ¶ /fig / table
Comparison group type *(placebo, no treatment, different drug)*		
Type of surgical procedure and method *(e.g. tonsillectomy by electrocautery)*		
No. randomized to group *(specify whether no. people or clusters)*		
Description *(type, dose)*		
Duration of treatment period		
Timing *(e.g. pre-operatively, intra-operatively, post-operatively)*		
Delivery *(e.g. mechanism, medium, intensity)*		

(Continued)

Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*
Co-interventions

7.3 Comparison groups

	Description as stated in report/paper	Location in text *(pg & ¶ /fig / table*
Comparison group type *(placebo, no treatment, different drug)*		
Type of surgical procedure and method *(e.g. tonsillectomy by electrocautery)*		
No. randomized to group *(specify whether no. people or clusters)*		
Description *(type, dose)*		
Duration of treatment period		
Timing *(e.g. pre-operatively, intra-operatively, post-operatively)*		
Delivery *(e.g. mechanism, medium, intensity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		

(Continued)

8.1 Outcomes (repeat for each outcome)

	Description as stated in report/paper	Location in text *(pg & ¶ /fig / table*
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome tool validated?	**Yes/No/Unclear**	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power		

9.1 Results (repeat for each outcome)

	Description as stated in report/paper		**Location in text** *(pg & ¶ /fig / table*
Comparison			
Outcome			
Subgroup			
Timepoint *(specify whether from start or end of intervention)*			
Results	**Intervention**	**Comparison**	
	No. events/no. participants	**No. events/no.participants**	
No. missing participants and reasons			
No. participants moved from other group and reasons			
Any other results reported			
Unit of analysis *(by individuals, cluster/ groups or body parts)*			
Statistical methods used & appropriateness of these methods *(e.g. adjustment for correlation)*			
Reanalysis required?	**Yes/No/Unclear**		

(Continued)

(specify)

Reanalysis possible?	**Yes/No/Unclear**
Reanalysed results	

10. Applicability

Have important population groups been excluded from the study? *(consider disadvantaged populations, and possible differences in the intervention effect)*	**Yes No Unclear**	
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	**Yes No Unclear**	
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	**Yes No Unclear**	

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶ /fig / table*
Key conclusion of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		

END

WHAT'S NEW

Date	Event	Description
1 July 2013	New search has been performed	A 'Summary of findings' table has been included.
1 July 2013	New search has been performed	We reconsidered a previously excluded subgroup analysis of timing of administration of the intervention drug. We were able to

Date	Event	Description
		conduct this subgroup analysis by considering the timing between studies as well as within studies.
1 July 2013	New citation required but conclusions have not changed	We updated our search from 2010 to 2012. We did a full paper review of 12 new studies of which we excluded 11. We included Rawlinson 2011. We arranged translation of Sun 2009, which was then excluded. We reconsidered Tawalbeh 2001 as not being eligible and removed this study from the included studies. Due to changes to the Cochrane risk of bias tables we chose to re-extract data from all existing studies as well as the new study. This resulted in some minor alterations to the data. Where studies had provided both pre and postoperative data (Kokki 2002; Romsing 1998), we included data in the analysis from both groups. We reconsidered and chose to include data from a particular surgeon (in Romsing 1998) in order to show any potential increased risk of bleeding.
1 July 2013	New search has been performed	We made revisions to the text and to the 'Risk of bias' tables in light of alterations as a result of data extraction. We made changes to the outcomes in order to improve clarity. For the vomiting outcome we also defined the timing in the text as being within 24 hours. This was then reflected in minor alterations to the data.
1 July 2013	New search has been performed	Additional authors were added to the review.

HISTORY

Protocol first published: Issue 2, 2002
Review first published: Issue 2, 2005

Date	Event	Description
24 August 2010	Amended	We included a study (Pickering 2002) which had been incorrectly excluded from our previous review (Cardwell 2005). This study had been excluded because it studied COX-2 inhibitors; but it also had an ibuprofen group and a placebo group, so data were used from these two groups.
24 August 2010	Amended	We completed a risk of bias table, risk of bias graph and risk of bias summary.
24 August 2010	New search has been performed	We updated our search from 2004 to 2010. We did a full paper review of 11 new studies from our updated search of which we excluded 10 (Bhattacharya 2005; Bhattacharya 2009; Hardy 2010; Heaney 2007; Hiller 2004; Jeyakumar 2008; Kedek 2005; Louizos 2006; McKean 2008; Nikanne 2005) and included one (Antila 2006). An additional paper is awaiting further assessment as it needs to be translated (Sun 2009). This new study does not change our conclusions.
1 August 2008	New search has been performed	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Updated review

Sharon R Lewis (SL), Amanda Nicholson (AN), Mary E Cardwell (MC), Gretchen Siviter (GS), Andrew F Smith (AFS)

Conceiving the original review: MC, GS

Designing the original review: MC, Dr G Siviter, AFS

Co-ordinating the 2012 update: SL

Undertaking manual searches: SL, AN

Screening search results: SL, MC, AFS

Organizing retrieval of papers: SL

Screening retrieved papers against inclusion criteria: MC, SL

Appraising quality of papers: SL, AN

Extracting data from papers: SL, AN

Writing to authors of papers for additional information: SL

Providing additional data about papers: MC

Obtaining and screening data on unpublished studies: SL, AN

Data management for the review: AN, SL

Entering data into Review Manager (RevMan 5.2): SL, AN

RevMan statistical data: AN, SL

Double entry of data: (data entered by person one: SL; data entered by person two: AN)

Interpretation of data: AN, SL, AFS

Statistical inferences: AN, SL, AFS

Writing the review: SL, AN

Providing guidance on the review: AFS

Securing funding for the review: AFS

Guarantor for the review (one author): AFS

Person responsible for reading and checking review before submission: AN

Original review (Cardwell 2005)

GS and MC conceived the idea for the review and wrote the protocol. AFS helped to design the protocol.

SL and AN wrote the review update with advice and editing from AFS and MC.

DECLARATIONS OF INTEREST

Sharon R Lewis: see Sources of support

Amanda Nicholson: AN worked for the Cardiff Research Consortium, which provided research and consultancy services to the pharmaceutical industry, from March to Septmber 2011. Cardiff Research Consortium has no connection with AN's work with The Cochrane Collaboration. AN's husband has small direct holdings in several drug and biotech companies as part of a wider balanced share portfolio

Mary E Cardwell: none known

Gretchen Siviter: none known

Andrew F Smith: see Sources of support

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Health Research (NIHR), UK.

  This review forms part of the NIHR Cochrane Collaboration Programme Grant 10/40001/04 entitled Enhancing the safety, quality and productivity of perioperative care

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol, we stated that if there were enough data we would create subgroups for individual drugs. After our search, we found that we had inadequate numbers of papers to do this for all the NSAIDs. However, we were able to do this for ketorolac.

In the 2012 update we renamed the original outcomes. In particular the second outcome was changed from 'bleeding not requiring surgical intervention' to 'perioperative bleeding requiring non-surgical intervention'. Although we considered the same types of examples given in the original protocol (intravenous fluid therapy, prolonged observation and non-surgical haemostasis), this change in the wording improved clarity for data extraction purposes. We also changed the third outcome to only include reported data on vomiting and added the time to event as within 24 hours.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*adverse effects]; Pain, Postoperative [*drug therapy]; Postoperative Hemorrhage [*chemically induced]; Postoperative Nausea and Vomiting [prevention & control]; Randomized Controlled Trials as Topic; Tonsillectomy [*adverse effects]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant