Diclofenac for acute pain in children (Review)

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[Intervention Review]

Diclofenac for acute pain in children

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ABSTRACT

Background

Diclofenac is commonly used for acute pain in children, but is not licensed for this indication in all age groups.

Objectives

1) Assess the efficacy of diclofenac for acute pain in children.

2) Assess the safety of diclofenac for short-term use in children.

3) Identify gaps in the evidence to direct future research.

Search strategy

Seventeen databases indexing clinical trial reports were searched in February 2005 (with an update search as part of this first review in May 2008). A hand search of Paediatric Anaesthesia was undertaken and summaries obtained of adverse reaction reports from the UK Yellow Card Scheme and World Health Organization (WHO) Monitoring Centre. The reference lists of included studies were also searched.

Selection criteria

Any published report, in any language, involving the administration of diclofenac to a patient aged 18 years or younger for acute pain and detailing either monitoring of efficacy or safety.

Data collection and analysis

Two review authors independently assessed study quality and extracted the data. Authors were contacted where necessary. Review Manager version 5 was used for analysis.

Main results

1) Efficacy: randomised controlled trials (RCTs) comparing diclofenac with placebo/any other treatment by using pain scores (assessed or reported), or need for rescue analgesia.

2) Safety: any type of study seeking adverse events (regardless of cause). An adverse event was defined as any reported adverse or untoward happening to a patient being treated with diclofenac for acute pain.

Seven publications on diclofenac efficacy and 79 on safety (74 studies plus five case reports) were included in the final analysis. Compared with placebo/no treatment, diclofenac significantly reduced need for post-operative rescue analgesia (relative risk [RR] 0.6; number needed to treat to benefit [NNT] 3.6; 95% confidence interval [CI] 2.5 to 6.3).

Compared with any other non-NSAID, patients receiving diclofenac suffered less nausea or vomiting, or both (RR 0.6; NNT 7.7 [5.3 to 14.3]). There appeared to be no increase in bleeding requiring surgical intervention in patients receiving diclofenac in the peri-operative period. Serious diclofenac adverse reactions occurred in fewer than 0.24% of children treated for acute pain. The types of serious adverse reactions were similar to those reported in adults.

Authors' conclusions

Diclofenac is an effective analgesic for perioperative acute pain in children. It causes similar types of serious adverse reactions in children as in adults, but these are rare. More research on optimum dosing and safety in asthmatic children is required.

PLAIN LANGUAGE SUMMARY

Diclofenac for pain relief in children

Diclofenac is commonly used for short-term pain relief in children, particularly around the time of surgery. There is good evidence that diclofenac is effective for pain relief in adults, and side effects such as stomach upset are well known. However, developmental differences mean that children may sometimes react differently to medicines than adults do. It is important to assess whether diclofenac is also effective in children, and to understand the type and frequency of adverse reactions that diclofenac causes in children. This review has found that, as with adults, diclofenac is effective for the relief of pain after an operation. If it is given at the time of an operation, it will halve the number of children needing extra pain relief. Diclofenac seems to be twice as effective as paracetamol (acetaminophen) for surgical pain, and this is also true for adults. Diclofenac appears to cause similar types of serious adverse reactions (such as bleeding of the stomach and allergic-type reactions), but these are rare and occur in fewer than 3 in 1000 children who take the drug. We had hoped to investigate whether diclofenac made children with asthma more wheezy, but there was not enough information for us to do this. The main conclusions of this review are that diclofenac is effective for relief of acute pain arising from operations in children, with a low risk of serious adverse reactions. Intramuscular injections of diclofenac should be avoided, due to risk of injection site problems. The main questions still to be answered are: What is the best dose to give and should diclofenac be avoided in children with asthma?

BACKGROUND

The non-steroidal anti-inflammatory drug (NSAID) diclofenac, is a phenylacetic acid derivative used to treat pain and inflammation, usually in the form of the sodium salt. It is readily absorbed orally, rectally and by an intra-muscular injection; these constitute the main routes of systemic administration (Sweetman 2002). The analgesic and anti-inflammatory action of NSAIDs are mainly due to cyclo-oxygenase inhibition, although decreased leukotriene and arachidonic acid production may also contribute. NSAIDs also have a central antinociceptive action, the mechanism for which is poorly understood (Cashman 1995).

Two isoforms of cyclo-oxygenase (COX-1 and COX-2) have been extensively studied and diclofenac inhibits both (Van 2000). COX-2 is expressed at low levels in various cell types. It is induced at sites of tissue injury and catalyses prostaglandin formation from arachidonic acid and causes pain by generating action potentials in nociceptive neurons (Cashman 1995). It is probably the inhibition of COX-2 that gives diclofenac its analgesic and anti-inflammatory properties. COX-1 is expressed in most tissues and catalyses the formation of prostaglandins with homeostatic functions such as maintaining gastric mucosa, renal blood flow and platelet activation. Some of diclofenac's adverse effects may be mediated by COX-1 inhibition (Cashman 1995).

The main adverse effects of diclofenac are upper gastro-intestinal tract disturbances including bleeding and ulceration. In adults, the risk of such bleeding with NSAIDs seems to increase with

dose and age (Garcia 2004) and chronic NSAID exposure may be the cause rather than short-term acute use. Prolonged bleeding time, vomiting, impaired renal function and bronchospasm (Sweetman 2002) are other reported adverse reactions to diclofenac which may be of particular importance to its use in acute pain such as in the post-operative period. Previous systematic reviews have established diclofenac efficacy in adults with post-operative pain (Barden 2004; Collins 2004) and NSAIDs have been recommended in adults suffering acute pain arising from renal colic (Holdgate 2004).

Despite not being licensed for acute pain in children, diclofenac is commonly used for this indication (Conroy 2001; Turner 1998). Drugs used outside the terms of their product license carry a greater potential for adverse reactions (Choonara 2002), highlighting the importance of safety for the use of diclofenac in children. The increasing recognition of pain suffered by children has led to better management and increased use of pharmacological interventions in this age group (Howard 2003; Lloyd-Thomas 1999). NSAIDs including diclofenac are seen as simple, cheap, and relatively safe options and they are often recommended for acute pain relief in children (AAP 2001; Lloyd-Thomas 1999; Zacharias 1998). Such recommendations need to be supported by sound evidence on safety and efficacy.

Diclofenac undergoes extensive first-pass metabolism (Todd 1988), primarily through 4'-hydroxylation by cytochrome P450 (CYP) 2C9 although 5'-hydroxylation by CYP3A4, CYP2C19, CYP2C8 and CYP2C18 also occurs (Kirchheiner 2003). Diclofenac is highly plasma protein bound, mainly to albumin, and is excreted in both the bile and urine as the glucuronide and sulphate conjugates (Todd 1988). Children at varying developmental stages have varying capacities for metabolising, conjugating and eliminating drugs (Kearns 2003; Morselli 1980) meaning that adult data cannot be extrapolated to determine whether diclofenac is safe and effective in children.

Previous paediatric reviews have tended to focus on peri-operative use of NSAIDs in general (Krishna 2003; Romsing 1997). As diclofenac is widely used for children with acute pain (Conroy 2001; Turner 1998), it is necessary to produce a systematic review on its safety and efficacy in this group of patients.

OBJECTIVES

1. Assess the efficacy of diclofenac for acute pain in children.

2. Assess the safety of diclofenac for short-term (three months or less) use in children.

3. Identify gaps in the evidence for diclofenac use in children to direct future research.

METHODS

Criteria for considering studies for this review

Types of studies

1. **Efficacy:** To investigate the efficacy of diclofenac for acute pain in children, we searched for randomised controlled trials (RCTs) comparing diclofenac with placebo or any other treatment. Pain scoring by patient report or by an assessor, or the use of rescue analgesia, were the measures of efficacy used.
2. **Safety:** To investigate adverse reactions caused by diclofenac in children being treated for acute pain, we searched for any type of study in which adverse events (regardless of their cause) were sought. An adverse event was defined as any reported adverse or untoward happening to a patient being treated with diclofenac for acute pain.

RCTs in which adverse event rates are monitored in patients who have and have not received diclofenac allow event rates to be compared. However, adverse events may not be documented systematically in RCTs (Ioannidis 2002), so we reviewed a broader range of study designs in a teleometric analysis (Aronson 2005). We included any study in which the total number of children exposed to diclofenac for treatment of acute pain was known. This included blind and open RCTs, prospective and retrospective cohort studies, and RCTs of other interventions in which diclofenac was used as an adjuvant therapy to manage acute pain.

All fatal, life-threatening and serious adverse effects (prolonging hospitalisation, causing permanent or significant incapacity or requiring medical or surgical intervention) were reported, regardless of whether diclofenac was thought to be causative. The importance of reporting such events for the purpose of pattern recognition is highlighted by the practolol disaster (Abraham 2006), when an unexpected adverse reaction was grossly under-reported because practolol was not suspected as the causative agent.

Types of participants

Children (participants aged 18 years or younger).

Types of interventions

Diclofenac given systemically for acute pain by the following routes: oral, rectal, intramuscular, intravenous. Acute pain was defined as any situation where diclofenac is required for a short duration e.g.: peri-operative pain; migraine; renal colic; soft tissue injury/fractures.

Types of outcome measures

Efficacy:

- patient-reported pain intensity,
- pain relief scales,
- pain scoring by third party,
- need for opioid analgesia,
- time elapsed to administration of rescue analgesia,
- opioid-sparing effects.

Safety:

Any adverse reaction in patients receiving a short course (three months or less) of diclofenac, defined either as a) a statistically significant increase in events versus placebo or b) a causal link between an adverse event and diclofenac made in the report. In the case of placebo-controlled trials, adverse events in the placebo group were recorded and reported.

Search methods for identification of studies

Electronic searches

The following data sources were searched in February 2005 (with an update search in May 2008).

1. EMBASE
2. MEDLINE
3. CINAHL
4. CENTRAL
5. *The Cochrane Library*
6. Pascal (French)
7. Lilacs (South American)
8. Sigle (grey literature)
9. Dissertation abstracts
10. ISI (conference abstracts)
11. National Research Register
12. Current Controlled Trials
13. Clinicaltrials.gov
14. IPA (International Pharmaceutical Abstracts)
15. Pharmline
16. BIOSIS
17. Pharmaceutical companies marketing diclofenac 25 mg tablets or 12.5 mg/25 mg suppositories in the UK approached for unpublished data in children
18. Hand search of Paediatric Anaesthesia (1970 to 2004)

The general principle of the search used for all databases was as follows:

[Diclofenac text word (not exploded as may get other NSAIDs) OR Diclofenac and related subject headings OR Brand names] AND [Terms for pain (exploded) OR Pain and management OR Cause/type of pain text words OR Cause/type of pain subject headings OR Treatments for pain text word and subject heading] AND Children

The studies selected for the efficacy section were also considered for the safety study. The search terms were modified according to the constraints of each database (Please see Appendix 1 for the EMBASE search strategy). The resulting titles with abstracts where appropriate were put into Reference Manager and duplicates searched for and removed. We used a Microsoft Excel spreadsheet to manage the results of the initial search, with the data analysis and results managed using Review Manager version 4.2.10, the final version being exported to Review Manager version 5.

Data collection and analysis

The search strategy identified studies in which diclofenac had been used for children as a short-term analgesic. Two sets of inclusion criteria were applied to the identified studies: one for efficacy and one for safety. Efficacy studies were identified and data extracted independently by JFS and DP. The safety studies were identified and data extracted independently by JFS and IS.

Efficacy:

RCTs which used diclofenac as a short-term analgesic. Some measure of pain relief was required (e.g. pain score, need for rescue analgesia, patient questioning). Where possible, studies using the same efficacy measures were combined. A quality assessment of the randomisation process, allocation concealment and follow up was made and recorded.

In practice, diclofenac is often combined with other analgesics such as opioids, paracetamol (acetaminophen) and local anaesthetic blocks. Ideally, studies comparing diclofenac with placebo (to show its efficacy as an analgesic) and diclofenac with other NSAIDs/COX 2 inhibitors (to inform choices in practice) were sought. However, as only a small number of studies done exclusively in children were of sufficient methodological quality, well-designed studies comparing diclofenac with any other treatment were also included. Studies were grouped into the following categories: Diclofenac versus no treatment/placebo; other NSAIDs/COX-2 inhibitors; opioids; paracetamol (acetaminophen); others (e.g. local anaesthetic blocks, complementary therapies).

Safety:

Three types of analysis were done to estimate the frequency and kinds of adverse drug reactions to short-term diclofenac in children under 18 years old:

1. A quantitative comparison of adverse reactions in patients who had and had not received diclofenac in RCTs.

2. An analysis of adverse events reported in all studies in which the total number of children exposed to diclofenac was known. This included blind and open RCTs, open unrandomised comparisons, and prospective and retrospective audits.

3. A qualitative analysis of case reports of adverse reactions to diclofenac reported in the literature, and to regulatory authorities. The Medicines and Healthcare Regulatory Authority (MHRA) was approached to do a search on diclofenac-related adverse reactions in children under 18 using data from the Yellow Card scheme. The World Health Organization (WHO) Uppsala Monitoring centre was also approached. These data were combined with case reports found in the literature review. Studies included in 1 and 2 above were ranked as high, moderate or low quality using the criteria shown in additional Table 1.

Table 1. Quality analysis of safety study papers

Quality categories	High	Moderate	Low
Study design	Prospective, number of patients exposed to diclofenac given	Prospective, number of patients exposed to diclofenac given	Prospective or retrospective, number of patients exposed to diclofenac given
Adverse event monitoring	Evidence of monitoring for adverse events	Evidence of monitoring for adverse events	Spontaneous reporting of adverse events
Adverse event reporting	Specific adverse events reported	Adverse events may be grouped by system	Adverse events may be grouped by system
Assessment of causality linking adverse events and adverse drug reactions	Use of causality algorithm or difference versus placebo in double-blind RCT	Causality may be attributed by clinical judgement or difference versus placebo in double-blind RCT	Causality may be attributed by clinical judgement or difference versus placebo in double-blind RCT
Follow-up	Post-discharge follow-up on at least one occasion	No evidence of follow-up	No evidence of follow-up

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The search yielded 1094 studies (not including the hand-search of Paediatric Anaesthesia). Initial screening of the abstracts of these studies was undertaken by JFS and IS. Where it was unclear from the abstract that a study should be included, or if no abstract was available, the full paper was obtained.

A total of 142 papers were taken forward for detailed assessment; of these, 63 were excluded (Characteristics of excluded studies) and 79 (74 trials plus five case reports) fitted the inclusion criteria (Characteristics of included studies). These 79 papers provided data on 3616 participants who had been exposed to diclofenac.

Efficacy:

Seven studies (Baer 1992; Bone 1988; Littlejohn 1996; Nishina 2000; Samarkandi 2005; Tay 2002; Watters 1988) were RCTs comparing peri-operative diclofenac (168 children) with either placebo/no treatment (178) or another analgesic (58 children). Unfortunately each study used a different scale or method for rating pain, meaning that these results could not be combined. However, these studies did report the number of participants requiring rescue analgesia in each group, allowing a combined comparison to be done (Analysis 1.1; Analysis 2.1; Figure 1; Figure 2).

Figure 1. Forest plot of comparison: 1 Diclofenac vs no treatment/placebo, outcome: 1.1 Number of patients requiring rescue analgesia.

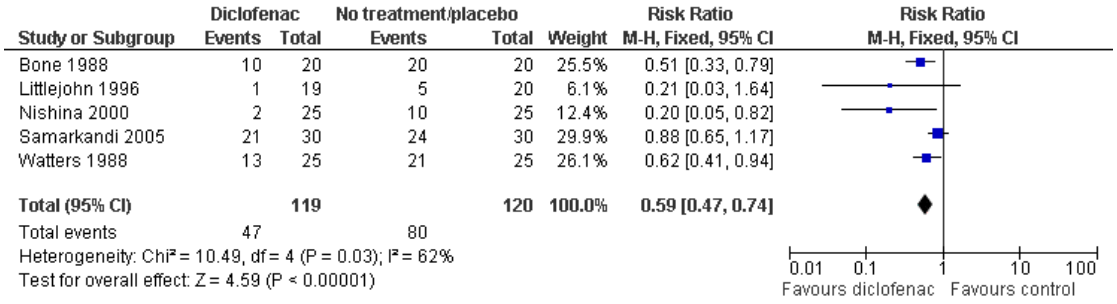
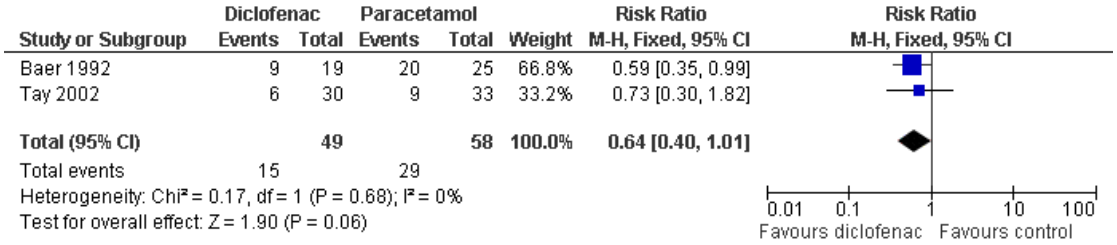


Figure 2. Forest plot of comparison: 2 Diclofenac vs paracetamol, outcome: 2.1 Number of patients requiring rescue analgesia.



Safety:

1. Eighteen RCTs (including those included in the efficacy analysis) reported monitoring of adverse events (Analysis 3.1; Analysis 3.2; Analysis 4.1; Analysis 4.2; Figure 3; Figure 4; Figure 5).

Figure 3. Forest plot of comparison: 3 Diclofenac vs any other treatment, outcome: 3.1 Nausea and/or vomiting.

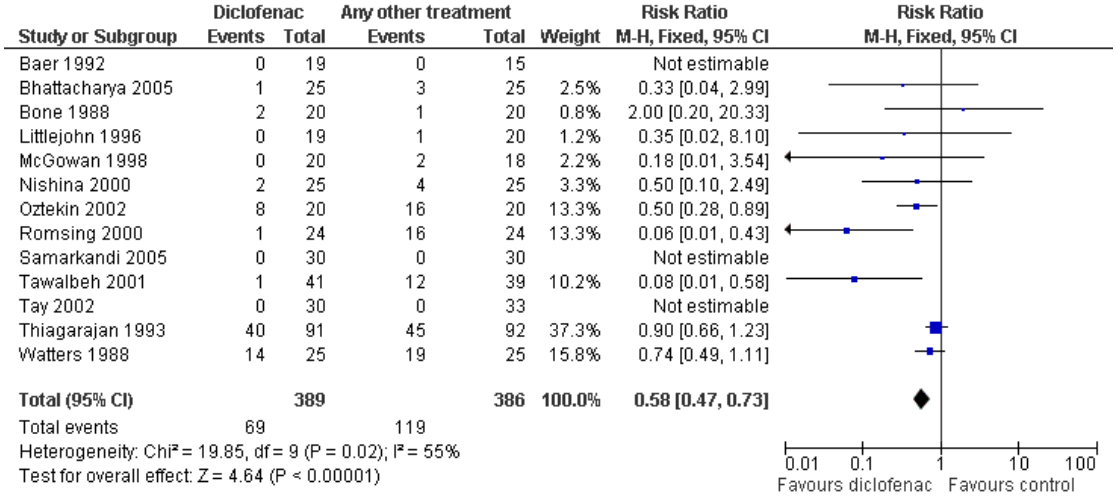


Figure 4. Forest plot of comparison: 3 Diclofenac vs any other treatment, outcome: 3.2 Bleeding requiring surgical intervention.

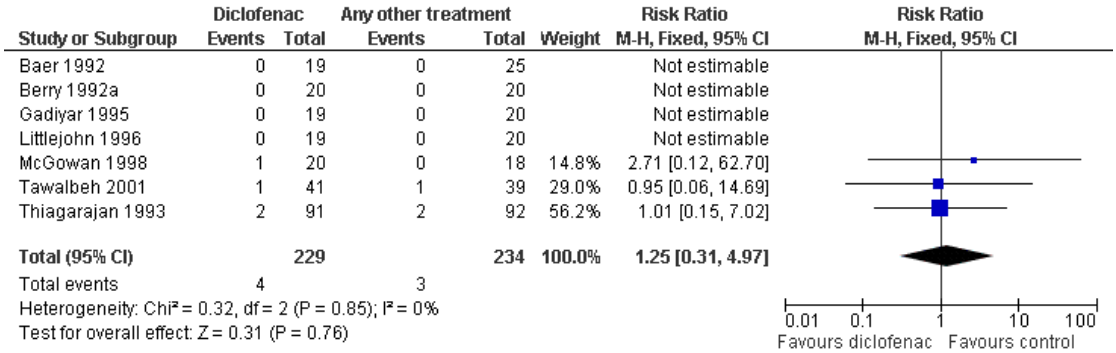
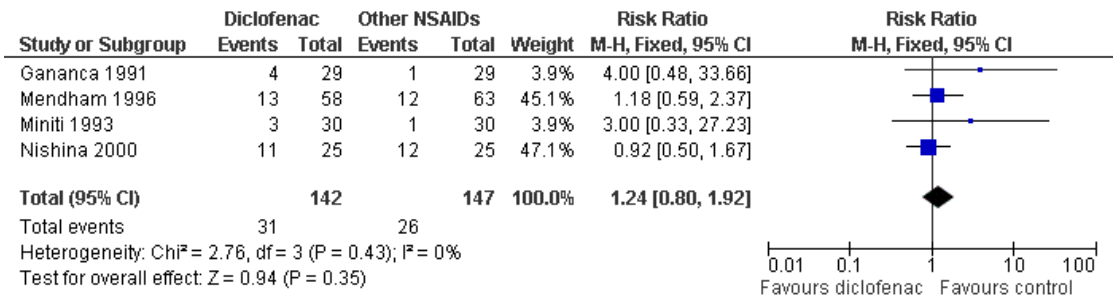


Figure 5. Forest plot of comparison: 4 Diclofenac vs other NSAIDs, outcome: 4.1 Nausea and/or vomiting.



1. Seventy-four studies (the 18 RCTs above plus 56 others) contained information on the total number of children exposed to diclofenac (3611), plus evidence of monitoring for adverse effects.

2. Five additional case reports were identified: (Lai 2005; Nikolic 2001; Seaton 2000; Sen 2001; Robinson 1994). In addition to these case reports, data on 77 adverse reactions to diclofenac were included from Medicines and Healthcare products Regulatory Agency (MHRA) from the Committee of Safety of Medicine Yellow Card scheme. The data from the WHO Uppsala Monitoring centre were not included in the final analysis, for the reasons stated below.

In total, 63 studies were excluded on detailed assessment. The main reason for exclusion was that participants were all over 18 years old, or, where some were children and some adults, it was not possible to extract the paediatric data. A small number of papers concerned use of diclofenac by the topical route.

Risk of bias in included studies

Details of the quality assessment for each of the 74 studies included in this review can be found in the 'Characteristics of included studies' table.

Only 18 studies were of sufficient quality to use in a comparative analyses of safety (all18) or efficacy (7 of 18). All but two of these involved administration of diclofenac in the peri-operative period; the remaining studies (Gananca 1991; Miniti 1993) involved participants with tonsillitis receiving antibiotic and analgesic therapy only. The authors of any study in which participants had been excluded from the analysis were contacted. If no reply was received, or if insufficient information was provided, the study was excluded (no intention-to-treat analysis was performed).

Efficacy:

The main efficacy measure which allowed study results to be combined was use of rescue analgesia given by a person who was blind to treatment allocation. Only seven studies met these criteria in a RCT. Five studies (Bone 1988, tonsillectomy; Littlejohn 1996, dental extraction; Nishina 2000, eye surgery; Samarkandi 2005, herniotomy; Watters 1988, tonsillectomy) were placebo/no treatment control studies in which the study drugs were given in theatre post-induction. This makes patient bias unlikely, but other types of bias are still possible as the authors gave little or no information on who held the treatment allocation codes, or on how treatment blinding was maintained once the child had left the theatre.

The two studies comparing diclofenac against paracetamol (Baer 1992, adenoidectomy; Tay 2002, myringotomy) were of lower quality, as the drugs were not necessarily given in theatre and there was more uncertainty over treatment blinding.

We imposed slightly different criteria for including studies for the efficacy and safety comparative analyses. As rescue analgesia was used to mark efficacy, only studies where the person administering rescue analgesia was blind to treatment were included. For comparisons of adverse effects (nausea and/or vomiting, and bleeding requiring surgical intervention), unblinded studies were included.

Safety:

1. Four unblinded studies were included in the comparative analysis of safety (Gananca 1991; McGowan 1998; Miniti 1993; Tawalbeh 2001). Two studies stated that blinding was used but gave no further details of how it was achieved (Baer 1992; Tay 2002), so were included in both comparative analyses of efficacy and safety but with a risk of investigator bias.

2. Most of the 74 studies providing denominator data for adverse reactions were rated as moderate according to our criteria of safety quality (*see additional*Table 1), most failing on the criteria of not following participants up post discharge.

3. The WHO data were not included in the final analysis of case reports of serious reactions . Firstly no indication of whether diclofenac was prescribed for acute pain or chronic conditions is given, and this review is focused on diclofenac for acute pain only. Secondly, it was not possible to ascertain which of the reports in the WHO list were duplicates from the Yellow Card data.

Effects of interventions

Efficacy:

As stated earlier, the only measure of pain which could be used to compare studies was the decision, by a blinded assessor, to give rescue analgesia. Comparison 01/01 (Analysis 1.1; Figure 1) includes 239 participants from five studies (Bone 1988; Watters 1988; Littlejohn 1996; Nishina 2000; Samarkandi 2005) comparing a peri-operative analgesic regime with or without diclofenac, and showed that diclofenac significantly decreased the number of children requiring rescue analgesia (RR 0.6; 95% CI 0.5 to 0.7). The proportion of participants requiring rescue analgesia after diclofenac was 39.5% (47/119); range 5% (dental extractions) to 70% (herniotomy). The proportion of participants requiring rescue analgesia with placebo/no treatment was 67% (80/120); range 25% (extraction) to 100% (tonsillectomy). These figures give a NNT to prevent need for rescue analgesia of 3.6 (95% CI 2.5 to 6.3).

The two studies (Baer 1992; Tay 2002) comparing 107 children randomised to either diclofenac or paracetamol (Analysis 2.1; Figure 2) showed a similar, but non-significant, reduction in need for rescue analgesia.

Safety:

Only one study (Romsing 2000) provided a direct comparison between diclofenac and another (non-NSAID) treatment with standardisation of all other medicines administered. However, an intention-to-treat type analysis of the prevalence of the adverse events nausea and/or vomiting, and bleeding requiring surgical intervention were performed (Analysis 3.1; Analysis 3.2; Analysis 4.1; Analysis 4.2). A combination of 13 studies (Bhattacharya 2005; Baer 1992; Bone 1988; Littlejohn 1996; McGowan 1998; Nishina 2000; Oztekin 2002; Romsing 2000; Samarkandi 2005; Tawalbeh 2001; Tay 2002; Thiagarajan 1993; Watters 1988) including 775 children randomised to diclofenac or any other non-NSAID (placebo, paracetamol or opioid) treatment (Analysis 3.1; Figure 3) found diclofenac significantly reduced the incidence of nausea and/or vomiting. The proportion of participants experiencing nausea and vomiting after peri-operative diclofenac was 18% (69/389); range 0% (andenoidectomy; dental extraction; circumcision; myringotomy; herniotomy) to 56% (tonsillectomy). The proportion of participants with nausea and vomiting after any other non-NSAID treatment was 31% (119/386); range 0% (myringotomy; adenoidectomy) to 80% (tonsillectomy). These figures give a NNT to prevent of 7.7 (5.3 to 14.3).

Bleeding requiring surgical intervention was assessed in seven studies (Baer 1992; Berry 1992a; Gadiyar 1995; Littlejohn 1996; McGowan 1998; Tawalbeh 2001; Thiagarajan 1993) including 463 children randomised to diclofenac or any other non-NSAID treatment (Analysis 3.2; Figure 4), and no significant difference was seen with either treatment arm. The incidence of nausea and/or vomiting was compared in 289 participants randomised to receive either diclofenac or another NSAID in four studies (Gananca 1991; Mendham 1996; Miniti 1993; Nishina 2000). These studies found no significant difference in the incidence of nausea and/or vomiting with diclofenac and with other NSAIDs (Analysis 4.1; Figure 5).

In the analysis of serious adverse events, 3611 children received at least one dose of diclofenac for acute pain and were monitored for adverse events in 74 studies (all studies are listed in the 'Characteristics of included studies' table). There were 26 serious adverse events (*see* additional Table 2). All but three were post-operative complications and the authors did not state that they considered they were caused by diclofenac. Three cases from two studies (*see* additional Table 2) involved the use of diclofenac for non-surgical management of pain in tonsillitis. Both authors (Duarte 1997; Kierszenbaum 1991) considered these events to have been caused by diclofenac, and stopped the drug. The incidence (95% confidence interval (CI)) of serious diclofenac adverse reactions is therefore 0.08% (0.02 to 0.24%).

Five case reports of serious adverse events were identified: Lai 2005 (tissue necrosis following intramuscular injection), Nikolic 2001 (tubulointerstitial nephritis), Seaton 2000 (gastrointestinal vasculitis), Sen 2001 (fatality from allergic-type reaction) and Robinson 1994 (three cases of post-tonsillectomy bleeding attributed to diclofenac in retrospective review).

Table 2. Serious adverse events in 3611 participants given diclofenac for acute pain

Study	Number of Events	Description
Duarte 1997*	1	Palpebral oedema "of serious intensity". Diclofenac stopped
Fischer 1992	1	Unclear as refers to table grouping moderate/severe as rated by patient. Reaction is one of: vomiting, headache, stomach pain or erythema.
Kierszenbaum 1991*	2	Hypothermia "obliging the suspension of treatment"
Kokinsky 1999	1	Protracted vomiting requiring prolonged hospitalisation.
Kokinsky 1999	1	Bleeding after penile surgery requiring re-operation.
Leontev 2005	5	Allergic skin reaction, reversed with injected chlorpyramine
McGowan 1998	2	Late haemorrhage after day-case circumcision requiring hospital admission.
Mendham 1996	3	Haemorrhage after tonsillectomy requiring re-operation.
Oztekin 2002	1	Bleeding after tonsillectomy requiring prolonged hospitalisation.

Table 2. Serious adverse events in 3611 participants given diclofenac for acute pain (*Continued*)

Tawalbeh 2001	1	Bleeding requiring re-hospitalisation after tonsillectomy.
Tewary 1993	6	Bleeding causing prolonged or re-hospitalisation after tonsillectomy.
Thiagarajan 1993	1	Bleeding requiring re-operation after tonsillectomy.
Vuori 2004	1	Bleeding requiring blood transfusion following major surgery.
TOTAL	26	NOTE: Only two studies * reported that they considered these serious adverse events to be adverse drug reactions caused by diclofenac.

Additional Table 3 gives a summary of published case reports combined with the Yellow Card data. Of these 77 cases, 29 were related to children treated with diclofenac for chronic conditions, the indication was unclear for 12 cases, and 36 cases were in participants being treated for acute pain. Eight of the reactions were classified by the reporter as not serious, 49 were not classified, and 20 were reported to be serious. Of these, six were serious intramuscular injection site reactions.

Table 3. Summary of case reports sorted by indication

Reaction type	Chronic treatment	Indication unknown	Acute pain
Acute allergic-type reaction	0	1	4
Cardiovascular	0	0	1
Central nervous system	5	2	5
Dermatological	7	4	3
Endocrine	1	1	0
Genitourinary	3	0	1
Gastrointestinal - bleeding	3	3	7
Gastrointestinal - general	3	1	5
Haematological	1	0	5
Hepatic	2	0	0
Injection site reactions	0	0	6

Table 3. Summary of case reports sorted by indication (*Continued*)

Muscular	0	0	2
Renal	0	1	0
Respiratory	4	1	3

There were two fatalities, one due to an acute allergic-type reaction causing an inflammatory response and bronchospasm, and one gastric bleed causing peritonitis; both in participants being treated with diclofenac for acute pain. No denominator was available for these data so an incidence of these adverse reactions cannot be ascertained.

There was a five-fold range in the single doses of diclofenac used for acute pain in children in the studies we have reviewed: from 0.5 mg/kg (Tay 2002) to 2.5 mg/kg (McGowan 1998). The pharmacokinetic studies were all descriptive (Korpela 1990; Murphy 2000; van der Marel 2004), and none sought to recommend a dose.

No studies reported the use of diclofenac for acute pain in asthmatic children; asthmatics were either excluded or no information was given. Each author who was contacted for other reasons was asked whether any participants were asthmatic, none were able to provide actual numbers of participants who were.

DISCUSSION

This review has focused on assessing diclofenac's place in the management of acute pain in children using endpoints with relevance to clinical situations. Whilst we aimed to include all types of acute pain, the vast majority of studies were conducted in the peri-operative period. This probably reflects the fact that conditions such as renal colic are relatively uncommon in children, and that such sudden onset conditions are difficult to study in a clinical trial. Conversely post-operative pain is common in most children undergoing surgery, and surgery is generally planned and undertaken in a controlled environment that lends itself to clinical studies.

For the assessment of efficacy, no studies using pain scores could be combined because of the range of different methods employed. Administration of supplementary or rescue analgesia by an investigator blind to treatment allocation did provide a consistent measure of pain which could be compared across studies of post-operative pain. The comparison of analgesic regimes that only differed in the administration of diclofenac (Analysis 1.1; Figure 1) showed diclofenac halved the number of participants requiring rescue analgesia.

In adults diclofenac (50 mg) has been found to be about twice as effective as paracetamol (1 g) for post-operative pain (McQuay 1998). We have shown that when diclofenac (0.5 mg/kg or fixed dose 12.5 mg) is compared with paracetamol (15 mg/kg or fixed dose 125 mg) (Analysis 2.1; Figure 2) half the number of children on diclofenac required rescue analgesia. However, the numbers in this analysis were small and the comparison was not statistically significant.

From the published reports it was not possible to determine whether participants with an adverse event (such as nausea and/or vomiting) had also received rescue analgesia. This means that the two groups may not have received exactly the same treatments. In comparing participants randomised to receive diclofenac with any other non-NSAID (placebo, paracetamol or opioid) we found less nausea and/or vomiting recorded (Analysis 3.1; Figure 3) and no difference in the rate of bleeding requiring surgical intervention (Analysis 3.2; Figure 4).

There are several possible explanations as to why participants randomised to diclofenac had less nausea and/or vomiting. As diclofenac provided better analgesia (Analysis 1.1; Figure 1), this meant more participants in the control group received rescue analgesia, which in itself could be emetogenic. Even where rescue analgesia does not cause nausea and/or vomiting, it has been suggested that adequate analgesia can decrease the incidence of nausea in the peri-operative period (Michaloliakou 1996), meaning differences in efficacy can possibly influence differences in adverse events.

As with a previous review on NSAIDs in children (Cardwell 2005) we looked for bleeding requiring surgical intervention and found no difference in the rates between participants randomised to diclofenac and non-NSAIDs. Amongst those contributing to Comparison 03/02 (Analysis 3.1), three studies (Berry 1992a; Tawalbeh 2001; Thiagarajan 1993) included children undergoing a high-

risk surgery in terms of post-operative bleeding (tonsillectomy). Whilst this may indicate that at therapeutic dosing diclofenac does not inhibit COX-1 dependent platelet aggregation to a clinically significant degree, it is possible that factors such as restlessness due to inadequate analgesia in the post-operative period may contribute to bleeding. The analgesic effects of diclofenac could therefore lead to less restlessness, and therefore may offset any increased risk of bleeding.

Our safety data comes from 74 studies in which the total number of children exposed to diclofenac for treatment of acute pain was known and there was evidence that adverse events were looked for. The majority (56) of these studies were not controlled trials; the intention was to carry out a telemetric analysis as described by Aronson 2005, in which every study was considered to exist in order to contribute to the overall picture of diclofenac safety in children treated for acute pain. The contribution that each study made was the study authors' own assessments of the likely cause of the adverse reactions that they reported.

By including a range of study types in which adverse events were monitored and the number of participants given diclofenac for acute pain was known, we were able to estimate the incidence of serious adverse drug reactions caused by diclofenac. There were 26 serious adverse events in a total of 3611 children (see additional Table 2 for references). As stated above, the judgement on whether the adverse events were caused by diclofenac was made by the study author. Most adverse events were typical post-operative complications and none were attributed by the authors to have been caused by diclofenac. Three other events were considered to be caused by diclofenac (*see* additional Table 2). The incidence (95% CI) of serious adverse reactions caused by diclofenac when used for acute pain is therefore 0.08% (0.02 to 0.24%).

The qualitative analysis of case reports shows children appear to suffer similar types of serious adverse reactions to diclofenac as adults. Bleeding following tonsillectomy was attributed to diclofenac in three cases in a retrospective review (Robinson 1994). The cause of post-operative bleeding is likely to be multifactorial, and may include depletion of clotting factors, restlessness in the post-operative period, and haematological disorders such as inhibited platelet aggregation. To identify whether diclofenac is a causative factor in post-operative bleeding, comparative studies were analysed (Analysis 3.2; Figure 4), and no increased bleeding risk in 463 children given either diclofenac or any other non-NSAID was found. A systematic review of comparative studies on NSAIDs and bleeding requiring surgical intervention in 955 children undergoing tonsillectomy (Cardwell 2005) also found no increase in bleeding with NSAIDs. The six case reports of serious intramuscular injection site reactions indicate that this route of administration is inappropriate in children.

AUTHORS' CONCLUSIONS

Implications for practice

Diclofenac is an effective analgesic for acute pain in children, and its use as part of the analgesic regime in the peri-operative period seems to reduce the incidence of nausea or vomiting, or both. Diclofenac does not appear to increase the incidence of peri-operative bleeding requiring surgical intervention, although more patients need to be studied to confirm this. The incidence (95% CI) of serious adverse reactions caused by diclofenac when used post-operatively is 0.08% (0.02 to 0.24%).

Implications for research

The optimum dose of diclofenac for acute pain in children still needs to be ascertained, this review found a five-fold range in the single doses being used (0.5 to 2.5 mg/kg). The prevalence of bronchospasm in asthmatic children given diclofenac is unknown. It would be helpful if future studies on NSAIDs in children reported the number of asthmatics included; a study aimed at ascertaining the frequency of bronchospasm in asthmatic children would be very useful in that it would guide prescribers as to whether asthmatic children should be denied an effective analgesic.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Akinci 2005

Methods	Randomized controlled trial
Participants	22 children needing ventilation after orthopedic spinal surgery
Interventions	1. remifentanil infusion (11) 2. fentanyl infusion (11) for postop analgesia/sedation in PICU. All patients received IM diclofenac 1 mg/kg before extubation
Outcomes	1. Pain 2. PONV
Notes	Asthmatics: not clear. Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Andrzejowski 2002

Methods	Randomised controlled trial.
Participants	133 children (ASA 1-2) undergoing dental surgery.
Interventions	1. Swab soaked in bupivacaine 0.25% (60) 2. Swab soaked in saline (60). All patients received rectal diclofenac 1 mg/kg.
Outcomes	1. Pain 2. Bleeding
Notes	13 dropouts due to inability to self-score pain. Wrote to authors: all these patients received diclofenac and none had any serious adverse events. Adverse events monitored for, no serious adverse events occurred in the 133 receiving diclofenac. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Azuma 1982

Methods	Comparative trial of analgesia, diclofenac pharmacokinetics. Not randomised or blinded.
Participants	40 children post-tonsillectomy.
Interventions	1. Rectal diclofenac 1 mg/kg (20) 2. Non-NSAID group (20).
Outcomes	1. Analgesia 2. Pharmacokinetics 3. Adverse events.
Notes	Not enough information to include in comparative study. Adverse events monitored for, no serious adverse events occurred in the 20 receiving diclofenac. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Baer 1992

Methods	Randomised controlled trial, investigator blind.
Participants	44 children (ASA 1) undergoing adenoidectomy.
Interventions	1. Rectal diclofenac 12.5 mg (19) 2. Rectal paracetamol 125 mg (25).
Outcomes	1. Pain 2. Bleeding 3. Behaviour 4. Post-operative complications
Notes	Adverse events monitored for, no adverse events in either group and no serious adverse events. States is blinded study but no details on how blinding done. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bebawy 2005

Methods	Randomised controlled trial
Participants	80 children, 2-6 years old undergoing inguinal hernia repair
Interventions	1. Sevoflurane (40) 2. Halothane (40). All patients received rectal diclofenac sodium 2 mg/kg as pre-med. Post-op local wound infiltration using ropivacaine.
Outcomes	1. Pain
Notes	Asthmatics: excluded (C/Is to NSAIDs). Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Berry 1992a

Methods	Randomised controlled trial, investigator blind.
Participants	40 children (ASA 1-2) undergoing adenotonsillectomy.
Interventions	1. Intravenous diclofenac 1 mg/kg (20) 2. Intravenous papaveretum 0.2 mg/kg (20).
Outcomes	1. Pain 2. Bleeding 3. Vomiting 4. Venous irritation.
Notes	Wrote to author of letter on venous sequelae of diclofenac in children which mentioned a clinical study - directed to paper in The Journal of the Pain Society. Blinding centralised with hospital pharmacy prepared doses. Papaveretum and paracetamol rescue analgesia used. Adverse events monitored for, 20 children had diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bhattacharya 2005

Methods	Randomised controlled trial. Assessor (nurse) blind
Participants	50 children aged 8-12 undergoing tonsillectomy and/or adenoidectomy
Interventions	1. rectal diclofenac 2 mg/kg post induction (25) 2. IV pethidine 0.5 mg/kg (25)
Outcomes	1. Pain 2. Adverse events
Notes	Asthmatics: excluded. Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bone 1988

Methods	Randomised controlled trial, investigator blind.
Participants	60 children undergoing tonsillectomy.
Interventions	1. Rectal diclofenac 2 mg/kg (20) 2. Intramuscular papaveretum 0.2 mg/kg (20). 3. No treatment (20).
Outcomes	1. Pain 2. Nausea and vomiting 3. Respiratory rate 4. Restlessness
Notes	Paracetamol and papaveretum rescue analgesia used. Risk of bias as no placebo injection/suppositories used. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Borkar 2005

Methods	Randomised controlled trial
Participants	50 children aged 3-13 years undergoing laparoscopy

Borkar 2005 (*Continued*)

Interventions	1. caudal block (25) 2. rectal diclofenac (25) All children also received metoclopramide and pentazocine post-induction
Outcomes	1. Pain 2. PONV
Notes	Study said to be randomised but blinding not mentioned. Adverse events monitored; 25 children received diclofenac; no reports of serious adverse events

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Duarte 1997

Methods	Randomised comparative open study.
Participants	60 children with swollen glands, with and without sore throat and laryngitis
Interventions	1. nimesulide (n = 21), 2.5 mg/kg bd; 2. dipyrone 25 mg/kg qds (n = 19) 3. diclo 0.5 mg/kg bd (21); all for 4-10 days
Outcomes	1. Pain 2. Adverse events 1. Pain 2. Adverse events
Notes	Adverse events monitored for; 21 children received diclofenac; 1 case of palpebral oedema, treatment stopped. Asthmatics: no information. Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Elhakim 2003

Methods	Randomised controlled trial.
Participants	50 children (ASA 1-2) undergoing tonsillectomy.
Interventions	1. Intramuscular ketamine 0.1 mg/kg (25). 2. Intramuscular saline, equivalent volume to ketamine dose (25). All children received rectal diclofenac 2 mg/kg.
Outcomes	1. Pain. 2. Adverse events.

Elhakim 2003 (*Continued*)

Notes	Evidence of monitoring for adverse events, no serious adverse events reported. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Engelhardt 2001

Methods	Randomised controlled trial.
Participants	29 children undergoing adenotonsillectomy.
Interventions	1. Sublingual morphine 0.1mg/kg (14). 2. Intravenous morphine 0.1 mg/kg (15). All patients received rectal diclofenac 1 mg/kg.
Outcomes	1. Pain 2. Sedation 3. Adverse events.
Notes	Adverse events monitored for, 29 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Engelhardt 2003

Methods	Randomised controlled trial.
Participants	60 children undergoing tonsillectomy +/- adenoidectomy.
Interventions	1. Intravenous morphine 0.1mg/kg (20). 2. Intravenous tramadol 1mg/kg (20). 3. Intravenous tramadol 2mg/kg (20). All (60) received rectal diclofenac 1mg/kg.
Outcomes	1. Pain. 2. Adverse events until discharge.
Notes	Adverse events monitored for, 60 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Engelhardt 2003 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Ericsson 2006

Methods	Randomized open comparative study of two surgical methods.
Participants	Ninety-two children (5-15 years) with sleep-disordered breathing
Interventions	1. Rectal diclo 1-2.5 mg/kg end of op, repeated after 8 hours. 2. post-op paracet and diclo for at least 3 days; route not clear
Outcomes	1. Pain 2. Adverse events
Notes	Evidence of monitoring for adverse events over 4-10 days. 1 report of pain and nausea at day 3; diclofenac stopped needing change in analgesic medication

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Filatov 2000

Methods	Randomised controlled trial.
Participants	126 children (ASA 1) undergoing adenoidectomy.
Interventions	1. Rectal diclofenac 12.5 mg, rectal diazepam 0.5 mg/kg, intravenous glycopyrrolate 5µg/kg, topical EMLA® to hand (20) 2. Rectal diclofenac 12.5 mg, rectal diazepam 0.5 mg/kg topical EMLA® to hand (21) 3. Oral ketamine in cola drink 6 mg/kg, intravenous glycopyrrolate 5 µg/kg (30) 4. Oral ketamine in cola drink 6 mg/kg (29). Placebo local anaesthetic cream, suppository, rectal fluid, oral cola drink and injection used.
Outcomes	1. Pain 2. Adverse events
Notes	Wrote to authors as 26 patients excluded causing risk of bias, no reply therefore cannot include in comparative analysis. Adverse events monitored for, 41 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: Low

Risk of bias

Item	Authors' judgement	Description

Filatov 2000 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Findlow 1997

Methods	Randomised controlled trial.
Participants	40 boys undergoing orchidopexy.
Interventions	1. Caudal bupivacaine 0.25% 0.5 mL/kg and ketamine 0.5 mg/kg. (20) 2. Ilioinguinal block bupivacaine 0.25% 0.5 mL/kg (20). All (40) received rectal diclofenac 1-2 mg/kg.
Outcomes	1. Pain 2. Adverse events including follow-up
Notes	Drop-outs: two did not undergo surgery or receive diclofenac, two no follow-up was possible but received diclofenac. Adverse events monitored for, 38 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Fischer 1992

Methods	Randomised controlled trial.
Participants	60 children undergoing orthopaedic surgery.
Interventions	1. Oral diclofenac 50 mg twice or three times daily (50). 2. Oral serrapeptase 5 mg 1-2 tablets three times daily (50).
Outcomes	1. Pain. 2. Swelling. 3. Adverse events.
Notes	Cannot use for comparative analysis - five serrapeptase and three diclofenac drop-outs, unaccounted for and no blinding. Adverse events monitored for, 47 patients received diclofenac, one event rated by patient as severe but unclear which one from table, could be: vomiting, headache, stomach pain or erythema. Asthmatics: unknown. Safety quality: Low.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Fosel 2005

Methods	Prospective cohort
Participants	100 children aged between 6 and 14 years post tonsillectomy
Interventions	Combined regime including an opioid (piritramid), and rectal paracetamol 1 mg/kg diclofenac orally 3 times a day from 2nd postop day
Outcomes	1. Pain 2. Vomiting 3. Bleeding
Notes	Adverse events monitored for, 100 patients received diclofenac, no reports of serious adverse events. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Funk 2008

Methods	Randomised placebo-controlled trial. Nurse giving drug blinded.
Participants	40 children (1-5 yr) undergoing ENT, hernia repair, and urology surgery
Interventions	1. Physostigmine 30 mcg/kg IV (20) 2. Saline (20) All children received. rectal diclo 1-2 mg/kg post induction as part of combined regime including regional/local bupivacaine
Outcomes	1. Agitation 2. PONV 3. Sleep disturbances
Notes	Adverse events monitored for post-operation and at day 7 and 28. 20 children r received diclofenac. No reports of severe adverse events. Asthmatics: unknown. Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Gadiyar 1995

Methods	Randomised controlled trial, investigator blinded.
Participants	39 children (ASA 1 or 2) undergoing day case surgery.
Interventions	1. Rectal diclofenac 1 mg/kg plus caudal bupivacaine 0.125% plus adrenaline 1:400 000 1 mL/kg (19). 2. Caudal bupivacaine 0.125% plus adrenaline 1:400 000 1 mL/kg only (20).

Gadiyar 1995 (*Continued*)

Outcomes	1. Pain. 2. Sedation. 3. Time to passing urine. 4. Time to eating/drinking. 5. Excessive bleeding.
Notes	Paracetamol rescue analgesia used. Adverse events monitored for including post-discharge follow-up. No mention of nausea and vomiting but subjectively looked at bleeding, no increase in the diclofenac group. No reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gananca 1991

Methods	Randomised controlled trial.
Participants	58 children with pharyngo-tonsillitis.
Interventions	1. Oral diclofenac resinate 0.5 mg/kg (29). 2. Oral nimesulide 5 mg/kg (29). Seven day treatment, all patients also received oral amoxicillin 30 mg/kg/day.
Outcomes	1. Pain. 2. Adverse events. 3. Taste of medication.
Notes	Include in comparative study but open study with no blinding so risk of bias. Specifically mentions no other medicines used during treatment course, adverse events monitored for, 29 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Hanafy 2004

Methods	Randomised controlled trial.
Participants	51 children (ASA 1-2) undergoing adenotonsillectomy.
Interventions	1. Intravenous dexmedetomidine 0.5 μg/kg (23). 2. Intravenous saline (23). All patients received rectal diclofenac 1 mg/kg.
Outcomes	1. Post-operative agitation. 2. Adverse events.
Notes	Wrote to authors (as 5 patients excluded - risk of bias) no response. Adverse events monitored for, 46 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality:

	Low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Holder 1997

Methods	Randomised controlled trial.
Participants	45 boys (ASA 1-2) undergoing circumcision.
Interventions	1. Subcutaneous ring block with bupivacaine 0.25% 2 mg/kg (16). 2. Subpubic penile block using bupivacaine 0.5% 0.2 mL/kg (24). Seven patients received diclofenac 1 mg/kg rescue analgesia.
Outcomes	1. Pain. 2. Adverse events.
Notes	Adverse events monitored for, seven patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Homer 2002

Methods	Audit.
Participants	100 children undergoing tonsillectomy.
Interventions	77 received diclofenac.
Outcomes	1. Pain. 2. Haemorrhage rate.
Notes	Retrospective audit, adverse events monitored for, 77 patients received diclofenac, no reports of serious adverse events (mentions one patient with reactionary haemorrhage settled with conservative treatment). Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Hultcrantz 2004

Methods	Randomised controlled trial.
Participants	150 children undergoing tonsillectomy.
Interventions	1. Radiofrequency technique (49). 2. Standard technique (43). All children received diclofenac (route not stated) 0.7-1 mg/kg/dose.
Outcomes	1. Pain. 2. Adverse events including follow-up.
Notes	Only 92 of the 150 randomised were operated on. Five were excluded for not accepting randomisation, five operated on without being randomised and the rest had surgery cancelled. Adverse events monitored for, 92 patients received diclofenac, no reports of serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Kierszenbaum 1991

Methods	Randomised comparative study.
Participants	60 children aged 1-12 years with upper respiratory tract infections
Interventions	1. diclofenac resinate orally 0.5 mg/kg tid for 7 days (30) 2. nimesulide 1% oral suspension 5 mg/kg bd for 7 days (30)
Outcomes	1. Throat pain 2. Dysphagia 3. Adverse events
Notes	Adverse events monitored for; 30 children received diclofenac; treatment stopped in two cases because of hypothermia. Asthmatics: unknown. Safety quality: moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kokinsky 1999

Methods	Audit.
Participants	200 children undergoing day case surgery.
Interventions	68 children received rectal diclofenac 0.8-2 mg/kg intra-operatively, and 10 post-operatively

Kokinsky 1999 (*Continued*)

Outcomes	1. Pain. 2. Adverse events.
Notes	Wrote to authors for clarification on adverse events. Two patients who received diclofenac had serious adverse events (one protracted vomiting requiring prolonged admission, one re-operated due to bleeding in penile surgery). Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Korpela 1990

Methods	Pharmacokinetic study.
Participants	10 children undergoing minor surgery.
Interventions	1. Intravenous diclofenac 0.5 mg/kg infused over five minutes (5). 2. Intravenous diclofenac 0.5 mg/kg infused over 15 minutes (5).
Outcomes	1. Pharmacokinetics. 2. Adverse events.
Notes	Adverse events monitored for and contacted authors, 10 patients received diclofenac, no serious adverse events. Asthmatics: excluded. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Kurokawa 2002

Methods	Case series.
Participants	Girls undergoing laparoscopic nephroureterectomy.
Interventions	Laparoscopic nephroureterectomy, two received rectal diclofenac 12.5 mg.
Outcomes	1. Post-operative complications. 2. Pain.
Notes	Adverse events monitored for, two patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: low.

Risk of bias

Kurokawa 2002 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Lai 2005

Methods	Comparative study.
Participants	19 children and 23 adults undergoing appendicectomy.
Interventions	Standardised analgesia including diclofenac 1.5 mg/kg in children.
Outcomes	1. Pain measured by PCA morphine consumption. 2. Adverse events.
Notes	Some evidence of monitoring for adverse events, contacted author for confirmation, no serious adverse events occurred in the paediatric patients. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Lambert 2000

Methods	Comparative study.
Participants	19 children and 23 adults undergoing appendicectomy.
Interventions	Standardised analgesia including diclofenac 1.5 mg/kg in children.
Outcomes	1. Pain measured by PCA morphine consumption. 2. Adverse events.
Notes	Some evidence of monitoring for adverse events, contacted author for confirmation, no serious adverse events occurred in the paediatric patients. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Leontev 2004

Methods	Comparative study.
Participants	57 children undergoing minor surgery.
Interventions	1. Rectal or intramuscular diclofenac 1 mg/kg (47). 2. Analgin and Promedol (10).
Outcomes	1. Pain. 2. Adverse events.
Notes	Some evidence of monitoring for adverse events, no serious adverse events in 47 patients receiving diclofenac. no mention of blinding. Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Leontev 2005

Methods	Open comparative study
Participants	92 children aged 11-15 years undergoing minor surgical procedures
Interventions	1. diclofenac 1.5-2.0 mg/kg, rectally (n=22) 2. diclofenac IM injection 1-1.5 mg/kg (n=21) 3. rectal paracetamol 25-30 mg/kg (20) ; 4. IM promedol (meperidine) dose not clear (12) ; 5. dipyrone 5-10 mg/kg (14)
Outcomes	1. Pain 2. PONV 3. Bleeding 4. Allergy
Notes	Adverse events monitored for; 43 children received diclofenac; 5 cases of allergic skin rash, reverse d with chlorpyramine

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Littlejohn 1996

Methods	Randomised controlled trial, investigator blind.
Participants	60 children undergoing day case dental extractions.
Interventions	1. Rectal diclofenac 1-2 mg/kg (19). 2. Intravenous nalbuphine 0.3 mg/kg (21). 3. No analgesia (20).
Outcomes	1. Pain. 2. Subjective bleeding. 3. Time to waking. 4. Nausea.

Littlejohn 1996 (*Continued*)

Notes	Paracetamol rescue analgesia. Adverse events monitored for and no serious adverse events. Asthmatics: excluded. Safety quality: moderate, no evidence of follow-up.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mak 2001

Methods	Randomised controlled trial, investigator blind.
Participants	187 boys undergoing circumcision.
Interventions	1. Rectal diclofenac 1 mg/kg and intravenous fentanyl 0.5 µg/kg (61). 2. Dorsal penile nerve block with 0.5% bupivacaine (63). 3. Caudal block with bupivacaine 0.5 mL/kg (61).
Outcomes	1. Pain. 2. Adverse events.
Notes	Cannot use in comparative section as comparison was diclofenac plus fentanyl (one patient in each group suffered bleeding, three in each of the local block groups vomited versus one in diclofenac/fentanyl group). Drop-outs in caudal group due to inability to perform caudal block. Adverse events monitored for, 61 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Martindale 2004

Methods	Randomised controlled trial.
Participants	60 children undergoing day case surgery.
Interventions	1. Caudal bupivacaine 0.25% 1 mL/kg (20). 2. Caudal bupivacaine 0.25% 1 mL/kg plus S(+)-ketamine 0.5mg/kg (20). 3. Caudal bupivacaine 0.25% 1 mL/kg plus intravenous S(+)-ketamine 0.5 mg/kg. All patients received rectal diclofenac 1 mg/kg.
Outcomes	1. Pain. 2. Adverse events.
Notes	One patient was withdrawn - did not have surgery so 59 received diclofenac. Adverse events monitored for, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Martindale 2004 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

McGowan 1998

Methods	Randomised controlled trial.
Participants	61 boys (ASA 1-2) undergoing circumcision.
Interventions	1. Rectal diclofenac 2-2.5 mg/kg plus penile block with bupivacaine 0.5% 0.3 mL/kg (20). 2. Penile block with bupivacaine 0.5% 0.3 mL/kg (18). 3. Rectal diclofenac 2-2.5 mg/kg (20).
Outcomes	1. Pain. 2. Bleeding. 3. Nausea and vomiting.
Notes	Got raw data. Include the diclofenac plus penile block vs penile block in the comparative analysis. Three dropouts - penile block failed. Adverse events monitored for and two diclofenac patients had serious adverse events, both late haemorrhage requiring overnight hospitalisation and reoperation in one case. Asthmatics: unknown. Safety quality: moderate.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Mendham 1996

Methods	Randomised controlled trial, investigator blind.
Participants	127 children undergoing tonsillectomy or adenotonsillectomy.
Interventions	1. Rectal diclofenac 1 mg/kg (25). 2. Rectal diclofenac 1 mg/kg plus intravenous fentanyl 0.75µg/kg (33). 3. Intravenous tenoxicam 0.4 mg/kg (35). 4. Intravenous tenoxicam 0.4 mg/kg plus intravenous fentanyl 0.75 µg/kg (28).
Outcomes	1. Pain. 2. Bleeding. 3. Sedation.
Notes	Wrote to author for more detail on exclusions and drop-outs. Six patients excluded - two from group 1, one from group 2 and two from group 3 returned to theatre with post-operative bleeding, one from group 2 was excluded due to insufficient data. Morphine rescue analgesia used. Adverse events monitored for, 62 patients received diclofenac, three serious adverse events. Asthmatics: excluded severe. Safety quality: Moderate.

Risk of bias

Mendham 1996 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Menezes 2002

Methods	Comparative study.
Participants	100 children (ASA 1-3) undergoing orthopaedic surgery.
Interventions	1. Rectal diclofenac 1 mg/kg (20). 2. Caudal bupivacaine 0.25% plus adrenaline (1:400000) 0.5-1 mL/kg (20). 3. Caudal fentanyl 1.5 ?g/kg (20). 4. Caudal morphine 30 ?g/kg (20). 5. Caudal sulfentanil 0.3 ?g/kg (20).
Outcomes	1. Pain. 2. Adverse events.
Notes	Randomisation by order of admission and no blinding. Some patients received midazolam pre-medication but cannot tell who - exclude from comparative analysis. Adverse events monitored for, 20 patients received diclofenac with no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Mikawa 1995

Methods	Randomised placebo controlled trial.
Participants	140 children (ASA 1) undergoing strabismus surgery.
Interventions	1. Diazepam 0.4 mg/kg (35). 2. Clonidine 2µg/kg (35). 3. Clonidine 4 µg/kg (35) all dissolved in apple juice. 4. Placebo (35). All patients received rectal diclofenac 12.5 or 25 mg.
Outcomes	1. Vomiting. 2. Adverse events.
Notes	Adverse events monitored for, 140 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Miniti 1993

Methods	Open randomised comparative study
Participants	60 children with tonsillitis attending a walk-in ENT clinic
Interventions	1. nimesulide 5% oral suspension 2.5 mg/kg bd for 7 days (30) 2. diclofenac resinate 0.5 mg/kg tds for 7 days. All children also received amoxicillin
Outcomes	1. Throat pain 2. Dysphagia 3. Adverse events
Notes	Include in quantitative adverse events comparison but not blind so risk of bias. Adverse events monitored for; 30 children received diclofenac, no reports of serious adverse events

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Moores 1990

Methods	Randomised controlled trial, investigator blinded.
Participants	43 children undergoing day case herniotomy.
Interventions	1. Rectal diclofenac 2.5 mg/kg (20). 2. Caudal bupivacaine 0.25% 1 mL/kg (18).
Outcomes	1. Pain. 2. Vomiting. 3. Oral intake. 4. Mobility. 5. Passing urine. 6. Sleep disturbance.
Notes	Paracetamol rescue analgesia used. Wrote to authors, no response. Five dropouts, three incomplete questionnaires, one discharged early, one surgical complications caused overnight admission, original allocation unclear. Blinding maintained by placing gauze over sacral hiatus for all patients. Asthmatics: unknown. Safety quality: Low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Morton 1999

Methods	Randomised controlled trial.
Participants	80 children undergoing appendicectomy.

Morton 1999 (*Continued*)

Interventions	1. Rectal diclofenac 1 mg/kg 8 hourly (20). 2. Rectal paracetamol 20 mg/kg loading dose than 15 mg/kg 6 hourly (20). 3. Diclofenac plus paracetamol in the doses above (20). 4. No simple analgesic (20). All patients on patient controlled morphine infusions.
Outcomes	1. Pain. 2. Adverse events.
Notes	No information on blinding. Differential morphine consumption used as efficacy measure. Cannot compare number of adverse events between groups. Adverse events monitored for, 40 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Mukherjee 2001

Methods	Randomised controlled trial.
Participants	60 children (ASA 1-2) undergoing tonsillectomy or adenotonsillectomy.
Interventions	1. Intramuscular morphine 100 µg/kg (27). 2. Intravenous fentanyl 1µg/kg (29). All patients received rectal diclofenac 1-1.5 mg/kg.
Outcomes	1. Pain. 2. Adverse events.
Notes	Wrote to authors, four drop-outs did receive diclofenac and did not suffer any serious adverse events. Adverse events monitored for, 60 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Murphy 2000

Methods	Pharmacokinetic study.
Participants	20 children undergoing adenotonsillectomy.
Interventions	Rectal diclofenac 2 mg/kg.
Outcomes	1. Pharmacokinetics. 2. Adverse events.

Murphy 2000 (*Continued*)

Notes	Conference abstract, little detail but does mention no patients suffered any adverse effects. Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Nakayama 1982

Methods	Prospective cohort.
Participants	40 children undergoing tonsillectomy.
Interventions	Rectal diclofenac 25 mg.
Outcomes	1. Pain. 2. Adverse events.
Notes	Adverse events monitored for, 40 patients received diclofenac, no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Nikolic 2001

Methods	Case series.
Participants	28 children admitted with acute tubulointerstitial nephritis.
Interventions	None.
Outcomes	1. Description of treatment and outcome
Notes	One case was attributed to diclofenac, no details on length of treatment given. Child made a full recovery with supportive therapy.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Nishina 2000

Methods	Randomised controlled trial, investigator blind.
Participants	125 children (ASA 1) undergoing ophthalmological surgery.
Interventions	1. Rectal diclofenac 2 mg/kg (25). 2. Intravenous flurbiprofen 1 mg/kg (25). 3. Oral clonidine 4 µg/kg (25). 4. Rectal diclofenac plus oral clonidine (25). 5. Intravenous flurbiprofen plus oral clonidine (25). Placebos used for pre-medication where patient was awake.
Outcomes	1. Pain. 2. Vomiting. 3. Time to eye opening. 4. NSAID complications (rash, pruritus, bronchospasm, convulsions).
Notes	Paracetamol and diclofenac rescue analgesia used. NSAID complications looked for. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nordman 2006

Methods	Randomised controlled trial. Observer blind
Participants	54 children (ASA 1 and 2) aged 4 months-12 years having elective surgery
Interventions	1. isoflurane (27) 2. desflurane (27) All received oral paracetamol 20 mg/kg with pre-med and diclofenac 1 mg/kg rectally during operation
Outcomes	1. Anaesthetic recovery 2. Adverse events
Notes	Evidence of monitoring for adverse events. 54 children received diclofenac, no serious events reported. Asthmatics: unknown. Safety quality:moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Nze 2006

Methods	Randomised placebo-controlled trial
Participants	74 children aged 1-7 years day-case adenoidectomy

Nze 2006 (*Continued*)

Interventions	1. 1 mg/kg i.v. after induction of anaesthesia followed by an infusion of diclofenac 1 mg/kg over 2 hours (74) 2. placebo 0.9% saline (76)
Outcomes	1. pain 2. Bleeding 3. Adverse events
Notes	Evidence of monitoring for adverse events. Cannot use for comparative analyses as blinding is unclear and placebo data is missing from Table in paper. Authors contacted but no response. Asthmatics excluded. safety quality:moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

O'Donnell 2007

Methods	Prospective cohort study with three groups
Participants	210 children (ASA 1 or 2) aged between 3 and 12 years, having routine extractions of primary teeth in three hospitals using three different pain regimes
Interventions	"Usual care" for the hospital concerned 1. Voltarol suppository (70) 2. Paracetamol (70) 3. No analgesia (70)
Outcomes	1. Pain
Notes	This was a tri-site study with each hospital using its usual pain regime. Children compared on gender only; no data on ages. 70 children received diclofenac; adverse event monitoring unclear; no adverse events reported. Asthmatics: unknown. Safety quality: low

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Oztekin 2002

Methods	Randomised controlled trial, investigator blind.
Participants	40 children (ASA 1-2) undergoing tonsillectomy.
Interventions	1. Rectal diclofenac 1 mg/kg (20). 2. No treatment (20).
Outcomes	1. Pain. 2. Adverse events.

Oztekin 2002 (*Continued*)

Notes	Morphine as rescue analgesia. Adverse events monitored for, 20 patients received diclofenac, one serious adverse event from each group required nasal packaging and prolonged hospitalisation. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Riad 2007

Methods	Randomised controlled trial. Assessors blinded
Participants	108 children (ASA 1) aged 3-8 undergoing inguinal hernia repair
Interventions	1. rectal diclofenac 1 mg/kg 1 hr pre-op (36) 2. rectal paracetamol 40 mg/kg (36) 3. both drugs (36)
Outcomes	1. Pain
Notes	Differential morphine consumption used as efficacy measure. Adverse event monitoring unclear; no adverse events reported. Asthmatics: excluded. Safety quality: low

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Robinson 1994

Methods	Retrospective cohort (case note review)
Participants	366 patients undergoing tonsillectomy.
Interventions	Cases of post-tonsillectomy haemorrhage reviewed, not all received diclofenac.
Outcomes	Four children identified to have had post-tonsillectomy haemorrhage, three received diclofenac.
Notes	Include in qualitative review - authors state that they believe the incidence of post-operative bleeding increases with diclofenac use and these cases were likely to be caused by diclofenac.

Risk of bias

Item	Authors' judgement	Description

Robinson 1994 (*Continued*)

Allocation concealment?	Unclear	D - Not used

Romsing 2000

Methods	Randomised controlled trial, investigator blind.
Participants	52 children undergoing tonsillectomy.
Interventions	1. Oral diclofenac 2-3 mg/kg/24 hours (24). 2. Paracetamol 90 mg/kg/24 hours (24). Placebo tablets and oral liquid used to maintain blinding.
Outcomes	1. Pain. 2. Bleeding. 3. Nausea and vomiting.
Notes	Four patients (two from each group) excluded as unwilling to take oral analgesics - no risk of bias as patients did not receive study medication. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Ryhanen 1994

Methods	Randomised controlled trial, investigator blind.
Participants	299 children (ASA 1) undergoing herniotomy or orchidopexy.
Interventions	1. Intramuscular diclofenac 1 mg/kg (70). 2. No analgesia (73). 3. Caudal bupivacaine 0.25% 1 mL/kg (57). 4. Caudal bupivacaine 0.25% with adrenaline 5µg/mL 1 mL/kg (50).
Outcomes	1. Pain. 2. Adverse events. 3. Diclofenac pharmacokinetics.
Notes	Wrote to author, original data destroyed. 49 drop-outs cannot account for all but author states no patients had serious adverse events. Cannot compare post-operative complication rates as no numbers given (overall percentages). Gauze placed over sacral hiatus to maintain blinding. Adverse events monitored for, 70 patients received diclofenac with no serious adverse events. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Sahajananda 2003

Methods	Case report.
Participants	Eight year old boy with Kartagener's syndrome.
Interventions	Lobectomy, received diclofenac for acute pain.
Outcomes	Post-operative complications.
Notes	Description of anaesthesia in difficult case. Received diclofenac, no serious adverse events. Asthmatic: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Samarkandi 2005

Methods	Randomised controlled trial, investigator blind.
Participants	92 children (ASA 1) undergoing herniotomy.
Interventions	1. Rectal diclofenac 1 mg/kg (32). 2. Caudal bupivacaine 0.25% 0.75 mL/kg (30). 3. Combination of the above (30).
Outcomes	1. Pain. 2. Vomiting. 3. Urinary retention. 4. Time to ambulation. 5. Sleep on night after operation.
Notes	Pethidine and paracetamol rescue analgesia used. Gauze covering sacral hiatus used for all patients to maintain blinding. Adverse events monitored for, 63 patients received diclofenac with no serious adverse events. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Schiffmann 2005

Methods	Case report.
Participants	16 year-old girl two weeks post wisdom teeth removal.
Interventions	Oral diclofenac 75 mg twice daily for five days and clindamycin 300 mg three times daily for 10 days.

Schiffmann 2005 (*Continued*)

Outcomes	Colon perforation causing peritonitis and requiring peritoneal lavage and colostomy formation, closed after three months with no further complications.
Notes	Include in qualitative review. Diclofenac implicated as lesions typical of NSAID-associated damage and showed no signs of pseudomembranous colitis possibly induced by clindamycin.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Seaton 2000

Methods	Case report.
Participants	15 year old boy with meningococcaemia.
Interventions	Received diclofenac for arthralgia.
Outcomes	Developed widespread limb purpura, protracted immunological phenomena and late-onset gastrointestinal vasculitis.
Notes	Include as case report but note causality uncertain. Contacted author, unsure as to the most likely cause for gastrointestinal pathology - either diclofenac or meningococcal related arthropathy.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Selin 2004

Methods	Comparative study.
Participants	86 children undergoing orthopaedic surgery.
Interventions	1. Intramuscular diclofenac 50-75 mg (50). 2. No additional treatment (36).
Outcomes	1. Pain. 2. Bleeding.
Notes	No information on randomisation or blinding. Some evidence adverse events monitored for, 50 patients received diclofenac with no serious adverse events. Asthmatics: unknown. Safety quality: low.

Risk of bias

Selin 2004 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sen 2001

Methods	Case report.
Participants	Nine year-old girl hospitalised for transient synovitis.
Interventions	Discharge medication: oral diclofenac 25 mg twice daily.
Outcomes	On the first dose at home patient developed body aches, rash, itching, cutaneous flushing and became febrile. A second dose was administered two hours later (to treat these symptoms) and developed generalised rash and choking. Prompt hospitalisation with haemodynamic and respiratory support, but resuscitation failed.
Notes	Include in qualitative review.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Swanepoel 1999

Methods	Randomised trial, investigator blinded.
Participants	80 children undergoing tonsillectomy.
Interventions	1. Rectal diclofenac 1 mg/kg on induction of anaesthesia (40). 2. Oral diclofenac suspension 1 mg/kg two hours before surgery (40).
Outcomes	1. Pain.
Notes	Letter describing study, unclear whether adverse events looked for but states all patients discharged home the following day and no problems with haemostasis occurred. Wrote to author who confirmed no serious adverse events occurred. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sylaidis 1998

Methods	Prospective cohort
Participants	20 children undergoing cleft palate repair.
Interventions	Rectal diclofenac 1 mg/kg in theatre and further post-operative doses if required.
Outcomes	1. Post-operative complications.
Notes	Two non-serious adverse events noted, neither attributed to diclofenac. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Tawalbeh 2001

Methods	Randomised controlled trial.
Participants	80 children undergoing tonsillectomy.
Interventions	1. Rectal diclofenac 0.5-1.5 mg/kg/dose (41). 2. Oral paracetamol 10-15 mg/kg (39).
Outcomes	1. Pain. 2. Prolonged hospitalisation. 3. Bleeding requiring surgical intervention. 4. Nausea and vomiting.
Notes	Uses rescue analgesia. Risk of bias as treatment allocation known. Two serious adverse events (re-hospitalisation) one in each group. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Tay 2002

Methods	Randomised controlled trial, investigator blind.
Participants	63 children (ASA 1-2) undergoing bilateral myringotomy.
Interventions	1. Oral diclofenac resinate 0.5 mg/kg (30). 2. Oral paracetamol 15 mg/kg (33).
Outcomes	1. Pain. 2. Vomiting.

Tay 2002 (*Continued*)

Notes	Fentanyl rescue analgesia used, some evidence of adverse event monitoring, no serious adverse events reported. Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tewary 1993

Methods	Retrospective case record review.
Participants	363 children undergoing tonsillectomy.
Interventions	All patients received rectal diclofenac 25 mg on induction of anaesthesia.
Outcomes	1. Reactionary haemorrhage. 2. Return to hospital due to bleeding.
Notes	Six patients either had prolonged hospitalisation or were rehospitalised within 24 hours for reactionary haemorrhage. Five patients returned to hospital with bleeding between days two and eight (11 serious adverse events in total). Asthmatics: unknown. Safety quality: low.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Thiagarajan 1993

Methods	Randomised controlled trial, investigator and anaesthetist blinded.
Participants	198 children (ASA 1-2) undergoing tonsillectomy.
Interventions	1. Intramuscular diclofenac 1 mg/kg (91). 2. Intramuscular papaveretum 0.2 mg/kg (92).
Outcomes	1. Pain. 2. Bleeding requiring surgical intervention. 3. Subjective blood loss. 4. Nausea and vomiting.
Notes	15 withdrawals, 10 did not receive the study drug and record sheets of five were incomplete. Wrote to authors - none of these five excluded patients had a serious adverse event, but unclear whether they received diclofenac. Can use recovery area adverse events for comparative analysis without rescue analgesia. Evidence of monitoring for adverse events, 91 patients definitely received diclofenac, one serious adverse event - bleeding requiring re-operation. Asthmatics: excluded. Safety quality: moderate.

Risk of bias

Thiagarajan 1993 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

van der Marel 2004

Methods	Pharmacokinetic study
Participants	26 children undergoing tonsillectomy.
Interventions	Rectal diclofenac 2 mg/kg followed by 1 mg/kg eight hourly.
Outcomes	1. Pharmacokinetics.
Notes	Wrote to authors, no serious adverse events. Study also pooled pharmacokinetic data from 11 patients from Romsing 2000. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Varvinski 2001

Methods	Case report.
Participants	13 year old girl with Soto's syndrome.
Interventions	Orthopaedic surgery, rectal diclofenac (2 mg/kg) for acute pain.
Outcomes	Post-operative complications.
Notes	Description of anaesthesia in difficult case. Child received diclofenac and did not have a serious adverse event. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Viitanen 2000

Methods	Randomised controlled trial.
Participants	80 children (ASA 1-3) undergoing adenoidectomy with or without myringotomy.
Interventions	1. Sevoflurane 8% (40). 2. Halothane 5% (40). All received rectal diclofenac 12.5 mg.
Outcomes	1. Recovery characteristics. 2. Adverse events.
Notes	Evidence of monitoring for adverse events, 80 patients received diclofenac, no serious adverse events. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Vuori 2004

Methods	Randomised controlled trial.
Participants	51 children (ASA 1-2) undergoing elective major abdominal, thoracic or orthopaedic surgery.
Interventions	1. Intravenous diclofenac1.5 mg/kg followed by rectal diclofenac 2mg/kg twice daily (17). 2. Intravenous oxycodone 0.1 mg/kg followed by a continuous infusion of 0.03 mg/kg/hr (16). 3. Epidural bupivacaine 0.25% 0.1-0.2 mL/kg followed by an epidural infusion of bupivacaine 0.125% plus fentanyl 50 µg (15). Each treatment lasted for three days after the operation.
Outcomes	1. Systemic and local immune response. 2. Pain. 3. Diclofenac pharmacokinetics. 4. Adverse events.
Notes	Main study focus on immune response to surgery, no detail on adverse events. However, adverse events were monitored for and one serious adverse event (bleeding requiring transfusion) occurred in diclofenac group. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Walmsley 1997

Methods	Audit
Participants	30 children undergoing ENT surgery.
Interventions	Soluble oral diclofenac 12.5 mg or 25 mg.

Walmsley 1997 (*Continued*)

Outcomes	1. Pain.
Notes	Wrote to author, no serious adverse events occurred. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Watters 1988

Methods	Randomised controlled trial, investigator blind.
Participants	75 children (ASA 1-2) undergoing tonsillectomy.
Interventions	1. Intramuscular diclofenac 1 mg/kg (25). 2. Pethidine 1 mg/kg (25). 3. No analgesia (25).
Outcomes	1. Pain. 2. Drowsiness. 3. Vomiting.
Notes	Pethidine rescue analgesia used. Adverse events monitored for and no serious adverse events occurred. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Wennstrom 2002

Methods	Randomised controlled trial.
Participants	50 children (ASA 1-2) undergoing strabismus surgery.
Interventions	1. Rectal diclofenac 1 mg/kg (25). 2. Intravenous morphine 0.05 mg/kg (25).
Outcomes	1. Pain. 2. Nausea and vomiting.
Notes	Risk of bias as no allocation blinding, morphine used for rescue analgesia. Cannot include in comparative analysis as gives number of episodes not number of patients with vomiting. Adverse events monitored for and no serious adverse events occurred. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description

Wennstrom 2002 (*Continued*)

Allocation concealment?	No	C - Inadequate

Willey 2005

Methods	Randomised comparative study. Not blind
Participants	31 children aged 4-16 years admitted to two hospitals with a diagnosis of appendicitis
Interventions	Postoperative paracetamol 90 mg/kg/24 hours and diclofenac 3 mg/kg/24 hours via 1. rectal route (11) 2. oral route (18). All children received one diclofenac suppository pre-op.
Outcomes	1. Pain 2. PONV
Notes	Allocation to oral or rectal treatment said to be randomised but marked imbalance of numbers. Evidence of monitoring for adverse events. Asthmatics:unknown. Safety quality: medium

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Williams 2002

Methods	Randomised controlled trial.
Participants	98 children (ASA 1-2) undergoing adenotonsillectomy.
Interventions	1. Intramuscular codeine 1.5 mg/kg (48). 2. Intramuscular morphine (0.15 mg/kg) (48). All patients received rectal diclofenac 1 mg/kg.
Outcomes	1. Pain. 2. Adverse events. 3. CYP2D6 genotype.
Notes	Two withdrawals, neither received diclofenac. Adverse events monitored for, 96 received diclofenac and no serious adverse events occurred. Safety quality: moderate.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Yamamoto 1994

Methods	Comparative study.
Participants	74 children undergoing minor surgery.
Interventions	1. Sevoflurane. 2. Isoflurane. 3. Halothane. Rectal diclofenac 1 mg/kg was given to 23 patients.
Outcomes	1. Pain. 2. Adverse events.
Notes	Adverse events monitored for and no serious adverse events occurred. Asthmatics: unknown. Safety quality: moderate.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Yoo 1999

Methods	Randomised placebo-controlled trial
Participants	60 patients, aged 3-13 years, day-case tonsillectomy with or without adenoidectomy.
Interventions	1. IV fentanyl 1 mcg/kg (20) ; 2. IM diclofenac 1 mg.kg (20) 3. PLACEBO injection (20) route not stated. Post-induction
Outcomes	1. Pain 2. PONV 3. Bleeding
Notes	Study translated from Korean; blinding unclear. Evidence of monitoring for adverse events but cannot use for comparative analysis as not known if post-op bleeds required surgical intervention. Asthmatics: unknown. safety quality:moderate

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Anon 2005	(French) No mention of diclofenac use of adverse effects
Arundel 2007	Review. No cases involving diclofenac-induced liver disease in children
Bano 2004	Diclofenac as rescue analgesia, cannot tell number who received it
Baroni 1983	(Italian) Adult and paediatric patients, cannot separate out paediatric data
Berry 1992b	Letter relating to Berry 1992a
Bertin 1991	Diclofenac not used
Bruce 2006	Some children probably received diclofenac but individual cases cannot be identified
Camera 1992	Adult and paediatric patients, cannot separate out data on children
Campbell 1990	Adult patients only
Castro 1995	Translated from Spanish - adult patients
Courtney 2001	Adult and paediatric patients, cannot separate out data on children
Cuvellier 2005	(French) Clinical review. No case reports involving diclofenac use
Farsi 2007	Data relates to patients over 17 years old
Fender 1992	Translated from French - adult patient
Garcia-Alonso 1991	Adult patients only
Gold 2007	Clinical update. No specific cases involving diclofenac in children
Han 2005	Adult patients only
Hernandez 1997	Translated from Spanish - adult patients
Hicklin 1999	'Most' children given diclofenac, wrote to authors, no response
Karachalios 1992	Adult patients only
Keohane 1995	Not all patients received diclofenac, cannot separate out those who did
Kokki 1994	Diclofenac not used
Kurimoto 1993	Translated from Japanese - not all patients received diclofenac, cannot separate out those who did

(*Continued*)

Kuzelova 2004	Accidental intoxications, not a study of acute pain in children
Lankinen 2006	Diclofenac use is mentioned in abstract but there is no mention at all in the main paper
Lau 2002	Adult patients only
Leaper 2006	Spme children received diclofenac but not possible to identify data on individual cases
Lemelle 1998	Translated from French - review article
Machida 2004	Adult and paediatric patients, cannot separate out data on children
Majid 2004	Number of patients receiving diclofenac unclear, wrote to authors, no response
Mannion 1994	No mention of adverse events or blinding, wrote to authors, no response
Marczyk 1992	Translated from Portugese - adult patients
Maunuksela 1991	Review article
McEwan 2000	Diclofenac as rescue analgesia, not all patients received it and cannot separate out adverse event data in the ones that did
Miralles 1987	Adult patients only
Mitic 2007	Some patients received diclofenac but not possible to identify data on specific cases
Moore 1985	Diclofenac not used
Mostaque 1998	No mention of adverse events, wrote to authors, no response
Nordbladh 1991	Adult and paediatric patients, cannot separate out data on children
Ozcan 2002	Adult patients only
Parker 1986	Diclofenac not used
Pendeville 2001	Adult and paediatric patients, cannot separate out data on children
Roelofse 1993	Adult patients only
Roelofse 1996	Adult patients only
Romej 1996	Paitients did not receive diclofenac
Romsing 2001	Pharmacokinetic data from Romsing 2000 - further analysis on same study/patients

(*Continued*)

Rozhkova 1983	Translated from Russian - adult patients only
Schachtel 1993	Does not fit criteria for this review (Diclofenac not used for treating acute pain in children)
Schaller 1998	Case reports of NSAID renal toxicity in children - none were diclofenac
Schwentner 2006	Cannot determine number of patients receiving diclofenac
Shah 2001	Number of patients receiving diclofenac unclear, wrote to authors, no response
Sheppard 1993	Not all patients received diclofenac, cannot separate out those who did
Silvasti 1999	Adult patients
Stanley 2002	Case report, child received diclofenac but cannot ascertain when or what dose. Adverse events mentioned but no link to diclofenac made in text
Taneja 2004	Adult and paediatric patients, not all received diclofenac and cannot separate out data on children
Teiria 1994	Patients received diclofenac or ibuprofen, cannot tell numbers receiving diclofenac
Thomaser 2004	Translated from German - 70 dropouts, cannot tell total number of children exposed to diclofenac
Tuzuner 2007	Adult patients only
Valladares 2004	Adult and paediatric patients, cannot separate out data on children
van den Berg 1999	Adult and paediatric patients, cannot separate out paediatric data
Verheggen 1994	Adult and paediatric patients, not all received diclofenac and cannot separate out data on children
Walton 1993	Adult patients only
Weber 2007	Mix of children and adults. Cannot separate out data on children

DATA AND ANALYSES

Comparison 1. Diclofenac vs no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia	5	239	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.47, 0.74]

Comparison 2. Diclofenac vs paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients requiring rescue analgesia	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.01]

Comparison 3. Diclofenac vs any other treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea and/or vomiting	13	775	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.47, 0.73]
2 Bleeding requiring surgical intervention	7	463	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.31, 4.97]

Comparison 4. Diclofenac vs other NSAIDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea and/or vomiting	4	289	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.80, 1.92]
2 Bleeding requiring surgical intervention	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.28, 9.41]

Analysis 1.1. Comparison 1 Diclofenac vs no treatment/placebo, Outcome 1 Number of patients requiring rescue analgesia.

Review: Diclofenac for acute pain in children

Comparison: 1 Diclofenac vs no treatment/placebo

Outcome: 1 Number of patients requiring rescue analgesia

Study or subgroup	Diclofenac n/N	No treatment/placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bone 1988	10/20	20/20		25.5 %	0.51 [0.33, 0.79]
Littlejohn 1996	1/19	5/20		6.1 %	0.21 [0.03, 1.64]
Nishina 2000	2/25	10/25		12.4 %	0.20 [0.05, 0.82]
Samarkandi 2005	21/30	24/30		29.9 %	0.88 [0.65, 1.17]
Watters 1988	13/25	21/25		26.1 %	0.62 [0.41, 0.94]
Total (95% CI)	**119**	**120**		**100.0 %**	**0.59 [0.47, 0.74]**

Total events: 47 (Diclofenac), 80 (No treatment/placebo)

Heterogeneity: Chi^2 = 10.49, df = 4 (P = 0.03); I^2 =62%

Test for overall effect: Z = 4.59 (P < 0.00001)

Analysis 2.1. Comparison 2 Diclofenac vs paracetamol, Outcome 1 Number of patients requiring rescue analgesia.

Review: Diclofenac for acute pain in children

Comparison: 2 Diclofenac vs paracetamol

Outcome: 1 Number of patients requiring rescue analgesia

Study or subgroup	Diclofenac n/N	Paracetamol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baer 1992	9/19	20/25		66.8 %	0.59 [0.35, 0.99]
Tay 2002	6/30	9/33		33.2 %	0.73 [0.30, 1.82]
Total (95% CI)	**49**	**58**		**100.0 %**	**0.64 [0.40, 1.01]**

Total events: 15 (Diclofenac), 29 (Paracetamol)

Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%

Test for overall effect: Z = 1.90 (P = 0.057)

Analysis 3.1. Comparison 3 Diclofenac vs any other treatment, Outcome 1 Nausea and/or vomiting.

Review: Diclofenac for acute pain in children

Comparison: 3 Diclofenac vs any other treatment

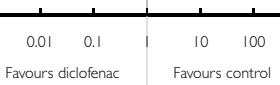
Outcome: 1 Nausea and/or vomiting

Study or subgroup	Diclofenac n/N	Any other treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Baer 1992	0/19	0/15		0.0 [0.0, 0.0]
Bhattacharya 2005	1/25	3/25		0.33 [0.04, 2.99]
Bone 1988	2/20	1/20		2.00 [0.20, 20.33]
Littlejohn 1996	0/19	1/20		0.35 [0.02, 8.10]
McGowan 1998	0/20	2/18		0.18 [0.01, 3.54]
Nishina 2000	2/25	4/25		0.50 [0.10, 2.49]
Oztekin 2002	8/20	16/20		0.50 [0.28, 0.89]
Romsing 2000	1/24	16/24		0.06 [0.01, 0.43]
Samarkandi 2005	0/30	0/30		0.0 [0.0, 0.0]
Tawalbeh 2001	1/41	12/39		0.08 [0.01, 0.58]
Tay 2002	0/30	0/33		0.0 [0.0, 0.0]
Thiagarajan 1993	40/91	45/92		0.90 [0.66, 1.23]
Watters 1988	14/25	19/25		0.74 [0.49, 1.11]
Total (95% CI)	**389**	**386**		**0.58 [0.47, 0.73]**

Total events: 69 (Diclofenac), 119 (Any other treatment)

Heterogeneity: Chi^2 = 19.85, df = 9 (P = 0.02); I^2 =55%

Test for overall effect: Z = 4.64 (P < 0.00001)



Analysis 3.2. Comparison 3 Diclofenac vs any other treatment, Outcome 2 Bleeding requiring surgical intervention.

Review: Diclofenac for acute pain in children

Comparison: 3 Diclofenac vs any other treatment

Outcome: 2 Bleeding requiring surgical intervention

Study or subgroup	Diclofenac n/N	Any other treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Baer 1992	0/19	0/25		0.0 [0.0, 0.0]
Berry 1992a	0/20	0/20		0.0 [0.0, 0.0]
Gadiyar 1995	0/19	0/20		0.0 [0.0, 0.0]
Littlejohn 1996	0/19	0/20		0.0 [0.0, 0.0]
McGowan 1998	1/20	0/18		2.71 [0.12, 62.70]
Tawalbeh 2001	1/41	1/39		0.95 [0.06, 14.69]
Thiagarajan 1993	2/91	2/92		1.01 [0.15, 7.02]
Total (95% CI)	**229**	**234**		**1.25 [0.31, 4.97]**

Total events: 4 (Diclofenac), 3 (Any other treatment)

Heterogeneity: $Chi^2 = 0.32$, df = 2 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.76)

Analysis 4.1. Comparison 4 Diclofenac vs other NSAIDs, Outcome 1 Nausea and/or vomiting.

Review: Diclofenac for acute pain in children

Comparison: 4 Diclofenac vs other NSAIDs

Outcome: 1 Nausea and/or vomiting

Study or subgroup	Diclofenac n/N	Other NSAIDs n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gananca 1991	4/29	1/29		3.9 %	4.00 [0.48, 33.66]
Mendham 1996	13/58	12/63		45.1 %	1.18 [0.59, 2.37]
Miniti 1993	3/30	1/30		3.9 %	3.00 [0.33, 27.23]
Nishina 2000	11/25	12/25		47.1 %	0.92 [0.50, 1.67]
Total (95% CI)	**142**	**147**		**100.0 %**	**1.24 [0.80, 1.92]**

Total events: 31 (Diclofenac), 26 (Other NSAIDs)

Heterogeneity: Chi^2 = 2.76, df = 3 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 0.94 (P = 0.35)

Analysis 4.2. Comparison 4 Diclofenac vs other NSAIDs, Outcome 2 Bleeding requiring surgical intervention.

Review: Diclofenac for acute pain in children

Comparison: 4 Diclofenac vs other NSAIDs

Outcome: 2 Bleeding requiring surgical intervention

Study or subgroup	Diclofenac n/N	Other NSAIDs n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mendham 1996	3/58	2/63		100.0 %	1.63 [0.28, 9.41]
Total (95% CI)	**58**	**63**		**100.0 %**	**1.63 [0.28, 9.41]**

Total events: 3 (Diclofenac), 2 (Other NSAIDs)

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.59)

APPENDICES

Appendix 1. EMBASE search strategy

1. diclofenac$ (textword)
2. diclofenac (subject heading) or diclofenac-potassium (subject heading) or diclofenac-diethylamine (subject heading) or diclofenac colestyramine (subject heading)
3. voltarol$ (textword) or Voltaren$ (textword) or diclomax (textword) or motifene (textword)
4. 1 or 2 or 3
5. (explode) pain subject heading
6. (explode) neuralgia (subject heading)
7. (explode) nociception (subject heading)
8. (pain or neuralgia or nociception or nociperception) and (manag$ or control$ or relief or relieve$) (textwords)
9. injur$ (textword) or fracture (textword) or headache (textword) or migraine (textword) or cephalalgia (textword) or hemicrania (textword) or neuralgi$ (textword) or hyperalgesi$ (textword) or earache (textword) or toothache (textword) or colic (textword)
10. postoperative-pain (subject heading) or kidney-colic (subject heading) or migraine (subject heading) or soft-tissue-injury (subject heading)
11. analgesi$ (textword) or antinocicept$ (textword)
12. (explode) analgesia (subject heading)
13. (explode) antinociception (subject heading)
14. postoperative-analgesia (subject heading)
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. child (textword) or adolescent (textword) or infant (textword) or paediatric (textword)
17. child (subject heading) or infant (subject heading) or baby (subject heading) or preschool-child (subject heading) or school-child (subject heading) or adolescent (subject heading)
18. 16 0r 17
19. 4 and 15 and 18

$ = truncation adj = adjacent to

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

MW undertook the literature search. IS and JS searched the references, extracted and analysed the data and wrote the review. All authors collectively designed the protocol and contributed comments. IS will be responsible for conducting the update of this review.

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INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adolescent; Anti-Inflammatory Agents, Non-Steroidal [adverse effects; *therapeutic use]; Diclofenac [adverse effects; *therapeutic use]; Pain [*drug therapy]; Pain, Postoperative [drug therapy]; Pain Measurement; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans