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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
Figure 1.	6
RESULTS	8
Figure 2.	8
Figure 3.	9
DISCUSSION	11
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	13
REFERENCES	14
CHARACTERISTICS OF STUDIES	16
APPENDICES	20
WHAT'S NEW	24
HISTORY	24
CONTRIBUTIONS OF AUTHORS	24
DECLARATIONS OF INTEREST	24
SOURCES OF SUPPORT	24
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	25
NOTES	25
INDEX TERMS	25

[Intervention Review]

As required versus fixed schedule analgesic administration for postoperative pain in children

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ABSTRACT

Background

Acute postoperative pain occurs as a result of tissue damage following surgery. Administering the appropriate analgesia to children is a complex process and it is unclear whether children's postoperative pain is more successfully treated by using 'as required' (when pain occurs) (termed '*pro re nata*' or PRN) or fixed scheduled 'around the clock' (ATC) analgesic administration (irrespective of pain at the time of administration).

Objectives

To assess the efficacy of as required versus fixed schedule analgesic administration for the management of postoperative pain in children under the age of 16 years.

Search methods

On 2 July 2014, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and CINAHL databases. We reviewed the bibliographies of all included studies and of reviews, and searched two clinical trial databases, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform, to identify additional published or unpublished data.

Selection criteria

We included randomised controlled trials (RCTs) comparing PRN versus ATC analgesic administration for postoperative pain in children under the age of 16 years who had undergone any surgical procedure requiring postoperative pain relief, in any setting.

Data collection and analysis

Two review authors (AH, PW) independently extracted efficacy and adverse event data, examined issues of study quality, and assessed risk of bias as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

We included three RCTs (four reports) of 246 children aged under 16 years undergoing tonsillectomy. Children were given weight-appropriate doses of the study medication, either PRN or ATC, by a parent or carer at home for up to four days following surgery. We did not identify any studies assessing the management of postoperative pain in children in any other setting (i.e. as an inpatient). All studies included in this review were based on the use of paracetamol, and an opioid was added to paracetamol in two studies. Analgesics were administered either orally (tablet or elixir) or rectally (suppository). Reporting quality was poor and there were fewer than 50 children in each arm. Mean pain intensity scores decreased over time, as did medication use. However, children were still reporting pain at the final assessment, suggesting that no administration schedule provided adequate analgesia. There were no significant differences in pain

intensity scores at any time point. The studies reported adverse events that may have been related to the study medication, such as nausea and vomiting, and constipation, but no statistically significant differences were noted between the groups. There were too few data from only three small studies and meta-analysis was not possible. One study reported that a higher amount of analgesics was consumed in the ATC group compared with the PRN group: it would have been helpful to show that the higher volume in the ATC group led to better analgesia but we were not able to demonstrate this.

Authors' conclusions

There was limited evidence available to draw any conclusions about the efficacy of PRN versus ATC analgesic administration for the management of postoperative pain in children.

PLAIN LANGUAGE SUMMARY

Postoperative pain relief for children

Pain is commonly experienced after surgery. Children tend to rely on a parent or carer to give medication to help relieve the pain. Medication can either be given when the child complains of pain (as required), or 'around the clock' (fixed schedule, e.g. every four hours).

In July 2014, we found three studies (randomised controlled trials) of 246 children under the age of 16 years. All studies compared the two ways of giving medicine for pain relief after tonsillectomy (an operation to remove the tonsils). The studies were small, and generally of low quality.

One study showed that the children in the 'around the clock' group took more medication, but they did not have better pain relief. There were no differences in pain relief or side effects between the two groups. There was not enough evidence to be sure which method is better for a child's pain relief after surgery. More high quality, large studies are needed.

BACKGROUND

Description of the condition

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury or nerve injury, or both. The management of postoperative pain and inflammation is a critical component of patient care (Derry 2013), and if treated inadequately can significantly affect recovery (Apfelbaum 2003).

The World Health Organization (WHO) guidelines for pharmacological treatments for children's pain acknowledge that pain in children is a public health concern of major significance in most parts of the world (WHO 2012). These guidelines state that the principle for treating pain at regular intervals is to administer analgesics 'around the clock' (ATC) rather than on an 'as required' (termed '*pro re nata*' or PRN) basis. It has also been suggested that ATC dosing should be used when pain itself is continuous or present for 12 hours or more each day, since postoperative pain will most likely be continuous for at least 24 hours following surgery (Pasero 2010). However, there is a need to understand the risks and benefits of time-contingent (ATC) dosing because of fears of over-medication or unwanted adverse effects (Sutters 2005). It is unclear whether PRN or ATC analgesic administration is more successful at preventing or reducing postoperative pain in children.

A report for the Department of Health (DoH) in the UK stated that approximately half a million children and young people undergo anaesthesia and surgery each year in England and Wales (Cochrane 2007). In the US, tonsillectomy is one of the most common surgical procedures, with more than 530,000 procedures performed annually in children younger than 15 years (Baugh 2011). In the early 1980s, a survey on the incidence of postoperative pain in children showed that on the first postoperative day, 17% reported severe pain (Mather 1983). More recent evaluations of the prevalence of acute pain in hospitalised children have shown that children on surgical units, for example, reported higher rates of moderate to severe pain (44%) than children on medical units (13%) (McGrath 2013). Another survey of 290 medical and surgical inpatients in Canada concluded that pain was infrequently assessed, yet occurred commonly across all age groups and services, and was often moderate or severe; analgesic therapy was largely single-agent and intermittent (Taylor 2008). A range of postoperative analgesic techniques have been developed to recognise, minimise, and control pain in children (Lönnqvist 2005). However, it is still reported that children remain under-treated and that more research in this area is needed (Lee 2014; Schechter 2003).

Description of the intervention

Self report is the primary source of information for measuring pain intensity in children (McGrath 2013), and analgesic doses can be adjusted in response to reports of intensity (von Baeyer 2009).

Cognitive developmental factors can impact children's understanding of pain and their ability to describe it effectively, and a good measure "should accurately reflect the individual's subjective experience" (Schechter 2003). Age-appropriate measurement tools are used to assess a child's self report, and can assist the person administering the analgesics

in selecting and evaluating treatments. The numerical rating scale (NRS) and the visual analogue scale (VAS) are validated measurement scales commonly used by children over the age of eight years, whereas the Faces Pain Scale - Revised (FPS-R) or the Poker Chip Tool (PCT) may be implemented for much younger children. NRS and VAS require the individual to be able to estimate quantities along a numerical or spatial dimension, hence are more appropriate for older children (von Baeyer 2013).

Administering appropriate analgesia to paediatric patients is a complex process and multiple strategies may be required (Smyth 2011). Participation of the parents and carers, or proxy measures (e.g. observational, behavioural or physiological), may be utilised in order to manage children's postoperative pain (APA 2012; Lee 2014; Lönnqvist 2005). Behavioural measures may be helpful when the child is sedated, in distress, or believed to be under-reporting their pain (MacLaren Chorney 2013). Physiological biomarkers of pain, such as cortisol levels or heart rate, may also be utilised, but the process of identifying and measuring biomarkers for such a diverse and subjective experience as pain is still under development and may be neither possible or practical (Brummelte 2013).

PRN analgesic administration can be used to manage children's postoperative pain. It provides flexible dosing that can be adapted to the needs of an individual (Gordon 2008). Self administration is not always possible, especially in very young children, and the patient may need to signal to the person administering the analgesic (e.g. a parent or nurse) to indicate that they are in pain and require another dose.

ATC analgesia is also used to manage children's postoperative pain, and this can provide continuous relief by preventing the pain from recurring (Chiaretti 2013). The website for the Great Ormond Street Hospital in the UK describes planned pain relief for children after surgery, indicating that the effects of analgesics such as paracetamol, ibuprofen, or oral morphine last for four to six hours (GOSH 2014). For most people receiving scheduled analgesia for postoperative pain, a supplemental dose is also offered on a PRN basis, although the route of administration and time to peak effect will dictate how often the rescue dose can be offered (Chiaretti 2013). Clinical concerns for the people administering analgesics can include whether to wake children up in order to maintain ATC dosing, and whether the child's self report makes sense and can be accurately interpreted.

Regardless of the means of administering pain relief, it is acknowledged that good communication between the child, the parents and carers, and the healthcare team is vital in helping to manage a child's postoperative pain (APA 2012).

This review compared PRN analgesia and scheduled analgesic administration for postoperative pain as two distinct intervention arms.

Why it is important to do this review

This review was commissioned by the National Institute for Health Research (NIHR) in the UK in response to a National Health Service (NHS) 'decision problem' regarding outpatient management of postoperative pain in children. This topic was identified in September 2013 during consultation with the NIHR. This review aimed to assess the comparative benefits of PRN analgesia and

scheduled analgesic administration for postoperative pain in children who have recently undergone surgery, in both inpatient and outpatient settings.

The NIHR commission stated: "Guidelines on postoperative management of paediatric pain recommend time-contingent analgesic dosing to reduce or prevent pain before it begins. Potential benefits of this approach include the maintenance of therapeutic levels of opioids, the facilitation of routine postoperative activities (e.g., oral intake, activity, sleep), and the avoidance of delays in analgesic administration because of inaccurate parental assessment of children's pain behaviours. However, many clinicians and parents fear that regularly scheduled administration of analgesics may result in the administration of unnecessary and/or excessive amounts of analgesics, which may cause undesirable and potentially harmful adverse effects. As a result, children are often not given enough pain control in the post-operative period. It is therefore necessary to evaluate the current evidence to determine the benefits and/or harms of regular dosing of analgesics versus 'when needed' following surgery in children."

This review assessed analgesic administration for children, and has been directly commissioned for completion by March 2015.

OBJECTIVES

To assess the efficacy of as required versus fixed schedule analgesic administration for the management of postoperative pain in children under the age of 16 years.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) assessing participant outcomes based on validated age-appropriate pain scales.

Types of participants

Children under the age of 16 years, who had undergone any surgical procedure requiring postoperative pain relief, in any setting.

Types of interventions

Interventions of interest included:

1. the use of as required or 'pro re nata' (PRN) analgesia administered by any route, in any dosage, and prescribed to treat pain postoperatively;
2. fixed analgesic administration schedules for postoperative pain management.

We did not plan to include studies of patient-controlled analgesia as these are not 'PRN' in the true sense of the term and this topic will be considered for a separate review.

Types of outcome measures

We planned to include a 'Summary of findings' table as set out in the Cochrane Pain, Palliative and Supportive Care Review Group's author guide (AUREF 2011), and recommended in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Primary outcomes

1. Pain intensity and pain relief, assessed using validated tools such as NRS, VAS, FPS-R, Colour Analogue Scale (CAS), or any other validated NRS. We searched for participant-reported pain, but accepted observer-reported outcomes if no data were available for participant-reported pain.
2. Any reported adverse events.

Secondary outcomes

We identified the following outcomes with reference to the PedIMPACT (Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) recommendations, which suggest core outcome domains and measures for consideration in paediatric acute and chronic/recurrent pain clinical trials (PedIMPACT 2008).

1. Participant global impression, measured using the Patients' Global Impression of Change (PGIC) scale (Hurst 2004).
2. Carer global impression; see point 1 above.
3. Medication use.
4. Requirement for rescue analgesia.
5. Length of postoperative stay.
6. Sleep duration and quality.
7. Acceptability of treatment.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL; on *The Cochrane Library*) Issue 6 of 12, 2014;
2. MEDLINE and MEDLINE in Process 1946 to 29 July 2014;
3. EMBASE 1947 to 29 July 2014;
4. CINAHL 1982 to July 2014.

We used Medical Subject Headings (MeSH) or equivalent and text word terms. There were no language restrictions. We tailored searches to individual databases. Appendix 1 shows the search strategies.

Searching other resources

We searched ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials, on 1 December 2014. We planned to search the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), but the website was unavailable. In addition, we checked reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles.

Data collection and analysis

Selection of studies

Two review authors (AH, PW) independently assessed the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria. Disagreements would have been resolved by discussion with the third review author if necessary (JC). We documented the selection process in sufficient

detail to complete a PRISMA flowchart ([Liberati 2009](#)) ([Figure 1](#)), and

[Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables.

Figure 1. Study flow diagram.

Data extraction and management

We obtained full copies of 11 studies and assessed them against the inclusion criteria. We extracted data on study design, participants, interventions, reported postoperative pain intensity and pain relief, adverse events, participant and carer global impressions, medication use, requirement for rescue analgesia, length of hospital stay, sleep duration and quality, and acceptability of treatment. We used a template data extraction form and checked for agreement before entry into The Cochrane Collaboration's statistical software Review Manager 5.3 (RevMan 2014).

We included three RCTs. Rømsing 1998 had two study arms, where the study group received analgesics ATC and the control group received them PRN. The other two included studies had three arms, of PRN or ATC with or without nurse coaching (Sutters 2004; Sutters 2010). We did not utilise the data from the ATC with nurse coaching group. We only included intervention groups and control groups that met the eligibility criteria.

Assessment of risk of bias in included studies

Two review authors (AH, PW) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group.

We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, e.g. random number table; computer random number generator); or unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies at high risk of bias that used a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); or unclear risk of bias (when the method was not clearly stated). We excluded studies that did not conceal allocation and therefore were at a high risk of bias (e.g. open list).
3. Blinding of outcome assessment (checking for possible detection bias). For this review, it was unlikely that these studies would be blinded to the investigators or participants. We assessed any methods used to blind the outcome assessors from knowledge of which intervention a child received. We assessed the methods as: low risk of bias (e.g. study stated that it was single-blinded and described the method used to achieve blinding of the outcome assessor); unclear risk of bias (study stated that outcome assessors were blinded but did not provide an adequate description of how it was achieved); or high risk of bias (outcome assessors were not blinded). We excluded studies at a high risk of bias that were not single-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% of children did not

complete the study or the study used 'baseline observation carried forward' (BOCF) analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).

5. Size of study (checking for possible biases confounded by small-study size). We assessed studies as being at low risk of bias (200 children or more per treatment arm); unclear risk of bias (50 to 199 children per treatment arm); or high risk of bias (fewer than 50 children per treatment arm).
6. Selective outcome reporting (reporting bias).

Measures of treatment effect

Where dichotomous data were available, we planned to calculate a risk ratio (RR) with 95% confidence intervals (CIs) and meta-analyse the data as appropriate. We would have used a fixed-effect model unless we found significant statistical heterogeneity. We planned to calculate numbers needed to treat for an additional beneficial outcome (NNTB) where appropriate (McQuay 1998); for unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. Where continuous data were reported, we had planned to use appropriate methods to combine these data in the meta-analysis.

We did not identify any data for analysis.

Assessment of heterogeneity

We planned to identify and measure heterogeneity as recommended in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would have dealt with clinical heterogeneity by combining studies that examined similar conditions. We planned to undertake and present a meta-analysis only if we judged children, interventions, comparisons, and outcomes to be sufficiently similar to ensure a clinically meaningful answer. We planned to assess statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic. Where I^2 was greater than 50%, we would have considered the possible reasons.

Assessment of reporting biases

We used The Cochrane Collaboration's tool for assessing the risk of reporting bias, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The aim of this review was to use dichotomous data of known utility (Moore 2013a). The review did not depend on what authors of the original studies chose to report or not, though clearly difficulties may have arisen in studies not reporting any dichotomous results. We had planned to extract and use continuous data, which probably poorly reflect efficacy and utility, if useful for illustrative purposes only, but there were no data available for analysis.

Data synthesis

We planned to use a fixed-effect model for meta-analysis, but there were no data available for analysis. We planned to use a random-effects model for meta-analysis if there was significant clinical heterogeneity and we considered it appropriate to combine studies. We planned to conduct our analysis using the primary outcomes of pain and adverse events, and to calculate the NNTHs for adverse events.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses, where data were available, according to age (two to five years, five to 12 years) and types of surgery (e.g. tonsillectomy versus other surgery).

Sensitivity analysis

We did not intend to carry out any sensitivity analyses.

RESULTS

Description of studies

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables.

Results of the search

The searches identified 1289 reports after duplicates were removed ([Figure 1](#)). We examined 11 full-text articles in detail and assessed them for eligibility. We subsequently included three studies (four reports) and excluded seven studies.

Included studies

We included three studies (four reports) with 246 children undergoing tonsillectomy ([Rømsing 1998](#); [Sutters 2004](#); [Sutters 2010](#)). [Sutters 2005](#) provided additional information for the study by [Sutters 2004](#). Children were aged five to 15 years in one study ([Rømsing 1998](#)), and aged six to 15 years in the remaining two studies ([Sutters 2004](#); [Sutters 2010](#)). The [Characteristics of included studies](#) table provides details.

[Rømsing 1998](#) was conducted in Denmark; [Sutters 2004](#) and [Sutters 2010](#) took place in the US. Neither [Rømsing 1998](#) nor [Sutters 2004](#) declared a funding source; [Sutters 2010](#) was supported by a grant from the National Institute of Nursing Research, USA.

Boys and girls were evenly assigned to the randomisation groups for all three studies.

[Rømsing 1998](#) examined the outpatient management of post-tonsillectomy pain in 53 children randomly assigned to two groups. Children were given paracetamol (acetaminophen) in weight-appropriate doses for the first three days following discharge from

hospital. The study reported that in Denmark, recommended dose ranges for this population were 60 mg/kg per 24 hours orally or 90 mg/kg per 24 hours rectally divided into four to six daily doses. The children in both groups were able to choose the route of administration, either oral (tablet (125 or 500 mg) or elixir (120 mg/5 mL)) or rectal (suppository (125, 250, 500, or 1000 mg)). The study group followed an ATC analgesic administration. The control group used paracetamol PRN (i.e. when the child complained of pain or was thought to be in pain by the parent or carer).

[Sutters 2004](#) randomised 88 children to one of three groups. All children received elixir of paracetamol with codeine in weight-appropriate doses (paracetamol 120 mg/5 mL with codeine 12 mg/5 mL) for three days after surgery. The first group ('PRN group') received analgesics every four hours PRN, without nurse coaching; parents were given instructions on dose measurement. The second group ('ATC group') received analgesics every four hours ATC, without nurse coaching. The third group ('ATC + coaching group') received analgesics every four hours ATC with nurse coaching. Children in all three groups were provided with a teaching booklet. Nurse coaching involved reviewing the pain management guidance in the booklet, and providing further information about postoperative pain (e.g. rationale for combining opioids and non-opioids, and strategies for improving the participants' adherence to analgesic consumption).

[Sutters 2010](#) randomised 123 children to one of three study groups as described above in [Sutters 2004](#). All children received elixir of paracetamol with hydrocodone in weight-appropriate doses (maximum daily paracetamol dose approximately 73 mg/kg and hydrocodone approximately 0.2 mg/kg/dose) for three days after surgery.

Excluded studies

We excluded seven studies after reading the full reports ([Bean-Lijewski 2007](#); [Higgins 1999](#); [King 1967](#); [Najafi 2010](#); [Patterson 2002](#); [Smyth 2004](#); [Tubbs 2007](#)). Four studies were not RCTs, two did not assess PRN versus ATC analgesic administration, and one included a different population. The [Characteristics of excluded studies](#) table provides details.

Risk of bias in included studies

[Figure 2](#) and [Figure 3](#) show the summary graphs.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Size
Rømsing 1998	?	?	+	+	?
Sutters 2004	+	?	+	+	-
Sutters 2010	+	+	+	+	-

Allocation

All three included studies were randomised.

Two studies were at low risk of random sequence generation (selection) bias, as they used an SPSS software-generated random selection process (Sutters 2004; Sutters 2010). Rømsing 1998 was at unclear risk of bias as the sequence was only described as 'randomly assigned'.

Allocation concealment (selection) bias was low for Sutters 2010, but it was unclear for the remaining two studies.

Blinding

It was not possible to assess the included studies for blinding of the investigators or participants. We assessed any methods used to blind the outcome assessors from knowledge of which intervention

a child received. Parents were asked to record the child's pain scores in a home diary or medication log; the studies did not report how these documents were assessed or whether the assessors were blinded to the intervention.

Incomplete outcome data

All three included studies were at low risk of attrition bias: in Rømsing 1998, 13/53 children or parents 'did not complete the forms'; in Sutters 2004, 8/88 children withdrew due to intolerable adverse effects; in Sutters 2010, 10/123 children became ineligible or parents withdrew consent.

Size of study

We assessed the size of the study as a potential source of bias. All studies were at high risk of bias due to size: there were fewer than 50 children in total in Rømsing 1998, and fewer than 50 children

per treatment arm in [Sutters 2004](#). More than 123 children were randomised in [Sutters 2010](#), but there were fewer than 50 children in one arm, and a combined total of 81 children randomised to the other two arms; therefore, we assumed the children were divided evenly between arms two and three, hence the high risk of bias assessment.

Selective reporting

All included studies were at low risk of reporting bias.

Effects of interventions

Pain intensity and pain relief

[Rømsing 1998](#): pain intensity was measured by the children using the poker chip tool (PCT), where one chip was 'a little piece of hurt' and four chips were 'the most hurt a child could have'. The scores were given on a 5-point scale of 0 to 4, with scores of 3 and 4 classified as severe pain. Pain intensity scores were recorded by the parents based on child self report twice a day for three days following surgery.

For both ATC and PRN groups, mean pain intensity scores tended to be higher in the morning than the evening, except on day one where the mean pain scores were lower in the morning. A higher pain score in the morning is expected due to the length of time between doses overnight. A lower pain score on the morning after surgery is also expected due to the effects of preoperative analgesia given on the day of surgery.

On day two, the study authors stated that the ATC group reported lower mean pain scores than the PRN group both in the morning and the evening, but this was not statistically significant. These data were derived from tables 2 and 3 on page 237.

Pain relief was not reported.

[Sutters 2004](#): pain intensity, with and without swallowing, was measured by the children using a descriptive NRS from 0 (no pain) to 10 (worst pain imaginable), prior to bedtime and upon awakening, on the evening of the day of surgery and twice a day for the following three days. Pain relief was rated using a 0 (no change) to 10 (pain gone) NRS at the same time. Mean pain intensity scores ranged from approximately 5 to 8 on the evening of the day of surgery, and had reduced to a range of approximately 2 to 5 on the evening of day three. There were no differences in pain intensity or pain relief scores between groups. There were no differences between pain intensity with swallowing and without swallowing. These data were derived from figure 2 on page 54.

[Sutters 2010](#): pain intensity, with and without swallowing, was measured by the children using a descriptive NRS from 0 (no pain) to 10 (worst pain imaginable), prior to bedtime and upon awakening, on the evening of the day of surgery and twice a day for the following three days. Pain intensity scores were higher for both ATC and PRN groups in the morning than in the evening for all three days. The mean pain intensity scores were numerically but not significantly higher in the PRN group than the ATC group, both with swallowing (3.9 with PRN versus 3.0 with ATC) and without swallowing (4.2 with PRN and 3.2 with ATC). Pain relief was not reported.

Both [Sutters 2004](#) and [Sutters 2010](#) also assessed the impact of nurse coaching of parents. Although not a critical part of this review,

they showed that compliance with the ATC regimen was high and not improved by nurse coaching. These data were derived from table 2 on page 16.

No data were available for analysis.

Adverse events

[Rømsing 1998](#): two children experience nausea and vomiting (one in each group). Two children reported otalgia (one in each group). One child reported a sore tongue (control group).

[Sutters 2004](#) reported adverse events in the secondary paper [Sutters 2005](#): assessed frequency of adverse events; believed that increased analgesics according to an ATC regimen, would mean increased adverse effects.

There were no differences between groups in the following symptoms: lightheadedness, feeling dizzy (approximately 4% to 32% of children across groups); nightmares (occurred infrequently); nausea (12% to 43%); vomiting (2% to 29%); doses of antiemetics (30%); and constipation (6% to 24%). There was no difference for sedation, and across groups there were significant decreases in sedation over the four postoperative assessments; 14% to 37% of children experienced daytime sedation. However, on day three, the ATC groups experienced significantly more sedation (7/52 with ATC versus 0/52 with PRN).

The study authors reported that nausea and vomiting may have been related to the study medication.

[Sutters 2010](#): assessed sedation, lightheadedness, dizziness, nightmares, nausea, vomiting, and constipation: there were no significant between-group differences, except that children in the ATC group did experience increased constipation. Adverse events were rated by the child before bedtime and upon awakening, using a 0 (did not have) to 4 (very severe) NRS.

Child and carer global impression

Not reported.

Medication use

[Rømsing 1998](#): reported the mean cumulative dose in milligrams per kilogram of paracetamol (acetaminophen) administered orally and rectally during the first three days following discharge.

Oral administration: on day two, the mean cumulative dose (for days one and two) was reported as 120.5 mg/kg (standard deviation (SD) 20.9) with ATC (study group) and 48.6 mg/kg (SD 22.9) with PRN (control group). On day three, the mean cumulative dose (for days one to three) was reported as 180.7 mg/kg (SD 31.8) with ATC and 69.7 mg/kg (SD 24.6) with PRN.

For rectal administration: on day two, the mean cumulative dose was reported as 172.3 mg/kg (SD 22.8) with ATC and 69.8 mg/kg (SD 26.5) with PRN. On day three, the mean cumulative dose was reported as 253.8 mg/kg (SD 32.7) with ATC and 81.8 mg/kg (SD 37.4) with PRN.

The study authors reported that the dose administered orally to the PRN group represented 39% of the dose administered to the ATC group, and that the dose administered rectally to the control group represented 32% of the dose administered to the study group.

In [Sutters 2004](#) and [Sutters 2010](#), the parents or nurses recorded the volume in millilitres when administering medication. [Sutters 2004](#) reported that medication use decreased over time for both groups. It was not clear to the study investigators what criteria were used by parents in the PRN group when decreasing the amount of analgesic given to their child over time. There were no differences in the total amount of analgesic administered over time for the ATC groups (with and without coaching). [Sutters 2010](#) reported that a higher amount of analgesics was consumed in the ATC group compared with the PRN group.

Requirement for rescue analgesia

Not reported.

Length of postoperative stay

All children were discharged home on the day of surgery.

Sleep duration and quality

Only [Sutters 2010](#) reported night-time doses, sedation, and nightmares. There were no differences between groups for sedation and nightmares. Across the three postoperative days, children in the ATC group received a mean nine night-time doses of the analgesic, whereas the PRN group received only four on average. Both groups reported pain on waking.

Acceptability of treatment

No study specifically reported acceptability of treatment.

In [Rømsing 1998](#), parents reported that children experienced nausea and vomiting (two children, one from each group), sore tongue (one child from control group), and otalgia (two children, one from each group). The study authors did not comment on whether these symptoms may have been caused by the study medication.

In [Sutters 2004](#), eight children developed intolerable adverse effects (i.e. persistent nausea and vomiting); these children were withdrawn from the study and given different medication. Nausea and vomiting were also measured each evening on a scale of 0 (none) to 4 (severe). There were no between-group differences for severity of nausea and vomiting reported.

DISCUSSION

The process of reviewing the question of whether ATC analgesia is more beneficial than PRN raised important issues that need careful consideration.

Assessing whether ATC is better than PRN for treating pain after surgery in children is not straightforward. The assessment is of methods that can be used in everyday clinical situations, which is very different from the efficacy of a particular intervention.

All studies included in this review were based on the use of paracetamol, despite there being a poor evidence base for paracetamol as an analgesic ([Moore 2014](#)).

An opioid was added to paracetamol in two studies ([Sutters 2004](#); [Sutters 2010](#)). [Sutters 2004](#) used codeine, which is now contraindicated for use in children ([FDA 2013](#)). We could find no systematic reviews on the comparison of effective analgesic administration for tonsillectomy in children. Non-steroidal anti-

inflammatory drugs might be an option but concern has been expressed about the risk of increased bleeding with these drugs. One review of 15 randomised studies and 1100 children by [Lewis 2013](#) showed that there was a non-significant increase in bleeding. The authors stated that an increased risk of bleeding could not be ruled out. Other interventions, such as dexamethasone, have been variously reported to increase bleeding or have little effect ([Czarnetzki 2008](#); [Gallagher 2012](#); [Bellis 2014](#)).

A second concern is linked to the use of mean pain data. Mean data hides the true picture in terms of how many participants achieved mild pain or less and how many had moderate pain or more ([Moore 2013b](#)). Of concern is that mean pain scores indicated that participants were generally still in moderate pain at the end of the studies, and several days after the surgery. This suggests that paracetamol was insufficient to control pain post tonsillectomy, and is in accord with the poor performance of paracetamol compared with other analgesics in postoperative pain in adults ([Moore 2011](#)).

A third and major concern is the paucity of the evidence base. The question posed is very important, and yet we identified only three small studies. While it is appreciated that ethical concerns are always greater in paediatric studies, children will continue to have inadequate pain relief unless questions are answered by randomised trials of large size, and using robust methods and reporting useful outcomes.

Summary of main results

We cannot draw any conclusions from the included studies. We noted the following points.

Pain intensity scores decreased over time, as did medication use. However, children were still reporting pain at the final assessment, suggesting that no administration schedule provided adequate analgesia.

There were no significant differences in pain intensity scores at any time point between the groups receiving analgesics administered ATC versus PRN.

Mean pain intensity scores were generally higher in the morning than in the evening regardless of the method, route, or type of analgesics administered. This is explained in part due to the longer gap between doses while the children slept during the night compared with the dose interval in the daytime.

A higher dose of analgesics was consumed by the ATC groups compared with the PRN groups. The studies reported adverse events that may have been related to the study medication, such as nausea and vomiting, and constipation, but there were no numerically significant differences noted between the groups. It would have been helpful to show that the higher volume in the ATC group led to better analgesia but we were unable to demonstrate this. It should be noted that [Rømsing 1998](#) reported that children in the PRN group received 'inadequate' doses of analgesics. The authors reported that many parents were reluctant to treat their children even when they recognised that they were in significant pain.

An increase in many surgical procedures being performed as day cases (at least in the UK ([NHS 2008](#))) may restrict the opportunities for staff to educate parents in analgesic administration and the

interpretation of pain scores. As a result, pain intensity scores may be higher at home due to the lack of supervision by trained staff. Two studies provided nurse coaching for parents in one of the ATC arms, but the authors reported that this did not impact parents' adherence to ATC dosing schedules (Sutters 2004; Sutters 2010).

Two of the three included studies reported pain intensity and pain relief scores with and without swallowing (Sutters 2004; Sutters 2010): while this is important in tonsillectomy studies, it was not important for this review.

All three included studies were of small size with fewer than 50 children in each arm, and therefore were at a high risk of bias. All children were administered analgesics for the management of postoperative pain following tonsillectomy. Children were given weight-appropriate doses of the study medication, either ATC or PRN, by a parent or carer at home for up to four days following surgery.

The initial report by NIHR and NHS (see [Why it is important to do this review](#)) highlighted the concerns of clinicians and parents regarding the frequency of analgesic administration, and associated adverse effects, when treating postoperative pain in children. Specifically there was a concern that "many clinicians and parents fear that regularly scheduled administration of analgesics may result in the administration of unnecessary and/or excessive amounts of analgesics, which may cause undesirable and potentially harmful adverse effects." There were too few data from only three small studies to address these concerns adequately.

Overall completeness and applicability of evidence

Overall completeness and applicability of evidence were inadequate. We identified only three small RCTs comparing PRN versus ATC analgesic administration for postoperative pain in children, and all three focused on post-tonsillectomy pain.

Quality of the evidence

All included studies were randomised, but reporting quality was poor. Only mean pain intensity scores were available, either in graphs or tables. All three included studies were of small size with fewer than 50 children in each arm. It was not stated whether the outcome assessors were blind to the children's group allocation. The complexity of children's self reports of pain intensity is widely accepted, as these self reports are potentially influenced by various social and developmental factors (von Baeyer 2009). The tendency of young children to use the bottom and top extremes rather than the middle of rating scales is well known (von Baeyer 2009).

Potential biases in the review process

We carried out a broad search of studies, in line with The Cochrane Collaboration's policy, and we consider it is unlikely that significant amounts of relevant data remain unknown to us.

Agreements and disagreements with other studies or reviews

We did not identify any other similar studies or reviews comparing PRN versus ATC analgesic administration for postoperative pain in children. However, there are a number of reviews on postoperative pain in children, typically following tonsillectomy (Hamunen 2005; Wiggins 2007; Lönnqvist 2005; Sutters 1997; Howard 2014; Dorkham 2014; Wilson 2006; Martin 2014). All reviews agreed that children

experience significant pain after surgery and that continuing adequate pain control at home is essential.

Some reviews also identified the issue of under-treating pain in this population, and that parents often gave fewer doses of analgesics than were prescribed. Unlike Sutters 2004 and Sutters 2010, Wilson 2006 found that pain scores were higher with swallowing than without swallowing. Martin 2014 reported that the most serious adverse effect of opioids, as prescribed for paediatric pain, was respiratory depression; none of the included studies in this review reported this outcome.

AUTHORS' CONCLUSIONS

Implications for practice

1. For children under the age of 16 years with postoperative pain, we could not determine whether the 'around the clock' method was any different from the 'as required' method, for outpatients given oral or rectal analgesics.
2. For clinicians, at present there is insufficient evidence to recommend one approach over another. Around the clock would appear to be a logical approach based on adult studies but we have not been able to demonstrate superiority.
3. For policy-makers and funders, there can be no implications for policy-makers making recommendations on the management of postoperative pain based on this review.

Implications for research

1. General: there is an urgent need for the adoption of a sensible pain assessment outcome for use by children that can be used both in clinical trials and in clinical practice. The outcome of mild or no pain has been suggested as being a target important to (adult) patients. It has the advantage of being useful as a dichotomous outcome to determine efficacy. Failure to attain the outcome is a marker of poor treatment.
2. Design: there is a need for randomised controlled trials of large size, and using robust methods and reporting useful outcomes. These should use analgesic efficacy with known endpoints, and take into account concerns about safety and serious adverse events such as postoperative bleeding.
3. Measurement (endpoints): we recommend that future studies aim to measure patient self report of pain relief or pain intensity, or both, using validated scales appropriate for use in children, ideally as a primary outcome. Parent-reported pain (such as the Parents' Post-operative Pain Measure (PPPM)) could also be a helpful secondary outcome, particularly in younger children as parents may have a better sense of their child's state than the child is able to report. Observer-reported pain scores could be a primary outcome measure if self report is not available. Investigators in future studies could also consider measuring the timing of pain ratings, whether pain is provoked or not, and the location and the spread of pain.
4. It is recommended that funding bodies work on three levels. First to generate agreement, based on evidence, of outcomes to be used in clinical trials of pain in children. Second, to generate agreement, based on evidence, of interventions that should be both effective and safe, and with protocols concerning how they may be used. Third, based on this, to commission several large studies in a number of different painful surgical interventions in children of various ages.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Rømsing 1998

Study characteristics

Rømsing 1998 (Continued)

Methods	Randomised parallel group of 3 days postoperative
Participants	53 children: 54 approached; 40 completed ('One parent was unwilling to participate and 13 failed to complete the forms') Aged 5-15 years Eligibility: scheduled for tonsillectomy
Interventions	"Scheduled administration of acetaminophen [paracetamol] 60mg/kg/day oral or 90mg/kg/day rectal...or acetaminophen 'as needed' " Paracetamol tablets (20 children): 125 mg or 500 mg Paracetamol suppositories (20 children): 125 mg, 250 mg, 500 mg, or 1 g Both groups received IV fentanyl and paracetamol 20 mg/kg rectally during surgery
Outcomes	Pain intensity: 'a 4 point pain intensity scale, the poker chip tool (PCT) was used to examine the children's postoperative pain'
Notes	Funding source not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% (13/53) 'did not complete the forms'
Selective reporting (reporting bias)	Low risk	'PCT pain scores'
Size	Unclear risk	< 50 children completed the study

Sutters 2004

Study characteristics

Methods	Randomised parallel group study of 4 days postoperatively
Participants	88 children undergoing tonsillectomy; 80 children completed Aged 6-15 years
Interventions	Weight-appropriate dose of paracetamol with codeine (120 mg/12 mg/5 mL) for 3 days after surgery PRN (28 children): every 4 hours PRN, with standard postoperative instructions, without nurse coaching

Sutters 2004 (Continued)

ATC without nurse coaching group (26 children): every 4 hours ATC, with standard postoperative instructions and no nurse coaching

ATC with nurse coaching group (26 children): every 4 hours ATC, with standard postoperative instructions and nurse coaching

Dose stated to be based on codeine 1 mg/kg but not stated if this is per dose or per day

No other analgesics allowed during study period

All children received fentanyl or morphine IV immediately postoperative for pain

Outcomes	Pain intensity with and without swallowing: 11-point NRS (0-10) Pain relief: 11-point NRS (0-10), and increased analgesic consumption Severity of nausea and vomiting
Notes	Funding source not declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised...using an SPSS software-generated random selection process
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/88 children withdrew due to intolerable adverse effects (i.e. persistent nausea and vomiting)
Selective reporting (reporting bias)	Low risk	Analgesic consumption, pain intensity, pain relief, and severity of nausea and vomiting all analysed/reported
Size	High risk	< 50 children in each arm

Sutters 2010
Study characteristics

Methods	Randomised parallel group study of 4 days postoperatively
Participants	123 children; 113 completed Aged: 6-15 years
Interventions	Weight-appropriate dose of paracetamol with hydrocodone elixir (167 mg/2.5 mg/5 mL) for 3 days after surgery Group A (39 children): every 4 hours PRN, with standard postoperative instructions Group B (34 children): every 4 hours ATC, with standard postoperative instructions, without nurse coaching Group C (40 children): every 4 hours ATC, with standard postoperative instructions, with nurse coaching

Sutters 2010 (Continued)

Doses based on approximately 0.2 mg/kg/dose of hydrocodone with maximum daily dose of paracetamol of 73 mg/kg

All groups received fentanyl or morphine IV immediately postoperatively for pain

No other analgesics allowed during study period

Outcomes	Pain intensity with and without swallowing: 11-point NRS (0-10) Severity of opioid-related adverse effects evaluated including nausea, vomiting, constipation, daytime sedation, dizziness, and nightmares
Notes	Supported by a grant from the National Institute of Nursing Research (NR04826)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised...using an SPSS software-generated random selection process
Allocation concealment (selection bias)	Low risk	A computer-generated randomisation list was drawn up by the statistician and given to an administrative assistant who prepared 2 sets of serially numbered sealed envelopes, 1 for boys and 1 for girls, each containing the random group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/123 children withdrew (became ineligible or withdrew consent)
Selective reporting (reporting bias)	Low risk	Reported analgesic consumption, pain intensity, and adverse effects
Size	High risk	< 50 children in each arm

ATC: around the clock; IV: intravenous; NRS: numerical rating scale; PRN: as required.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bean-Lijewski 2007	Did not compare PRN with scheduled analgesics
Higgins 1999	Not an RCT
King 1967	Did not compare PRN with scheduled analgesics
Najafi 2010	Not an RCT
Patterson 2002	Burn pain, not postoperative pain
Smyth 2004	Not an RCT
Tubbs 2007	Not an RCT

PRN: as required; RCT: randomised controlled trial.

APPENDICES

Appendix 1. Search strategies

CENTRAL (*The Cochrane Library*)

#1 MeSH descriptor: [Pain, Postoperative] this term only

#2 ((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or "post-operative analgesi*"):ti,ab,kw (Word variations have been searched)

#3 ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)):ti,ab,kw (Word variations have been searched)

#4 ("pain-relief after surg*" or "pain following surg*" or "pain control after"):ti,ab,kw (Word variations have been searched)

#5 ("post surg*" or post-surg*) and (pain* or discomfort):ti,ab,kw (Word variations have been searched)

#6 ((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)

#7 ((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*")):ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 MeSH descriptor: [Analgesia] this term only

#11 MeSH descriptor: [Analgesia, Patient-Controlled] this term only

#12 PRN:ti,ab,kw (Word variations have been searched)

#13 "pro re nata":ti,ab,kw (Word variations have been searched)

#14 PCA:ti,ab,kw (Word variations have been searched)

#15 patient controlled analg*:ti,ab,kw (Word variations have been searched)

#16 required analg*:ti,ab,kw (Word variations have been searched)

#17 #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #9 and #17

#19 MeSH descriptor: [Child] explode all trees

#20 child*:ti,ab,kw (Word variations have been searched)

#21 #19 or #20

#22 #18 and #21

MEDLINE (via OVID)

1 Pain, Postoperative/ (27231)

2 ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (47695)

3 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (338)

4 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (605)

- 5 (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (1302)
- 6 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (2803)
- 7 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (586)
- 8 exp Surgical Procedures, Operative/ (2400632)
- 9 or/1-8 (2420214)
- 10 analgesia/ or analgesia, patient-controlled/ (16633)
- 11 PRN.tw. (1208)
- 12 "pro re nata".tw. (194)
- 13 required analg*.tw. (227)
- 14 10 or 11 or 12 or 13 (18100)
- 15 9 and 14 (7354)
- 16 child/ or child, preschool/ (1551429)
- 17 child*.tw. (1004275)
- 18 16 or 17 (1870247)
- 19 15 and 18 (795)
- 20 randomized controlled trial.pt. (379463)
- 21 controlled clinical trial.pt. (88883)
- 22 randomized.ab. (300411)
- 23 placebo.ab. (156435)
- 24 drug therapy.fs. (1718784)
- 25 randomly.ab. (217206)
- 26 trial.ab. (312139)
- 27 or/20-26 (2352062)
- 28 exp animals/ not humans.sh. (3970931)
- 29 27 not 28 (2106550)
- 30 19 and 29 (391)

EMBASE (OVID)

- 1 Pain, Postoperative/ (42053)
- 2 ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi* or (post-operative adj4 analgesi*) or "post-operative analgesi*")).mp. (85022)
- 3 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (714)
- 4 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (803)
- 5 (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (2705)
- 6 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (3741)

7 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (758)

8 exp Surgical Procedures, Operative/ (3387468)

9 or/1-8 (3411336)

10 analgesia/ or analgesia, patient-controlled/ (83256)

11 PRN.tw. (1742)

12 "pro re nata".tw. (216)

13 PCA.tw. (29766)

14 patient controlled analg*.tw. (4185)

15 required analg*.tw. (309)

16 or/10-15 (112605)

17 9 and 16 (40996)

18 child/ or child, preschool/ (1447956)

19 child*.tw. (1223934)

20 18 or 19 (1906550)

21 17 and 20 (3096)

22 random\$.tw. (892607)

23 factorial\$.tw. (23412)

24 crossover\$.tw. (49689)

25 cross over\$.tw. (22268)

26 cross-over\$.tw. (22268)

27 placebo\$.tw. (203813)

28 (doubl\$ adj blind\$).tw. (147649)

29 (singl\$ adj blind\$).tw. (14596)

30 assign\$.tw. (241698)

31 allocat\$.tw. (84763)

32 volunteer\$.tw. (181481)

33 Crossover Procedure/ (39320)

34 double-blind procedure.tw. (219)

35 Randomized Controlled Trial/ (347139)

36 Single Blind Procedure/ (18456)

37 or/22-36 (1428811)

38 (animal/ or nonhuman/) not human/ (4624844)

39 37 not 38 (1262559)

40 21 and 39 (687)

41 limit 40 to embase (653)

CINAHL (EBSCO)

S33 S23 AND S32

S32 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31

S31 (allocat* random*)

S30 (MH "Quantitative Studies")

S29 (MH "Placebos")

S28 placebo*

S27 (random* allocat*)

S26 (MH "Random Assignment")

S25 (Randomi?ed control* trial*)

S24 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)

S23 (S11 AND S19 AND S22)

S22 S20 OR S21

S21 child*

S20 (MH "Child, Preschool") OR (MH "Child")

S19 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18

S18 required analg*

S17 patient controlled analg*

S16 PCA

S15 "pro re nata"

S14 PRN

S13 (MH "Patient-Controlled Analgesia")

S12 (MH "Analgesia")

S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10

S10 (MH "Surgery, Operative+")

S9 ((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*"))

S8 ((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*"))

S7 ((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*"))

S6 (("post surg*" or post-surg*) and (pain* or discomfort))

S5 ("pain-relief after surg*" or "pain following surg*" or "pain control after")

S4 ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*))

S3 ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*))

S2 ((postoperative near/4 pain*) or (post-operative near/4 pain*) or post-operative-pain* or (post* near/4 pain*) or (postoperative near/4 analgesi*) or (post-operative near/4 analgesi*) or "post-operative analgesi*")

S1 (MH "Postoperative Pain")

WHAT'S NEW

Date	Event	Description
14 May 2020	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 11, 2014

Review first published: Issue 2, 2015

Date	Event	Description
28 May 2019	Amended	Contact details updated.
13 March 2017	Review declared as stable	See Published notes .
23 June 2016	Amended	Flowchart amended.
1 April 2016	Amended	Contact Person name updated.
18 March 2015	Amended	Minor wording error amended in Abstract.

CONTRIBUTIONS OF AUTHORS

AH and PW were responsible for writing the protocol, data extraction, and completion of the full rapid review.

AH will be responsible for the completion of updates.

JC contributed to data extraction, analysis, and writing of the discussion for the full review.

All review authors agreed the final version.

DECLARATIONS OF INTEREST

AH is the Managing Editor of the PaPaS Group and contribution to this review was solely as an author; the NIHR Incentive Grant will be added to the Group's core infrastructure funding.

PW received funding from the Cochrane PaPaS Group for work on this review.

JC has no known conflicts of interest related to this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK

NIHR Directly Commissioned Cochrane Incentive Scheme, Award Reference Number: 13/180/13.

As required versus fixed schedule analgesic administration for postoperative pain in children (Review)

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were not able to include a 'Summary of Findings' table as planned at protocol stage. We added selective outcome reporting (reporting bias) to the 'Assessment of risk of bias in included studies' section at full review stage.

NOTES

2017

A search in February 2017 identified one potentially relevant study (Friedrichsdorf 2015) which did not meet the inclusion criteria. We identified no studies with the potential to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

We considered Friedrichsdorf 2015 in some detail. The study compares tramadol with a codeine-paracetamol mixture. Although there is an 'as required' element to both arms, there is no comparison undertaken between the fixed dose period and the 'as required' period. On this basis the study would be excluded.

Friedrichsdorf SJ, Postier AC, Foster LP, Lander TA, Tibesar RJ, Lu Y, et al, Tramadol versus codeine/acetaminophen after pediatric tonsillectomy: A prospective, double-blinded, randomized controlled trial. *Journal of Opioid Management*. 2015 Jul-Aug;11(4):283-94. doi: 10.5055/jom.2015.0277.

2020

We performed a restricted search in March 2020 and identified one potentially relevant study (Czarnecki 2018) but this would not change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Michelle L. Czarnecki, Keri R. Hainsworth, Pippa M. Simpson, Steven J. Weisman. Parent/Nurse-Controlled Analgesia Compared with Intravenous PRN Opioids for Postsurgical Pain Management in Children with Developmental Delay: A Randomized Controlled Trial. *Pain Medicine* 2018; 19: 742-752

DOI: 10.1093/pm/pnx257

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [administration & dosage]; Acute Pain [*drug therapy] [etiology]; Analgesia [methods]; Analgesics [*administration & dosage]; Analgesics, Opioid [administration & dosage]; Drug Administration Schedule; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Tonsillectomy [*adverse effects]

MeSH check words

Adolescent; Child; Child, Preschool; Humans