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Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery (Protocol)

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[Intervention Protocol]

Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate in adult participants undergoing all types of surgery, the effects of pre-emptive and preventive non-steroidal anti-inflammatory drugs (NSAIDs) compared with post-incision NSAIDs for reducing postoperative pain and opioid consumption.

BACKGROUND

This protocol contains text from a previous Cochrane protocol (Doleman 2017a).

Description of the condition

Postoperative pain is a common consequence of surgery that affects around 80% of patients. The severity of postoperative pain is variable, with 18% of patients suffering extreme pain (Apfelbaum 2003). Pain can have deleterious effects during the postoperative period, including patient dissatisfaction (Myles 2000), interference with daily activities (Strassels 2002), pulmonary complications (Desai 1999), increases in the stress response to surgery (Desborough 2000), and an increased risk of chronic postsurgical pain (Kehlet 2006). Risk factors for severe postoperative pain include the presence of pre-operative pain, pre-operative anxiety and the type of surgery (Ip 2009). Intravenous opioids are commonly used to treat pain in the postoperative period (Benhamou 2008), however their use is associated with many side effects such as vomiting, pruritus (itching), sedation (drowsiness) and patient concerns over addiction (Apfelbaum 2003). Therefore, alternative strategies to manage both postoperative pain and reduce postoperative opioid consumption may have important benefits for patients undergoing surgery (Zhao 2004).

Description of the intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) are a commonly used analgesic during the peri-operative period. The mechanism of action of NSAIDs involves inhibition of cyclooxygenase

(COX) enzymes, which are involved in the formation of hyperalgesic compounds called prostaglandins (Burian 2005). NSAIDs are effective in reducing postoperative pain, even when added to standard regimens including paracetamol (Ong 2010). Adverse events around the peri-operative period include possible increases in bleeding (Warltier 2003), and acute kidney injury and gastrointestinal ulceration (Gilron 2003). However, newer COX-2 specific agents that do not target gastrointestinal COX-1 may offer lower incidences of gastrointestinal ulceration compared with traditional NSAIDs (Jüni 2002), although studies have suggested an increased risk of cardiac events in high-risk patients (Nussmeier 2005).

Pre-emptive analgesia involves the initiation of an analgesic agent (painkiller) prior to surgical incision (before the surgeon cuts the skin). It is thought that by initiating analgesic interventions before surgical injury, the analgesic can provide reductions in intra-operative nociception to the central nervous system and therefore provide superior pain relief compared with the same analgesic given post-incision (after the surgeon has cut the skin) (Kissin 2000). Preventive analgesia extends this definition to include increasing the intensity and duration of pre-emptive analgesic interventions until final wound healing (Dahl 2011). The first review to examine the clinical effects of pre-emptive analgesia showed pre-emptive NSAIDs were ineffective in reducing pain scores or analgesic consumption in most of the included trials when compared to post-incision NSAIDs (Møiniche 2002). A second review, published a few years later, demonstrated a lower analgesic consumption and delayed time to first analgesic request with pre-emptive NSAIDs (Ong 2005). However, these reviews are now outdated and importantly, did not evaluate reductions in opioid side effects (from reduced postoperative consumption) and potential intervention adverse events.

How the intervention might work

Surgical incision promotes changes in both the central and peripheral nervous system, called sensitization. Such sensitization can cause biochemical changes which manifest as hyperalgesia (the same pain stimulus causing increased pain), and allodynia (normal sensations causing pain). It is thought that by initiating analgesia before surgical incision, both peripheral and central sensitization can be reduced, resulting in reductions in intra-operative nociception, and later, both acute and chronic postoperative pain. Preventive analgesia extends this reduction in sensitization to include the postoperative period. This enhanced definition came from an increased understanding of the development of persistent post-surgical pain, which is associated with postoperative sensitization, which may only be reduced by continuing analgesia longer into the postoperative period (Dahl 2011). As opioids are commonly used to treat pain postoperatively (Benhamou 2008), any reductions in opioid use may also result in a reduction in opioid adverse events (Doleman 2015b; Zhao 2004), and improve the patient experience.

Why it is important to do this review

Due to both its common occurrence (Apfelbaum 2003), and potential deleterious effects during the postoperative period, reducing postoperative pain is an important clinical issue. A simple change in clinical practice, such as changing the timing of administration of analgesics, could have important implications for postoperative pain management. Moreover, such a change is cost-neutral and therefore may benefit both anaesthetists in low-income countries and those working within healthcare systems with finite resources (such as the National Health Service (NHS) in the United Kingdom). A previous review has highlighted a potential effect of pre-emptive analgesia (Ong 2005), although most of the data were published over a decade ago, which mandates an updated review of the evidence.

OBJECTIVES

To evaluate in adult participants undergoing all types of surgery, the effects of pre-emptive and preventive non-steroidal anti-inflammatory drugs (NSAIDs) compared with post-incision NSAIDs for reducing postoperative pain and opioid consumption.

METHODS

Criteria for considering studies for this review

Types of studies

We will include parallel group, randomized controlled trials (RCTs) only. We will consider studies that did not use a double dummy placebo (for example, intervention group receives active drug before incision and placebo after incision; control group receives placebo before incision and active drug after incision). We will exclude studies that include paediatric participants and pharmacokinetic studies not reporting any clinical outcomes.

Types of participants

Adult patients (18 years and above) undergoing any type of surgery. We will not include studies that include both adult and paediatric participants.

Types of interventions

We will compare both pre-emptive non-steroidal anti-inflammatory drugs (NSAIDs) and preventive NSAIDs (intervention groups) with post-incision NSAIDs (control group). We define:

1. pre-emptive NSAIDs as NSAIDs initiated before incision but not continued postoperatively;
2. preventive NSAIDs as NSAIDs initiated before surgical incision and continued postoperatively; and
3. post-incision NSAIDs as the same analgesic intervention initiated after surgical incision, whether single dose (as comparator with pre-emptive analgesia) or continued postoperatively (as comparator with preventive analgesia) (control group).

We will only compare interventions if identical analgesics with identical dosages are used. In addition, we will only include studies if concurrent use of other multimodal analgesic agents during the peri-operative period is identical, in order to avoid confounding. If the studies report multiple intervention subgroups that have comparable control groups (identical interventions), we will combine these into one group using recommended methods (Higgins 2011a). We will include all types of NSAIDs and COX-2 inhibitors, at any dose, via any route of administration (oral and parenteral) and all types of regimen (pre-emptive or preventive) in the analysis.

Types of outcome measures

Primary outcomes

1. Early acute postoperative pain (measured within six hours postoperatively using a validated pain scale; converted to a 0 to 10 scale where a 0 to 100 scale is used; and where multiple time points are reported, we will include the earliest time point reported).
2. Adverse events (re-operation for major bleeding within 30 days (yes/no)); acute kidney injury within 48 hours (defined using published criteria (Mehta 2007) (yes/no)); gastrointestinal ulceration or bleeding requiring endoscopy within 30 days (yes/no); myocardial infarction within 30 days (defined as two of three of the following: chest pain, electrocardiogram (ECG) changes indicating ischaemia, or > 20% rise in high sensitivity troponin (yes/no)). We will report these adverse events separately.

Secondary outcomes

1. Nausea and vomiting (self-reported by the patient or requirement for anti-emetic; we will report nausea and vomiting both separately and aggregated (yes/no)).
2. Late acute postoperative pain (measured at 24 to 48 hours postoperatively using a validated pain scale; converted to a 0 to 10 scale where a 0 to 100 scale is used; and where multiple time points are reported, we will include the earliest time point reported).
3. 24-hour morphine consumption (mg) (if alternative opioids are used, we will convert these to morphine-equivalents using standard conversion factors (Doleman [in press])).
4. Time to first analgesic request (minutes).
5. Pruritus (self-reported by the patient (yes/no)).
6. Sedation (measured on a continuous scale such as the Ramsay Sedation Scale 0 to 6 with sedation defined as 3 or more (yes/no)).
7. Patient satisfaction (self-reported by the patient within 24 hours; converted to a 0 to 10 scale where a 0 to 100 scale is used).
8. Chronic pain (yes/no, measured three to six months postoperatively using a validated scale, such as the Visual Analogue Scale or the McGill Pain Questionnaire; we will include the earliest time point closest to three months). We will report this outcome as a separate dichotomous and continuous outcome.
9. Time to first bowel movement (hours).

For the secondary outcomes where time points are not specified, we will use the end point closest to two hours (one to six hours) to assess immediate short-term effects, and the end point closest to 24 hours (six to 48 hours) to assess longer-term effects. We will consider a reduction in pain score of 1.5 (on a 0 to 10 scale) (Gallagher 2001; Myles 2017), a reduction in the time to first analgesic request of one hour, a time to first bowel movement of 12 hours and a 10 mg reduction in morphine consumption (Doleman 2015a), as clinically significant. Outcomes will not form part of the study eligibility assessment, and so we will include studies that meet the participant, intervention and comparison criteria in the review even if they report no relevant outcomes.

Search methods for identification of studies

Electronic searches

We will identify RCTs through literature searching designed to identify relevant trials as outlined in Chapter 6.4 of the *Cochrane Handbook of Systematic reviews of Interventions* (Lefebvre 2011). We will not apply restrictions to language or publication status. We will search the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL, latest Issue) in the Cochrane Library.
2. MEDLINE (Ovid SP, 1946 onwards).
3. Embase (Ovid SP, 1974 onwards).
4. CINAHL (1982 onwards).
5. AMED (1985 onwards).

We developed a draft search strategy for MEDLINE (Appendix 1). We will used this as the basis for the search strategies in the other databases listed.

We will scan the following trials registries for ongoing and unpublished trials.

1. World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en);
2. ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We will conduct a search of the OpenSIGLE database to identify grey literature sources. We will scan the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials. When necessary, we will contact trial authors for additional information. In addition, we will search the following conference proceedings to identify further unpublished studies (all years considered).

1. World Congress on Pain (International Association for the Study of Pain).
2. Anaesthetic Research Society Meetings.
3. Association of Anaesthetists of Great Britain and Ireland Winter Symposium and Annual Congress.
4. American Society of Anesthesiologists Annual Meeting.
5. European Society of Anaesthesiologists Euroanaesthesia Conference.

Data collection and analysis

Selection of studies

We will use two review authors (BD and JPW) to independently screen the identified studies using the inclusion criteria to assess eligibility. BD and JPW will resolve any disagreements by consensus. If disagreement still exists following discussion, we will consult a third review author (JLB). BD and JPW will use the information from the retrieved reports to help identify any duplicate publications, such as author name, study centre, type and dose of interventions used and study dates. We will link any duplicate publications. We will input details of all potentially eligible studies into PubMed to identify any retracted publications and we will exclude these (Eisenach 2009).

Data extraction and management

We will extract data onto an electronic database using standardized data extraction forms (Appendix 2). We will perform this independently using two review authors (BD and TH), and will resolve any disagreements by consensus. If disagreement still exists, we will consult a third review author (JPW). We will perform the analysis using one review author (BD). We will translate non-English language studies and extract data following translation. If data are not contained within the original research report, we will contact the corresponding author, irrespective of the age of publication. We will extract the following information.

1. Bibliographic data, including date of completion/ publication.
2. Country.
3. Publication status.
4. Source of funding.
5. Trial design, e.g. parallel.
6. Study setting.
7. Number of participants randomized to each trial arm and number included in final analysis.
8. Eligibility criteria and key baseline participant data, including sex and age.
9. Details of treatment regimen received by each group.
10. Details of any co-interventions.
11. Primary and secondary outcome(s) (with definitions and, where applicable, time points).
12. Outcome data for primary and secondary outcomes (by group).
13. Duration of follow-up.
14. Number of withdrawals (by group) and number of withdrawals (by group) due to adverse events.
15. Adverse events.

Assessment of risk of bias in included studies

We will assess risk of bias in the included studies using the Cochrane tool for assessing risk of bias (Higgins 2011b). Two review authors (BD and JPW) will independently undertake assessment of risk of bias and reach agreement by consensus. We will assess risk of bias in the domains of sequence generation, allocation concealment, blinding of participants, study personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We will assess each domain as low-, unclear- or high-risk of bias (Higgins 2011b). We will present the results in both a 'Risk of bias' summary and a 'Risk of bias' graph. We will interpret risk of bias across studies by reducing the quality of evidence if there is potential risk of bias in the studies included in each analysis.

Measures of treatment effect

We will present dichotomous outcomes as risk ratios (RRs). For continuous outcomes, we will present these as mean differences (MDs), or if non-comparable scales are used across studies but still presented as continuous data, we will present these as standardized mean differences (SMDs). We will present the outcomes of time to first analgesic and time to first bowel movement as hazard ratios (HRs) where reported. If HRs are not reported, we attempt to calculate these from reported data using published methods (Tierney 2007). We will present the precision of effect estimates using 95% confidence intervals (CIs).

Unit of analysis issues

As we will include parallel-group RCTs only; unit of analysis issues are not expected for the main analysis (Higgins 2011c). For the main results, we will combine different dose subgroups into one treatment group, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If it is not possible to combine groups (for example, for continuous outcomes where the combined standard deviation (SD) cannot be estimated), we will treat these as separate studies and distribute the control group participants between these treatment groups to avoid analysing them twice (Higgins 2011c).

Dealing with missing data

We will contact corresponding authors for any data missing from the original publication, irrespective of publication date. If we do not receive a response, we will extract data from published graphs. If SDs are not reported, we will attempt to calculate these from other reported statistics. If this is not possible, we will instead discuss these in the narrative synthesis.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining study characteristics, such as the type of population, type of surgery and intervention used. We will assess statistical heterogeneity using the I^2 statistic. We will use the following recommended cut-off values in the interpretation of the I^2 statistic (Deeks 2011).

1. > 50% may represent moderate heterogeneity.
2. > 85% considerable heterogeneity.

In addition to the cut-off values, we will examine the direction of the effect in the individual studies. For clinically meaningful magnitudes of the pooled effect, we will explore heterogeneity using meta-regression when the criteria set out in Subgroup analysis and investigation of heterogeneity section are fulfilled.

Assessment of reporting biases

If we include 10 or more studies in the meta-analysis, we will assess publication bias graphically using funnel plots and quantitatively using Egger's linear regression test (Egger 1997). Due to the low power of this test, we will regard $P < 0.1$ as evidence of imprecise study effects and possible publication bias.

Data synthesis

We will use Review Manager 5 to aggregate study data (Review Manager 2014). We will conduct separate analyses for pre-emptive and preventive interventions. We will aggregate data using the adapted DerSimonian and Laird random-effects model (for continuous and categorical outcomes), as currently available in Review Manager 5. This is because we expect the treatment effect to vary with respect to the different populations within each study, and therefore there is no single underlying effect to estimate, making the random-effects model more appropriate. We will aggregate reported log hazard ratios and their associated standard errors using the generic inverse variance method. If we are unable to synthesize results, we will discuss them in a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

If there are sufficient included studies, we will consider conducting two separate subgroup analyses for the type of NSAIDs (non-COX-2 versus COX-2 inhibitor) and trials with different baseline pain levels (mean pain scores in the control group of < 3 (mild), 3 to 6 (moderate) and > 6 (severe)) (Moore 2013). If we include 10 studies or more in a meta-analysis and the included studies have a sufficient number of events, we will explore reasons for heterogeneity by performing a restricted maximum likelihood, random-effects meta-regression using the covariates: type and dose of NSAIDs; type of anaesthesia; and type of surgery (Thompson 2002). For dummy variables, we will use the least effective subgroup as the reference category. We will present the R^2 analogue with a corresponding P value for each covariate. We will use the Knapp-Hartung method to calculate P values (as this method more appropriately uses the t-distribution for the between-study variance). We will perform this analysis using the software STATA Version 15 (Stata 2017). If there is a low number of studies, or events, or both, we will only perform traditional subgroup analysis, and report the P value for subgroup differences.

Sensitivity analysis

We will perform a sensitivity analysis by restricting the analysis to studies at low-risk of bias (defined as low-risk for randomization and allocation concealment). As we will judge studies that did not use a double dummy design at high-risk of bias for blinding, we will assess the impact of excluding these from the analysis. We will also perform a further sensitivity analysis by excluding studies where SDs were estimated. As a further sensitivity analysis, we will analyse only the participants whose outcomes were measured (available case analysis) to assess the robustness of the findings.

'Summary of findings' table and GRADE

We will present outcomes in a 'Summary of findings' table. We will produce two 'Summary of findings' tables, one for each comparison.

1. Pre-emptive NSAIDs versus single dose post-incision NSAIDs.
2. Preventive NSAIDs versus continuous post-incision NSAIDs.

The outcomes for each comparison will include: early acute postoperative pain; adverse events: nausea and vomiting; late acute postoperative pain; 24-hour morphine consumption; time to first

analgesic request; and chronic pain. We will present these using the GRADE approach (Schünemann 2011). We will downgrade the quality of evidence from high-quality to moderate-, low- or very low-quality. Downgrading will be undertaken independently by two review authors (BD and JPW) and agreement reached by consensus. Characteristics of the evidence that will cause downgrading include:

1. limitations in the design and implementation of available studies, suggesting a high likelihood of bias (for example, studies not using a double dummy placebo design);
2. indirectness of evidence (indirect population, intervention, control or outcomes);
3. inconsistency of results;
4. imprecision of results (wide confidence intervals);
5. evidence of publication bias from asymmetry of the funnel plot.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Anti-Inflammatory Agents, Non-Steroidal/
2. (NSAID* or non-steroidal anti-inflammatory drug* or cyclooxygenase enzyme* or cox or ibuprofen or ketoprofen or diclofenac or indomethacin or ketorolac or naproxen or celecoxib or parecoxib or valdecoxib).tw
3. 1 or 2
4. exp Pain, Postoperative/
5. ((postoperati* or post-operati*) adj6 (pain* or recover*)).ti,ab
6. 4 or 5
7. 3 and 6
8. ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)
9. 7 and 8
10. (exp child/ or exp infant/) not exp adult/
11. 9 not 10
12. exp Preanesthetic Medication/ or (pre-emptive or preemptive or preventive or preoperati* or pre-operat* or preincision or pre-incision or perioperati* or peri-operati* or intraoperati* or intra-operati* or prophylactic* or ((before or prior) adj3 (surg* or operat*))).ti,ab
13. 11 and 12

Appendix 2. Data Extraction Form

Data collection form

Review title or ID

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

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

Notes:

1. General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Report title *(title of paper/ abstract/ report that data are extracted from)*	
Report ID *(ID for this paper/ abstract/ report)*	
Reference details	
Report author contact details	
Publication type *(e.g. full report, abstract, letter)*	

(*Continued*)

Study funding sources *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	
Notes:	

2. Study Eligibility

Study Characteristics	**Eligibility criteria** *(Insert eligibility criteria for each characteristic as defined in the protocol)*	Yes	No	Unclear	**Location in text** *(pg & /fig/table)*
Type of study	Randomized Controlled Trial				
	Controlled Clinical Trial *(quasi-randomized trial)*				
Participants					
Types of intervention					
Types of outcome measures					

INCLUDE	**EXCLUDE**
Reason for exclusion	
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	Location in text *(pg & ¶/fig/table)*
Population description *(from which study participants are drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Notes:		

4. Methods

	Descriptions as stated in report/ paper	Location in text *(pg & ¶/fig/table)*
Aim of study		
Design *(e.g. parallel, cross-over, cluster)*		
Unit of allocation *(by individuals, cluster/ groups or body parts)*		
Start date		
End date		
Total study duration		

(*Continued*)

Ethical approval needed/ obtained for study	Yes No Unclear		
Notes:			

5. Risk of bias assessment

See Chapter 8 of the Cochrane Handbook

Domain	Risk of bias			Support for judgement	Location in text *(pg & ¶/fig/table)*
	Low-risk	High-risk	Unclear		
Random sequence generation *(selection bias)*					
Allocation concealment *(selection bias)*					
Blinding of participants and personnel *(performance bias)*				**Outcome group: All/**	
(if required)				**Outcome group:**	
Blinding of outcome assessment *(detection bias)*				**Outcome group: All/**	
(if required)				**Outcome group:**	
Incomplete outcome data *(attrition bias)*					
Selective outcome reporting? *(reporting bias)*					
Other bias					
Notes:					

6. Participants

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

	Description as stated in report/paper	**Location in text** (pg & ¶/fig/table)
Total no. randomized *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/ethnicity		
Severity of illness		
Comorbidities		
Other treatment received *(additional to study intervention)*		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

7. Intervention groups

Copy and paste table for each intervention and comparison group
Intervention group 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Group name		
No. randomized to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Resource requirements to replicate intervention *(e.g. staff numbers, cold chain, equipment)*		
Notes:		

8. Outcomes

Copy and paste table for each outcome.
Outcome 1

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

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.
Dichotomous outcome

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
Comparison		
Outcome		

(*Continued*)

Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis *(by individuals, cluster/groups or body parts)*					
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*					
Reanalysis required? *(specify)*	Yes No Unclear				
Reanalysis possible?	Yes No Unclear				
Reanalysed results					

(*Continued*)

Notes:

Continuous outcome

	Description as stated in report/paper						**Location in text** *(pg & ¶/fig/table)*
Comparison							
Outcome							
Subgroup							
Time point *(specify whether from start or end of intervention)*							
Post-intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis *(individuals, cluster/groups or body parts)*							
Statistical methods used and appropriateness of these							

(*Continued*)

methods *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	Yes No Unclear		
Reanalysis possible?	Yes No Unclear		
Reanalysed results			
Notes:			

Other outcome

	Description as stated in report/paper				**Location in text** *(pg & ¶/fig/table)*
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					

(*Continued*)

No. participants moved from other group and reasons			
Any other results reported			
Unit of analysis *(by individuals, cluster/groups or body parts)*			
Statistical methods used and appropriateness of these methods			
Reanalysis required? *(specify)*	Yes No Unclear		
Reanalysis possible?	Yes No Unclear		
Reanalysed results			
Notes:			

10. Applicability

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

(*Continued*)

Notes:

11. Other information

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

CONTRIBUTIONS OF AUTHORS

Brett Doleman (BD), John P Williams (JPW), Jon Lund (JL), Jo Leonardi-Bee (JLB), Thomas Heinink (TH).

Conceiving the review: BD, JPW

Co-ordinating the review: BD, JPW, JL, JLB, TH

Undertaking manual searches: BD

Screening search results: BD

Organizing retrieval of papers: BD

Screening retrieved papers against inclusion criteria: BD, JPW, TH, JLB

Appraising quality of papers: BD, JPW, TH, JLB

Abstracting data from papers: BD, JPW, TH

Writing to authors of papers for additional information: BD

Providing additional data about papers: BD

Obtaining and screening data on unpublished studies: BD

Data management for the review: BD, JPW

Entering data into Review Manager 5 (RevMan 5): BD, JPW

RevMan statistical data: BD, JPW

Other statistical analysis not using RevMan 5: BD

Interpretation of data: BD, JPW, JLB

Statistical inferences: BD, JPW, JLB

Writing the review: BD, JPW

Securing funding for the review: N/A

Performing previous work that was the foundation of the present study: BD, JPW, JL, TH

Guarantor for the review (one author): BD

Person responsible for reading and checking review before submission: BD, JL, JPW, JLB, TH

DECLARATIONS OF INTEREST

Brett Doleman: has received a grant from Association of Anaesthetists of Great Britain and Ireland (AAGBI) for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

John P Williams: has received a grant from AAGBI for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

Jon Lund: has received a grant from AAGBI for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

Jo Leonardi-Bee: is a co-applicant of an Educational Grant from Roche to carry out further research in the area of pandemic influenza. Dr. Leonardi-Bee will be using this to carry out a systematic review and individual patient meta-analysis of the evidence (published and unpublished) of the impact of antiviral use on public health outcomes for 2009 pandemic influenza A/H1N1. This systematic review has been registered with PROSPERO (International prospective register of systematic reviews).

Thomas Heinink: no declarations of interest.