Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review

Hyllested M, Jones S, Pedersen J L, Kehlet H

Authors' objectives
To compare the safety and efficacy of paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and their combinations in post-operative pain management.

Searching
MEDLINE (from 1966 to January 2001) and the Cochrane Library (January 2001) were searched for articles published in full in the English language. The search strategy used pain terms combined with the keywords 'paracetamol', 'acetaminophen', 'proparacetamol', 'non-steroidal anti-inflammatory drugs (NSAID)', or individual drug names. The reference lists from identified studies were also examined.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible if the statistical method used for the analysis was fully described.

Specific interventions included in the review
Comparisons of paracetamol with NSAIDs (including acetylsalicylic acid), or paracetamol plus an NSAID with either paracetamol or NSAID alone, were eligible. Paracetamol had to be administered in a dose of at least 1,000 mg when given as a single agent in adults. Lower doses of paracetamol were included when the drug was used in combination with another agent or was administered to children. Drugs administered at different times and by different routes were eligible.

The NSAIDs studied included: oral aspirin (650 mg); diclofenac as a suppository (12.5 to 100 mg) or oral dose (2 to 3 mg/kg, and 100 mg); naproxen as a suppository (1,000 mg) or oral dose (440 to 500 mg); ketorolac as an intravenous (30 mg) or oral (5 to 20 mg, and 1 mg/kg) dose; ibuprofen as oral (200 to 800 mg) or sustained release (1,600 mg and 10 mg/kg) dose; oral bromfenac (5 to 25 mg); oral ketoprofen (12.5 to 200 mg); oral tenoxicam (0.5 mg/kg and 40 mg); oral meclofenamate (100 to 200 mg); oral flurbiprofen (50 mg) oral difusinal (500 mg); and oral indoprofen (800 mg). Paracetamol was administered in suppository form (1,300 to 4,000 mg and 35 mg/kg), as an oral dose (500 to 8,000 mg, and 10 to 35 mg/kg), and as proparacetamol (2,000 mg intravenously). The drugs were given as a single pre-emptive dose, as a single post-operative dose, and on up to 7 consecutive days.

Participants included in the review
The inclusion criteria were not defined in terms of the participants. The patients included adults and children who had undergone one of the following surgical procedures: major surgery, including abdominal and gynaecological surgery; orthopaedic surgery; gynaecological surgery including episiotomy and tubal ligation; ear, nose and throat surgery; and dental surgery.

Outcomes assessed in the review
Studies that assessed post-operative pain were eligible. Analgesic efficacy was assessed by standard pain measures, through quality of sleep, and through consumption of opioids or rescue analgesia. The standard pain measures included visual analogue scales, a variety of scoring systems, and objective and behavioural scores.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
Validity was assessed and scored using a 3-item, 5-point scale (see Other Publications of Related Interest no.1) on the basis of the following criteria: adequacy of randomisation; degree and adequacy of blinding; and adequacy of description of withdrawals and drop-outs. Two of the authors assessed and scored validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information were tabulated in the review: author and year of publication; sample size; type of surgery; treatment groups; method of administration of drug; treatment duration and timing; outcome measures; and adverse effects.

Methods of synthesis
How were the studies combined?
The studies were classified into the following comparisons: paracetamol versus NSAIDs; paracetamol plus NSAIDs versus paracetamol; and paracetamol plus NSAIDs versus NSAIDs. Within each comparison, the studies were grouped according to the type of surgery and a narrative synthesis was undertaken.

How were differences between studies investigated?
Evidence from higher quality studies was highlighted in the text of the review. The methodological quality scores of studies reporting positive and negative analgesic effects were compared statistically.

Results of the review
Thirty-six double-blind RCTs (3,362 patients, excluding the number of patients receiving placebo) were included.

The methodological quality scores ranged from 2 to 5 (out of a possible 5). There was no statistically significant difference between the studies showing a difference in analgesic effect and studies showing a negative effect (p=1.0).

The methodological flaws included: baseline difference between the treatment groups; use of a relatively insensitive pain scale; the possibility of low study sensitivity (suggested by no significant difference between the active drugs and placebo); low bioavailability of rectal paracetamol; and the use of insufficient doses of paracetamol.

Paracetamol versus NSAIDs (33 RCTs).
Major surgery (5 RCTs, 398 patients): 4 of the 5 RCTs showed no significant difference between paracetamol and NSAID in pain scores or post-operative morphine requirements.

Orthopaedic surgery (3 RCTs, 270 patients): none of the 3 studies showed any differences on pain scores at rest. One of the 3 RCTs showed reduced pain on movement after disk surgery with ketoprofen, compared with paracetamol.

Gynaecological surgery (3 RCTs, 178 patients): 2 of the 3 RCTs showed that NSAIDs improved pain scores in two different surgical procedures in comparison with paracetamol.

Ear, nose and throat surgery (6 RCTs, 408 children): 5 of the 6 studies included no placebo control and showed no difference between paracetamol and NSAIDs. One RCT with a placebo control showed that ketorolac was superior to a relatively low dose of paracetamol (10 mg/kg).

Dental surgery (16 RCTs): the results were inconsistent. Eight RCTs showed NSAIDs were associated with lower pain scores than paracetamol; 5 RCTs showed no difference; 2 RCTs showed that 1,000 mg paracetamol was superior to 650 mg aspirin and 100 mg diclofenac; and one study did not compare the two treatments statistically.

Paracetamol plus NSAIDs versus paracetamol (7 RCTs): each study involved a different surgical procedure. Four of the
7 RCTs showed that combinations of paracetamol with NSAIDs (aspirin, ketoprofen and diclofenac) were associated with lower pain scores than paracetamol alone; 2 RCTs involving gynaecological surgery showed no differences between the treatment groups; and in one study, the pain scores were not measured. Five of the 7 RCTs showed significant reductions in opioid consumption for combinations of drugs when compared with paracetamol alone; and one RCT showed no difference between the treatment groups.

Paracetamol plus NSAIDs versus NSAIDs (4 RCTs, 190 patients): one of the 4 RCTs showed a reduction in pain scores at rest and on movement for the combination of paracetamol and ketoprofen, compared with ketoprofen alone; one RCT showed diclofenac plus paracetamol reduced pain after dental surgery in comparison with diclofenac alone; and 2 RCTs showed no difference between the treatment groups.

Adverse effects.

Relatively few studies compared the adverse effects of NSAIDs with paracetamol. Adverse reactions that have been reported in the literature were discussed. These related to gastrointestinal hepatic, renal and haematological effects, allergic reactions and miscellaneous. The latter included heterotopic bone formation, sleep disturbance, modification of body temperature, and drug interactions.

Authors' conclusions

Paracetamol is a viable alternative to NSAIDs, especially because of the low incidence of adverse effects, and should be the preferred choice in high-risk patients. It may be appropriate to combine paracetamol with NSAIDs, but future studies are required.

CRD commentary

The aims were stated clearly, and the inclusion criteria were defined in terms of the study design, intervention and outcomes. Two relevant sources of literature were searched, but the methods used to select the studies were not described. Limiting the eligible studies to those published in the English language may have resulted in the omission of other relevant studies. In addition, the lack of an attempt to locate unpublished material raises the possibility of publication bias. The included studies were limited to double-blind RCTs and validity was assessed and scored using defined criteria. The methods used to assess validity were described, the results of the assessment were reported, and other potential sources of bias were discussed in the text.

Relevant data were tabulated although there were no details of the methods used to extract the data. The studies were grouped appropriately and a narrative synthesis was undertaken, with a summary of results provided for each subgroup. Attention was drawn to higher quality studies in the narration.

This review is clearly structured and presented. The evidence presented supports the authors' conclusions.

Implications of the review for practice and research

Practice: The authors state that NSAIDs are more effective than paracetamol in some situations, e.g. dental surgery, but differences are less obvious after other types of surgery. Paracetamol should be considered the preferred choice in high-risk patients. In addition, paracetamol should be considered instead of NSAIDs after major or orthopaedic surgery, and is to be recommended after tonsillectomy because of less bleeding.

Research: The authors state that future studies are required to examine the use of combinations of paracetamol with NSAIDs, especially after major surgery. The studies should focus specifically on a potential increase in side-effects, as a result of the combined use of these drugs.

Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetaminophen /therapeutic use; Analgesics, Non-Narcotic /therapeutic use; Anti-Inflammatory Agents, Non-Steroidal /therapeutic use; Double-Blind Method; Drug Therapy, Combination; Female; Humans; Pain, Postoperative /drug therapy; Randomized Controlled Trials as Topic

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.