Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain: a meta-analysis

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Authors' objectives
To quantify the analgesic efficacy of paracetamol and its combination with codeine or caffeine.

Searching
MEDLINE was searched from 1966 to May 1996 using MeSH first, when possible, followed by a keyword search of both titles and abstracts. EMBASE and the ISI database, both on BIDS, were also searched up to May 1996. Additional material was obtained by historical searches of the reference lists of retrieved articles, and by contacting the manufacturers. Only publications written in English were retrieved.

Study selection
Study designs of evaluations included in the review
Double-blinded randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Paracetamol, codeine and caffeine.

Participants included in the review
Participants were in the age range 13 to 87 years with a mean weight ranging from 46 to 81 kg. All had severe pain before taking the study drug or placebo (mean baseline pain score 0.54 to 0.87%); pain could originate from episiotomy, postpartum uterine cramp, dental or miscellaneous post-operative pain.

Outcomes assessed in the review
Total pain relief (TOTPAR) and pain intensity difference (SPID). The higher the recorded value of the outcome measure, the greater the pain relief. Response rate ratio (ResRR), and the re-medication rate (RemRR) were also assessed.

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 authors performed the selection. All studies had to be RCTs; those using formulations for non-oral routes, or where paracetamol was administered prior to surgery, were excluded. All included studies had to deal with post-operative acute pain including dental pain and postpartum pain. Studies involving orthopaedic surgery, general surgery, rectal surgery, hysterectomy, mastectomy, osteotomy and Caesarean section were included for comparative purposes.

Assessment of study quality
The authors do not report a method for assessing validity.

Data extraction
The scores of individual studies were standardised to take account of different scales, differences in the calculation of TOTPAR and SPID values, and the different time intervals used by different investigators. A standard score (TOTPAR% and SPID%) was calculated using a modified version of the equation first proposed by Eisenberg et al. (see Other Publications of Related Interest no.1).

Efficacy was estimated using the ResRR for patients receiving the treatment relative to the placebo (proportion of patients reporting moderate-to-excellent or greater than 50% pain relief during in the observation period). RemRR was calculated from the proportion of patients requiring rescue analgesics during the observation period.
Methods of synthesis
How were the studies combined?
Primary studies were pooled to estimate the effect size for the outcome measures. The formula used for these calculations is given in the authors' text. The individual log rate ratio, weighted by the inverse of the variance, was used for the pooling of rate ratios. For interval estimation and calculation of the 95% confidence intervals (CIs) of the pooled estimates, the method of DerSimonian and Laird was used (see Other Publications of Related Interest no.2).

The dose-response relationship was determined by regression analysis of dose versus response (differences of TOTPAR%), weighted by the inverse of response variance.

How were differences between studies investigated?
The chi-squared statistic for heterogeneity was employed, and where heterogeneity was found the random-effects model was used to investigate differences between studies.

Results of the review
Eighty studies were included containing 103 placebo comparisons and 26 head-to-head comparisons.

Paracetamol versus placebo:
TOTPAR% difference, 14 (95% CI: 12, 16);
SPID% difference, 12 (95% CI: 11, 13);
ResRR, 2.39 (95% CI: 1.89, 3.02); and
RemRR, 0.78 (95% CI: 0.69, 0.88).
Differences in TOTPAR%:
paracetamol and codeine versus paracetamol, 7.39 (95% CI: 2.62, 12.16);
paracetamol and caffeine versus paracetamol, 3.97 (95% CI: 0.57, 7.37).

Authors' conclusions
Paracetamol is an effective analgesic in a wide range of post-operative pain, including that associated with dental surgery, episiotomy and childbirth. There was some evidence of superiority of the combinations over paracetamol, but the effects were weak and probably not clinically significant. There is some evidence that 60 mg codeine adds to the analgesic effect of 600 mg paracetamol when using pain relief or pain intensity scores as the outcomes, but this is not necessarily translated into an increase in the number of patients who obtain moderate-to-excellent pain relief.

CRD commentary
A well-documented report that provides extensive details about the included studies. Results for adverse events and head-to-head comparisons are also given in the authors' text and may be of interest to the reader. It is unfortunate that the authors do not comment on the quality of the individual trials, particularly in light of the results from the tests for heterogeneity. It is also worth noting that although a good literature search was conducted, the included trials were restricted to those written in English. Since paracetamol is a widely-used and well-researched drug it is likely that many relevant trials have been overlooked; this could have important implications for the validity of the meta-analysis.

Bibliographic details
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetaminophen /adverse effects /therapeutic use; Administration, Oral; Analgesics, Non-Narcotic /adverse effects /therapeutic use; Analgesics, Opioid /adverse effects /therapeutic use; Caffeine /adverse effects /therapeutic use; Codeine /adverse effects /therapeutic use; Dose-Response Relationship, Drug; Drug Therapy, Combination; Humans; Pain, Postoperative /drug therapy; Randomized Controlled Trials as Topic; Regression Analysis

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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.