Paracetamol with and without codeine in acute pain: a quantitative systematic review

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Authors’ objectives
To assess the analgesic effect obtained from single oral doses of paracetamol alone, and in combination with codeine, in post-operative pain.

Searching
The following sources were searched: MEDLINE from 1966 to May 1996, EMBASE from 1980 to 1996, the Cochrane Library (March 1996), and the Oxford Pain Relief Database from 1950 to 1994. The words ‘paracetamol’, ‘acetaminophen’ and ‘trial’ were used in a free text search for studies published in any language. Additional reports were identified from reference lists of retrieved articles, review articles and textbooks. Neither pharmaceutical companies nor authors of papers were contacted for unpublished reports. Abstracts and review articles were not considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of paracetamol in post-operative pain (postdental extraction, postsurgical or postpartum pain). Inclusion criteria were: full journal publication, acute post-operative pain with total pain relief as a derived pain outcome, oral administration, adult patients, baseline pain of moderate-to-severe intensity, blinded design and randomised allocation to treatment groups. Exclusion criteria were: relief of other pain conditions, paracetamol used in combination with drugs other than codeine, and trials with less than 10 patients per treatment group.

Specific interventions included in the review
Oral administration of paracetamol, paracetamol plus codeine or placebo. Doses of paracetamol alone were 500, 600 or 650, or 1000 mg. Doses of paracetamol plus codeine were 300 plus 30 mg, 600 or 650 plus 60 mg, 1000 plus 60 mg.

Participants included in the review
Adults with pain rated as moderate to severe were included.

Outcomes assessed in the review
Pain relief: number of patients with at least 50% pain relief over 4 to 6 hours.

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.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
For each report, the mean total pain relief score was converted to the proportion of patients in each treatment group who achieved at least 50% pain relief. Details of the calculations are given.

Methods of synthesis
How were the studies combined?
Relative risk (RR) estimates were calculated with 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model (see Other Publications of Related Interest). Number-needed-to-treat (NNT) and 95% CIs were also calculated.

How were differences between studies investigated?
The homogeneity or heterogeneity between the studies was reported, but no details are provided of the tests used.
Results of the review
Paracetamol versus placebo: 31 trials (1,338 patients given paracetamol, 1,177 given placebo), of which 19 trials investigated oral surgery, 8 postsurgical and 4 postpartum pain.

Paracetamol plus codeine versus placebo: 19 trials (631 patients given paracetamol plus codeine, 573 given placebo), of which 14 trials investigated oral surgery and 5 postsurgical pain.

Paracetamol plus codeine versus paracetamol: 13 trials (435 patients given paracetamol plus codeine, 439 given paracetamol alone), of which 10 trials investigated oral surgery and 3 postsurgical pain.

Paracetamol versus placebo (all conditions). 500 mg paracetamol versus placebo: the RR and NNT were 1.6 (95% CI: 0.8, 3.5) and 3.6 (95% CI: 2.5, 6.5), respectively. 600 or 650 mg paracetamol versus placebo: the RR and NNT were 1.7 (95% CI: 1.3, 2.2) and 5.0 (95% CI: 4.1, 6.9), respectively. 1000 mg paracetamol versus placebo: the RR and NNT were 2.5 (95% CI: 1.9, 3.3) and 3.6 (95% CI: 3.0, 4.4), respectively.

Paracetamol plus codeine versus placebo. 300 mg paracetamol plus 30mg codeine versus placebo: the RR and NNT were 3.0 (95% CI: 1.8, 5.0) and 5.3 (95% CI: 3.8, 8.0), respectively. 600 or 650 mg paracetamol plus 60mg codeine versus placebo: the RR and NNT were 2.6 (95% CI: 2.1, 3.2) and 3.1 (95% CI: 2.6, 3.8), respectively. 1000 mg paracetamol plus 60 mg codeine versus placebo: the RR and NNT were 2.8 (95% CI: 1.2, 6.8) and 2.4 (95% CI: 1.5, 5.7), respectively.

Paracetamol plus codeine versus paracetamol. 300 mg paracetamol plus 30 mg codeine versus same dose paracetamol alone: the RR and NNT were 1.2 (95% CI: 1.0, 1.4) and 10 (95% CI: 5.9, 43), respectively. 600 or 650mg paracetamol plus 60 mg codeine versus same dose paracetamol alone: the RR and NNT were 1.3 (95% CI: 1.1, 1.5) and 6.7 (95% CI: 3.4, 174), respectively. 1000 mg paracetamol plus 60 mg codeine versus same dose paracetamol alone: the RR and NNT were 1.2 (95% CI: 1.0, 1.4) and 9.1 (95% CI: 5.8, 24), respectively.

The 18 trials combined for all conditions for 600 or 650 mg paracetamol versus placebo were found to be heterogeneous, as were the 3 trials of postpartum pain comparing 1000 mg paracetamol versus placebo. All other combinations of trials were homogeneous.

Authors' conclusions
The results confirm that paracetamol is an effective analgesic, and that 60 mg codeine added to paracetamol produces worthwhile additional pain relief even in single oral doses.

CRD commentary
This is a thorough and well-written review, with clear inclusion and exclusion criteria. Details of the primary studies are not given in the paper, but are available on the Bandolier website. See Web Address at end of abstract.

Restriction of the search to articles published in full means that publication bias cannot be ruled out, which may limit the completeness of the review and the reliability of the results. The strict inclusion criteria mean that only rigorous RCTs were included, but even so there is no discussion of the quality of the included studies or the way in which decisions were made, e.g. about the inclusion of studies or the way in which data were extracted. More explanation of the rationale behind the outcome measure would be useful.

The review addresses a clearly-defined intervention, i.e. oral administration of paracetamol alone or in combination with codeine for the treatment of post-operative pain in adults, and utilises a consistent pain relief outcome measure. The authors' conclusions follow from the results presented in the review.

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Other publications of related interest

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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.