Do codeine and caffeine enhance the analgesic effect of aspirin: a systematic overview

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Authors' objectives
To assess whether codeine and caffeine enhance the analgesic effect of aspirin in post-operative pain.

Searching
Computerised searches of MEDLINE and BIDS (EMBASE and ISI databases) were conducted from 1966 to the end of October 1996. Searches were carried out using MeSH terms (on MEDLINE) and, if possible, keyword searches on both the titles and abstracts. In addition, historical searches were made through the reference lists of the reports retrieved and review articles. Only articles in the English language were included in the review.

Study selection
Study designs of evaluations included in the review
Double-blinded randomised controlled trials (RCTs) undertaken between 1975 and 1995 were included. The observation period in the trials ranged from 2 to 12 hours. Studies were excluded on the basis of the following: relevant data were not extractable; there was self-controlled dose adjustment; syrup or buffered formulations were used; or the report of the trial was unobtainable. Abstracts and reports from multi-dose trials were also excluded.

Specific interventions included in the review
Oral formulations of aspirin, aspirin and codeine, aspirin and caffeine, and placebo.

Participants included in the review
Mild to severe pain. The participants had mild to severe pain before taking the study drugs: the mean baseline pain score was 0.30 to 1.00%. The types of pain were categorised as dental, episiotomy, postpartum uterine cramp and other. The mean age of the participants in the study ranged from 20 to 46 years, and their mean weights ranged from 55 to 74 kg.

Outcomes assessed in the review
Pain relief, pain intensity, and side-effects were assessed. Total pain relief (TOTPAR) and the sum of pain intensity difference (SPID) were measured. Both of these were calculated from pain scores collected in the studies. Pain was measured on a scale where the highest values indicated the most severe pain.

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 inclusion criteria represented the authors’ quality criteria. The authors do not state how the quality assessment was performed.

Data extraction
The data were extracted by one of the authors and a 10% random sample was cross-validated by the second author. The authors made an a priori decision to cross-validate the complete data set if any obvious error was identified. Any ambiguity in data interpretation identified by the first author was discussed and resolved by consensus. A customised form was used to record the details of each individual study included in the review.

Methods of synthesis
How were the studies combined?

Efficacy was measured using the response rate ratio. The pooled effect difference between the two treatments was calculated to estimate the effect size for the outcome measures. The formulae used for these calculations were provided.

The method of DerSimonian and Laird, as implemented by Whitehead and Whitehead (see Other Publications of Related Interest no.1), was used to estimate the interval and to calculate the 95% confidence interval (CI) of the pooled estimates.

The numbers-needed-to-treat (NNT) and side-effects were also calculated. The dose-response relationship was determined by regression analysis of the dose versus response, 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.

**Results of the review**

Placebo-controlled trials: there were 90 trials with aspirin (6,567 participants) versus placebo (6,497 participants), 4 trials with aspirin plus codeine (148 participants) versus placebo (145 participants), and 3 trials with aspirin and caffeine (215 participants) versus placebo (222 participants).

Head-to-head comparisons: there were 4 trials of aspirin plus codeine (148 participants) versus aspirin (140 participants), and 2 trials of aspirin plus caffeine (156 participants) versus aspirin (163 participants).

The pooled estimate for the effect (TOTPAR) of aspirin at a single dose of 650 mg was 14.05% (95% CI: 12.27, 15.83); the NNT was 3.57 (95% CI: 3.08, 4.23). A visual inspection showed no obvious dose-response relationship for aspirin, whereas the weighted regression analysis using the inverse of the response variance as the weight showed a significant effect (P<0.00001).

The corresponding estimate for the aspirin (650 mg)-codeine (60 mg) combination was 27.25% (95% CI: 19.77, 34.74); the NNT was 2.67 (95% CI: 1.67, 6.55). A further study showed another aspirin (650 mg)-codeine (30 mg) combination to have a positive effect relative to placebo (TOTPAR 20.03%, 95% CI: 7.18, 32.90).

The positive effects of TOTPAR (%) were confirmed by the pooled estimates obtained when using SPID (%) and the proportion of patients responding with at least moderate pain relief as the outcome measure. All three formulations (aspirin alone, aspirin plus codeine, and aspirin plus caffeine) were more effective than placebo.

The combination aspirin (650 mg)-codeine (60 mg) was more effective than aspirin (650 mg) in the indirect comparison using TOTPAR as an efficacy end point: TOTPAR was 27.25% (95% CI: 19.77, 34.74) for the combination compared with 14.05% (95% CI: 12.27, 15.83) for aspirin alone. The combination was not more effective when SPID (%) or the proportion of patients responding with moderate to excellent pain relief were used. Aspirin (650 mg)-caffeine (65 mg) was no more effective than aspirin (650 mg) on any of the efficacy end points studied; the NNT was 2.55 (95% CI: 1.89, 3.93).

In head-to-head comparisons, neither the aspirin-codeine nor the aspirin-caffeine combinations were more effective than aspirin alone for any of the efficacy variables. None of the three formulations showed any more side-effects than placebo, when expressed as a rate ratio with a 95% CI.

**Authors' conclusions**

Codeine (60 mg) may add to the analgesic effect of aspirin (650 mg) when administered as a single dose. However, the effect is modest and is unlikely to be of clinical significance, because the proportion of patients reporting moderate or excellent pain relief was not increased. Caffeine exerted no discernible additional analgesic effect when added to aspirin. The combination products did not cause any more short-term side-effects than aspirin alone.
CRD commentary
This was a thorough review with details of all the primary studies included. The review made a wide search of the available literature, both electronically and by examining the references in the primary studies. However, the authors limited themselves to papers in the English language and may, therefore, have missed studies from other sources. Aspirin and codeine alone or in combination are widely used, and it is likely that there would be studies available in languages other than English. No attempt was made to identify unpublished literature.

The paper stated the inclusion criteria and gave reasons for excluding studies; however, there were no stated inclusion criteria relating to the participants. The authors relied on the quality of the study design of the included trials (i.e. RCTs) and did not, therefore, assess the quality of the included trials.

The data from the individual studies were drawn primarily from studies of aspirin versus placebo; there were very few studies for the combination-dose comparisons. The synthesis of the data was comprehensive, but the results obtained could be altered if additional combination-dose studies could be found from non-English sources. The authors’ conclusions follow from the results presented.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Analgesia; Analgesics, Opioid /adverse effects /therapeutic use; Anti-Inflammatory Agents, Non-Steroidal /adverse effects /therapeutic use; Aspirin; Caffeine /adverse effects /therapeutic use; Central Nervous System Stimulants /adverse effects /therapeutic use; Codeine /adverse effects /therapeutic use; Drug Synergism; Drug Therapy, Combination; Humans; Pain, Postoperative /drug therapy; Randomized Controlled Trials as Topic

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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.