Analgesic efficacy of ibuprofen alone and in combination with codeine or caffeine in post-surgical pain: a meta-analysis

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Authors' objectives
To estimate the analgesic effect of ibuprofen, and to test whether codeine and caffeine enhance its effect on postsurgical pain.

Searching
MEDLINE, Excerpta Medica and the ISI database (from 1966 to December 1996) were searched using MeSH and keywords (not given). The reference lists of retrieved reports and review articles were also checked. Only English language articles were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of placebo and headtohead evaluations. Double-blind, single-blind, crossover and parallel studies were included. The observation period ranged from 3 to 10 hours.

Specific interventions included in the review
Oral formulations of ibuprofen, ibuprofen plus codeine, ibuprofen plus caffeine, and placebo. Ibuprofen doses ranged from 50 to 900 mg, codeine from 15 to 60 mg, and caffeine from 50 to 200 mg.

Participants included in the review
Adults with mild to severe pain resulting from dental, episiotomy, postpartum and other post-operative pain. Patients in eligible ibuprofen and caffeine trials took no caffeine-containing products during the 4 to 12 hours prior to administration of the test medication and during the study period. The mean age of the included patients ranged from 20 to 44 years, and the mean weight ranged from 60 to 74 kg.

Outcomes assessed in the review
The outcomes assessed were pain relief, pain intensity, and remedication (use of rescue analgesics). Adverse effects were also reported.

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 state that they assessed validity.

Data extraction
One author extracted the data onto a customised form, whilst a 10% random sample was cross-validated by the other author.

Methods of synthesis
How were the studies combined?
The efficacy was estimated using the response-rate ratio, whilst the effects were estimated using the rate-ratio or relative risk. Rothman's method (see Other Publications of Related Interest no. 1) was used to estimate the individual
effects, and the method of DerSimonian and Laird (see Other Publications of Related Interest no. 2) was used to estimate the confidence intervals (CIs). Dose-response was investigated by weighted regression analysis.

Comparisons of ibuprofen alone with ibuprofen plus codeine or ibuprofen plus caffeine were undertaken both directly and indirectly.

How were differences between studies investigated?
The studies were analysed according to the type of pain and analgesic dose. A chi-squared test for heterogeneity was performed.

**Results of the review**
Forty RCTs containing 75 placebo comparisons and 10 head-to-head comparisons were included.

There were 58 comparisons of ibuprofen versus placebo, involving 4,832 patients.

There were 11 comparisons of ibuprofen and codeine versus placebo, involving 699 patients.

There were 6 comparisons of ibuprofen and caffeine versus placebo, involving 415 patients.

There were 6 comparisons of ibuprofen and codeine versus ibuprofen, involving 414 patients.

There were 4 comparisons of ibuprofen and codeine versus ibuprofen and caffeine, involving 331 patients.

**Efficacy of ibuprofen.**
Ibuprofen was effective in dental pain, episiotomy pain and other post-operative pain at all the doses administered. Detailed results were presented for the trials of dental pain.

For ibuprofen compared with placebo:
the difference in the percentage total pain-relief score was 27.52 (95% CI: 24.76, 34.32);  
the difference in the percentage sum of pain intensity was 21.59 (95% CI: 19.05, 24.12); and  
the number-needed-to-treat for one more patient to obtain moderate-to-excellent pain relief was 2.44 (95% CI: 2.19, 2.77).

There was a dose-response relationship over the range 50 to 400 mg.

**Additive effects of codeine and caffeine.**
When pooling across all types of pain, the difference in percentage total pain-relief score was 8.48 (95% CI: 0.95, 16.01) for ibuprofen (400 mg) plus codeine (60 mg), compared with ibuprofen (400 mg) alone.

Indirect comparisons of the addition of codeine were not statistically significant.

The additive effect of caffeine was inconsistent.

**Adverse effects.**
Patients were more likely to experience drowsiness with both ibuprofen (400 mg) alone and the ibuprofen-codeine combination than with placebo; the relative risks were 2.33 (95% CI: 1.27, 4.27) and 3.74 (95% CI: 1.03, 13.56), respectively.

**Authors’ conclusions**
Ibuprofen was an effective analgesic for pain associated with dental surgery, episiotomy and other types of surgery. There was a significant dose-response relationship over the range 50 to 400 mg. Codeine (60 mg) enhanced the analgesic effect of ibuprofen (400 mg), but also increased the risk of inducing drowsiness. There was insufficient consistent data to demonstrate any additive efficacy with caffeine treatment.

CRD commentary
This was a thorough and clearly presented review with well-defined inclusion criteria. However, the search was quite restrictive and the search terms used were not given. In addition, the possibility of publication bias cannot be ruled out since only English language articles were sought and no attempt was made to identify unpublished studies.

Only RCTs were considered, but even so the included studies were not assessed for validity. Results should be treated with caution, since pain-relief scores were combined despite the differences in the way they were measured in the primary studies. There were a few inconsistencies between the tabulated data and the main text in terms of the characteristics of the primary studies.

The authors’ conclusions appeared to follow from the results presented. It would be interesting to see if the same results were found in older patients or patients with other causes of pain.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anesthetics, Combined /adverse effects /therapeutic use; Caffeine /administration & dosage; Codeine /administration & dosage; Dose-Response Relationship, Drug; Drug Synergism; Humans; Ibuprofen /administration & dosage; Pain, Postoperative /drug therapy; Randomized Controlled Trials as Topic; Sleep Stages

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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.