Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs

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Authors' objectives
To review the effectiveness and safety of topical non-steroidal anti-inflammatory drugs (NSAIDs) in acute and chronic pain conditions.

Searching
MEDLINE (from 1966 to September 1996), EMBASE (from 1981 to September 1996) and the Oxford Pain Relief Database (from 1950 to 1994) were searched for reports published in any language, using the individual drug names (generic and proprietary) together with the words 'administration, topical', 'gel', 'ointment', 'aerosol', 'cream', and combinations of these. Additional studies were identified from the reference lists of retrieved reports and review articles. Librarians and medical directors of the 12 UK pharmaceutical companies marketing topical NSAIDS were contacted for RCTs of their products, including any unpublished reports. Abstracts were not sought.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included since it had been agreed earlier that trials without randomisation, or with an inadequate randomisation method (without concealment of treatment allocation), would be excluded from further analysis.

Specific interventions included in the review
Topical NSAIDs with particular emphasis on ketoprofen, felbinac, ibuprofen, and piroxicam.

Participants included in the review
Patients with acute conditions (strains, sprains, sports injuries) or chronic conditions (arthritis, rheumatism) were eligible for inclusion. Those in vaginitis, oral or buccal conditions, thrombophlebitis, or experimental pain settings were excluded.

Outcomes assessed in the review
Measures of treatment success approximating at least a 50% reduction in pain, local and systemic adverse effects. Analyses were performed at 1 and 2 weeks for acute and chronic conditions, respectively.

How were decisions on the relevance of primary studies made?
Two reviewers screened the reports.

Assessment of study quality
Studies described as randomised were given 1 point; a further point was awarded if the method of randomisation was described and was considered adequate (e.g. a table of random numbers). Studies described as blinded were given 1 point; an additional point was awarded if the method of blinding was described and was considered adequate (e.g. identical appearance of preparation). Studies describing the number of withdrawals, along with the reasons for withdrawal, were given 1 point. Thus, the minimum score of an included RCT was 1 and the maximum score was 5. Each report was read by all of the authors independently to assess the adequacy of randomisation and blinding, and to assess the description of withdrawals. Any disagreements were resolved by consensus.

Data extraction
Information was extracted by the reviewers who met to concur decisions.
Methods of synthesis

How were the studies combined?
Relative risks with 95% confidence intervals (CIs) were calculated for placebo-controlled studies, and were combined by a random-effects model.

How were differences between studies investigated?
Differences between the studies were investigated by pooling all the data, by pooling the data for an individual drug for which there were at least three trials, and by sensitivity analyses based on the quality score and size of treatment group. Heterogeneity was assumed when the P-value was less than 0.1.

Results of the review

Forty placebo-controlled trials of topical NSAIDs were found. Dichotomous pain outcomes were available from 1,747 patients on active treatment and 1,492 on placebo. An additional 24 trials (4,171 patients) compared different topical NSAIDs, formulations, or routes of drug administration. Topical and oral NSAIDs were compared in 3 studies, one of which also had a placebo control.

Acute conditions (soft tissue trauma, strains, and sprains).

The pooled relative benefit for all 37 placebo-controlled comparisons was 1.7 (95% CI: 1.5, 1.9) and the number-needed-to-treat (NNT) was 3.9 (95% CI: 3.4, 4.4). The same results were produced when pooling the data from only those trials with a quality score of at least 3. The sensitivity analysis based on treatment group size showed that trials with fewer than 40 treated patients produced a significantly lower (better) NNT (2.6, 95% CI: 2.3, 3.1) than either larger trials or all trials. Larger trials with 40 to 80 treated patients produced higher (worse) estimates for the NNT (5.0, 95% CI: 3.7, 7.4) than all trials together, whilst the largest trials (more than 80 treated patients) produced an intermediate NNT (4.6, 95% CI: 3.7, 5.9). For the sensitivity analysis based on the drug (at least 3 trials), ketoprofen, felbinac, ibuprofen and piroxicam showed significant efficacy; the NNT values were 2.6, 3.0, 3.5 and 4.2, respectively. Benzydamine and indomethacin were no different from the placebo.

Chronic conditions (osteoarthritis, tendinitis).

The pooled relative benefit for all 12 comparisons was 2.0 (95% CI: 1.5, 2.7) and the NNT was 3.1 (95% CI: 2.7, 3.8). The sensitivity analyses based on quality score or treatment group size produced no significant change in these estimates; only one trial had a treatment group size of more than 80 patients, and the NNT for this trial was similar to that of the pooled estimate for all trials of more than 40 treated patients. No single topical NSAID was tested in as many as 3 placebo-controlled studies; combined estimates could not, therefore, be calculated for any single drug.

Comparison with oral NSAIDs.

Five studies compared topical with oral NSAIDs; 3 studies in acute conditions and 2 in chronic conditions. None showed significant benefit of oral over topical preparations.

Authors' conclusions

Topical NSAIDs were effective in relieving pain in both acute and chronic conditions when compared with a placebo.

CRD commentary

This was a very well-written and comprehensive review. As the reviewers report, the funnel plot they presented may be interpreted as showing publication bias. However, they did make strenuous efforts to unearth unpublished studies.

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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.