Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain


CRD summary
This review evaluated the efficacy and safety of topical rubefacients in the treatment of acute and chronic pain. The authors concluded that topically applied rubefacient may be efficacious in the treatment of acute pain. However, they acknowledge that estimates for the efficacy of rubefacients are unreliable, owing to the lack of good clinical trials.

Authors' objectives
To determine the efficacy and safety of topical rubefacients containing salicylates in the treatment of acute and chronic pain.

Searching
MEDLINE, PREMEDLINE, EMBASE, PubMed and the Cochrane Library were searched up to April 2003; the search strategy was provided. No language restrictions were applied. An in-house database of RCTs was also searched and the reference lists of retrieved articles were checked. Forty-eight pharmaceutical companies were also contacted.

Study selection
Study designs of evaluations included in the review
Double-blinded, randomised controlled trials (RCTs) with either placebo or an active control, and at least 10 participants in each arm of the trial, were eligible for inclusion.

Specific interventions included in the review
Studies of counter irritant or rubefacient, applied at least once daily, were eligible for inclusion. Studies of preparations containing only or mainly capsaicin, or its derivatives, were excluded. The included studies evaluated a range of salicylate-containing gels, creams and ointments. The comparators for studies of acute pain were placebo cream or gel, or homeopathic gel; for studies of chronic pain, the comparators were placebo cream or gel, or 5% etofenamate gel.

Participants included in the review
Studies of people with chronic or acute pain were eligible for inclusion. Studies of oral conditions were excluded. Studies of chronic pain included osteoarthritis, rheumatic disorders and unspecified chronic disorders. Studies of acute pain included low back pain, ankle sprain and unspecified sports injuries. Where reported, the age of the participants ranged from 14 to 86 years.

Outcomes assessed in the review
The primary outcome was improvement in pain. The hierarchy of outcomes in order of preference was: number of patients with a 50% or more reduction in pain (if given), patient-reported global assessment of treatment, pain on movement, pain on rest or spontaneous pain, and physician or investigator global assessment of treatment. The secondary outcomes were adverse events and withdrawal due to adverse events. To be eligible for inclusion, studies had to report the outcomes after at least 3 days for acute conditions and after at least 7 days for chronic conditions. Only trials reporting dichotomous data were included in the efficacy analysis; those reporting only mean or median pain relief, reduction in pain, or continuous data were excluded from this analysis.

How were decisions on the relevance of primary studies made?
At least two reviewers independently assessed trials for inclusion, which were verified by another reviewer. Any disagreements were resolved by consensus.
Assessment of study quality
The criteria used to assess the quality of the included studies were randomisation, blinding and withdrawals; the maximum quality score attainable was 5. The authors also assessed validity using a 16-point scale. At least two reviewers independently assessed study quality, which was verified by another reviewer. Any disagreements were resolved by consensus.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the number of patients responding to treatment, using an intention-to-treat format.

Methods of synthesis
How were the studies combined?
The authors calculated the number-needed-to-treat (NNT) or harm with 95% confidence intervals (CIs) for efficacy and adverse event data, respectively. For efficacy data, pooled relative risks (RRs) with 95% CIs were calculated separately for studies of acute and chronic pain using a fixed-effect meta-analysis.

How were differences between studies investigated?
The authors investigated heterogeneity visually using L’Abbe plots. Statistical tests of homogeneity (chi-squared and I² tests) were performed as part of the meta-analysis. Sensitivity analyses were conducted to investigate the effect of the outcome measured, type of placebo used and the validity score.

Results of the review
Twelve studies (n=862) were included in the review.

The quality scores ranged from 2 to 4 out of a possible 5. On the 16-point validity assessment, the scores ranged from 5 to 14.

Efficacy.

Based on 182 patients in 3 studies, rubefacient resulted in a statistically significant improvement in acute pain compared with placebo (RR 3.6, 95% CI: 2.4, 5.6, P<0.00001) and the corresponding NNT was 2.1 (95% CI: 1.7, 2.8). There was evidence of statistical heterogeneity (P<0.00001; I²=91.9%).

Based on 455 patients in 6 studies, rubefacient resulted in a statistically significant improvement in chronic pain compared with placebo (RR 1.5, 95% CI: 1.3, 1.9, P<0.0001) and the corresponding NNT was 5.3 (95% CI: 3.6, 10.2). There was no evidence of statistical heterogeneity (P=0.15; I²=38.3%). Subgroup analyses of studies of chronic pain showed no significant effect of outcome measured (P=0.76) or type of placebo (P=0.58). However, the analgesic effect was lower in studies with higher validity scores (P=0.009).

Adverse events.

There was no significant difference in the number of local adverse events between rubefacient and placebo. The quality of the reporting was poor and insufficient data were provided for statistical analysis. No withdrawals related to adverse events were reported.

Authors' conclusions
Topically applied rubefacient may be efficacious in the treatment of acute pain. However, estimates for the efficacy of rubefacients were unreliable because of a lack of good clinical trials.

CRD commentary
The authors carried out an extensive search with no language restrictions, thus minimising the possibility of publication bias.
and language bias. The study selection and quality assessment processes were carried out in duplicate, but since the authors did not report how the data were extracted, the possibility of error and bias being introduced at this stage of the review cannot be ruled out. Details of each included study were given.

Heterogeneity was assessed as part of the meta-analysis, which suggested statistical differences between studies of acute pain. Therefore, the decision to statistically combine these studies might not have been appropriate. The authors appropriately considered the limitations of the evidence presented, and indicated that the lack of high-quality clinical trials means that the results and conclusions of the review may be unreliable.

**Implications of the review for practice and research**

The authors did not state any implications for practice or further research.

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