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Primary care

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

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Abstract

Objective To determine the efficacy and safety of topical rubefacients containing salicylates in acute and chronic pain.
Data sources Electronic databases and manufacturers of salicylates.
Study selection Randomised double blind trials comparing topical rubefacients with placebo or another active treatment, in adults with acute or chronic pain, and reporting dichotomous information, around a 50% reduction in pain, and analyses at one week for acute conditions and two weeks for chronic conditions.
Data extraction Relative benefit and number needed to treat, analysis of adverse events, and withdrawals.
Data synthesis Three double blind placebo controlled trials had information on 182 patients with acute conditions. Topical salicylate was significantly better than placebo (relative benefit 3.6, 95% confidence interval 2.4 to 5.6; number needed to treat 2.1, 1.7 to 2.8). Six double blind placebo controlled trials had information on 429 patients with chronic conditions. Topical salicylate was significantly better than placebo (relative benefit 1.5, 1.3 to 1.9; number needed to treat 5.3, 3.6 to 10.2), but larger, more valid studies were without significant effect. Local adverse events and withdrawals were generally rare in trials that reported them.
Conclusions Based on limited information, topically applied rubefacients containing salicylates may be efficacious in the treatment of acute pain. Trials of musculoskeletal and arthritic pain suggested moderate to poor efficacy. Adverse events were rare in studies of acute pain and poorly reported in those of chronic pain. Efficacy estimates for rubefacients are unreliable owing to a lack of good clinical trials.

Introduction

Rubefacients may work by counter irritation to relieve pain in muscles, joints, and tendons and in non-articular musculoskeletal conditions.[1] By contrast, topical non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase, responsible for the biosynthesis of prostaglandin which mediates inflammation.[2] Rubefacients are usually used as adjuvants to other therapies, such as oral analgesics, support bandages, rest, ice, and compression and may be useful for patients who cannot tolerate oral analgesics.

Although most sources stated that rubefacients act by counter irritation, it is less clear which drugs fall into this category. Salicylates are particularly difficult to categorise.[3 4] They do not seem to work in the same way as other NSAIDs.[3 4] There is still no common agreement about the mechanisms of action of salicylates.[5] Thus the ability of topical salicylates to relieve pain through inhibition of cyclo-oxygenase is unclear.

We have included in our review only rubefacients (salicylate and nicotinate esters). Other categories of topical analgesics include capsaicin and capsicum; newer NSAIDs (diclofenac, felbinac, ibuprofen, ketoprofen, piroxicam); and a miscellaneous group including benzydamine, mucopolysaccharide polysulphate, salicylamide, and cooling sprays.[6]

We found no systematic reviews of rubefacients alone, other than one that included some salicylates with topical NSAIDs.[7] Another review reported that there were no randomised controlled trials of rubefacients[8]; we believe this was due more to problems of definition than to absence of trials. We performed a meta-analysis of randomised controlled trials to determine the efficacy of topical rubefacients for the relief of acute or chronic pain.

Methods

Relevant studies were sought through the Cochrane Library (Issue 2, 2003), Medline, PreMedline, Embase, and PubMed up to March 2003, regardless of publication date, type, status, or language. We also searched an in-house database of 13 000 randomised clinical trials in pain research from 1950 identified through a refined Medline search strategy together with handsearching of 40 biomedical journals.[9] We searched for all products in which the principal active ingredient was listed as a counter irritant or rubefacient in Martindale's pharmacopoeia.[4] The search strategy (see bmj.com) contained "rubefacient" and "counter-irritant" together with generic and proprietary preparations.[1 4] We did not include preparations containing only or mainly capsaicin or its derivatives. We asked 48 pharmaceutical companies (Europe, the United States, Canada, Australia, and South Africa) known to manufacture rubefacients if they could supply trials. Reference lists of retrieved articles were searched.

Selection criteria and trial validity

Trials were included if they were randomised, active or placebo controlled in which patients were treated for acute pain (strains, sprains, sports injuries) or chronic pain (arthritis, musculoskeletal problems). We excluded trials for oral conditions. Other inclusion criteria were outcomes closest to seven days (but at least three days) for acute conditions and closest to 14 days (but at least seven days) for chronic conditions, a minimum of 10 patients per group, and treatment applied at least once daily.

P+ *Details of the search strategy and studies are on bmj.com*

For efficacy analysis, we included trials only if they reported dichotomous information; we excluded trials reporting only mean or median pain relief, reduction in pain, or continuous data because we were unable to calculate numbers needed to treat. Trials that did not contain extractable information on efficacy but met all other inclusion criteria could be included for analysis of adverse events or withdrawals.

We assessed the quality of each potentially relevant trial using a scale with a maximum score of five.[10] Studies had to score at least two points (randomised and double blind) to be included for efficacy analysis. Trial validity was assessed on a 16 point scale.[11]

Data abstraction and study characteristics

At least two reviewers independently assessed the trials for inclusion and quality, which were verified by another reviewer. Disputes were settled by consensus.

We defined our own outcome of clinical success as around a 50% reduction in pain. This was the number of patients with either a "good" or "excellent" global assessment of treatment or "none" or "slight" pain on rest or movement (or comparable wording), measured on a categorical scale. A hierarchy of outcomes was used to extract efficacy information (see bmj.com).[7] We also accepted trials of patients showing undefined improvement; we performed a separate sensitivity analysis for these trials as the outcome may not have represented a 50% or more reduction in pain.

Quantitative data synthesis

For the efficacy analysis we took the number of patients randomised into each treatment group (intention to treat). Numbers needed to treat with 95% confidence intervals were calculated from data for patients obtaining at least 50% pain relief for both active treatment and control.[12] The fixed effects model was used to calculate relative benefits with 95% confidence intervals.[13] Homogeneity of trials was assessed visually.[14] Numbers needed to harm and relative risks for local adverse events were calculated in the same way as for numbers needed to treat. All calculations were performed in Microsoft Excel and RevMan 4.2. The z test was used in sensitivity analyses.[15] QUOROM guidelines were followed.[16]

Our prior intention was to perform separate sensitivity analyses on pooled information for trial size (<40 *v* >40 patients), type of placebo (undefined or defined as vehicle *v* described as vehicle with principal active ingredient removed, leaving some other potentially active counter irritants), type of outcome, quality score (low quality trials (≤ 3 points) *v* higher quality trials), validity score (≤ 8 *v* ≥ 9 points out of 16), and product type (salicylates alone *v* other products alone in a given pain condition).

Results

Two of 48 pharmaceutical companies responded to our request for studies, but neither provided data. Overall, we identified 29 potential papers (fig 1). Fifteen other trials failed to meet the inclusion criteria (see table A on bmj.com).

Twelve studies, totalling 862 patients, met the inclusion criteria (see table B on bmj.com).[17–28] Three were active controlled trials and were not included in the meta-analysis.[20 27 28] Two additional reports in acute conditions contained extractable information for only adverse events.[29 30]

Quality scores ranged from two to four; all trials were double blind. Of the 14 studies, 11 had quality scores of three or more and six had validity scores of nine or more. The participants' age ranged from 14 to 86 years. All treatments contained salicylate as the principal ingredient. In some of the trials patients took concomitant physical therapy or oral drugs.

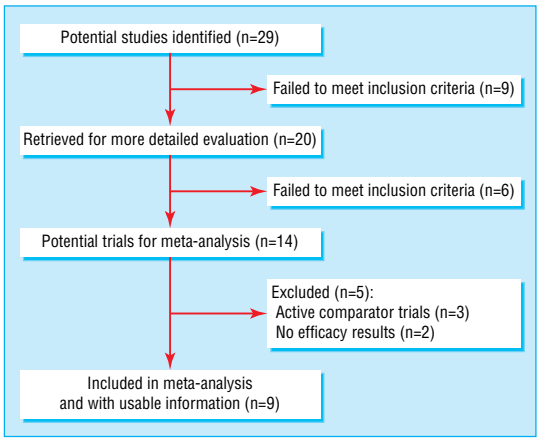

Fig 1 Flow diagram of papers in review

Efficacy analysis

Acute conditions

Three placebo controlled trials had information on 182 patients with acute pain,[17–19] one of which had a low validity score.[18] The mean treatment response rate (percentage of patients with at least 50% pain relief) was 67% (range 25% to 90% in individual trials). The mean response rate with placebo was 18% (range 0% to 59%). Treatment with rubefacient was significantly better than placebo (relative benefit 3.6, 95% confidence interval 2.4 to 5.6). The number need to treat was 2.1 (1.7 to 2.8) for at least 50% pain relief at seven days compared with placebo (table and figures on bmj.com). Sensitivity analyses were not performed owing to lack of data. One larger trial (161 patients) could not be classified as either active or placebo controlled because of a supposed homoeopathic control; there were more local adverse events with salicylate but with no greater efficacy.[20] We identified no conventional active controlled trials in acute conditions.

Chronic conditions

Six placebo controlled trials had information on 429 patients with chronic pain (26 of whom received both treatment and placebo in a crossover study).[21–26] Three of the trials had low validity scores (see table B on bmj.com). The mean treatment response rate was 54% (range 35% to 80% in individual trials; fig 2). The mean response rate with placebo was 36% (range 20% to 53). Treatment with rubefacient was significantly better than treatment with placebo (relative benefit 1.5, 1.3 to 1.9). The number needed to treat was 5.3 (3.6 to 10.2) for at least 50% pain relief at 14 days compared with placebo (see table and figures on bmj.com). Two small active controlled trials with low validity scores and outcomes at seven days provided no helpful information (see table B on bmj.com).[27 28]

In sensitivity analyses of pooled information for placebo controlled trials in chronic conditions, there was no significant difference between type of outcome ($z=0.34$, $P=0.76$) or type of placebo ($z=0.55$, $P=0.58$) (table), but higher validity scores produced statistically less analgesic effect ($z=2.61$; $P=0.009$). Better trials had less effect. Owing to insufficient data, we could not perform sensitivity analyses for size, quality score, or type of rubefacient.

Relative benefit of rubefacients containing salicylate in patients with acute or chronic pain and numbers needed to treat

Condition	No of trials	No of patients	No (%) responding to intervention		Relative benefit (95% CI)	Number needed to treat (95% CI)
			Treatment	Placebo		
Acute pain						
Efficacy (all trials)	3	182	60/90 (67)	17/92 (18)	3.6 (2.4 to 5.6)	2.1 (1.7 to 2.8)
Local adverse event	5	418	4/208 (2)	4/210 (2)	1.1 (0.4 to 3.5)	Not calculated
Chronic pain						
Efficacy (all trials)	6	429*	125/230 (54)	80/225 (36)	1.5 (1.3 to 1.9)	5.3 (3.6 to 10.2)
Sensitivity analysis (chronic pain trials)						
Outcome:						
Improvement	2	72	17/36 (47)	9/36 (25)	1.9 (0.98 to 3.6)	Not calculated
Global or categorical assessment	4	383	108/194 (56)	71/189 (38)	1.5 (1.2 to 1.9)	5.5 (3.6 to 12.1)
Placebo:						
Inactive or undefined	4	241	76/122 (62)	49/119 (41)	1.5 (1.2 to 2.0)	4.7 (3.0 to 11.4)
Salicylate removed	2	214	49/108 (45)	31/106 (29)	1.6 (1.1 to 2.2)	6.2 (3.5 to 29.8)
Validity score:						
≤8	3	176	55/92 (60)	22/84 (26)	2.2 (1.5 to 3.3)	3.0 (2.1 to 5.0)
≥9	3	279	70/138 (51)	58/141 (41)	1.3 (0.98 to 1.6)	Not calculated

*26 patients part of cross over study; all received treatment and placebo.

Adverse events and withdrawals

Local adverse events were rare, with no significant difference between treatment and control groups (table). No withdrawals related to adverse events were reported.

The quality of reporting was poor, and there were insufficient data for statistical analysis. Adverse events were rare in trials that did report them, with the exception of one study using copper salicylate gel (see table B on bmj.com).[25]

Discussion

Trials of rubefacients are limited by number, size, quality, and validity, which weakens assessment of their efficacy. We included trials of seven types of rubefacients, found as principal ingredients in more than 30 counter irritant preparations available in Britain through pharmacies.[1] For almost all of these products, specific evidence of effect is lacking.

The best assessment of limited information suggests that rubefacients containing salicylates may be efficacious in acute pain and moderately to poorly efficacious in chronic arthritic and rheumatic pain. In acute conditions, the number needed to treat was 2.1 (95% confidence interval 1.7 to 2.8) for at least 50% pain relief compared with placebo at seven days. For chronic conditions, the number needed to treat for topical salicylate compared with placebo was 5.3 (3.6 to 10.2), compared with that for topical NSAIDs of 3.1 (2.7 to 3.8) with the same comparator (placebo) and with similar outcomes in similar conditions and trials of similar duration.

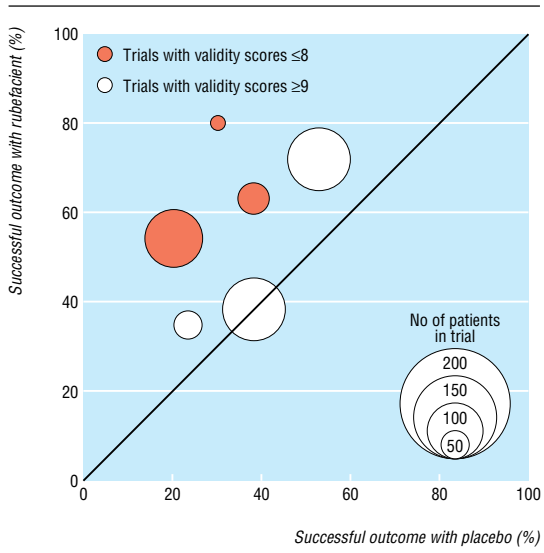

Fig 2 L'Abbé plot for rubefacient *v* placebo in trials on chronic pain

Insufficient data precluded us from accurately judging the effect of trial size or quality score, but high validity trials of chronic pain showed significantly less analgesic effect than low validity trials. Small, low quality trials are more likely to overestimate efficacy.[7 11] Half of all trials contained 50 or fewer patients. Although a meta-analysis may be more robust than relying on the results from a single small trial, limited data may still not overcome chance effects.[31] In addition there was considerable variability in outcomes, scales for recording outcomes, and quality of reporting, in common with older trials on arthritis.[32]

The longest trial lasted only 28 days, and most lasted 14 days or less. For chronic conditions in particular, information is needed on long term efficacy and adverse events. In acute pain, local adverse events seemed to be rare (2% of patients). Data on chronic pain were insufficient to evaluate the long term effects of continuous irritation on the skin, which may vary according to drug and vehicle. Less rigorous reporting of adverse events and withdrawals compared with data on efficacy is not unusual in randomised controlled trials.[33]

It has been suggested that topical analgesics owe much of their efficacy to rubbing during application, giving a high placebo response rate.[34] Evidence suggests otherwise. The placebo gels were rubbed on to the skin in the same way as active treatments, and we found that active treatments were significantly better than placebo in double blind clinical trials.

Creating double blind conditions in trials of counter irritants can be problematic; rubefacients irritate the skin whereas inactive placebos do not. Some studies tried to allow for this by removing the principle active ingredient from the treatment, leaving a placebo vehicle containing some other potentially irritant ingredients. Although the number needed to treat for combined outcomes of trials of this type was greater (worse) than for trials with inactive placebo, the difference was not statistically significant and there was insufficient evidence to draw conclusions.

Only two of 48 pharmaceutical companies replied to our request for studies. Our electronic and in-house searches identified few suitable studies. The inability to uncover any trials in the

What is already known on this topic

No systematic reviews have studied topical rubefacients containing salicylates for the treatment of acute or chronic pain

A seeming lack of clinical trials may be partly due to lack of consensus on a definition for rubefacients

What this study adds

Randomised double blind trials have studied topical salicylates in acute and chronic pain

Trials were limited by small size, inadequate design, and validity, making results tentative

Topical salicylate may have efficacy in acute pain at seven days but poor to moderate efficacy in chronic pain at 14 days

Better trials showed little difference from placebo

past may be due to a lack of consensus on the definition of rubefacients. Flawed search strategies may therefore have led to the assumption that the only evidence in support of rubefacients was anecdotal.[8] It is more than likely that nobody really looked for the evidence until now.[35]

Contributors: LM was involved with planning, searching, reading the papers, quality scoring, data extraction, analysis, and writing. RAM was involved with planning, reading the papers, quality scoring, analysis, and writing. JE was involved with reading the papers, quality scoring, data extraction and analysis, and commenting on the text. HJM was involved with planning and commenting on the text. SD was involved with analysis and checking and revising. PJW was involved with planning and commenting on the text. RAM and HJM will act as guarantors for the paper. The guarantors accept full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

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Ethical approval: Not required.

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