

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

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Abstract

Objectives 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 musculoskeletal pains.¹ By contrast, topical non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase, indirectly responsible for inflammation.² Rubefacients are usually used as adjuvants to other therapies and may be useful for patients intolerant to oral analgesics.

Most sources state that rubefacients act by counter irritation, but it is unclear which drugs this includes. Salicylates are particularly difficult to categorise.^{3,4} They do not seem to work in the same way as other NSAIDs.^{3,4}

We performed a meta-analysis of randomised controlled trials to determine the efficacy of topical rubefacients for the relief of acute or chronic pain. 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, keto-

profen, piroxicam); and a miscellaneous group including benzydamine, mucopolysaccharide polysulphate, salicylamide, and cooling sprays.

Methods

Relevant studies were identified through the Cochrane Library (Issue 2, 2003), Medline, PreMedline, Embase, and PubMed up to March 2003. 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 hand-searching of 40 biomedical journals.⁵ Further searches identified more than 13 000 relevant studies. The trials had to include a product in which the principal ingredient was listed as a counter irritant or rubefacient in Martindale's pharmacopoeia.⁴ Preparations containing only or mainly capsaicin or its derivatives were excluded.

Inclusion criteria were randomised, active or placebo controlled trials in which patients were treated for acute or chronic pain, 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 in each group, and treatment applied at least once daily.

For efficacy analysis, we included trials only if they reported dichotomous information. 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.⁶ Studies scoring at least two points were included for efficacy analysis.

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

Our definition of clinical success was around a 50% reduction in pain—that is, the number of patients with either a “good” or “excellent” global assessment of treatment or “none” or “slight” pain on rest or movement. We also accepted trials of patients showing undefined improvement; as the outcome may not have been a 50% or more reduction in pain, we performed a separate sensitivity analysis for these trials.

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.⁷ The fixed effects model was used to calculate relative benefits with 95% confidence intervals.⁸ Homogeneity of trials was

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



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assessed visually.⁹ Numbers needed to harm and relative risks for local adverse events were calculated in the same way as for numbers needed to treat.

Results

Twelve studies (862 patients) met the inclusion criteria (see [bmj.com](#)).¹⁰⁻²¹ Three were active controlled trials and were not included in the meta-analysis.^{13 20 21}

Quality scores ranged from two to four. The participants' age ranged from 14 to 86 years. All treatments contained salicylate as the principal ingredient.

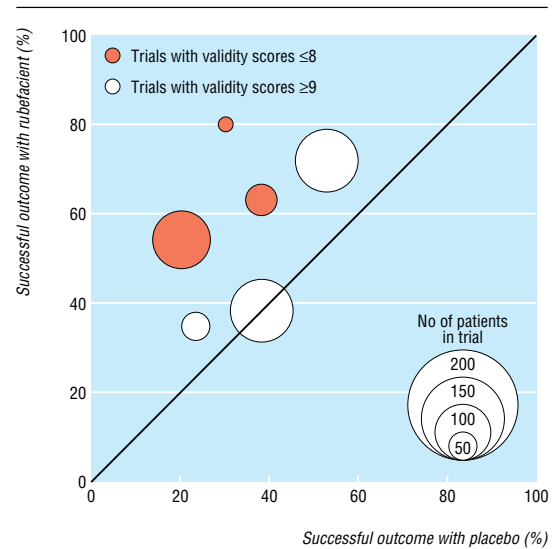
Three placebo controlled trials had information on 182 patients with acute pain,¹⁰⁻¹² one of which had a low validity score.¹¹ The mean treatment response rate was 67% (range 25% to 90% in individual trials). The mean response rate with placebo was 18% (range 0% to 59%). Treatment with rubefacient was significantly better than with placebo (relative benefit 3.6, 95% confidence interval 2.4 to 5.6). The number needed 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](#)). We identified no active controlled trials in acute conditions.

Six placebo controlled trials had information on 429 patients with chronic pain.¹⁴⁻¹⁹ Three of the trials had low validity scores (see table A on [bmj.com](#)). The mean treatment response rate was 54% (range 35% to 80% in individual trials; figure). 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](#)).

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

Discussion

Trials of rubefacients are limited by number, size, quality, and validity, which weaken assessments of their efficacy. We included trials of seven types of rubefacients, found as principal ingredients in more



L'Abbé plot for rubefacient versus placebo in trials on chronic pain

than 30 counter irritant preparations available in Britain.¹ For almost all of these products, 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.

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. Half of all trials contained 50 or fewer patients. Also there was considerable variability in outcomes, scales for recording outcomes, and quality of reporting, in common with older trials on arthritis.²²

The longest trial lasted only 28 days, and most lasted 14 days or less. Data on chronic pain was insufficient to evaluate the long term effects of continuous irritation on the skin, which may vary according to drug and vehicle.

It has been suggested that topical analgesics owe much of their efficacy to rubbing during application, giving a high placebo response rate.²³ Although the

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.

What is already known on this topic

No systematic reviews have studied topical rubefaciants 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 rubefaciants

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

placebo gels were rubbed onto the skin in the same way as active treatments, we found that active treatments were significantly better than placebo.

Creating double blind conditions in trials of counter irritants can be problematic as rubefaciants irritate the skin whereas inactive placebos do not. Some studies allowed for this by removing the principle 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.

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Ethical approval: Not required.

- 1 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary*. London: BMA, RPS, 2003. (No 45.)
- 2 Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971; 231:232-5.
- 3 Morton I, Hall J. *The Royal Society of Medicine: medicines*. 6th ed. London: Bloomsbury, 2002.
- 4 Reynolds JEF, ed. *Martindale: the extra pharmacopoeia*. 32nd ed. London: Royal Pharmaceutical Society, 1999.
- 5 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- 6 Cook D, Sackett DL. On the clinically important difference. *Ann Intern Med* 1992;117:A16-7.
- 7 Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. In: Gardner MJ, Altman DG, eds. *Statistics with confidence—confidence intervals and statistical guidelines*. London: British Medical Journal, 1995:50-63.
- 8 L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med* 1987;107:224-33.
- 9 Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;66:239-46.

- 10 Ginsberg F, Famaey JP. A double-blind study of topical massage with Rado-Salil ointment in mechanical low-back pain. *J Int Med Res* 1987;15:148-53.
- 11 Lester AA, Geller O, Bach GL, Fotiadis P. Management of sprained ankles. A double-blind study. *Practitioner* 1981;225:935-6.
- 12 Rothhaar J, Thiel W. Percutaneous gel therapy of blunt athletic injuries. *Med Welt* 1982;33:1006-10. (In German.)
- 13 Stam C, Bonnet MS, van Haselen RA. The efficacy and safety of a homeopathic gel in the treatment of acute low back pain: a multi-centre, randomised, double-blind comparative clinical trial. *Br Homeopath J* 2001;90:21-8.
- 14 Algozzine GJ, Stein GH, Doering PL, Araujo OE, Akin KC. Trolamine salicylate cream in osteoarthritis of the knee. *JAMA* 1982;247:1311-3.
- 15 Bach GL, Fotiadis P, Wanet G. Enelbin rheumatism ointment in rheumatic diseases. Results of a double-blind study for the determination of efficacy. *Fortschr Med* 1979;97:1249-52. (In German.)
- 16 Camus JP. Action de la myrtécaine associée au salicylate de diéthylamine, en traitement local, dans diverses affections rhumatismales. *Rheumatologie* 1975;27:61-6.
- 17 Rutner M, Fitzek J, Jahnel-Kracht H, Otto J, Krause W. Treatment of rheumatism with a hydroxyethylsalicylate gel. Results of 2 clinical studies of effectiveness and bioavailability. *Fortschr Med* 1995;113:111-3. (In German.)
- 18 Shackel NA, Day RO, Kellett B, Brooks PM. Copper-salicylate gel for pain relief in osteoarthritis: a randomised controlled trial. *Med J Aust* 1997;167:134-6.
- 19 Wanet G. Controlled clinical study of a topic associating nopoxamine with diethylamine salicylate (Algesal suractive) in physical medicine and rehabilitation. *J Belge Med Phys Rehabil* 1979;2:119-26. (In French.)
- 20 Geller O, Bach GL, Fotiadis P. Comparison of a salicylate-heparin gel with a monosubstance preparation. Results of a double-blind cross-over study. *Munch Med Wochenschr* 1980;122:1231-2. (In German.)
- 21 Golden EL. A double-blind comparison of orally ingested aspirin and a topically applied salicylate cream in the relief of rheumatic pain. *Curr Ther Res* 1978;24:524-9.
- 22 Göttsche PC. Reporting of outcomes in arthritis trials measured on ordinal and interval scales is inadequate in relation to meta-analysis. *Ann Rheum Dis* 2001;60:349-52.
- 23 Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. *Drugs* 1998;56:783-99.

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Corrections and clarifications

Intimate partner violence

In this editorial by Lorraine E Ferris (13 March, pp 595-6) we let a wrong reference number slip through. The reference number in the title of the box should be 9 (not 8, as we stated).

Smoking and blindness

In the "web extra" material for this editorial by Simon P Kelly and colleagues, we forgot to make some final small amendments that the authors had told us about (6 March, pp 537-8). In the third sentence of the section headed "sensitivity analysis," 61 800 should be 53 900 (consistent with elsewhere in the text and web extra material). The last part of the URL for the web reference W7 where it appears after the table (the second time it appears in the web extra material) is wrong; the correct URL is www.statistics.gov.uk/census2001/pop2001/united_kingdom.asp (as it appears in the list of web references).

This week in the BMJ: Children treated for heart conditions survive equally well across UK

We mixed up survival and mortality to produce a rather alarming sentence in this summary paragraph for the paper by John L Gibbs and colleagues ("Survival after surgery or therapeutic catheterisation for congenital heart disease in children in the United Kingdom: analysis of the central cardiac audit database for 2000-1," 13 March, pp 611-5). We also omitted the word infant. So the third sentence should read: "Infant mortality [not "Survival"] at one year was double that at 30 days and may be a better descriptor of overall outcome."