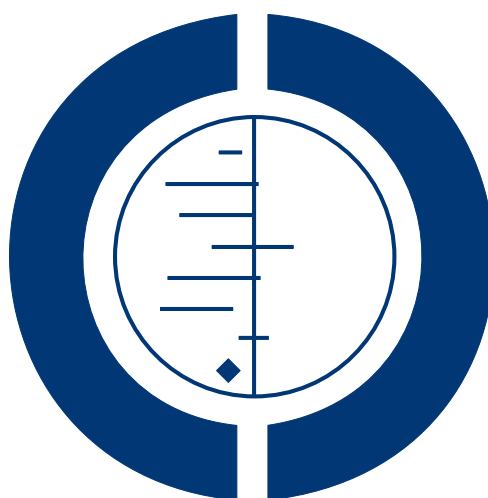


Topical agents or dressings for pain in venous leg ulcers (Review)

Briggs M, Nelson EA, Martyn-St James M



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[Intervention Review]

Topical agents or dressings for pain in venous leg ulcers

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ABSTRACT

Background

Venous leg ulcers affect up to 1% of people at some time in their lives and are often painful. The main treatments are compression bandages and dressings. Topical treatments to reduce pain during and between dressing changes are sometimes used.

Objectives

To determine the effects of topical agents or dressings for pain in venous leg ulcers.

Search methods

For this third update the following databases were searched: Cochrane Wounds Group Specialised Register (searched 9 May 2012); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4); Ovid MEDLINE (2009 to April Week 4 2012); Ovid MEDLINE (In-Process & Other Non-Indexed Citations May 08, 2012); Ovid EMBASE (2009 to 2012 Week 18); and EBSCO CINAHL (2009 to May 2 2012). No date or language restrictions were applied.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) that evaluated the effects of topical agents or dressing for the treatment of pain in venous ulcers were included.

Data collection and analysis

Two review authors independently performed trial selection, data extraction and risk of bias assessment.

Main results

Six trials (343 participants) evaluated Eutectic Mixture of Local Anaesthetics (EMLA): lidocaine-prilocaine cream for the pain associated with ulcer debridement. The between-group difference in pain measured on a 100 mm scale was statistically significant in favour of EMLA (MD -20.65, 95% CI -12.19 to -29.11). No significant between-group differences in burning or itching were observed.

Two trials (470 participants with venous leg ulcers) evaluated ibuprofen slow-release foam dressings for persistent venous leg ulcer pain. Compared with local best practice, significantly more participants in the ibuprofen dressing group achieved the outcome of >50% of the total maximum pain relief score between day 1 and day 5 than participants in the local best practice group (RR 1.63, 95% CI 1.24 to 2.15). The number needed to treat was 6 (95% CI 4 to 12). In the second trial, compared with an identical non-ibuprofen foam dressing, there was no statistically significant difference in the proportion of participants experiencing slight to complete pain relief on the first evening of treatment. Limited data were available to assess healing rates or adverse events.

Topical agents or dressings for pain in venous leg ulcers (Review)

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Authors' conclusions

There is some evidence to suggest that ibuprofen dressings may offer pain relief to people with painful venous leg ulcers. EMLA (5%) appears to provide effective pain relief during the debridement of venous leg ulcers. Further research should consider standardised pain assessment methods and assess both the effect on ulcer healing and the impact of long term use of these treatments.

PLAIN LANGUAGE SUMMARY

Topical agents or dressings for reducing pain in venous leg ulcers

Venous leg ulcers are often painful, both during and between dressing changes, and during surgical removal of dead tissue (debridement). Dressings, topical creams and lotions have been promoted to reduce the pain of ulcers. Two trials tested a dressing containing ibuprofen, however, the pain measures and time frames reported were different. One trial indicated that pain relief achieved over 5 days with ibuprofen dressings could represent a clinically relevant reduction in pain. The other trial found no significant difference in the chance of pain relief, measured on the first night of treatment, for ibuprofen dressings compared with foam dressings. This trial, however, was small and participants were only followed for a few weeks, which may not be long enough to assess whether the dressing affects healing. There was evidence from five trials that a local anaesthetic cream (EMLA 5%) reduces the post-procedural pain of debriding leg ulcers but there was insufficient evidence regarding any side effects of this cream and its impact on healing.

BACKGROUND

Description of the condition

Leg ulceration is estimated to have a point prevalence in Europe and Australia of 0.1% to 0.2% of the adult population (Callam 1985; Graham 2003; O'Brien 2000). Prevalence increases with age, and the condition is a chronic recurring problem with people experiencing episodes of open leg ulceration lasting from a few weeks to 50 years (Callam 1987; Noonan 1998). Given this pattern of ulceration, healing and recurrence, it has been estimated that up to 1% of the population will be affected by leg ulceration at some point. The majority of leg ulcers are caused by (are secondary to) venous disease, other causes include arterial disease, vasculitis and diabetes.

Pain is a frequently reported feature of venous leg ulceration (Hamer 1994; Hofman 1997; Hyland 1994; Lindholm 1993; Nelzen 1994; Noonan 1998; Phillips 1994). The precise prevalence of pain is difficult to determine due to methodological differences between the trials and the use of predominantly hospital populations. Reported figures for people experiencing severe or continuous pain associated with a leg ulcer range from 17% to 65% (Franks 1994; Hofman 1997; Hyland 1994; Nelzen 1994; Phillips 1994). It is accepted that when pain is a feature it has a major impact on both sufferers' and carers' quality of life, with sufferers stating that the worst aspect of having a leg ulcer is the

pain (Briggs 2007; Chase 1997; Douglas 2001; Ebbeskog 2001; Hyde 1999; Lindholm 1993; Phillips 1994; Walshe 1995).

The cause of pain in people with venous leg ulcers is complex and often poorly defined. The pathologies associated with leg ulceration (e.g. rheumatoid arthritis, vascular disease and diabetes) cause pain with or without an ulcer present (Gibson 1998; Noonan 1998). The presence of an ulcer can cause additional pain through two mechanisms. Firstly, pain is produced by the patient's normal response to wounding (i.e. through the inflammatory process associated with injury), and secondly, pain is produced by damaged nerves. Leg ulceration may damage peripheral nerves by a variety of processes, such as ischaemia (lack of oxygen), infection and inflammation and this may cause a disruption in the way the nerves respond to stimuli. This disruption can lead to a neuropathic component to the pain, where sensitised nerves produce an exaggerated response to touch, i.e. a slightly painful stimulus may be felt as extreme pain (Briggs 2007). Furthermore, pain is a symptom of wound complications such as infection, skin maceration and contact dermatitis, which may contribute to the overall leg ulcer pain. In addition, leg ulcer treatments such as replacing dressings, removing dead tissue (debridement) and firm bandages may cause pain. In a recent international survey where practitioners from 11 European countries were questioned, leg ulceration was perceived to be more painful than other chronic wounds. The practitioners surveyed indicated that pain at dressing changes was common and was caused by dressing adherence and wound cleansing (Moffatt 2002). It is clear from this that dressing choice and method of

removal have an effect on venous leg ulcer pain, and there are a number of trials where pain scores are reported as one of the characteristics of dressing performance (Ohlsson 1994).

Another leg ulcer treatment is sharp debridement of slough and necrotic tissue. This is advocated by some clinicians as the fastest way of achieving a clean ulcer, which, in turn, is thought to improve healing. It is thought that debridement reduces odour, lowers the risk of infection and improves the results of skin grafting (Vanscheidt 2001). Debridement, however, is not without risks. It is an extremely painful procedure (Hansson 1993), and people with ulcers often ask clinicians to stop before the debridement is complete because they are unable to tolerate the pain (Enander Malmros 1990; Lok 1999). In addition, sharp debridement may delay wound healing, as there is a risk of damaging healthy tissue and underlying blood vessels (Vanscheidt 2001), and, as yet, there is no direct evidence that debridement decreases the time taken for a wound to heal (Bradley 1999).

Non-systematic literature reviews and case trial reports have advocated the use of occlusive dressings, such as semipermeable films and hydrocolloids, as a method of pain relief (Hermans 1993; Kannon 1995; Seeley 1994; Thomas 1989). There a number of postulated theories that attempt to explain how an inert dressing can provide pain relief. In a review of possible mechanisms, Richardson 2010 suggests that there could be as many as 10 discrete but interrelated mechanisms of action to explain pain relieving dressings. The authors suggest that it is possible that the pain relief associated with the application of a new dressing to a chronic wound could be due to both physiological and psychological factors, as opposed to the analgesic effect of the dressing alone.

Description of the intervention

Topical (external, surface) treatments such as the local anaesthetic EMLA cream (Eutectic Mixture of Local Anaesthetics: lidocaine-prilocaine cream) and analgesics have been applied directly into ulcers in an attempt to relieve pain (e.g. Agrifoglio 2000). The discovery of opiate receptors on peripheral nerve terminals has also lead to the topical use of morphine in wounds (using hydrogel as a carrier) (Stein 1995), and a number of trials have reported the analgesic effect of morphine when applied topically to painful wounds (Back 1995; Flock 2003; Twillman 1999; Zeppetella 2004). This is thought to work via local action on opioid receptors (Stein 1995). This hypothesis was tested in the Ribeiro 2004 trial, which studied the bioavailability of topically-applied morphine to six participants with cutaneous ulcers in a hospice setting. In five participants there was no evidence that the topical morphine had been systemically absorbed (i.e. into the body), which supports the view that the action is local. However, morphine metabolites were detected in one participant who had a large pressure sore, suggesting that morphine can be absorbed systemically via a wound with a large surface area. This underlines the importance of research de-

signed to test the safety and efficacy of all topical agents in chronic wounds.

Why it is important to do this review

This review aims to identify and summarise the evidence for the effects of different dressings and topical treatments in the management of pain associated with venous leg ulcers.

OBJECTIVES

To conduct a systematic review of the effects of topical analgesics, local anaesthetics and dressings used to manage the pain associated with venous leg ulceration (either persistent pain or treatment-related pain, e.g. pain on leg ulcer debridement).

Specific questions addressed by the review are:

1. Are topical analgesics/anaesthetics effective in relieving venous leg ulcer pain?
2. Which topical analgesics/anaesthetics are the most effective?
3. Are dressings effective in relieving the pain of venous leg ulceration?
4. Which dressings are the most effective in relieving pain in venous leg ulceration?
5. What is the relative effectiveness of topical analgesics or anaesthetics compared to dressings in relieving pain in venous leg ulceration?
6. What is the combined effect of dressings and topical analgesics/anaesthetics in relieving pain in venous leg ulceration?

METHODS

Criteria for considering studies for this review

Types of studies

Trials were eligible for inclusion if the following criteria applied:

- they were randomised controlled trials (RCTs) that evaluated dressings and/or topical analgesics/anaesthetics used to relieve the pain associated with venous leg ulceration. Either the allocation of participants had to be described as randomised, or it had to be evident that the intervention was assigned at random;
- cross-over trials were eligible, but only data from the first period (if reported) were extracted in order to avoid carry-over effects;

- there was no restriction on the basis of language or publication status.

Trials were excluded if the evaluation of pain was not the primary aim, or if the pain was measured as a feature of the dressing (e.g. pain on removal of the dressing).

Types of participants

We considered trials that recruited people of any age, in any care setting who were described as having venous leg ulcers. As the diagnosis of venous leg ulceration varied between trials, a standard definition of a venous leg ulcer was difficult to apply. Trials that included people with leg ulcers, where the ulceration was reported to be due to venous disease, were included irrespective of the method of diagnosis used. People with arterial, diabetic, and neuropathic ulcers were excluded, as it is unclear whether the nature of their pain is similar to that of venous leg ulceration. People with ulcers reported to be due to sickle cell disease or rheumatoid arthritis were also excluded, as the ulcer aetiology (cause) and systemic disease processes involved in these conditions may mean that the mechanisms and treatment of pain may differ from people with pain from venous leg ulceration.

Trials that included a mixture of people with the following ulcer aetiologies: arterial disease; mixed aetiology; neuropathic; and diabetes were included, if the outcomes for people with venous ulcers were reported separately, or the original data were available.

Trials were excluded if the trial sample comprised people with infected ulcers at baseline, as the nature of the pain associated with infection may differ from the pain of leg ulceration.

Types of interventions

The primary intervention was the application of a topical analgesic/anaesthetic or dressing with the aim of relieving the pain associated with venous leg ulceration.

Topical analgesics/anaesthetics were defined as liquids, gels, powders, creams, foams or aerosols containing an analgesic or anaesthetic agent applied on or around the wound site. They can be grouped into:

1. local anaesthetics;
2. non steroidal anti-inflammatory gels;
3. capsaicin;
4. opioids.

Dressings were defined as any dressing applied to the venous leg ulcer with the intention of relieving pain. The groups of products considered included:

1. film dressings;
2. hydrocolloids;
3. hydropolymer dressings;
4. foam dressings;
5. alginates;
6. gauze/gauze-type dressings;

7. hydrogels;
8. any other type of wound dressing.

Types of outcome measures

In order to be considered for inclusion a trial had to report at least one of the primary outcomes (below).

Primary outcomes

1. Patient-reported pain scores using visual analogue scales (VAS), verbal rating scales, numerical rating scales, pictorial rating scales.
2. Pain scores from pain questionnaires such as the McGill Pain Questionnaire, Brief Pain Inventory (Cleland 1994).
3. Subjective global rating of pain relief (better/unchanged/worse).
4. Summary measures such as SPID (Sum of Pain Intensity Differences) and TOTPAR (Total pain relief achieved) (McQuay 1997).

Secondary outcomes

1. Ulcer healing rates (time from trial entry to complete ulcer healing, proportion of ulcers completely healed in trial period or changes in ulcer size).
2. Quality of life measures.
3. Adverse effects.

Trials were excluded if surrogate measures of pain were used instead of pain scores. These included analgesic consumption which may not correlate with the amount of chronic pain experienced (Abbott 1992). Trials were excluded if they reported *only* data from quality of life questionnaires that may highlight a broad category of bodily pain, but are more likely to measure the impact of such pain rather than the intensity of the experience.

Search methods for identification of studies

Electronic searches

For an outline of the search methods used in second update of this review see [Appendix 1](#).

For this third update we searched the following electronic databases:

- Cochrane Wounds Group Specialised Register (searched 9 May 2012);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4);
- Ovid MEDLINE (2009 to April Week 4 2012);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations May 08, 2012);

- Ovid EMBASE (2009 to 2012 Week 18);
- EBSCO CINAHL (2009 to May 2 2012).

The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):

- #1 MeSH descriptor Analgesia explode all trees
- #2 MeSH descriptor Analgesics explode all trees
- #3 MeSH descriptor Capsaicin explode all trees
- #4 capsaicin:ti,ab,kw
- #5 MeSH descriptor Analgesics, Opioid explode all trees
- #6 opioid:ti,ab,kw
- #7 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
- #8 (non NEXT steroidal NEXT anti-inflammatory* or NSAID*):ti,ab,kw
- #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 MeSH descriptor Administration, Topical explode all trees
- #11 topical or local:ti,ab,kw
- #12 (#10 OR #11)
- #13 (#9 AND #12)
- #14 MeSH descriptor Anesthetics, Local explode all trees
- #15 ((topical or local) NEAR/3 (anaesthe* or aneshe*)):ti,ab,kw
- #16 ((topical or local) NEAR/3 analgesi*):ti,ab,kw
- #17 (#13 OR #14 OR #15 OR #16)
- #18 MeSH descriptor Bandages explode all trees
- #19 MeSH descriptor Hydrogels explode all trees
- #20 MeSH descriptor Alginates explode all trees
- #21 (dressing* or hydrocolloid* or alginate* or hydrogel* or “foam” or “bead” or “film” or “films” or tulle or gauze or non-adherent or “non adherent”):ti,ab,kw
- #22 MeSH descriptor Ointments explode all trees
- #23 (ointment* or “cream” or “creams” or “gel” or “gels”):ti,ab,kw
- #24 (#18 OR #19 OR #20 OR #21 OR #22 OR #23)
- #25 MeSH descriptor Pain explode all trees
- #26 pain*:ti,ab,kw
- #27 (#25 OR #26)
- #28 (#24 AND #27)
- #29 (#17 OR #28)
- #30 MeSH descriptor Leg Ulcer explode all trees
- #31 ((varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*)):ti,ab,kw
- #32 (#30 OR #31)
- #33 (#29 AND #32)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#) respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format ([Lefebvre 2011](#)). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) ([SIGN 2012](#)).

Searching other resources

We searched the bibliographies of all relevant studies to identify any further reports. The review authors also contacted other researchers in the field.

Data collection and analysis

Selection of studies

All articles identified by the search strategy were coded as either relevant, irrelevant, or uncertain by two review authors using the inclusion and exclusion criteria as the decision framework. We obtained copies of full papers for abstracts coded as relevant or uncertain, and sought translations, if necessary. Eligibility for inclusion was confirmed by two review authors who independently assessed the trials. Where uncertainty about inclusion remained, where possible, additional information was sought from the original authors and the review authors reached consensus through discussion.

Data extraction and management

Details of trials eligible for inclusion were summarised using a data extraction sheet. Research papers reporting the same trial were identified and all relevant data from the papers were extracted. For this third update, data extraction was completed by one review author (MMSJ) and checked by a second (MB).

Assessment of risk of bias in included studies

For this third update, each included trial was appraised according to the risk of bias assessment criteria described in the Cochrane Handbook ([Higgins 2011](#)). Each validity item was assessed separately; ratings for each item were not combined into an overall score. Each included trial was assessed by one author (MMSJ) and checked by a second (MB). All disagreements were resolved by discussion. The following criteria were applied:

1. Random sequence generation (selection bias)

Low risk of bias: adequate sequence generation was reported using random number tables, computer random number generator, coin tossing, or card/envelope shuffling.

High risk of bias: used a system involving dates, names, or admittance numbers for the allocation of participants. Such trials were considered as quasi-randomised and were excluded from the review.

Unclear risk of bias: did not describe one of the adequate methods, but mentioned randomisation.

2. Allocation concealment (selection bias)

Low risk of bias: a randomisation method was described that would not allow an investigator/participant to know or influence allocation to an intervention group before an eligible participant entered the trial, such as central randomisation or serially-numbered, sealed envelopes.

High risk of bias: an inadequate method of allocation was used, such as alternate medical record numbers or unsealed envelopes; or there was information in the trial report indicating that investigators or participants could have influenced group allocation.

Unclear risk of bias: the trial report mentioned randomisation but there was no information about the method used for allocation of participants to treatment groups, or a method was reported that was not clearly adequate.

3. Blinding of participants and personnel (performance bias)

This item was graded as 'Low risk of bias' for blinding participants, 'Unclear risk of bias' if the relevant information was not stated in the trial report and 'High risk of bias' for unblinded participants.

4. Blinding of outcome assessment (detection bias)

This item was graded as 'Low risk of bias' for blinded outcome assessment, 'Unclear risk of bias' if the relevant information was not stated in the trial report and 'High risk of bias' for unblinded outcome assessment.

5. Incomplete outcome data (attrition bias)

Low risk of bias: trial report included information on participant withdrawals and indicates that all participants randomised were included in the final analysis as either all participants completed the trial, or participants that did not complete the trial were accommodated in an intention-to-treat (ITT analysis).

High risk of bias: final analysis was based on only those participants who completed the trial, and did not include all participants randomised.

Unclear risk of bias: unable to determine whether participants included in final analysis were all participants initially randomised.

6. Selective reporting (reporting bias)

Low risk of bias: either the trial protocol was available and all of the trial's pre-specified outcomes were reported, or the trial report described evaluation of expected outcomes and presented results.

High risk: the trial report did not include results for a key outcome that would have been expected to be reported.

Unclear risk: insufficient information in the trial report to permit judgement of low or high risk of bias.

7. Other sources of bias

Low risk of bias: the trial appeared to be free of other sources of bias.

High risk of bias: there was a potential source of bias related to the trial design (e.g., stopping early), or the trial has been claimed to have been fraudulent, or had some other problem.

Unclear risk of bias: insufficient information to permit judgement of low or high risk of bias.

Measures of treatment effect

We have grouped results according to the type of treatment for pain relief (topical agents or dressings). We have undertaken statistical pooling of outcome data on groups of trials considered to be sufficiently similar in terms of trial design and characteristics of participants, interventions and outcomes. We have reported estimates for dichotomous outcomes (e.g. between-group differences in the proportions of participants experiencing pain relief) as a risk ratio (RR) with associated 95% confidence intervals (CI). We have reported estimates for continuous data outcomes (e.g. between-group differences in the change in pain score on a visual analogue scale) as a mean difference (MD) with 95% CI.

Assessment of heterogeneity

The presence of clinical heterogeneity was assessed by comparing the trials in terms of characteristics of co-interventions, setting and population. We assessed the extent of statistical heterogeneity by using the I-squared statistic (I^2) (Higgins 2002; Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). We considered values greater than 50% as being indicative of substantial heterogeneity, in which case a random-effects model was used to pool the results from different trials, otherwise a fixed-effect model was used.

Data synthesis

We have presented a narrative overview of the included trials. We analysed data using Cochrane RevMan software (version 5.1) (RevMan 2011). If the event rates were less than 30%, dichotomous outcomes for each trial were summarised as odds ratios with 95% confidence intervals (CI); if event rates exceeded 30% then risk ratio (RR) was used (Deeks 1998). Where continuous outcomes were measured in the same way across trials, we estimate a mean difference (MD) with 95% CI. We planned to present a standardised mean difference (SMD) where trials measured the same outcome using different methods. Where trials reported adverse events in sufficient detail (e.g. the number of participants who experienced at least one adverse event) or proportions of ulcers healed following treatment, we analysed these data as dichotomous. Results were pooled where a number of trials made the same

comparisons and reported the same outcome in similar participants, otherwise, a narrative review was undertaken.

Sensitivity analysis

Where there was evidence of statistical heterogeneity ($I^2 < 50\%$), the included trials were explored to see what factors could have contributed to the heterogeneity.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

One hundred eighty-five citations have been identified by the searches to May 2012. From this, the third update search (82 citations), one new trial was identified which met all of the inclusion criteria and was included ([Arapoglou 2011](#)). Eight RCTs are now included in this review (see [Characteristics of excluded studies](#)). Two further trials were identified as relevant, but included people with ulcers of mixed aetiology and did not present results separately for participants with venous leg ulcers ([Claeys 2011](#); [Mosti 2010](#)). We have contacted the trial authors for these data and the trials are now awaiting assessment (see [Characteristics of studies awaiting classification](#)). Forty-nine studies have been excluded to date (see [Characteristics of excluded studies](#)).

Results will be presented first for the evidence for *treatment*-related pain (section 1), and then for *persistent* pain (section 2).

Included studies

I. Interventions for treatment-related pain

1.1 EMLA compared with placebo or no anaesthesia (six RCTs, 343 participants)

Six RCTs were included ([Agrifoglio 2000](#); [Hansson 1993](#); [Holm 1990](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). Five trials were multi-centre RCTs undertaken in Canada ([Rosenthal 2001](#)), and EU countries ([Agrifoglio 2000](#); [Hansson 1993](#); [Johnson 1992](#); [Lok 1999](#)). One was undertaken as a single-centre trial in Sweden ([Holm 1990](#)). One trial was described as a two-part study, first an open part and then a double-blind placebo controlled RCT part ([Holm 1990](#)). Data from the RCT phase only were included in this

review. Where reported, treatment settings included dermatology clinics ([Hansson 1993](#); [Lok 1999](#); [Rosenthal 2001](#)) and outpatient departments ([Holm 1990](#)). Three trials specified participants with ulcers of venous aetiology ([Agrifoglio 2000](#); [Hansson 1993](#); [Lok 1999](#)). Three included participants with venous leg ulcers, arterial ulcers or ulcers of mixed aetiology ([Holm 1990](#); [Johnson 1992](#); [Rosenthal 2001](#)). Sample sizes ranged from 30 participants ([Holm 1990](#)) to 110 participants ([Agrifoglio 2000](#)). Five trials reported prescribing EMLA 5% cream ([Hansson 1993](#); [Holm 1990](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). [Agrifoglio 2000](#) did not state the concentration of the EMLA preparation used. EMLA was compared with a placebo cream in five trials ([Agrifoglio 2000](#); [Holm 1990](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). One trial reported that EMLA was compared with no other anaesthetic or cream vehicle ([Hansson 1993](#)). Where reported, treatment application time prior to debridement was either 30 minutes ([Holm 1990](#); [Johnson 1992](#); [Rosenthal 2001](#)) or 30 to 45 minutes ([Agrifoglio 2000](#); [Lok 1999](#)). Details of the sharp debridement were reported by five of the trials ([Agrifoglio 2000](#); [Hansson 1993](#); [Holm 1990](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). Pain after debridement was assessed by five trials using a visual analogue scale (VAS) ([Agrifoglio 2000](#); [Hansson 1993](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). Pain was assessed during the procedure using a VAS and a 4-point verbal rating scale in one trial ([Holm 1990](#)). Other outcomes included pain during re-dressing of the ulcer and an overall procedure (cleansing and dressing) pain score ([Johnson 1992](#)), the difficulty of performing the debridement ([Agrifoglio 2000](#)), local reactions to the treatment ([Holm 1990](#)), local adverse events ([Lok 1999](#)), number of ulcers healed ([Hansson 1993](#)), and participant-rated severity of local reactions ([Rosenthal 2001](#)).

All six trials of EMLA were sponsored by Astra Zeneca AB.

2. Persistent venous leg ulcer pain

2.1 Topical ibuprofen (two RCTs, 810 participants)

Two RCTs that described the use of ibuprofen as a topical agent in the form of a foam dressing that releases low-dose ibuprofen (Biatain-Ibu (Coloplast A/S)) were included ([Arapoglou 2011](#); [Gottrup 2008](#)). Four reports previously classified as 'awaiting assessment' ([Durante 2007](#); [Domenech 2008](#); [Jørgensen 2009](#); [Romanelli 2009b](#)), one previously included report ([Romanelli 2009a](#)), and the report identified for inclusion in this update ([Arapoglou 2011](#)), were judged to be reports from the same multi-centre trial. The previously included report by [Romanelli 2009a](#) presented results for people with venous leg ulcers from the Italian centre only. As the [Arapoglou 2011](#) report presented results from the multi-centre trial separately by wound aetiology (including venous leg ulcers), that were not available from the original report by

Domenech 2008, [Arapoglou 2011](#) was identified for this update as the primary reference for this trial.

[Arapoglou 2011](#) was a report of multicentre RCT across 12 EU countries recruiting 853 inpatients and outpatients with painful exuding wounds of various aetiologies. Results for 688 participants belonging to wound aetiology categories comprising more than 25 patients (venous leg ulcers, arterial ulcers, mixed aetiology, vasculitis and traumatic) were reported. Participants were randomised to either ibuprofen foam dressing (Biatain Ibu) (n = 386, of whom 189 had venous ulcers) or local best practice (n = 302, of whom 159 had venous ulcers). Pain relief was evaluated on a 5-point scale. Pain intensity was assessed using an 11-point scale. The trial authors reported pain outcomes, categorised using TOTPAR (total pain relief) and SPID (summed pain intensity difference).

[Gottrup 2008](#) was a multicentre RCT across EU countries that randomised 122 people with leg ulcers to receive either a foam dressing containing ibuprofen (Biatain-Ibu, Coloplast A/S, Denmark) (n = 62), or an identical foam dressing without ibuprofen (Biatain Non-Adhesive, Coloplast A/S, Denmark) (n = 60). The trialists assessed persistent pain relief on a 5-point scale and then categorised these data as the number of participants experiencing either pain relief or no pain relief.

The trials of ibuprofen foam were sponsored by Coloplast A/S and all authors were members of the International Pain Advisory Board for Coloplast A/S

2.2 Topical morphine (no trials)

One RCT was identified at the last review update which attempted to address the question of efficacy of topical morphine on chronic skin ulcers ([Vernassiere 2005](#)). The trial included people with leg ulcers and pressure ulcers and the authors were contacted during the last update to request data for only those people with leg ulcers alone when the trial was awaiting assessment. We repeated this request to the contact author for this update and did not receive a reply so have excluded it from this update.

2.3 Lidocaine-containing dressing (no trials)

One citation was identified for this update that evaluated lidocaine ([Alvarez 2010](#)). This was a conference abstract, and the trial authors were contacted with a request for further information. The trial author provided our group with the information required (email communication) and we were able to conclude that pain was a secondary outcome in this trial as the agent was not used primarily to relieve pain. This trial was excluded then from this review.

2.4 Hydrocolloid dressing (no trials)

Two trials, reported in abstract form only, that evaluated hydrocolloid dressings, were identified at the last update ([Bruckner 2009](#); [Meaume 2008](#)). Both trial authors were contacted during the last update to request further information. For this update, we identified a full trial report ([Bruckner 2010](#)) for the Bruckner 2009 abstract and were able to conclude from the full report that the dressing was not used primarily to relieve pain. A further request for information regarding the other conference abstract ([Meaume 2008](#)) was made (email communication), but we were still unable to confirm eligibility for inclusion in this review. Both trials were therefore excluded at this update ([Meaume 2008](#); [Bruckner 2010](#)).

Excluded studies

Forty-nine studies were excluded. Seven studies that were not RCTs were excluded ([Barghorn 1994](#); [Freidman 1984](#); [Lycka 1992](#); [Mancini 2010](#); [Ohlsen 1994](#); [Peschen 1997](#); [Wanger 1990](#)). One trial that was a cross-over design with no data reported by group at cross-over was excluded ([Jørgensen 2006](#)). One case series design study was also excluded ([Flanagan 2006](#)). Two trials were excluded as pain outcome data were not available ([Larsson-Stymne 1990](#); [Stacey 1999](#)) and five trials were excluded as the primary outcome was not pain ([Alvarez 2010](#); [Enander Malmros 1990](#); [Holst 1998](#); [Nowak 1996](#); [Romanelli 2008](#)). Twenty-one trials were excluded as the treatment evaluated was not a topical analgesic/anaesthetic or dressing for relieving pain ([Alvarez 2004](#); [Armstrong 1997](#); [Arnold 1994](#); [Brandrup 1990](#); [Bruckner 2010](#); [Falabella 1998](#); [Harcup 1986](#); [Harvey 1985](#); [Holloway 1989](#); [Klemp 1986](#); [Larsen 1997](#); [Laudanska 1988](#); [Meaume 2008](#); [Mulligan 1986](#); [Ohlsson 1994](#); [Oluwatosin 2000](#); [Poglinano 2010](#); [Romanelli 2010](#); [Sibbald 2011](#); [Smith 1992](#); [Woo 2009](#)). One trial was excluded as the sample were people with malignant ulcers ([MacGregor 1994](#)). Two trials including people with different ulcer types where the data for only those with venous leg ulcers was not available were excluded ([Sibbald 2006](#); [Vernassiere 2005](#)). One trial that included participants with infected wounds ([Allen 1982](#)) was excluded. Eight trials that did not include any participants with venous leg ulcers ([Carneiro 2003](#); [Culyer 1983](#); [Foster 1994](#); [Hughes 1989](#); [Skog 1983](#); [Twillman 1999](#); [Shun 1983](#)) were also excluded. One previously identified trial protocol was excluded as the trial was never undertaken ([Back 1995](#)).

Risk of bias in included studies

We evaluated the risk of bias for each of the included trials and the assessments are graphically represented in [Figure 1](#) and [Figure 2](#).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

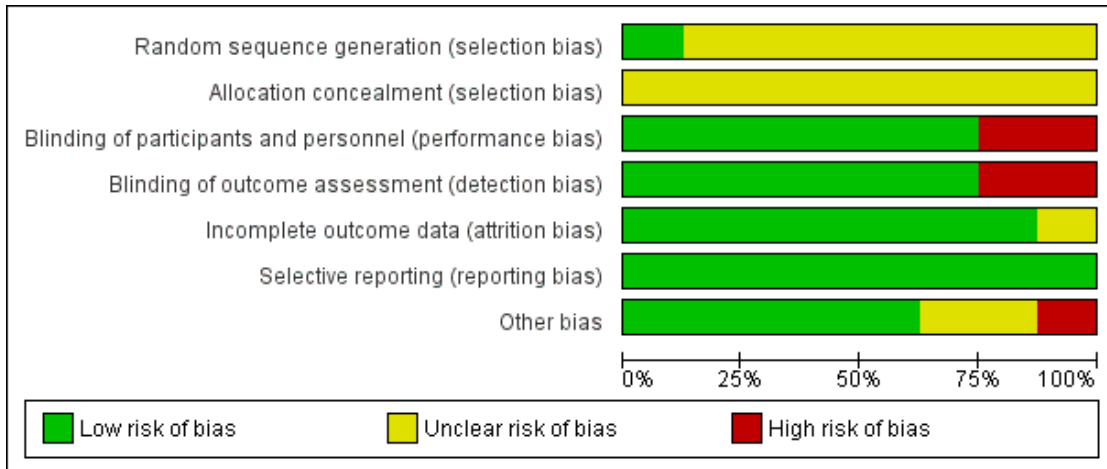


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Agrifoglio 2000	?	?	+	+	+	+	+
Arapoglou 2011	+	?	-	-	+	+	+
Gottrup 2008	?	?	+	+	+	+	+
Hansson 1993	?	?	-	-	+	+	?
Holm 1990	?	?	+	+	+	+	-
Johnson 1992	?	?	+	+	+	+	+
Lok 1999	?	?	+	+	?	+	+
Rosenthal 2001	?	?	+	+	+	+	?

Allocation

Random sequence generation (selection bias)

For the trial reported by [Arapoglou 2011](#) a computer-generated list was described as the method of generating the randomisation sequence and this trial was, therefore, classified as being at low risk of bias for this domain. None of the other reports of included trials described any details concerning the method for generation of the randomisation sequence, and the trials were, therefore, classified as being at an unclear risk of bias.

Allocation concealment (selection bias)

The [Arapoglou 2011](#), [Gottrup 2008](#) and [Hansson 1993](#) reports each described the use of sealed envelopes to conceal group allocation. The envelopes, however, were not described as opaque or sequentially numbered. These trials were classified as being at unclear risk of bias. No details regarding allocation concealment were reported by any of the other included trials. These were also classified as presenting an unclear risk of bias.

Blinding

Blinding of participants and personnel (performance bias)

[Arapoglou 2011](#) and [Hansson 1993](#) both reported results from open-label trials, and were, therefore, classified as being at high risk of bias for this domain. All of the other reports for included trials described them as being double-blind and were classified as being at low risk of bias.

Blinding of outcome assessment (detection bias)

[Arapoglou 2011](#) and [Hansson 1993](#) both reported results from open-label trials and were therefore classified as being at high risk of bias for this domain. All of the other reports for included trials described double-blind designs and were classified as being at low risk.

Incomplete outcome data

None of the included trial reports were considered at high risk of bias for this domain. One report contained insufficient detail regarding the presence, or absence, of withdrawals and was classified as being at unclear risk of bias ([Lok 1999](#)). All other included reports were classified as being at low risk of bias for this domain.

Selective reporting

A complete clinical report was available for one of the included trials that indicated there was no selective reporting bias evident ([Johnson 1992](#)). For the remaining seven included trials ([Agrifoglio 2000](#); [Arapoglou 2011](#); [Gottrup 2008](#); [Hansson 1993](#); [Holm 1990](#); [Lok 1999](#); [Rosenthal 2001](#)), the peer-reviewed report did not indicate that any selective reporting may have been evident, and these were also classified as being at low risk of bias.

Other potential sources of bias

In the [Holm 1990](#) trial, the trial authors reported that the randomisation process did not take into account people with diabetes, and that, as such, there was an imbalance of people with diabetes across the treatment groups. This trial was considered to be at high risk of other bias. No other sources of bias were detected in any of the other included trial reports.

Effects of interventions

The results of the review are presented with reference to the original questions posed.

1. Are topical analgesics/anaesthetics effective in relieving venous leg ulcer pain?

EMLA for debridement pain

Six trials involving 343 participants with venous leg ulcers compared EMLA cream with placebo cream or no anaesthetic for the treatment of pain caused by leg ulcer debridement ([Agrifoglio 2000](#); [Hansson 1993](#); [Holm 1990](#); [Johnson 1992](#); [Lok 1999](#); [Rosenthal 2001](#)). Five of the trials reported a statistically significant reduction in the pain outcome measured when EMLA (5%) was applied topically for 30 to 45 minutes under occlusion prior to debridement ([Agrifoglio 2000](#); [Hansson 1993](#); [Holm 1990](#); [Lok 1999](#); [Rosenthal 2001](#)). [Johnson 1992](#) reported no statistically significant between-group difference.

The characteristics of the trials are summarised in [Table 1](#). Methodologically the trials were considered similar. All six trials measured pain as the primary outcome using a 100 mm VAS. All the trials recruited people with venous leg ulcers of less than 50 cm² area from dermatology and vascular centres.

Outcome 1: pain score at debridement

The six trials were considered sufficiently similar to pool. The observed I² was 53%. Meta-analysis (random-effects) demonstrated that there was a statistically significant reduction in pain scores

measured on a VAS 0-100 mm at debridement associated with EMLA cream (MD -20.65, 95% CI -29.11 to -12.19; P value < 0.00001) (Analysis 1.1). This represents a clinically significant reduction in pain associated with EMLA.

The trials were explored to see what factors could have contributed to the statistical heterogeneity. Three trials included people with diabetes (Hansson 1993; Holm 1990; Lok 1999), whilst three excluded people with diabetes on the basis that diabetic neuropathy (which is frequently associated with reduced sensory perception) might confound the result (Agrifoglio 2000; Johnson 1992; Rosenthal 2001). Two trials restricted their sample to people who had previously experienced pain at debridement (Johnson 1992; Rosenthal 2001), whereas the other trials included all people with venous leg ulcers.

One trial administered the VAS during the debridement procedure (Holm 1990), whilst in the remainder the VAS was administered after the procedure. Excluding this trial from the analysis reduced both the observed between-trial heterogeneity ($I^2 = 29\%$) and the overall effect estimate (MD (fixed-effect) -18.72, 95% CI -24.41 to -13.02; P value < 0.00001).

One trial reported that participants were given oral analgesia in addition to the EMLA cream (Lok 1999). Excluding this trial from the analysis did not reduce the observed heterogeneity ($I^2 = 63\%$; MD -21.87 (random-effects), 95% CI -32.01 to -11.73; P value < 0.0001). None of the other trials recorded oral analgesic intake and therefore the impact of this is uncertain.

The Johnson 1992 trial may also account for some of the heterogeneity, because the cleansing did not only include sharp debridement, which is very painful, but also included rubbing the wound with gauze and irrigating the wound which are likely to be less painful procedures. Excluding this trial from the analysis reduced the observed heterogeneity ($I^2 = 18\%$) and increased the overall effect estimate (MD (fixed-effect) -23.38, 95% CI -29.43 to -17.14; P value < 0.00001).

The meta-analysis of the six trials suggests improved pain relief when EMLA is used, but the results should be viewed with caution, given the observed heterogeneity.

Outcome 2: ulcer healing

Only one trial reported healing outcomes. This trial favoured placebo in terms of the number of ulcers healed at the end of the trial; 1/22 healed in the EMLA group compared with 5/21 in the control group, although this is not a statistically significant difference (OR for healing with control 6.56, 95% CI 0.70 to 61.85) (Hansson 1993) (Analysis 1.2). The interpretation of this finding is not straightforward, however, since the groups were not matched for baseline ulcer duration (EMLA: median 9.5 months (range, 1-168); Control: 5 months (range, 1-504)). Findings from prognostic trials have suggested that the two most important predictors of delayed healing in participants with venous leg ulceration are baseline ulcer duration and wound surface area; people

with larger and more chronic wounds are more likely to experience longer times to healing (Margolis 2000; Margolis 2004). The period between individual debridement sessions ranged from two to nine days and the follow-up time varied considerably for each participant (one participant visited the clinic once a month with a follow-up time of 140 days. The range for the EMLA group was 38 to 40 days). Since the follow-up time varied considerably for each participant, the comparison of the healing outcomes may not be valid. The trial was also potentially underpowered to detect healing since only six events occurred.

No other included trial examined healing as an outcome and, therefore, the impact of the local anaesthetic on healing cannot be judged.

Outcome 3: adverse effects

Three trials reported the incidence of burning and itching in 233 participants (Agrifoglio 2000; Johnson 1992; Lok 1999). There was no statistically significant difference between rates of adverse events for EMLA and placebo creams (OR for burning with EMLA 1.72, 95% CI 0.74 to 4.01, Analysis 1.3; OR for itching with EMLA 1.68 95%CI 0.64 to 4.38, Analysis 1.4).

2. Which topical analgesics/anaesthetics are the most effective?

No trials were identified that could answer this question.

3. Are dressings effective in relieving the pain of venous leg ulceration?

Low-dose topical ibuprofen-containing dressings (Biatain-Ibu) for persistent pain

Outcome 1: pain relief/pain scores

We consulted members of the Cochrane Pain, Palliative & Supportive Care Review Group with a view to pooling the data from two trials evaluating ibuprofen-containing dressings (Arapoglou 2011; Gottrup 2008), however, it was agreed that the pain measures and time frames reported were too heterogeneous for the data to be pooled. Therefore, where the between-group difference was statistically significant, we have estimated a NNT (number needed to treat) with 95% CI. The NNT estimates the number of people who would need to use the topical ibuprofen dressing for one person to achieve significant pain relief.

Gottrup 2008 observed that on the first evening of treatment, 46 participants out of 62 (74%) achieved some pain relief with the ibuprofen-containing foam compared with 35/60 (58%) with the plain foam. The between-group difference was not statistically

significant although the comparison is underpowered (RR 1.27, 95% CI 0.98 to 1.65; $p=0.07$) (Analysis 2.1).

In the [Gottrup 2008](#) trial, the average pain scores reported indicated a reduction of 2.7 in the ibuprofen foam group (from 6.8 to 4.1) compared with 2.0 in the foam dressing group (6.6 to 4.6) (no variance data reported). This represents an overall percentage pain reduction of 40% and 30%, respectively, from baseline pain scores (i.e. a difference of 10% between the groups). A mean between-group difference with 95% CI could not be estimated for this review.

[Arapoglou 2011](#)

The proportion of patients with a summed pain relief score of more than 50% of the total maximum pain relief score from day 1 to day 5 was reported (TOTPAR_{D5>50%}). The authors reported that 49% of participants achieved more than 50% pain relief in the ibuprofen-containing dressing group compared to 30% in the comparator foam dressing group. The between-group difference was statistically significant in favour of the ibuprofen-containing dressing (RR 1.63, 95% CI 1.24 to 2.15; $p=0.0006$) (Analysis 3.1).

We estimated a NNT of 6 (95% CI 4 to 12). This can be interpreted as 19% more participants experienced greater than 50% pain relief in the ibuprofen-containing dressing group compared to the placebo group. This could represent a clinically relevant reduction in pain, especially if combined with other methods of pain relief ([Dworkin 2008](#)).

Outcome 2: ulcer healing

Gottrup reported similar rates of complete ulcer healing in the two groups after six weeks: 16% (10/62) with ibuprofen foam and 15% (9/60) with standard foam ([Gottrup 2008](#)). The between-group difference was not statistically significant (OR 0.85, 95% CI 0.32 to 2.26) (Analysis 2.2). [Arapoglou 2011](#) did not report ulcer healing.

Outcome 3: adverse effects

Gottrup reported that 12 participants experienced 21 adverse events in the ibuprofen foam group while in the comparator group there were 10 adverse events in seven participants ([Gottrup 2008](#)). There were no serious dressing-related events in the trial. The between-group difference in the proportion of participants experiencing adverse events was not statistically significant (OR 1.46, 95% CI 0.52 to 4.11) (Analysis 2.3). In the ibuprofen group there was local infection in three participants, eczema in two participants, blisters in two participants, urticaria in one patient, pain in one ulcer and 12 other participants had 13 incidences said to be unrelated to the dressing. In the standard foam group there were local wound infections in two participants, bullae in one patient, eczema in two participants, blisters in one patient, and another four participants had six events reported to be unrelated to the dressing. [Arapoglou 2011](#) did not report adverse events.

4. Which dressings are the most effective in relieving pain in venous leg ulceration?

No trials were identified that could answer this question. In section 3 above, the two trials evaluating dressings are summarised.

5. What is the relative effectiveness of topical analgesics or anaesthetics compared to dressings in relieving pain in venous leg ulceration?

No trials were identified that could answer this question.

6. What is the combined effect of dressings and topical analgesics/anaesthetics in relieving pain in venous leg ulceration?

No trials were identified that could answer this question.

DISCUSSION

Persistent pain

Two trials that evaluated low-dose ibuprofen releasing foam dressings reported this outcome. Both trials reported that the between-group difference in pain relief assessment scores was statistically significant. However, variance data for the differences were not presented. 'Pain relief achieved' was assessed in different ways across these trials; as pain scores on a visual analogue scale (11 points: 0 to 10), and as total pain relief achieved (TOTPAR_{D5<50%}). These differences in the way pain relief was assessed, coupled with the unavailability of variance data, limited any assessment of between-group differences in persistent pain across these trials for this review.

One trial indicated that there is a statistically significant between-group difference in favour of ibuprofen-containing dressings for TOTPAR_{D5<50%} ([Arapoglou 2011](#)). However, this trial was considered to be at a high risk of performance and detection bias as it was described as an open study design. As the primary outcome for this review, pain, whichever way it is measured, may be subject to observer or measurement bias, this should be taken into consideration when considering the pain outcomes reported by this trial. Both trials that evaluated low-dose ibuprofen releasing foam dressings were considered at unclear risk of bias for allocation concealment, as the method of treatment group allocation was not reported.

Both trials were of relatively short duration (only a few weeks long), and undertaken in people with chronic wounds where the dressing application was for the treatment of pain. One of the trials excluded participants who "had painful ulcers that had been resistant to analgesic treatment over the last six months" ([Gottrup 2008](#)). For this trial we were able to estimate the between-group

difference in the proportion of participants who achieved some pain relieve on the first evening of treatment, which was not statistically significant. This trial also reported the proportion of ulcers healed at follow-up. The between-group difference was not statistically significant.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). Systemic NSAIDs are associated with a number of important adverse effects including: effects on the kidneys, exacerbation of asthma in susceptible people, and problems in the gastrointestinal tract including ulceration (Bandolier Extra 2005). Topical NSAIDs can be given in lower doses, and their adverse event profile is better (Bandolier Extra 2005). This observation, however, is based on studies amongst people predominantly with arthritic pain, where topical NSAIDs are massaged into intact skin. Only one of the include trials in the present review that evaluated a topical NSAID reported on adverse events (Gottrup 2008), concluding that because there were few dressing-related events reported during the trial, that this indicated good dressing safety.

The variability in the pain assessment method and the reporting of pain outcomes across trials, coupled with the potential bias associated with un-blinded outcome assessment, makes interpretation of the current evidence-base for topical NSAIDs in the management of chronically painful leg ulcers difficult. We would recommend that future trials of topical NSAIDs for this condition need to consider a standardised pain assessment method to facilitate interpretation of results across trials, be of longer duration and be better reported, in order to assess both the efficacy for pain management and the safety and tolerability along with their effect on ulcer healing.

Treatment-related pain

Six trials focused on the relief of one aspect of pain, namely pain associated with leg ulcer debridement. These trials all evaluated EMLA cream versus placebo for the sharp debridement of venous leg ulcers. The rationale for the proliferation of research effort in this area appears to be based on two factors. Firstly, that debridement is a painful procedure (Hansson 1993), with participants often asking clinicians to stop before it is complete as they are unable to tolerate the pain (Lok 1999), and, secondly, the belief that the removal of necrotic and devitalised tissue improves the healing potential of a leg ulcer (Hansson 1993; Holm 1990; Lok 1999).

The pooled effect across the six trials for the mean between-group difference in the VAS score at debridement was statistically significant in favour of EMLA. The largest between-group effect estimate in favour of EMLA that was observed was for one trial that assessed pain during the ulcer debridement procedure (Holm 1990). This may in part be due to the specific effect of EMLA on the procedural pain associated with debridement, as opposed to the chronic, background pain that is associated with venous leg ulcers. The remaining five trials all assessed pain after debridement.

The between-trial heterogeneity that was observed for this comparison was reduced in the sensitivity analyses excluding the trial where pain was assessed during debridement (Holm 1990), and excluding one trial where the cleansing procedure included rubbing the wound (Johnson 1992). The effect estimates remained statistically significant.

Sharp debridement is an aggressive treatment involving scalpel, scissors, a sharp curette and forceps. The removal of necrotic and sloughy material from a wound bed is proposed to reduce the risk of infection, reduce odour and promote granulation tissue, and is an accepted therapeutic activity in wound healing (Lok 1999). It has been suggested that sharp debridement is the quickest way to achieve a clean ulcer and that it improves the result of skin grafting and the healing potential of the ulcer (Vanscheidt 2001). Steed 1996 reported the effect of extensive debridement on the healing of diabetic foot ulcers by pooling data from 10 treatment centres, reporting that those centres that performed more frequent debridement had better healing rates. The trial by Lok 1999 included in this review reported that the mean ulcer size at follow-up was inversely proportional to the number of debridements undertaken during the trial. However, the between-group difference in the proportion of ulcers healed at the end of treatment reported by another included trial (Hansson 1993) was not statistically significant. Improved healing may be attributable to aspects of wound care other than debridement.

The pooled effect estimate from five trials included in this review indicates that people with venous leg ulcers could expect their post-debridement pain to be reduced by 19 mm on a 100 mm VAS if given EMLA. Evidence from one trial indicates that the procedural pain associated with ulcer debridement is also significantly reduced with EMLA. However, none of the included trials provided adequate detail in the trial report regarding the randomisation sequence generation or any concealment of allocation procedure and are therefore considered to be at an unclear risk of selection bias. The results should therefore be interpreted with caution, given that there may be systematic differences in the characteristics of the participants receiving EMLA and those receiving placebo in these trials. One of the trials (Hansson 1993) was also considered to be at a high risk of performance and detection bias as it was described as an open trial.

The impact of local anaesthetics on ulcer healing was not sufficiently evaluated by the included trials in this review. A review of in vitro studies has suggested that local anaesthetics reduce granulocyte activity, inhibit fibroblast growth and collagen synthesis (Dahl 1994). A reduction in leukocyte activity in surgical wounds has also been reported (Eriksson 1992). Conversely, no significant differences between EMLA and placebo on the healing of experimentally-generated burns at two weeks were evident from one within-subject study (Pedersen 1996). The clinical implication of these experimental studies for the effects of EMLA on the healing of chronic wounds has yet to be determined through adequately designed randomised controlled trials.

There is still a paucity of evidence for the effects of topical agents or dressings for pain in venous leg ulcers from robust, adequately reported RCTs to inform this area of wound care practice. A possible reason could be that people with venous leg ulcers are not considered a sufficiently large, discrete group who have pain warranting study, unlike, for example, those with osteoarthritis, low back pain or postoperative pain. If a separate review was conducted exploring systemic analgesia or neuromodulation (e.g. Transcutaneous Electrical Nerve Stimulation (TENS)) the evidence base might be different. Pain specialists might not be aware of the need for robustly designed and clearly reported RCTs to evaluate the effects of topical agents and dressings for pain management and healing in people with venous leg ulcers. Similarly, wound care specialists may be aware of the need for well designed RCTs, but lack the specialist knowledge of pain management to develop and manage trials that evaluate analgesic interventions.

Limitations

There are limitations to the findings from this review. In addition to the electronic searches of bibliographic databases, the search for evidence for this review included handsearching and contact with trialists. Although this search strategy was comprehensive, the presence of a publication bias may still be evident. All of the published trials in this review reported statistically significant differences. The unpublished trial found during searching reported no difference (Johnson 1992). There may be other unpublished trials with similar results that we have been unable to identify.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of two trials, there is some evidence that foam dressings containing ibuprofen provide pain relief for some people with painful venous leg ulcers. The release of ibuprofen into the wound bed is dependent on the presence of wound exudate. This treatment would, therefore, not be an option for pain management for people with wounds that have low levels of, or no, exudate. Evidence from six trials indicates that EMLA (5%) significantly reduces pain during the debridement of venous leg ulcers compared with placebo or no anaesthetic. Existing trials examining EMLA versus placebo are designed to assess pain, but do not address the related question of whether debridement is necessary.

The decision to debride a venous leg ulcer needs to be made with knowledge of the evidence-base, clinical need and the risks associated. Severe pain is a clearly documented risk associated with debridement and EMLA 5% cream is the only topical anaesthetic for which this review has found evidence of analgesic efficacy. EMLA applied for 30 to 45 minutes in a dose of 1 g to 2 g/ 10 cm² significantly reduces the pain from sharp debridement and decreases

the incidence of post-debridement pain. However, most trials to date have excluded people with ulcers greater than 50 cm². The analgesic efficacy of EMLA in people with larger ulcers is currently not known.

It should be noted that in certain countries, specifically the UK, EMLA is not licensed to be applied directly to wounds. It is believed that EMLA is currently approved as a topical anaesthetic for the debridement of leg ulcers in Belgium, Denmark, Finland, France, Germany, Netherlands, Norway, Portugal, Spain, Sweden and Switzerland (Blanke 2003).

Implications for research

This review highlights the need for further randomised controlled trials to examine the effectiveness of local interventions to relieve the underlying pain of venous leg ulceration in long-term follow-up studies. Further research is required to determine whether dressings that incorporate ibuprofen reduce pain significantly. Further trials are also warranted to assess methods of pain relief during the actual debridement procedure and that evaluate EMLA in people with venous leg ulcers greater than 50 cm². Participants should be followed-up for sufficient time to assess healing and to measure the incidence of adverse effects. Further research is also required to determine whether debridement of venous leg ulcers aids healing.

The methodologies developed to assess interventions in the management of other chronic pain syndromes could be adapted to address questions related to leg ulcers (McQuay 1997). Specific outcome measures need to be developed for this group of people. In the absence of such measures, trials should follow the guidance outlined in the IMMPACT (Initiative on methods, measurement and pain assessment in clinical trials) recommendations. IMMPACT recommends four core chronic pain outcomes of which at least two should be measured in a trial (Dworkin 2008). These are:

1. Intensity of pain over time, assessed by a numerical rating scale.
2. Impact of physical functioning assessed by the multi-dimensional pain inventory, or the brief pain inventory.
3. Peoples' overall assessment of improvement assessed by the Patient Global Impression of Change scale.
4. Emotional functioning assessed by the Beck depression inventory and the profile of mood states.

In addition from a wound management perspective:

1. Time to complete healing.
2. Adverse effects.

Baseline comparability using the following criteria would also be desirable:

1. Baseline pain scores.
2. Psychological measures (anxiety, mood, depression).
3. Analgesic consumption.

Further trials should adopt a best practice methodology, use consistent outcomes and be better reported in line with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for the reporting of RCTs (Schulz 2010).

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Vanscheidt 2001

Vanscheidt W, Lillieborg S. EMLA anaesthetic cream for sharp debridement: a review of the clinical evidence for analgesic efficacy and tolerability. *European Journal of Dermatology* 2001;**11**(2):90–6.

Walshe 1995

Walshe C. Living with a venous ulcer: a descriptive study of patients' experiences. *Journal of Advanced Nursing* 1995;**22** (6):1092–100.

Zeppetella 2004

Zeppetella G. Topical opioids for painful skin ulcers; do they work?. *European Journal Palliative Care* 2004;**11**(3): 93–6.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agrifoglio 2000

Methods	Multicentred RCT (seven centres in Italy).
Participants	110 people with venous leg ulcers. Exclusion criteria: participants were excluded from the trial if diabetes or infection was noted, or if the area of the ulcer was greater than 50 cm ² Fifty-four participants were randomised to EMLA and 56 to placebo
Interventions	1. EMLA: % not stated (2.5g per 10 cm ² to a maximum 10g). 2. Placebo cream. EMLA (2.5 g per 10 cm ²) was applied as a cream for 30 to 45 minutes prior to debridement of the wound. 'Cling film' was used to occlude the ulcer during the application time The constituents of the placebo cream were not provided. The debridement was performed using a curette, scissors, lancets and forceps Baseline pain scores were not recorded.
Outcomes	Pain at debridement was measured by a VAS after debridement. The difficulty of performing the debridement was also explored by means of a physician-rated 3-point scale
Notes	Supported by Astra Pain Control AB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a randomised, double-masked, placebo-controlled trial" Comment: No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The study was a randomised, double-masked, placebo-controlled trial" Comment: Procedure for participant allocation to study groups not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Described as double-masked, placebo-controlled. Assume participants and personnel were blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: As it was a double-masked, placebo-controlled trial, outcome assessment (participant reported pain) would be

Agrifoglio 2000 (Continued)

		blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Sixty patients per group were planned for inclusion in the study, this sample size including a 20% increase to account for drop-outs." Quote: "Fifty-four patients were randomised to treatment with EMLA and 56 to placebo cream." Comment: Although no statement on numbers of patients completing/withdrawing from treatment, all patients randomised represented in results tables
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	Low risk	Comment: No other potential sources of bias evident.

Arapoglou 2011

Methods	Multicentred RCT conducted in 12 countries (184 centres). Setting: inpatients and outpatients
Participants	853 inpatients and outpatients with painful exuding wounds of various aetiologies were originally recruited (group 1 n = 189 with venous leg ulcers, group 2 n = 159 with venous leg ulcers). The trialists report data for 688 participants belonging to wound aetiology categories comprising more than 25 patients (venous leg ulcers, arterial ulcers, mixed aetiology, vasculitis and traumatic) People were excluded if they had hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatories (NSAIDs), if the trial ulcer was infected, discoloured, or odorous, if they had pressure ulcers of grade I, III or IV (according to NPUAP classification) or a diabetic foot ulcer grade 3, 4, 5 (according to Wagner classification) (reported in Domenech 2008)
Interventions	1. Foam dressing containing 0.5 mg/cm ² ibuprofen homogeneously dispersed (Biatain Ibu) 2. Local best practice - standard dressings at the investigator site used for painful exuding wounds Mean (SD) treatment duration was 7(±2) days. All concomitant treatments were allowed, although patients were asked not to alter the dosage of any pain-relieving medication Pain was assessed twice daily using a 5-point scale (0 = no relief, 1 = slight, 2 = moderate, 3 = marked, 4 = complete pain relief)

Arapoglou 2011 (Continued)

Outcomes	<p>Pain relief was evaluated on a 5-point scale (0 = no pain, 1 = slight, 2 = moderate, 3 = marked, 4 = complete relief)</p> <p>Pain intensity was assessed using an 11-point scale (0 = no pain, 10 = worse pain ever)</p> <p>The trial authors reported pain outcomes, categorised using TOTPAR (total pain relief) and SPID (summed pain intensity difference), as:</p> <p>Proportion of patients with > 50% pain relief score from day 1 to day 5 (TOTPAR_{D5>50%})</p> <p>·</p> <p>Proportion of patients with > 50% pain relief daily.</p> <p>Proportion of patients with > 50% reduction from baseline of pain intensity on day 5 (SPID_{D5>50%}).</p>
Notes	<p>Only reports outcomes for wound aetiology categories with >25 patients (688 patients)</p> <p>Other outcomes evaluated in the secondary reference by Domenech 2008 (quality of life, adverse events, the overall pain-relieving effect of the dressing, changes in the intake of pain-relieving medicine, condition of the peri-ulcer skin, leakage, and dressing time taken) were not reported</p> <p>Pain outcome data were available separately for venous leg ulcers (and other wound aetiologies)</p> <p>As outcome data for the venous leg ulcer participants alone was not reported by Domenech 2008 report, we have used the venous leg ulcer participant data presented by Arapoglou 2011 for our analysis.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Using a computer-generated list in sealed envelopes, patients were randomly assigned to either treatment with the ibuprofen-releasing foam (test) dressing or local best practice."</p> <p>Comment: reported in secondary reference (Domenech 2008).</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "Using a computer-generated list in sealed envelopes, patients were randomly assigned to either treatment with the ibuprofen-releasing foam (test) dressing or local best practice."</p> <p>Comment: envelopes not described as opaque or sequentially numbered. Reported in secondary reference (Domenech 2008)</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "As it was an open study design, there was the inherent possibility of treatment bias from patients or study personnel."</p>

Arapoglou 2011 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "As it was an open study design, there was the inherent possibility of treatment bias from patients or study personnel."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The analyses were performed on the intention-to-treat (ITT) population in accordance with the pre-specified statistical plan." (Reported in secondary reference (Domenech 2008)) Comment: numbers of patients not completing study and reasons for both groups reported in secondary reference (Domenech 2008). Low withdrawal rate (Group 1: 11%; Group 2: 8%). All patients randomised included in final analysis (Flow chart presented in Domenech 2008)
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	Low risk	Comment: No other potential sources of bias evident.

Gottrup 2008

Methods	Multicentred RCT. Setting not reported Performance and ascertainment biases were minimised by the trial being double-blind.
Participants	122 people with leg ulcers People were excluded if they had a contraindication to NSAIDs, had infected wounds or had painful ulcers that had been resistant to analgesic treatment over the last six months. 62 were randomised to receive a foam dressing containing ibuprofen (Biatain-Ibu, Coloplast A/S, Denmark) and 62 to receive an identical foam dressing without ibuprofen (Biatain Non-Adhesive, Coloplast A/S, Denmark)
Interventions	1. Foam dressing containing ibuprofen (Biatain-Ibu, Coloplast A/S, Denmark). 2. Identical foam dressing without ibuprofen (Biatain Non-Adhesive, Coloplast A/S, Denmark)
Outcomes	Persistent pain relief was assessed on a 5-point scale (no relief, slight relief, moderate relief, lots of relief, complete relief), that was then categorised to pain relief, yes (slight, moderate, lots, complete) or no pain relief in the final analysis Proportion of ulcers healed.
Notes	Sponsored by Coloplast A/S.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This randomised, controlled double-blind, parallel-group, multicenter, and multinational clinical investigation . . ." No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation in closed envelopes took place after inclusion and before study initiation." Comment: envelopes not described as opaque or sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study personnel and patients were blind to treatment from days 1 to 42 (double blind)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Persistent (relief and intensity) and temporary pain (dressing change related) were assessed at days 1-5 and at days 43-47." Comment: As participants were blind to treatment, outcome assessment (participant reported pain) would be blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All data analysis was performed..on the intention-to-treat (ITT) population." Comment: Numbers withdrawing and reasons reported. Numbers and reasons balanced across groups. Drop-out rate 23%
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	Low risk	Comment: No other potential sources of bias evident.

Hansson 1993

Methods	Single-centred, open, RCT (Sweden). Setting: dermatology and surgery departments of one hospital in Sweden
Participants	43 people with venous leg ulcers. Exclusion criteria were: ulcer > 50 cm ² ; history of sensitivity to local anaesthetics; previous treatment with EMLA; ongoing antibiotics or proteolytic enzyme treatment Twenty-two participants received EMLA, and, in the control group 21 participants did not receive either a “vehicle cream” (placebo) or anaesthesia
Interventions	1. EMLA 5%. 2. No treatment. Each participant underwent eight successive debridements separated by a period of two to nine days The debridement was performed using a curette, scissors, or a swab
Outcomes	Pain on debridement was measured using a visual analogue scale (VAS) after the procedure The occurrence of post-cleansing pain (up to four hours) was noted at each debridement session Additional data were collected about local reactions to the cream (patient-rated); reduction in necrotic tissue and ulcer size (using acetate tracing) Number of ulcers healed at the end of the trial.
Notes	Supported by Astra Pain Control AB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “The study had an open randomised parallel-group design with a control group” No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Quote: “A sealed envelope individual to each patient, containing information on allocation to EMLA allocation or control, was opened immediately before the first treatment.” Comment: envelopes not described as opaque or sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: Trial described as open.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Trial described as open.

Hansson 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No statement on whether analysis was ITT or per-protocol, but numbers withdrawing from study arms low (< 1%)
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	Unclear risk	Comment: No other potential sources of bias evident.

Holm 1990

Methods	Double-blind RCT (Sweden). Setting: outpatient department. The trial was described as a two-part study, first an open part and then a double-blind placebo controlled part	
Participants	30 patients (19 had venous leg ulcers and 11 arterial ulcers) 50 participants initially took part in the open phase (all received EMLA 5%), of which 30 then took part in the double-blind (RCT) phase. The trialists do not report at what point randomisation took place or why only 30 were included in the RCT No specific inclusion or exclusion criteria were reported.	
Interventions	1. EMLA 5%. 2. Placebo cream. The double-blind controlled trial evaluated a 30-minute exposure to placebo or active cream Both creams were identically packaged and applied in the same way, i.e. as a thick layer of cream under an occlusive dressing (Glad, Germany) for 30 minutes The ulcer was debrided using tweezers, scissors and a curette The treatments were randomised and stratified for types of ulcer (venous or arterial) but not for concomitant diabetes	
Outcomes	Debridement pain was assessed during the procedure using a 0 to 100 VAS and a 4-point verbal rating scale Local reactions to the cream were examined by asking participants about itching or burning, and observations of the area after removal of the cream The data for the venous ulcer participants was available separately	
Notes	Supported by Astra Pain Control AB.	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Holm 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "The treatments were randomised and stratified for type of ulcer (venous or arterial) but not for concomitant diabetes." Comment: No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Quote: "In the double-blind part, patients were treated with either EMLA cream or placebo" Comment: Procedure for concealment of participant allocation to study groups not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Trial described as double-blind. Assume participants and personnel were blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: As participants were blind to treatment, outcome assessment (participant reported pain) would be blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Single-dose study. One patient in the control arm missing VAS pain score
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	High risk	Quote: "In this study the randomisation protocol did not take account of diabetes. This resulted in an imbalance of patients with diabetes in the arterial ulcer group with the majority of diabetics in the placebo group." Quote: "This is probably the explanation why we could not find any significant effect of EMLA in the arterial ulcer group, since all the placebo group happened to be diabetics." Comment: Groups may not have been balanced for prognostic factors at baseline

Johnson 1992

Methods	Double-blind, parallel group, placebo-controlled, randomised trial conducted in four centres in Scotland, UK
Participants	41 people with venous leg ulcers of which 7 had arterial ulcers; 5 had mixed aetiology ulcers and 1 had a vasculitic ulcer Exclusion criteria were: ulcer > 50 cm ² ; history of sensitivity to local anaesthetics; diabetes; anyone whom the investigators deemed unsuitable due to pathological processes or anatomical variations People were only included in the trial if they had previously experienced pain during wound cleansing of greater than 25 mm (measured using a VAS) (Unpublished trial provided by Astra Zeneca)
Interventions	1. EMLA 5%. 2. Placebo cream. EMLA (5%) cream was applied for 30 minutes prior to debridement of the wound and covered with 'cling film' Participants received either EMLA (5%) or placebo packaged in identical aluminium tubes
Outcomes	Three pain assessments were recorded by means of a VAS: 1. pain during ulcer cleansing; 2. pain on re-dressing the ulcer; 3. overall pain score. The first two VAS scores were participant-generated, whilst the third was performed by the person performing the cleansing and re-dressing Local reactions were assessed after removal of the cream by means of a symptom checklist (e.g. burning, itching) and evidence of skin reaction The descriptions of ulcer cleansing were listed as wiping, dabbing, irrigating, removal of debris, cutting, scraping, and scraping until bleeding
Notes	Supported by Astra Pain Control AB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was designed as a multicentre trial, which was double-blind, parallel group, placebo controlled and randomised in blocks of two," No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to receive either EMLA or placebo before the cleansing and re-dressing of their leg ulcer." Comment: Procedure for concealment of participant allocation to study groups not

Johnson 1992 (Continued)

		reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Trial described as double-blind. Assume participants and personnel were blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: As participants were blind to treatment, outcome assessment (participant reported pain) would be blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty-four patients were included in the study. Of these 52 patients were eligible for both efficacy and safety analysis and 2 were eligible only for safety analysis as a result of insufficient pain on the comprehension VAS."
Selective reporting (reporting bias)	Low risk	Comment: Clinical report available. No selective reporting evident
Other bias	Low risk	Comment: No other potential sources of bias evident.

Lok 1999

Methods	Multicentred RCT, double-blind, placebo-controlled design (nine centres in France) Setting: departments of dermatology and phlebology
Participants	69 people with venous leg ulcers. Inclusion criteria were: ulcer area 5 -50 cm ² ; necrotic tissue over 50% of the ulcer; ulcer judged to require at least 3 debridement sessions in the first week; no previous treatment with EMLA Thirty-six participants received EMLA cream and 33 received placebo
Interventions	1. EMLA 5%. 2. Placebo cream. A thick layer of cream was administered to the wound and covered with 'cling film' for 30 to 45 minutes Standardised oral analgesia was administered one hour before treatment Debridement involved the use of curette and scissors. All participants received the treatment prior to debridement with a maximum of up to 15 treatments
Outcomes	Pain after debridement was measured using a VAS and the median number of debridements required to achieve a clean ulcer was reported Local reactions were assessed and adverse events noted.

Notes	The trial is limited by the length of follow-up, since only 30% of the control group achieved a clean ulcer by the end of the trial Median number of debridements to achieve a clean ulcer: EMLA: 11.5, Control: "more than 15". Number of participants with a clean ulcer at the end of the study: EMLA: 24 (66.7%) Control: 11 (33.3%).	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: The primary objective of this randomised, double-blind, placebo-controlled study was to assess the effect of EMLA cream on the number of mechanical debridement sessions required to obtain a clean ulcer." Comment: No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Comment: Procedure for concealment of participant allocation to study groups not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Trial described as double-blind. Assume participants and personnel were blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: As participants were blind to treatment, outcome assessment (participant reported pain) would be blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No statement on numbers of patients completing/withdrawing from treatment. No statement on whether analysis was ITT or per-protocol
Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non selective reporting
Other bias	Low risk	Comment: No other potential sources of bias evident.

Rosenthal 2001

Methods	Multicentred, double-blind, placebo-controlled, RCT (four centres in Canada) Setting: dermatology clinics.
Participants	101 people with leg ulcers - 61 had venous leg ulcers. All participants had previously experienced pain from leg ulcer debridement. People with diabetes, large ulcers (more than 50 cm ²) or a history of allergy were excluded 51 were randomised to receive EMLA cream and 50 to receive placebo
Interventions	1. EMLA 5%. 2. Placebo cream. A thick layer of cream was applied for approximately 30 minutes (range 25-37 minutes) and covered with an occlusive dressing (plastic wrap) Debridement involved the use of sharp curette, scissors, forceps or scalpel blade
Outcomes	After cream removal, participants rated the severity of local reactions on a 4-point scale (none, mild, moderate,severe) After debridement, participants were asked to assess the degree of pain using a VAS
Notes	Supported by Astra Pain Control AB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a randomised, double-blind, parallel-group, placebo controlled, multicenter trial." Cooment: No methods for generation of the randomisation sequence reported
Allocation concealment (selection bias)	Unclear risk	Comment: Procedure for concealment of participant allocation to study groups not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Trial described as double-blind. Assume participants and personnel were blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: As participants were blind to treatment, outcome assessment (participant reported pain) would be blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No data were excluded from the analysis." Comment: Single-dose study so no withdrawals would be anticipated

Rosenthal 2001 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: No protocol available but article title, study aims, treatment investigated and outcomes reported indicative of non-selective reporting
Other bias	Unclear risk	Comment: No other potential sources of bias evident.

Abbreviations used:

< - less than

> - greater than

EMLA - Eutectic Mixture of Local Anaesthetics (Lidocaine/Prilocaine Cream)

ITT - Intention-to-Treat

RCT - Randomised controlled trial

SPID - Sum of Pain Intensity Differences

TOTPAR - Total pain relief achieved

VAS - Visual Analogue Scale

VRS - Verbal Rating Scale (none, mild, moderate, severe)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allen 1982	Sample comprised people with infected wounds.
Alvarez 2004	Agent not used for pain relief.
Alvarez 2010	Agent not used for relieving pain. Pain measured as a secondary outcome
Armstrong 1997	Agent not used for relieving pain. Pain measured as a secondary outcome
Arnold 1994	Agent not used for relieving pain. Pain measured as a secondary outcome
Back 1995	Letter reporting ongoing trial. Contacted authors- trial was abandoned due to poor recruitment from centres
Barghorn 1994	Not a randomised controlled trial.
Brandrup 1990	Agent not used for pain relief. Pain measured as a secondary outcome
Bruckner 2010	Agent not used for relieving pain. Pain measured as a secondary outcome
Carneiro 2003	Sample population did not have venous leg ulcers - and primary aim healing, not pain

(Continued)

Culyer 1983	Sample population did not have venous leg ulcers.
Enander Malmros 1990	Outcome measure was plasma concentration, not pain.
Falabella 1998	Agent was not used for pain relief. Pain measured as a secondary outcome
Flanagan 2006	Case series.
Foster 1994	Sample population did not have venous leg ulcers. Participants had areas of diabetic neuropathic pain, but no wound
Freidman 1984	Not a randomised controlled trial.
Harcup 1986	Agent was not used for pain relief. Pain measured as a secondary outcome
Harvey 1985	The agent was not used for pain relief, and pain measures were a secondary outcome
Holloway 1989	Agent not used to relieve pain. Pain reported as a secondary outcome
Holst 1998	Outcome measure was plasma concentration, not pain.
Hughes 1989	Sample population did not have venous leg ulcers.
Jørgensen 2006	Cross-over design.
Klemp 1986	Agent not used for relieving pain. Pain measured as a secondary outcome
Larsen 1997	Agent was not used for pain relief. Pain measured as a secondary outcome
Larsson-Stymne 1990	No pain data available.
Laudanska 1988	Agent was not used for pain relief. Pain measured as a secondary outcome
Lycka 1992	Not a randomised controlled trial.
MacGregor 1994	Sample comprised malignant ulcers. Contacted authors, no further work planned
Mancini 2010	Not a randomised controlled trial.
Meaume 2008	Agent not used for relieving pain. Pain measured as a secondary outcome
Mulligan 1986	Agent was not used for pain relief. Pain measured as a secondary outcome
Nowak 1996	Pain measured as a secondary outcome.
Ohlsen 1994	Not a randomised controlled trial.

(Continued)

Ohlsson 1994	Agent not used for pain relief. Pain outcomes poorly reported
Oluwatosin 2000	Agent not used for relieving pain. Pain measured as a secondary outcome
Peschen 1997	Not a randomised controlled trial.
Poglinano 2010	Agent not used for relieving pain. Pain measured as a secondary outcome
Romanelli 2008	Pain measured as a secondary outcome.
Romanelli 2010	Agent not used for relieving pain. Pain measured as a secondary outcome
Shun 1983	Sample population did not have venous leg ulcers. Pain outcomes not reported
Sibbald 2006	Sample comprised people with different wound types. Data not available for venous leg ulcer participants only
Sibbald 2011	Agent not used for relieving pain. Pain measured as a secondary outcome
Skog 1983	Sample population did not have venous leg ulcers.
Smith 1992	Agent was not used for pain relief. Pain measured as a secondary outcome
Stacey 1999	Pain outcome not reported.
Twillman 1999	Sample population did not have venous leg ulcers.
Vernassiere 2005	Sample comprised people with different wound types. Data not available for venous leg ulcer participants only
Wanger 1990	Not a randomised controlled trial.
Woo 2009	Agent not used for relieving pain. Pain measured as a secondary outcome (at dressing change)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Claeys 2011

Methods	Randomised controlled trial.
Participants	41 people with venous, arterial or mixed leg ulcers.
Interventions	Nitrous oxide oxygen mixture or lidocaine-prilocaine cream.
Outcomes	Pain before and after debridement on VAS and VRS.

Claeys 2011 (Continued)

Notes	Contacted authors requesting results for VLU participants only. Awaiting reply
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Mosti 2010

Methods	Randomised controlled trial.
Participants	Inclusion criteria unclear from abstract.
Interventions	A hydrobalanced cellulose based dressing or a foam wound dressing with Ibuprofen
Outcomes	Pain on VAS, quality of life, wound size reduction or healing time
Notes	Contacted authors requesting results for VLU participants only. Awaiting reply

DATA AND ANALYSES

Comparison 1. EMLA compared with placebo or no anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score at debridement	6	317	Mean Difference (IV, Random, 95% CI)	-20.65 [-29.11, -12.19]
2 Number of healed wounds	1	43	Odds Ratio (M-H, Fixed, 95% CI)	6.56 [0.70, 61.85]
3 Incidence of burning at removal of cream	3	232	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.74, 4.01]
4 Incidence of itching at removal of cream	3	233	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [0.64, 4.38]

Comparison 2. Ibuprofen foam dressing compared with foam dressing alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number participants experiencing pain relief on the first evening of treatment	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.98, 1.65]
2 Number of healed wounds	1	122	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.32, 2.26]
3 Number participants experiencing adverse events	1	122	Odds Ratio (M-H, Fixed, 95% CI)	1.46 [0.52, 4.11]

Comparison 3. Ibuprofen foam dressing compared with local best practice

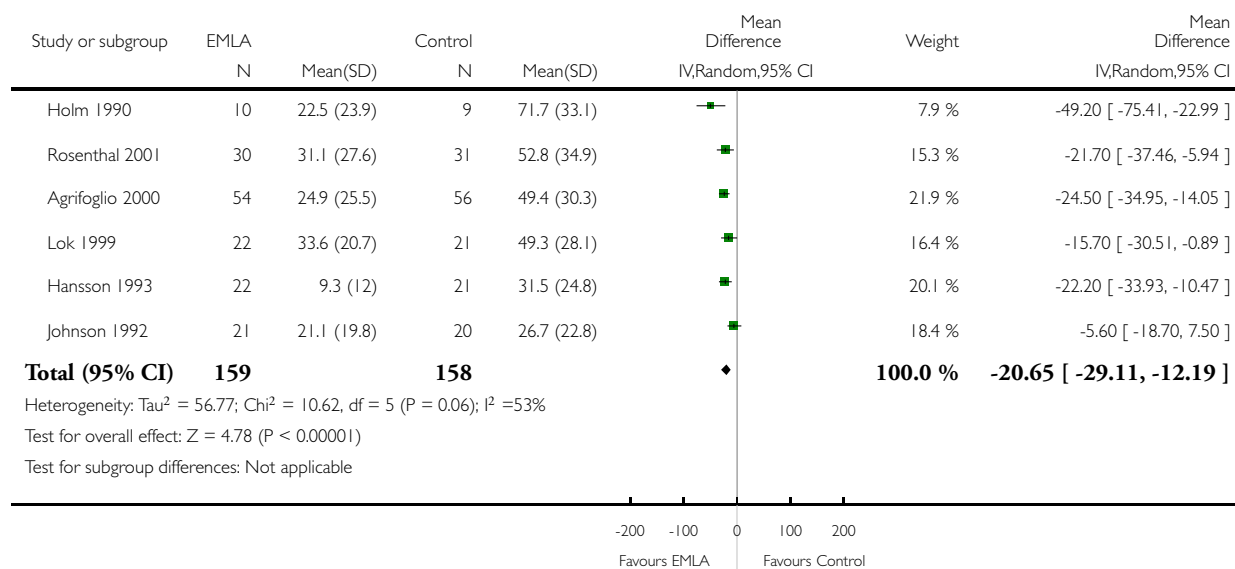
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number participants reporting TOTPAR _{D5} >50%	1	348	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.24, 2.15]

Analysis 1.1. Comparison 1 EMLA compared with placebo or no anaesthesia, Outcome 1 Pain score at debridement.

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 1 EMLA compared with placebo or no anaesthesia

Outcome: 1 Pain score at debridement

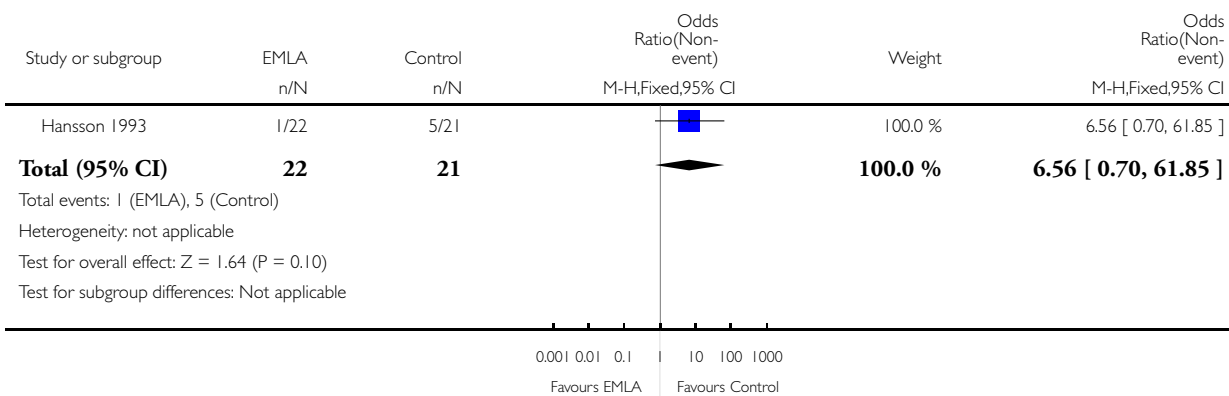


Analysis 1.2. Comparison 1 EMLA compared with placebo or no anaesthesia, Outcome 2 Number of healed wounds.

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 1 EMLA compared with placebo or no anaesthesia

Outcome: 2 Number of healed wounds

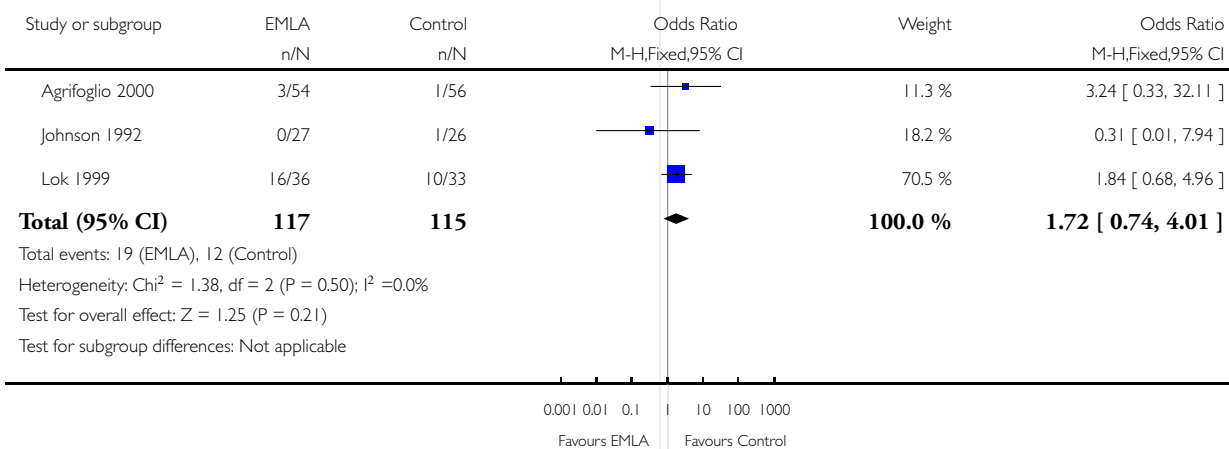


Analysis 1.3. Comparison 1 EMLA compared with placebo or no anaesthesia, Outcome 3 Incidence of burning at removal of cream.

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 1 EMLA compared with placebo or no anaesthesia

Outcome: 3 Incidence of burning at removal of cream

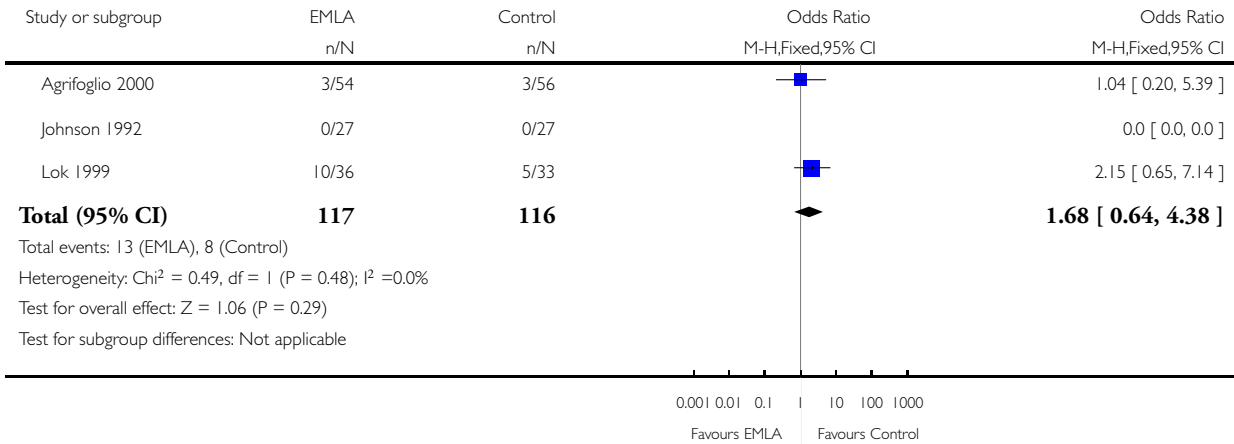


Analysis 1.4. Comparison 1 EMLA compared with placebo or no anaesthesia, Outcome 4 Incidence of itching at removal of cream.

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 1 EMLA compared with placebo or no anaesthesia

Outcome: 4 Incidence of itching at removal of cream

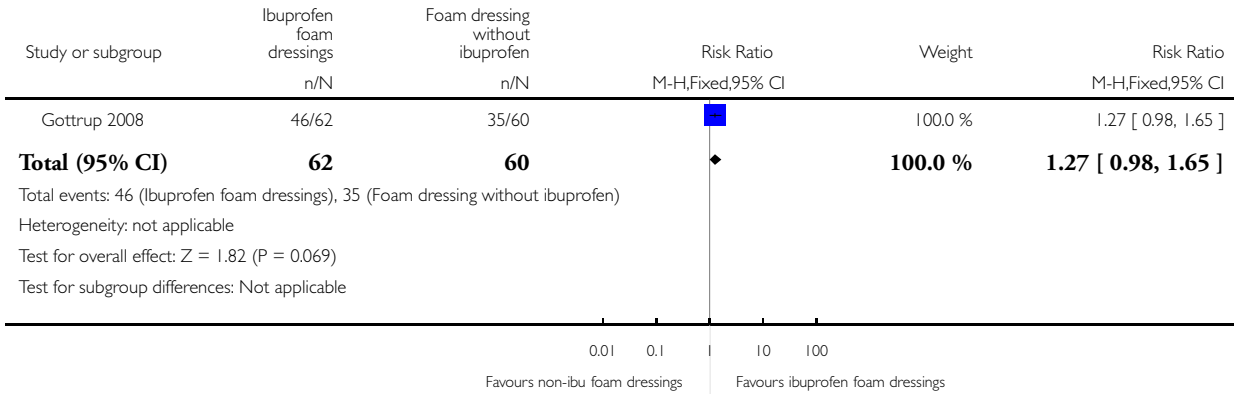


**Analysis 2.1. Comparison 2 Ibuprofen foam dressing compared with foam dressing alone, Outcome 1
Number participants experiencing pain relief on the first evening of treatment.**

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 2 Ibuprofen foam dressing compared with foam dressing alone

Outcome: 1 Number participants experiencing pain relief on the first evening of treatment

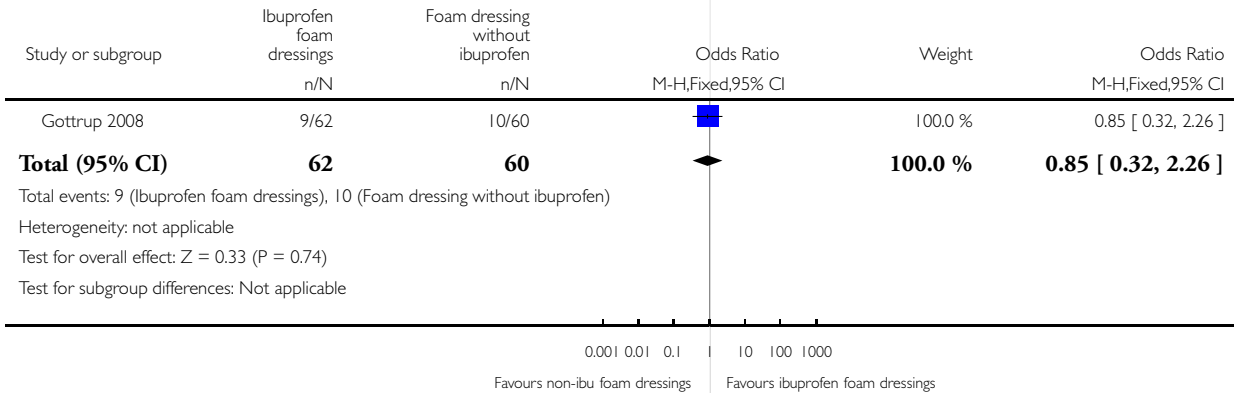


**Analysis 2.2. Comparison 2 Ibuprofen foam dressing compared with foam dressing alone, Outcome 2
Number of healed wounds.**

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 2 Ibuprofen foam dressing compared with foam dressing alone

Outcome: 2 Number of healed wounds

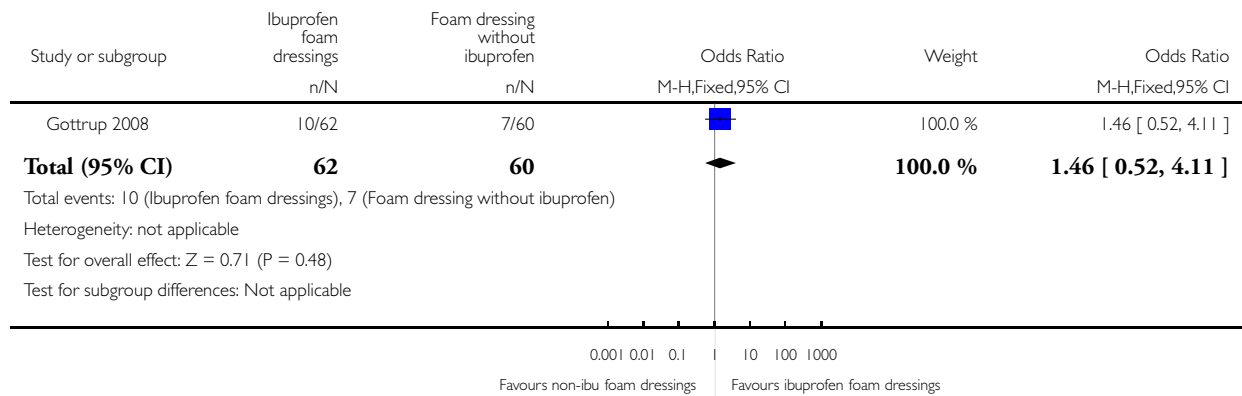


**Analysis 2.3. Comparison 2 Ibuprofen foam dressing compared with foam dressing alone, Outcome 3
Number participants experiencing adverse events.**

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 2 Ibuprofen foam dressing compared with foam dressing alone

Outcome: 3 Number participants experiencing adverse events

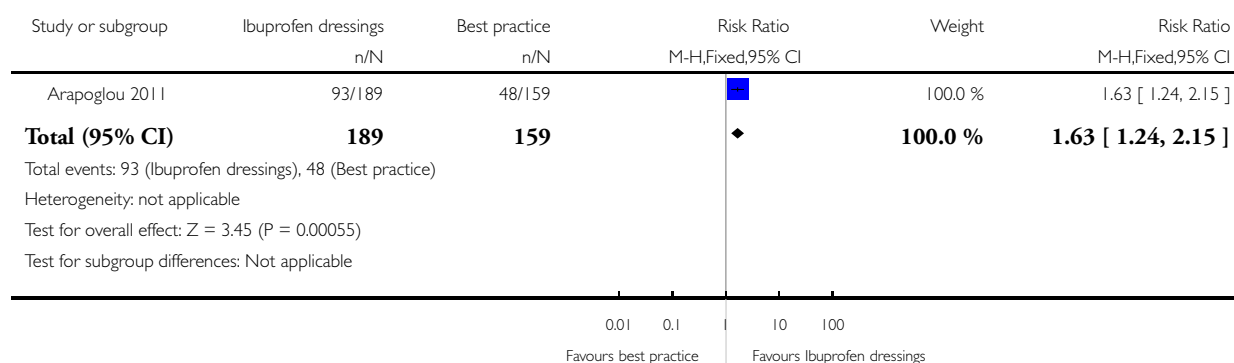


Analysis 3.1. Comparison 3 Ibuprofen foam dressing compared with local best practice, Outcome 1 Number participants reporting TOTPAR_{D5}>50%.

Review: Topical agents or dressings for pain in venous leg ulcers

Comparison: 3 Ibuprofen foam dressing compared with local best practice

Outcome: 1 Number participants reporting TOTPAR_{D5}>50%



ADDITIONAL TABLES

Table 1. Comparison of EMLA intervention studies for clinical heterogeneity

Rosenthal 2001	Agrifoglio 2000	Lok 1999	Hansson 1993	Johnson 1992	Holm 1990
Venous ulcers (from a mixed sample).	Venous ulcers.	Venous ulcers.	Venous ulcers.	Venous ulcers (from a mixed sample).	Venous ulcers (from a mixed sample).
Dermatology centres in Canada.	Vascular surgery centres in Italy.	Dermatology centres in France.	Dermatology and surgical centres in Sweden.	Health centres in Scotland.	Surgical centre in Sweden.
Included only patients with previous experience of painful debridement	All ulcers had previously been debrided.	Previous experience of debridement not stated.	Previous experience of debridement not stated.	Included only patients with previous experience of painful debridement	Previous experience of debridement not stated.
Diabetes excluded.	Diabetes excluded.	Not clear re diabetes.	Not clear re diabetes.	Diabetes excluded.	Not clear re diabetes.
Ulcers > 50 cm ² excluded.	Ulcers > 50 cm ² excluded.	Ulcers > 50 cm ² excluded.	Ulcers > 50 cm ² excluded.	Ulcers > 50 cm ² excluded.	Not clear.

Table 1. Comparison of EMLA intervention studies for clinical heterogeneity (Continued)

No concomitant analgesia given.	No concomitant analgesia given.	Concomitant analgesia given.	No concomitant analgesia given.	No concomitant analgesia given.	No concomitant analgesia given.
EMLA 5% for 30 minutes.	EMLA for 30 minutes.	EMLA 5% for 30 minutes.	EMLA 5% for 30 minutes.	EMLA 5% for 30 minutes.	EMLA 5% for 30 minutes.
Sharp debridement with curette, forceps and scissors.	Sharp debridement with curette, forceps and scissors.	Sharp debridement with curette, forceps and scissors.	Sharp debridement with curette, forceps and scissors.	All forms of ulcer cleansing.	Sharp debridement with curette, forceps and scissors.
VAS after debridement.	VAS after debridement.	VAS after debridement.	VAS after debridement.	VAS after debridement.	VAS during debridement.

APPENDICES

Appendix I. Search strategy for the second review update 2010

Search methods for identification of studies

Electronic searches

For this second update we searched the following electronic databases:

Cochrane Wounds Group Specialised Register (Searched 16/12/09)

The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library 2009 Issue 4

Ovid MEDLINE - 1950 to November Week 3 2009

Ovid MEDLINE - In-Process & Other Non-Indexed Citations (Searched 16/12/09)

Ovid EMBASE - 1980 to 2009 Week 50

EBSCO CINAHL - 1982 to December 16 2009

The following strategy was used to search The Cochrane Central Register of Controlled Trials (CENTRAL):

#1 MeSH descriptor Analgesia explode all trees

#2 MeSH descriptor Analgesics explode all trees

#3 MeSH descriptor Capsaicin explode all trees

#4 capsaicin:ti,ab,kw

#5 MeSH descriptor Analgesics, Opioid explode all trees

#6 opioid:ti,ab,kw

#7 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees

#8 (non NEXT steroidal NEXT anti-inflammatory* or NSAID*):ti,ab,kw

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

#10 MeSH descriptor Administration, Topical explode all trees

#11 topical or local:ti,ab,kw

#12 (#10 OR #11)

#13 (#9 AND #12)

#14 MeSH descriptor Anesthetics, Local explode all trees

Topical agents or dressings for pain in venous leg ulcers (Review)

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#15 ((topical or local) NEAR/3 (anaesthe* or anesthe*)):ti,ab,kw
 #16 ((topical or local) NEAR/3 analgesi*):ti,ab,kw
 #17 (#13 OR #14 OR #15 OR #16)
 #18 MeSH descriptor Bandages explode all trees
 #19 MeSH descriptor Hydrogels explode all trees
 #20 MeSH descriptor Alginates explode all trees
 #21 (dressing* or hydrocolloid* or alginate* or hydrogel* or “foam” or “bead” or “film” or “films” or tulle or gauze or non-adherent or “non adherent”):ti,ab,kw
 #22 MeSH descriptor Ointments explode all trees
 #23 (ointment* or “cream” or “creams” or “gel” or “gels”):ti,ab,kw
 #24 (#18 OR #19 OR #20 OR #21 OR #22 OR #23)
 #25 MeSH descriptor Pain explode all trees
 #26 pain*:ti,ab,kw
 #27 (#25 OR #26)
 #28 (#24 AND #27)
 #29 (#17 OR #28)
 #30 MeSH descriptor Leg Ulcer explode all trees
 #31 ((varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*)):ti,ab,kw
 #32 (#30 OR #31)
 #33 (#29 AND #32)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#) respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).

Searching other resources

Six additional records were identified from recent conference proceedings (European Wound Management Association, Lisbon 2008), and other studies known to the review authors from reading reference lists and discussions with researchers in the field.

Appendix 2. Ovid MEDLINE search strategy

- 1 exp Analgesia/
- 2 exp Analgesics/
- 3 exp Capsaicin/
- 4 capsaicin.ti,ab.
- 5 exp Analgesics, Opioid/
- 6 opioid\$.ti,ab.
- 7 exp Anti-Inflammatory Agents, Non-Steroidal/
- 8 (non steroidal anti-inflammatory\$ or NSAID\$).ti,ab.
- 9 or/1-8
- 10 exp Administration, Topical/
- 11 (topical or local).ti,ab.
- 12 or/10-11
- 13 9 and 12
- 14 exp Anesthetics, Local/
- 15 ((topical or local) adj3 (anaesthe\$ or anesthe\$)).ti,ab.
- 16 ((topical or local) adj3 analges\$).ti,ab.
- 17 or/13-16
- 18 exp Bandages/
- 19 exp Hydrogels/
- 20 exp Alginates/

21 (dressing\$ or hydrocolloid\$ or alginate\$ or hydrogel\$ or foam or bead or film or films or tulle or gauze or non-adherent or non adherent).ti,ab.
 22 exp Ointments/
 23 (ointment\$ or cream\$1 or gel\$1).ti,ab.
 24 or/18-23
 25 exp Pain/
 26 pain\$.ti,ab.
 27 or/25-26
 28 24 and 27
 29 17 or 28
 30 exp Leg Ulcer/
 31 (varicose ulcer\$ or venous ulcer\$ or leg ulcer\$ or foot ulcer\$ or (feet adj ulcer\$) or stasis ulcer\$).ti,ab.
 32 or/30-31
 33 29 and 32

Appendix 3. Ovid EMBASE search strategy

1 exp ANALGESIA/
 2 exp Analgesic Agent/
 3 exp CAPSAICIN/
 4 capsaicin.ti,ab.
 5 exp Opiate/
 6 opioid\$.ti,ab.
 7 exp Nonsteroid Antiinflammatory Agent/
 8 (non steroidal anti-inflammator\$ or NSAID\$).ti,ab.
 9 or/1-8
 10 exp Topical Drug Administration/
 11 (topical or local).ti,ab.
 12 or/10-11
 13 9 and 12
 14 exp Local Anesthetic Agent/
 15 ((topical or local) adj3 (anaesthe\$ or anesthe\$)).ti,ab.
 16 ((topical or local) adj3 analges\$).ti,ab.
 17 or/13-16
 18 exp Wound Dressing/
 19 exp Hydrogel Dressing/
 20 exp Hydrogel/
 21 exp Alginic Acid/
 22 (dressing\$ or hydrocolloid\$ or alginate\$ or hydrogel\$ or foam or bead or film or films or tulle or gauze or non-adherent or non adherent).ti,ab.
 23 exp Ointment/
 24 (ointment\$ or cream\$1 or gel\$1).ti,ab.
 25 or/18-24
 26 exp Pain/
 27 pain\$.ti,ab.
 28 or/26-27
 29 25 and 28
 30 17 or 29
 31 exp Leg Ulcer/
 32 (varicose ulcer\$ or venous ulcer\$ or leg ulcer\$ or foot ulcer\$ or (feet adj ulcer\$) or stasis ulcer\$).ti,ab.
 33 or/31-32
 34 30 and 33

Appendix 4. EBSCO CINAHL search strategy

S31 S27 and S30

S30 S28 or S29

S29 TI (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or feet N3 ulcer* or stasis ulcer) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or feet N3 ulcer* or stasis ulcer)

S28 Leg Ulcer

S27 S16 or S26

S26 S22 and S25

S25 S23 or S24

S24 TI pain* or AB pain*

S23 (MH "Pain+")

S22 S17 or S18 or S19 or S20 or S21

S21 TI (ointment* or cream* or gel or gels) or AB (ointment* or cream* or gel or gels)

S20 (MH "Ointments")

S19 TI (dressing* or hydrocolloid* or alginate* or hydrogel* or foam or bead or film or films or tulle or gauze or non-adherent or non adherent) or AB (dressing* or hydrocolloid* or alginate* or hydrogel* or foam or bead or film or films or tulle or gauze or non-adherent or nonadherent)

S18 (MH "Alginates")

S17 (MH "Bandages and Dressings+")

S16 S12 or S13 or S14 or S15

S15 TI (topical N3 analges* or local N3 analges*) or AB (topical N3 analges* or local N3 analges*)

S14 TI (topical N3 anaesthe* or topical N3 anesthe* or local N3 anaesthe* or local N3 anesthe*) or AB (topical N3 anaesthe* or topical N3 anesthe* or local N3 anaesthe* or local N3 anesthe*) S13(MH "Anesthetics, Local+")

S12 S8 and S11

S11 S9 or S10

S10 TI (topical or local) or AB (topical or local)

S9 (MH "Administration, Topical+")

S8 S1 or S2 or S3 or S4 or S5 or S6 or S7

S7 TI (non steroidal anti-inflammatory* or NSAID*) or AB (non steroidal anti-inflammatory* or NSAID*)

S6 (MH "Antiinflammatory Agents, Non-Steroidal+")

S5 TI opioid* or AB opioid*

S4 TI capsaicin or AB capsaicin

S3 (MH "Capsaicin")

S2 (MH "Analgesics+")

S1 (MH "Analgesia+")

WHAT'S NEW

Last assessed as up-to-date: 9 May 2012.

Date	Event	Description
6 June 2012	New search has been performed	Three new trials identified. One included for this update (Arapoglou 2011) and two added as awaiting assessment (Claeys 2011 ; Mosti 2010).
6 June 2012	New citation required but conclusions have not changed	Third update, new search, no change to conclusions.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 2, 1999

Date	Event	Description
11 March 2010	New citation required and conclusions have changed	Two additional studies included (Gottrup 2008; Romanelli 2009a).
11 March 2010	New search has been performed	2nd update, new searches.
11 October 2008	New search has been performed	Converted to new review format.
7 November 2002	New citation required and conclusions have changed	Substantive amendment, 5 additional trials included

CONTRIBUTIONS OF AUTHORS

MB and EAN developed the protocol, identified papers and extracted data for the original review. Both MB and EAN drafted the review, sifted the updated searches and contributed to the writing of the first and second review updates. For this, third, update, MB and MMSJ: appraised and data abstracted selected trial reports identified for inclusion, and drafted the update. MB undertook the statistical and narrative synthesis for this update. MB is the guarantor of the review.

Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review and review update prior to submission.

Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the review and the updated review.

Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section for the update.

DECLARATIONS OF INTEREST

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- NIHR Programme Grants for Applied Research, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bandages; *Debridement; Administration, Topical; Analgesics [*administration & dosage]; Anesthetics, Local [*therapeutic use]; Ibuprofen [administration & dosage]; Leg Ulcer [complications]; Lidocaine [administration & dosage; therapeutic use]; Ointments; Pain [drug therapy; etiology]; Prilocaine [administration & dosage; therapeutic use]; Randomized Controlled Trials as Topic; Varicose Ulcer [complications; *therapy]

MeSH check words

Humans