Topical Analgesic and Local Anesthetic Agents for Pain Associated with Chronic Leg Ulcers: A Systematic Review

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GENERAL PURPOSE: To provide information about the effectiveness of topical analgesic and local anesthetic agents for reducing pain associated with chronic leg ulcers.

TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant will:

1. Distinguish adverse reactions to topical analgesics and local anesthetic agents.
2. Evaluate the effectiveness of topical analgesics and local anesthetic agents for pain associated with chronic leg ulcers.
3. Identify substances used as topical analgesics and local anesthetic agents and the application of those agents.

ABSTRACT

OBJECTIVE: To examine the evidence related to the effectiveness of topical analgesic and topical local anesthetic agents for reducing pain associated with chronic leg ulcers.

METHODS: A systematic search and review of the literature were undertaken using key search terms such as leg ulcers, topical anesthetics, topical analgesics, and pain. Six databases were electronically searched for articles published between January 1990 and August 2019.

RESULTS: A total of 23 articles were identified that met the inclusion criteria. Data were extracted using content analysis. Most of the included studies were randomized controlled trials; however, the reported methodology for most of studies was poor, so the validity and reliability of the evidence are uncertain. Lidocaine/prilocaine cream, ibuprofen foam, and morphine gel were the most examined topical agents. Lidocaine/prilocaine cream significantly improved wound-related pain compared with all other studied agents. For topical analgesic agents, ibuprofen foam reduced chronic leg ulcer pain significantly, whereas morphine gel was ineffective.

CONCLUSIONS: Lidocaine/prilocaine cream and ibuprofen foam are effective agents for reducing wound-related pain associated with chronic leg ulcers. Effective use of topical agents could reduce the need for systemic pain relief agents, mitigating potential adverse effects, while giving clinicians another treatment option to manage wound-related pain associated with chronic leg ulcers.

KEYWORDS: analgesic, chronic ulcer, ibuprofen foam, lidocaine/prilocaine cream, leg ulcers, local anesthetic, morphine gel, pain, topical

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INTRODUCTION

Pain associated with chronic leg ulcers can be significant and impact wound healing and health-related quality of life. Although oral pain relief strategies are available, these are sometimes ineffective. Pain that lasts or recurs for more than 3 months is considered chronic and may result in the high consumption of oral opiates and other pain relievers, which can lead to misuse and the development of adverse effects, highlighting the need for alternative pain management strategies. Topical pain relief medications may be a promising alternative for the management of chronic painful leg ulcers.

Two previous reviews[1,2] have reported on the use of topical agents and dressings for the management of pain associated with debridement of chronic leg ulcers. Their findings suggest that topical lidocaine/prilocaine cream may be useful for reducing acute pain in the context of leg ulcer debridement and that ibuprofen is effective in reducing chronic leg ulcer pain. As suggested by Briggs et al,[1] there is a considerable lack of data regarding the effect of topical agents on leg ulcer healing and long-term use, causing them to recommend further research in this area.

Since Briggs et al's 2012 review,[1] the body of evidence for the use of topical analgesia and anesthetics for the management of wound-related pain associated with chronic leg ulcers has continued to grow. The purpose of this review is to assess whether topical anesthetic or local analgesic agents confer any benefit for these patients.

METHODS

A systematic approach informed by Pare and Kitsiou[3] was used for this review to ensure relevant literature was identified. The clinical problems that guided the literature review are as follows: (1) chronic leg ulcers are painful; (2) oral pharmacologic strategies for the treatment of wound-related pain associated with chronic leg ulcers are not always effective; and (3) topical agents and dressings may be useful in managing pain associated with chronic leg ulcers. These clinical problems led to the following question: In patients with chronic leg ulcers, is the application of topical local anesthetics or analgesics effective in reducing pain?

Search Strategy

An extensive literature review was conducted using the following electronic databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Joanna Briggs Institute, PubMed, and the Cochrane Library. To ensure that relevant literature had not been missed during the electronic search, authors hand-searched international consensus documents and position statements related to wound management and their reference lists.

The dates of the search ranged from January 1990 to August 2019. This time period was designed to predate the induction of lidocaine/prilocaine cream into the Australian Register of Therapeutic Goods in August 1991[4] and its approval by the US FDA in 1992.[5] Further, the use of topical opioids were first reported in the early 1990s.[6]

Search terms and combinations were as follows:

1. exp Foot Ulcer/ or Leg Ulcer/ or Varicose Ulcer/
2. (venous ulcer$ or varicose ulcer$ or arterial ulcer$ or mixed ulcer$ or leg ulcer$ or foot ulcer$ or stasis ulcer$ or (feet adj ulcer$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Anesthetics, Local/
5. Lidocaine/
6. Prilocaine/
7. topical local an?esthetics$.mp.
8. lidocaine.mp.
9. prilocaine.mp.
10. EMLA.mp.
11. eutectic mixture local an?esthetic$.mp.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Analgesics, Opioid/
14. exp Analgesics/
15. Administration, Topical/
16. 14 and 15
17. Anti-Inflammatory Agents, Non-Steroidal/
18. morphine.mp.
19. amitriptyline.mp.
20. capsaicin.mp.
21. ketamine.mp.
22. NSAIDs.mp.
23. non-steroidal anti-inflammator$.mp.
24. topical anti-inflammator$.mp.
25. 13 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 12 or 25
27. exp Pain/
28. pain$.mp.
29. 27 or 28
30. 3 and 26 and 29
31. limit 30 to yr="2018 - Current"

Eligibility and Quality Assessment

Titles, abstracts, and articles were screened against the following inclusion criteria:

- studies investigating topical local anesthetics lidocaine or prilocaine and topical analgesic agents such as ketamine, nonsteroidal anti-inflammatory drugs, opioids, tricyclic antidepressants (amitriptyline), or capsaicin on participants with chronic leg ulcers

• wound-related pain associated with chronic leg ulcers as a primary or secondary outcome
• studies where the topical local anesthetic or topical analgesic agent was the intervention or the control
• studies where at least one-third of participants had chronic leg ulcers
• human, adult, peer-reviewed studies published in the English language

Case series and case reports were excluded. In addition, even though tetracaine 0.5%/adrenaline 0.05%/cocaine 11.8% and lidocaine/epinephrine 0.1%/tetracaine 0.1% also provide anesthesia to nonintact skin, the evidence reports concerns regarding their toxicity and expense,[7] and therefore studies evaluating these products were not included.

Methodology assessment was guided by the CONSORT (Consolidated Standards of Reporting Trials) guidelines,[8] Critical Appraisal Skills Programme checklists,[9] and the wound component of the Cochrane Risk of Bias Tool.[10]

RESULTS

The literature review identified a total of 406 articles. The number identified in each database was as follows: MEDLINE, 69; EMBASE, 91; CINAHL, 35; Joanna Briggs Institute, 7; Cochrane, 6; and PubMed, 198. Sixteen additional articles were identified through hand searching of international consensus documents and position statements. The full texts of five studies[11–15] could not be obtained despite repeated attempts and were therefore not included.

A total of 23 articles met the inclusion criteria and were included in the full-text review (Figure 1). These studies were classified into two major categories: topical analgesics (Table 1) and topical local anesthetics (Table 2). There were 19 randomized controlled trials (RCTs), one quasi-experimental study, two crossover studies, and one retrospective, observational medical record review (Figure 2). One of the included articles[16] reported a subanalysis from a previous study. Topical analgesics were evaluated in 10 articles: ibuprofen foam was the intervention in seven articles, and morphine gel was evaluated in three articles. Local anesthetics were the interventions in 13 studies.

The majority of studies (n = 20) were conducted in Europe, most commonly in Sweden (n = 5). Outcome measurement time points ranged from 10 minutes to 12 weeks. Current research relating to topical local anesthetic or analgesic agents for painful chronic leg ulcers was limited; the majority of the literature was more than 5 years old (83%).

Category 1: Topical Analgesic Agents

For all studies investigating topical analgesic agents, pain was the primary outcome reported and a variety of pain assessment tools were used to assess pain, including the numeric rating scale, visual analog scale, visual rating sale, and numeric box scale. Venous leg ulcers were the predominant ulcer type, and the surface areas of leg ulcers were less than 54 cm^2. Wound size was reflected in the inclusion criteria in all of the studies except one.[17]

In six of the seven studies investigating ibuprofen foam, there was a statistically significant reduction in wound-related pain when compared with a placebo or standard care; the remaining study showed a reduction in wound-related pain compared with standard care. The dose of ibuprofen was the same in all studies (0.5 mg/cm^2 = 112.5 mg), although the dose was not reported in one study.[16] Half of the studies compared ibuprofen foam with a placebo, and the other half with standard care. Although half of the studies in this review had large sample sizes (range, 120–835), some had fewer than 25 participants.[17,18] These small studies were not sufficiently powered to show a difference, likely contributing to type II error. Only four of the studies investigating ibuprofen reported an a priori sample size calculation.[16,19–21]

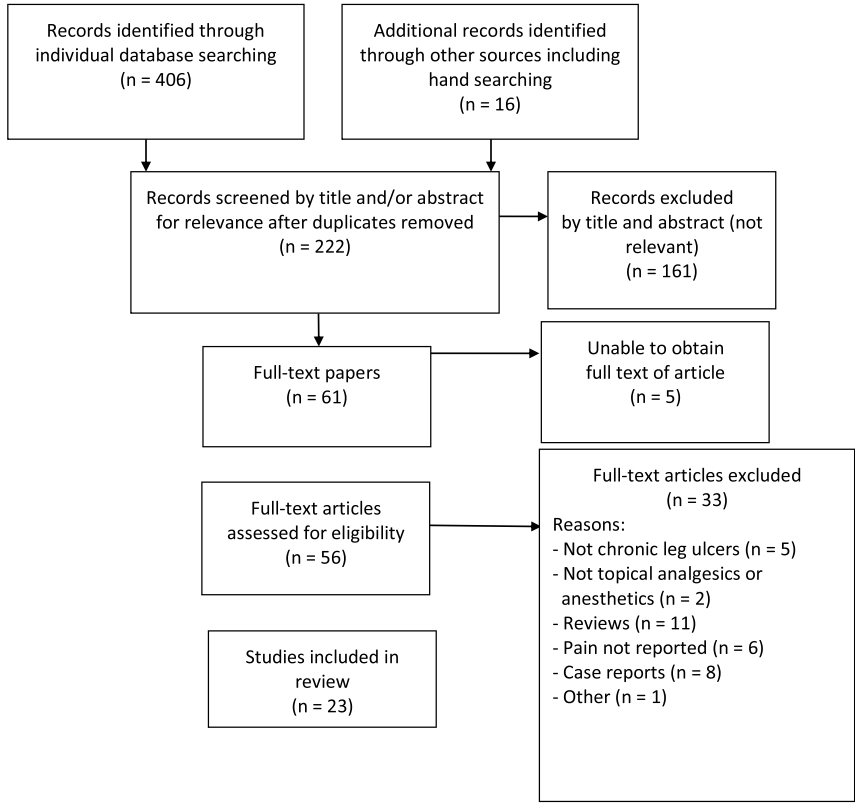
In general, the reporting of methodologies was poor in that important elements, such as method of randomization, allocation concealment, loss to follow-up, intention-to-treat analysis, blinding, and baseline comparability were not included. Gottrup et al[21] was the only group that reported methodology appropriately against recommended criteria,[8–10] so their study's level of bias could be determined more accurately.

Five of the seven studies in the ibuprofen group reported adverse events[16,17,19–21] related specifically to the intervention agent. These included local reactions such as infection, eczema, blisters, increased pain and wound size, erythema, bleeding, and periulcer deterioration. In one study, no adverse events relating to ibuprofen foam were reported during the study period,[18] and the final study[22] did not report on adverse effects at all.

It is unclear whether topical morphine gel was effective in reducing pain associated with venous, arterial, or mixed leg ulcers because of the small sample sizes in the three related studies. Morphine gel (morphine sulfate injection mixed with a hydrogel) is usually applied daily to painful chronic or palliative wounds for pain relief,[23,24] although twice-daily application is often required.[25] All studies investigating morphine gel used a placebo gel as the comparator.[25–27] A range of doses were reported, including 0.5 mg/cm^2, 10 mg, and 0.5%/g. All of these studies had fewer than 25 participants (Table 1), so type II error was likely. None reported undertaking a sample size calculation a priori, and the reporting of methodologies was poor.

All three studies investigating morphine gel reported adverse events associated with the intervention.[25–27] Local adverse reactions included itching, burning pain,

Figure 1. PRISMA FLOW DIAGRAM OF SEARCH OUTCOMES



stinging, eczema, ineffective pain relief, and infection. Systemic adverse reactions included dizziness, nausea, vomiting, and drowsiness.

Category 2: Topical Local Anesthetic Agents

Twelve studies investigated lidocaine/prilocaine cream (EMLA 5%) in the context of debridement of chronic leg ulcers (Table 2), and one study[28] investigated lidocaine/prilocaine cream for chronic pain associated with chronic leg ulcers. Pain was the primary outcome in all but two studies,[29,30] and the visual analog scale was the predominant pain assessment tool. The findings in this group suggest that lidocaine/prilocaine cream was effective in reducing wound-related pain associated with debridement of chronic leg ulcers in all but two studies,[31,32] although the reporting of methodologies in all but one study[28] was poor.

Venous leg ulcers were again the predominant leg ulcer type in studies included in this group. The surface area of each chronic leg ulcer was less than 50 cm^2 (86%) in most of the studies.

Nine studies compared lidocaine/prilocaine cream 5% with either a topical placebo,[29,33–35] lidocaine 10% spray,[31] lidocaine/prilocaine cream 2%,[32] or nitrous oxide-oxygen mixture inhalation;[36,37] the comparator in one study was unknown.[38] One RCT compared lidocaine/prilocaine cream to usual wound care.[28] One retrospective, observational study[39] evaluated the effectiveness of lidocaine/prilocaine cream 5% in a sample of 1,084 participants with a variety of wound types, including chronic leg ulcers. The number of total applications of the cream ranged from 1 to 28, and most studies applied it 30 minutes prior to debridement. Two studies extended the application time to 45 minutes,[29,35] and two studies to 60 minutes.[39,40] One study applied lidocaine/prilocaine cream for only 10 minutes,[31] and another repeated daily 24-hour doses for 4 weeks.[28] The maximum dose was 10 g in 69% of the studies.[28,30,32–35,37,40] However, in the medical record review conducted by Blanke and Hallern,[39] some participants received up to 150 g of lidocaine/prilocaine cream topically.

Findings from three studies measuring plasma concentrations of lidocaine and prilocaine in the 5% and 2% creams indicated that toxic levels are not reached after repeated applications for debridement.[30,32,33] In Enander et al,[32] plasma concentrations were higher for individuals with arterial leg ulcers compared with venous leg ulcers. However, this finding is not supported by a more recent study by Effendy et al,[30] which indicated that ulcer type does not have any affect on plasma concentrations, although leg ulcer size did have a significant impact.

Table 1. CHARACTERISTICS OF INCLUDED ARTICLES RELATED TO TOPICAL ANALGESIC AGENTS

Article	Design	Sample and Setting	CLU Type	Outcomes (Primary; Secondary)	Intervention and Dose	Results
Fogh et al, 2012[20]	Multicenter double-blind RCT	n = 120; hospitals, wound clinics, and community setting	Venous	Pain as measured with the NRS; healing rates, periulcer condition, local and adverse reactions	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 vs placebo foam	Pain relief was significantly greater in the intervention group (P = .04)
Arapoglou et al,[a] 2011[22]	Secondary analysis of data from a multicenter, parallel-group RCT	n = 688; 12 countries,184 centers in inpatient and outpatient departments	Venous, arterial, mixed, vasculitis and trauma	Pain as measured with the NRS and 5-point scale (relief); none	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 vs standard care	Statistically significant improvement in pain relief in all wound etiology subgroups compared with standard care (P < .0001)
Romanelli et al, 2009[16]	A subanalysis of a multicenter, open, comparative, parallel-group RCT	n = 185; 34 outpatient clinics	Venous, arterial, mixed, vasculitis	Pain as measured with the NRS and VAS; QOL, safety	Ibuprofen foam dressing 15 × 15 vs standard care; dose: NR	Intervention reduced pain intensity in all common leg ulcer etiologies
Domenech et al, 2008[19]	Multicenter, comparative, parallel-group RCT	n = 853; 12 countries, 184 centers in inpatient and outpatient departments	Venous, arterial, mixed and diabetic	Pain as measured with the VAS; QOL, local and adverse reactions, oral medications, exudate, healing rates, periwound condition	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 vs standard care	Total pain relief scores were significantly in favor of the treatment group (P < .0001); mean pain intensity reduction was significantly greater in the treatment group (P < .0001)
Gottrup et al, 2008[21]	Multicenter, double-blind, parallel-group RCT	n = 122; setting NR	Venous	Pain as measured with the VRS and NBS; QOL, local and adverse reactions	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 vs placebo foam	Statistically significant and sustained improvement in pain relief (P < .05) and pain intensity (P = < .001) in intervention group
Sibbald et al, 2007[18]	Open comparative and prospective, block- randomized study	n = 24; outpatient wound clinic	Painful CLUs	Pain as measured with the VAS and NBS; healing rates, periwound condition, nonviable tissue	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 vs standard care	Intervention decreased acute (P = .0405) and chronic wound pain (P = .0217) significantly compared with standard care
Jorgensen et al, 2006[17]	A single-blind crossover study	n = 10 + 2; A wound-healing outpatient center	Venous	Primary outcome: pain as measured with the VRS and NBS; secondary outcomes: safety, local and adverse reactions	Ibuprofen foam dressing 15 × 15; dose: 0.5 mg/cm^2 every 2nd or 3rd day vs foam without ibuprofen	Pain levels were significantly better during treatment with ibuprofen foam than before or after treatment with ibuprofen foam ($P \leq .0001$; $P \leq .005$)
Bastami et al, 2012[26]	Single center, double-blind, placebo-controlled, crossover pilot RCT	n = 21; a dermatology department and primary care centers	Venous; two CLUs not defined	Primary outcome: pain as measured with the VAS; secondary outcomes: local and adverse reactions	Morphine gel 0.5 mg/cm^2 for CLUs <1 cm^2 1 to 3 mg/mL vs placebo gel	No difference in pain between groups (P = .172)

(continues)

Table 1. CHARACTERISTICS OF INCLUDED ARTICLES RELATED TO TOPICAL ANALGESIC AGENTS, CONTINUED

Article	Design	Sample and Setting	CLU Type	Outcomes (Primary; Secondary)	Intervention and Dose	Results
Jansen et al, 2009[25]	Double-blind, placebo-controlled, three-way crossover pilot RCT	n = 10; two dermatology outpatient departments	Arterial	Pain as measured with the NRS; local and adverse reactions	Morphine gel (0.5% 1 g in hydrogel) compared with (1) morphine s/c infusion (5 mg) and placebo gel (hydrogel), (2) placebo gel plus s/c morphine infusion 5 mg, or (3) placebo gel plus s/c placebo infusion	No pain relief for participants with arterial CLUs
Vernassiere et al, 2005[27]	Prospective, bicenter, controlled, double-blind RCT	n = 24; two dermatology outpatient departments	Venous, arterial, and mixed	Pain as measured with the NRS; systemic tolerance, homogeneity of the morphine mixture, CLU characteristics	Morphine gel (10 mg morphine/gel) vs placebo gel	No statistical significance regarding the efficacy of topical morphine relating to pain

Abbreviations: CLUs, chronic leg ulcers; NBS, numerical box scale; NR, not reported; NRS, numerical rating scale; QOL, quality of life; RCT, randomized controlled trial; s/c, subcutaneous; VAS, visual analog scale; VRS, verbal rating scale.
[a]Arapoglou et al[22] is a secondary analysis of a previous study by Domenech et al.[19]

More than half of the studies reported minor adverse reactions, which were largely local skin reactions such as burning, pallor, erythema, itching, stinging, and edema.[28,29,32–34,37–39] No major adverse reactions to lidocaine/prilocaine cream were reported.

In the majority of studies, the sample sizes were small (range, 10–110), and there were fewer than 70 participants in 9 of 13 studies in this group. Only two studies reported undertaking a sample size calculation a priori.[35,37] However, a statistically significant reduction in pain during debridement was observed in all but two of the studies investigating debridement,[31,32] and a statistically significant reduction in chronic wound-related pain during and after dressing change was observed in one study.[28]

Assessment of Methodological Quality

Nineteen of the 23 studies included in this review were RCTs. The methodological quality of the RCTs related to topical analgesic and anesthetic agents is presented in Tables 3 and 4, respectively.

Two studies, one in the topical analgesic group[17] and one in the topical local anesthetic group,[36] were crossover studies. One study in the topical local anesthetic group[30] was a quasi-experimental study, and this was the only one that reported baseline comparability.[30] One study used a crossover design to compare ibuprofen foam with placebo foam as a primary dressing for painful chronic leg ulcers;[17] another compared lidocaine/prilocaine cream and nitrous oxide-oxygen mixture inhalation[36] as treatments for chronic leg ulcers before debridement. Two RCTs[32,33] included data from small preliminary observational studies. One investigated the application times of lidocaine/prilocaine cream;[33] the other, plasma concentrations.[32]

DISCUSSION

The findings suggest that ibuprofen foam may be successful in reducing chronic leg ulcer pain; however, there were insufficient data to suggest similar effectiveness for the application of morphine gel. Lidocaine/prilocaine cream was the local anesthetic agent used in all studies in the topical anesthetic group and was applied to chronic leg ulcers to prevent acute pain associated with debridement in all but one. These findings suggested that lidocaine/prilocaine cream was effective when used for this purpose. One study suggests that lidocaine/prilocaine cream may also be effective in reducing chronic pain associated with chronic leg ulcers when used daily as a primary dressing.

The majority of the studies in this review did not conform to CONSORT reporting requirements,[8] and therefore the risk of selection, detection, and performance biases often could not be determined. The insufficient information provided in most of the articles leads to the assumption of poor trial quality, but this cannot truly be assessed.[41] Nevertheless, only 43% of the RCTs blinded the participants and investigators, 12% reported how their allocation sequence was generated, and only 30% reported allocation concealment. The risk of attrition bias was also high, with fewer than 30% of RCTs reporting whether participants were accommodated in an intention-to-treat analysis and fewer than 15% reporting participant withdrawals. One study in this group had a dropout rate of 29%. Further, most studies included in this review were older than 5 years, although

TABLE 2. CLASSIFICATION OF INCLUDED STUDIES RELATED TO TOPICAL LOCAL ANESTHETIC AGENTS

Article	Design	Sample and Setting	CLU Type	Outcomes (Primary; Secondary)	Intervention and Dose	Results
Purcell et al, 2017[28]	RCT	N = 60; six clinics in a community setting	Venous, arterial, mixed, foot ulcers	Pain as measured with the NRS; wound healing, QOL	Lidocaine/ prilocaine cream, 1–2 g per 10 cm^2 versus usual wound care	During dressing change, mean pain scores across the 4-wk intervention period were significantly lower in the intervention (mean, 3.39 [SD, 2.16]) versus control (mean, 4.82 [SD, 2.27]; $P = .02$).
Traber et al, 2017[36]	Prospective, controlled, single-center, crossover design study	N = 21; specialist vein clinic outpatient unit	Venous, foot ulcers	Pain as measured with the VAS; pain after debridement, duration of treatment sessions	Lidocaine/prilocaine cream, NR dose for 30 min versus 50% N_2O/O_2 on demand	Lidocaine/prilocaine cream was more effective for reducing pain during sharp debridement of CLUs compared with inhaled gas ($P = .001$)
Effendy et al, 2015[30]	Quasi- experimental study	N = 25; five outpatient departments	Venous, mixed, vasculitic ulcers at least 50 cm^2	Plasma concentrations; pain as measured with the VAS	Lidocaine/prilocaine cream 10 g daily	Plasma concentrations were similar on days 1 and 10 for lidocaine, prilocaine, and both; ulcer size had a significant effect on peak values ($P = < .01$); Pain was significantly lower by day 10 ($P = < .01$)
Cuomo et al, 2014[31]	RCT	N = 50; setting NR	Venous	Pain as measured with the VAS; none	Lidocaine/prilocaine cream (dose NR) applied for 10 min versus topical lignocaine 10% spray (1 spray every 3 cm^2; each spray equals 10 mg)	Spray has a more immediate anesthetic effect (although superficial); lidocaine/ prilocaine cream penetrates deeper into the tissues when applied under occlusion with film, but requires a longer waiting time
Claeys et al, 2011[37]	Multicenter, prospective open-label pilot RCT	N = 4; setting NR	Venous, arterial, mixed	Pain as measured with the VAS and VRS; healing rates and quality of debridement	N_2O/O_2 mixture inhalation, dose: 9–12 L, 15 min prior to debridement versus lignocaine/prilocaine cream, dose: maximum 10 g for 30 min	Lignocaine/prilocaine cream was superior to N_2O/O_2 inhalation in reducing pain ($P = < .001$)
Blanke et al, 2003[39]	Retrospective observational study	N =1084, including CLUs and diabetic ulcers (n = 360); CLU size ranged between 5 – 360 cm^2	CLUs, diabetic ulcers, decubitus ulcers, abscess revisions, anal and coccyx fistulae, postoperative wounds, burns	Pain (measure -NR); adverse effects, dose, duration of application	Lidocaine/prilocaine cream, dose: 3 – 150 g per application; duration of application: 45 – 60 min	For all participants except three (arterial CLUs), analgesia was adequate for debridement; premature removal of Lidocaine/prilocaine cream was not required

(continues)

TABLE 2. CLASSIFICATION OF INCLUDED STUDIES RELATED TO TOPICAL LOCAL ANESTHETIC AGENTS, CONTINUED

Article	Design	Sample and Setting	CLU Type	Outcomes (Primary; Secondary)	Intervention and Dose	Results
Rosenthal et al, 2001[34]	Multicenter, double-blind, placebo-controlled, parallel RCT	n = 101; four outpatient dermatology centers	Venous, arterial, mixed	Pain as measured with the VAS; local and adverse reactions	Lidocaine/prilocaine cream versus placebo cream; both doses approximately 2 g/10 cm^2, maximum of 10 g for 30 minutes (range: 25–37)	Lidocaine/prilocaine cream significantly reduced pain scores versus placebo ($P < .0001$)
Agrifoglio et al, 2000[35]	A double- masked, placebo- controlled RCT	n = 110; seven angiology and vascular surgery outpatient centers	Venous	Pain as measured with the VAS; clinician judgment for the difficulty of debridement	Lidocaine/prilocaine cream versus placebo cream; both doses approximately 2.5 g/10 cm^2, maximum of 10 g for 30 – 45 minutes	A statistically significant improvement in pain scores observed in the lidocaine/prilocaine cream group ($P < .00001$); clinicians found debridement less difficult to perform as a result ($P < .01$)
Lok et al, 1999[29]	Multicenter, double-blind, placebo RCT	N = 69; outpatient dermatology or phlebology departments	Venous	No. of debridements required to clean CLU; pain as measured with the VAS and duration of debridement, local and adverse reactions, plasma concentrations	Lidocaine/prilocaine cream versus placebo cream; dose for both, 1–2 g/10 cm^2, max 10 g applied to CLU for 30 to 45 min before debridement	Lidocaine/prilocaine cream significantly decreased pain scores for debridement by 50% compared with placebo ($P = .003$)
Holst et al, 1998[40]	Single-blind, three-armed, parallel group RCT	n = 59; inpatients	Venous, arterial, diabetic	Pain as measured with the VAS; duration of the procedure	Lidocaine/prilocaine cream application times compared at different time points (10, 20, or 60 min of treatment); dose: 2 gm/10 cm^2, maximum 10 g	Pain intensity decreased significantly with increased lidocaine/prilocaine cream application time ($P = .001$)
Hansson et al, 1993[38]	Open, repeat dose, parallel-group RCT	n = 43; outpatient, multicenter dermatology and surgery departments	Venous	Pain as measured with the VAS; bacterial load, debridement efficacy, healing rates, local and adverse reactions	Lidocaine/prilocaine cream 5%; dose, thick layer, maximum 5 gm for 30 min versus unknown	Lidocaine/prilocaine cream significantly reduced pain scores from debridement ($P = .0008$); and postdebridement pain versus control group ($P = .021$)

(continues)

TABLE 2. CLASSIFICATION OF INCLUDED STUDIES RELATED TO TOPICAL LOCAL ANESTHETIC AGENTS, CONTINUED

Article	Design	Sample and Setting	CLU Type	Outcomes (Primary; Secondary)	Intervention and Dose	Results
Enander et al, 1990[32]	Part 1: observational study of plasma concentrations; part 2 double-blind, four-period crossover study of analgesic effect	Part 1 n = 8; part 2 n = 10; single site setting NR	Venous, immunologic origin	Two primary outcomes: plasma concentrations and pain as measured with the VAS; adverse reactions	Part 1: 8–10 g of lidocaine/prilocaine cream 2% applied for 60 min; part 2: lidocaine/prilocaine cream 2% versus 5% - each participant received both concentrations once during first and second treatment and once during third and fourth treatment; dose: a thick layer for 30 min before debridement	Part 1: maximum individual plasma concentrations - Lidocaine: 205 ng/mL Prilocaine: 79 ng/mL, 20 times lower than those associated with toxicity Part 2: No difference between the analgesic effect of 2% and 5% lidocaine/prilocaine cream; pain intensity was lower during the third and fourth debridement compared to first and second ($P = .039$)
Holm et al, 1990[33]	Part 1: Open, non-randomized study; part 2: double-blind, placebo-controlled RCT	Part 1, n = 50; part 2, n = 30; outpatient department	Venous, arterial	Pain as measured with the VAS; plasma concentrations, local and adverse reactions	Lidocaine/prilocaine cream on all participants; Dose: 5 – 10g; Application times: 10, 20 and 30 min	Part 1: Of the 50 participants, 41 reported no or slight pain; part 2: lidocaine/prilocaine cream significantly reduced pain scores versus placebo group ($P < .01$)

Abbreviations: CLUs, chronic leg ulcers; LMX-4, liposomal lidocaine cream N_2O/O_2, Nitrous oxide/oxygen mixture; NR, not reported; NRS numerical rating scale; QOL, quality of life; RCT, randomized controlled trial; VAS, visual analogue scale; VRS, verbal rating scale.

it is recognized that only valuing recent evidence over robust evidence may misinform practice.[42]

To improve the validity of a clinical trial, an appropriate sample size is important. A small sample size increases the potential for type II error, resulting in the decreased applicability and utility of findings in the clinical setting.[43] Conversely, clinical trials with larger sample sizes can result in wasted resources, decreasing the validity or accuracy because of low response rates and difficulty maintaining data quality.[43] In this review, 14 of the 23 studies had a sample size of fewer than 100. All 3 studies investigating morphine gel had sample sizes of fewer than 25, as did 2 of the 7 investigating ibuprofen foam and 9 of the 13 investigating lidocaine/prilocaine cream. Even though the retrospective, observational medical record review[39] included in this

Figure 2. CLASSIFICATION OF INCLUDED STUDIES

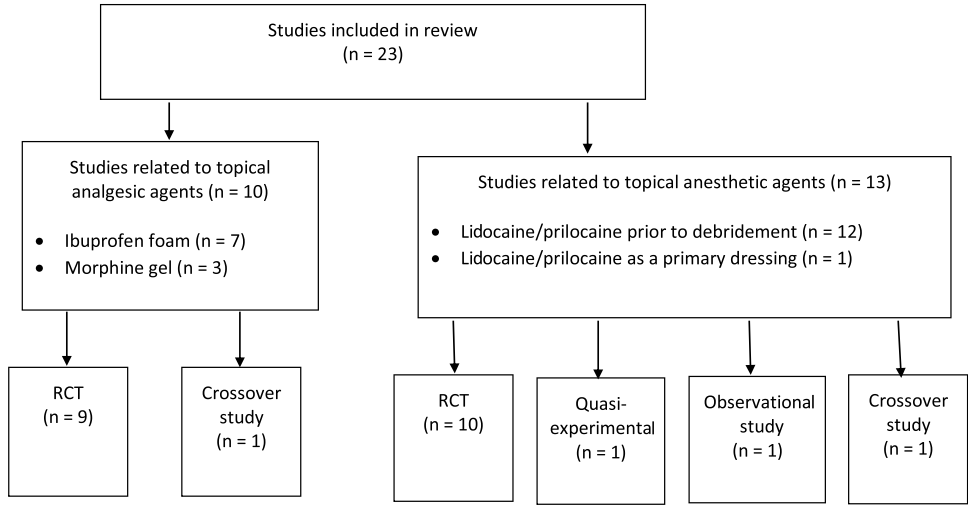


Table 3. ASSESSMENT OF METHODOLOGICAL QUALITY OF RANDOMIZED CONTROLLED TRIALS: TOPICAL ANALGESIC AGENTS

RCT	Randomized (Method)	Allocation Concealed	Loss to Follow-up	ITT Analysis	Double-blind	Baseline Comparability
Fogh et al, 2012[20]	No	Yes (telephone system)	27	NR	Yes	Yes—age, sex, height, weight, CLU size, ulcer duration, and compression type; CLU size statistically different at baseline ($P = .0009$)
Arapoglou et al, 2011[22]	No	NR	NR	NR	No	Yes—CLU type
Romanelli et al, 2009[16]	Yes (block randomization)	NR	22	Yes	No	Yes—age; sex; CLU size, duration, and type
Domenech et al, 2008[19]	No	Yes (sealed envelopes)	87	Yes	No	Yes—age, sex, CLU duration and size
Gottrup et al, 2008[21]	Yes (block randomization)	Yes (sealed envelopes)	29	Yes	Yes	Yes—age, sex, height, weight, medical history
Sibbald et al, 2007[18]	Yes (block randomization)	NR	1	NR	No	Yes—age; CLU duration, size, and type; pain medications and intensity; wound bed; periwound skin
Bastami et al, 2012[26]	No	NR	4	NR	Yes	NR
Jansen et al, 2009[25]	No	NR	1; 17 before baseline	NR	Yes	NR
Vernassiere et al, 2005[27]	No	NR	10	Yes	Yes	Yes—sex, age, CLU type and duration, pain intensity

Abbreviations: CLU, chronic leg ulcer; ITT, intent to treat; NR, not reported; RCT, randomized controlled trial.

analysis had a very large sample size, the study design has other inherent methodological limitations that sample size alone could not overcome.

In this review, the findings related to topical analgesic and topical local anesthetic agents for the relief of chronic leg ulcer pain indicate that topical agents (except for morphine gel) are effective. What this review has added to the body of knowledge is that, to date, the only topical formulations used as primary dressings for chronic leg ulcer pain have been ibuprofen foam and morphine gel, and rarely, lidocaine/prilocaine cream. For decades, lidocaine/prilocaine cream has been the predominant and most long-standing topical pain reliever for operative pain associated with the debridement of chronic leg ulcers. Only recently has it been investigated as a primary dressing to relieve chronic wound-related pain.

Limitations

Language bias was a limitation of this review, and publication bias was unclear. Further, interviews with trial investigators may have assisted in assessing study quality more accurately;[41] this was not carried out.

Literature Gaps

Topical analgesics and anesthetics provide an important pain relief alternative when oral analgesia is ineffective or results in significant adverse effects. There are a limited number of studies that examine the use of these agents to manage chronic leg ulcer pain. Available studies are limited mostly by small sample sizes and poor methodological quality. Accurate assessment of methodological quality was disadvantaged by the poor reporting outlined in the available literature.

The strongest evidence available supports intermittent, short applications of lidocaine/prilocaine cream prior to debridement for operative pain relief, which has been shown to be systemically safe without negatively impacting wound healing. The evidence for the effectiveness of lidocaine/prilocaine cream in debridement, together with one pilot RCT using it as a primary dressing, suggest that it may be effective in managing chronic pain for individuals with chronic leg ulcers. This strategy would lead to reduced wound-related pain for longer periods, which in turn may have a positive impact on wound healing and health-related quality of life.

CONCLUSIONS

This review has identified limited, inconsistent evidence for the use of topical analgesics and topical local anesthetic agents to treat painful chronic leg ulcers. Although there is the need for further research regarding the use of topical agents to relieve chronic wound-related pain lidocaine/prilocaine cream and ibuprofen foam appear to be effective agents for reducing wound-related pain associated with chronic leg ulcers. The effective use of

Table 4. ASSESSMENT OF METHODOLOGICAL QUALITY OF RANDOMIZED CONTROLLED TRIALS: TOPICAL LOCAL ANESTHETIC AGENTS

RCT	Randomized (Method)	Allocation Concealed	Loss to Follow-up	ITT Analysis	Double-blind	Baseline Comparability
Purcell et al, 2017[28]	Yes	Yes	Yes	Yes	No	Yes—age; CLU type, duration, and surface area; sex; whether patients had sharp debridement and/or compression therapy; pain medications
Cuomo et al, 2015[31]	NR	NR	NR	NR	No	NR
Claeys et al, 2011[37]	Yes (block randomization)	Yes (centralized, randomized process)	12	Yes	No	Yes—age; sex; MMS, CLU type, size, and duration; nonviable tissue type; VAS; VRS
Rosenthal et al, 2001[34]	NR	NR	NR	Unclear	Yes	Yes—sex, age, weight, treatment duration, CLU size and duration, diabetes, analgesics. and antibiotics
Agrifoglio et al, 2000[35]	NR	NR	NR	NR	Yes	Yes—age, sex, weight
Lok et al, 1999[29]	No	No	NR	No	Yes	Yes—age, sex, CLU type and size
Holst et al, 1998[40]	NR	Yes (sealed envelopes)	NR	NR	Single-blind (assessors blinded to application time)	Yes—CLU size and duration
Hansson et al, 1993[38]	NR	Yes (sealed envelopes)	3	NR	No	Yes—age, sex, CLU size and location, diabetes, antibiotics
Holm et al, 1990[33]	No (part 2 ulcer)	No	No	NR	Yes (part 2)	Yes—CLU duration, location and size
Enander et al, 1990[32]	NR	NR	NR	NR	Yes—analgesic effect only	Yes—age; CLU size, type, and duration

Abbreviations: CLU, chronic leg ulcer; NR, not reported; MMS, Mini-Mental Score; RCT, randomized controlled trial; VAS, visual analog scale; VRS, verbal rating scale.

topical agents could reduce the need for systemic pain relief agents, mitigating potential adverse effects.

PRACTICE PEARLS

- Pain associated with chronic leg ulcers can be significant and impact wound healing and health-related quality of life.
- Topical lidocaine/prilocaine 5% cream is effective for relieving pain during the debridement of chronic leg ulcers.
- Topical lidocaine/prilocaine 5% cream and ibuprofen foam may be promising alternatives to oral pain medications to treat chronic wound-related pain.
- Evidence for the use of topical analgesics and local anesthetic agents to treat painful chronic leg ulcers is inconsistent. Further research is needed.

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