MAYO CLINIC

REVIEW

Topical Analgesics in the Management of Acute and Chronic Pain

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Abstract

Oral analgesics are commonly prescribed for the treatment of acute and chronic pain, but these agents often produce adverse systemic effects, which sometimes are severe. Topical analgesics offer the potential to provide the same analgesic relief provided by oral analgesics but with minimal adverse systemic effects. This article describes the results of a systematic review of the efficacy of topical analgesics in the management of acute and chronic pain conditions. A literature search of MEDLINE/PubMed was conducted using the keywords *topical analgesic* AND *chronic pain* OR *acute pain* OR *neuropathic pain* and focused only on individual clinical trials published in English-language journals. The search identified 92 articles, of which 65 were eligible for inclusion in the review. The most commonly studied topical analgesics were nonsteroidal anti-inflammatory drugs (n=27), followed by lidocaine (n=9), capsaicin (n=6), amitriptyline (n=5), glyceryl trinitrate (n=3), opioids (n=2), menthol (n=2), pimecrolimus (n=2), and phenytoin (n=2). The most common indications were acute soft tissue injuries (n=18), followed by neuropathic pain (n=17), experimental pain (n=6), osteoarthritis and other chronic joint-related conditions (n=5), skin or leg ulcers (n=5), and chronic knee pain (n=2). Strong evidence was identified for the use of topical diclofenac and topical ibuprofen in the treatment of acute soft tissue injuries or chronic joint-related conditions, such as osteoarthritis. Evidence also supports the use of topical lidocaine in the treatment of postherpetic neuralgia and diabetic neuropathy. Currently, limited evidence is available to support the use of other topical analgesics in acute and chronic pain.

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Oral medications, including opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), are commonly prescribed for the treatment of acute pain. In addition to these agents, various types of oral neuromodulators, such as certain antidepressants and anticonvulsants, are often prescribed for chronic pain. Although potentially effective in providing meaningful pain relief, oral administration of these systemic agents frequently results in adverse events (AEs), which may preclude their ongoing use and result in discontinuation. For example, oral opioids are associated with a wide variety of AEs that affect the central and peripheral nervous systems, including potentially fatal respiratory depression, addiction, pruritus, nausea, and constipation.[1-7] Use of oral NSAIDs also can result in serious AEs, including gastrointestinal bleeding, cardiovascular complications (such as hypertension and increased risk for myocardial infarction), and renal dysfunction or failure.[8-13] Salicylates, such as acetylsalicylic acid (aspirin), produce analgesic effects through a mechanism similar to that of other NSAIDs and, therefore, are associated with similar AE profiles.[14,15] In addition, aspirin has been closely linked to the development of Reye syndrome, a rare but often fatal pediatric syndrome.[16]

Topical analgesics were developed, in part, to provide the symptomatic benefits seen with oral agents but without the systemic AEs associated with oral analgesics. Topical administration of analgesics can produce clinically effective drug concentrations at a peripherally located site of injury or inflammation, without resulting in high systemic concentrations that may increase the likelihood of AEs.[17-20] Not all topical analgesics produce therapeutic effects strictly at peripheral sites of action. For example, topical application of opioids, such as morphine or fentanyl, produces analgesia by both central and peripheral mechanisms of action,[21] although systemic concentrations are low after topical administration.[20,21] Various factors influence the penetration and absorption of topical analgesics, including the biochemical properties of any adjuvants included in the topical formulation and interindividual variability in skin absorption.[21] Topical analgesic

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therapy is nonetheless a potentially valuable strategy in the management of a variety of conditions associated with acute or chronic pain, including acute soft tissue injuries, chronic musculoskeletal pain, and various neuropathic pain disorders.[18,22-28]

Three systematic reviews or meta-analyses have investigated the efficacy of topical NSAIDs in the treatment of musculoskeletal pain[18,22,23]; however, no systematic review or meta-analysis has been conducted to examine the efficacy of other topical analgesics for other indications. Thus, a systematic review was conducted to evaluate the efficacy of topical analgesic therapy in the management of acute and chronic pain conditions.

METHODS

A MEDLINE/PubMed search, covering the period from inception through August 2011, was conducted using the keywords *topical analgesic* AND *chronic pain* OR *acute pain* OR *neuropathic pain*. The keyword *postoperative pain* was not included in the search, which largely restricted the search to acute pain conditions other than postoperative pain. In addition, the search was restricted to English-language articles describing individual clinical trials (not reviews of published clinical trials) in humans (patients or healthy volunteers). Evidence for efficacy and tolerability of a specific topical analgesic was reviewed only if 2 or more published clinical trials were available for that drug, irrespective of indication; in other words, if a particular disease state was the focus of only one published clinical trial but the topical analgesic that was studied in that clinical trial was studied in at least one other clinical trial, then that clinical trial was included in the review.

RESULTS

Study Identification

The literature search identified a total of 92 articles, of which 65 were eligible for inclusion (Figure).[29-92] A total of 27 articles were excluded: 7 articles[93-99] described studies in which the analgesic was not administered topically; 6 articles[100-105] described clinical trials of nonpharmacologic treatments (ie, ice, heat, or practitioner advice); 5 articles[106-110] focused on analgesics that were studied in only 1 clinical trial; 3 articles[111-113] dealt with ophthalmic indications rather than acute or chronic pain; 3 articles[114-116] were reviews; 1 article[117] described an experimental study in which capsaicin was used as a stimulus rather than as a therapy; 1 article[118] described a mathematical modeling study; and 1 article[119] dealt with a pharmacokinetic study with no pain assessment.

Study Characteristics

Detailed information can be found in the Supplemental Table (available online at http://www.mayoclinicproceedings.org). The most commonly studied agents were NSAIDs (n=26),[30-32,37,39,51,52,54,58,61,64,71,72,74,78,80-82,84-91] followed by lidocaine (n=9),[33,36,40-43,55,65,83] capsaicin (n=6),[29,35,38,53,73,75] and amitriptyline (n=5).[45,47,59,67,68] Other agents studied included glyceryl trinitrate (n=3),[44,48,69] opioids (n=2),[50,60] menthol (n=2),[62,92] pimecrolimus (n=2),[28,49] and phenytoin (n=2).[66,70]

The most common indications were soft tissue injuries and related conditions (n=17),[30,32,37,48,50,54,57,63,66,71,74,81,85,86,89-91] followed by neuropathic pain (n=17),[29,34,36,38,40-43,47,59,65,67,72,73,78,82,87] experimental pain (n=6),[45,53,56,64,68,76] osteoarthritis and other joint-related conditions (n=5),[44,58,77,80,84] skin or leg ulcers (n=5),[33,51,52,60,70] and chronic knee pain (n=2).[31,62]

NSAIDs

The most widely studied topical NSAIDs included diclofenac (n=14),[30,32,37,39,54,58,61,63,74,80-82,84,91] ibuprofen (n=5),[31,52,71,79,85] ketoprofen (n=4),[54,86,89,90] piroxicam (n=2),[81,88] and indomethacin (n=2).[82,89]

Diclofenac

Acute Soft Tissue Injury. In a study involving 222 patients with minor sports injuries, a diclofenac epolamine patch (1% diclofenac free acid) was found to be significantly more effective than placebo in relieving pain throughout the 2-week treatment period ($P \leq .05$).[74] Similar results were obtained in 2 studies that evaluated the efficacy of a patch formulation containing 140 mg of diclofenac sodium in patients with traumatic blunt soft tissue injuries.[37,63] A diclofenac epolamine plaster also has been reported to be effective in relieving pain in patients with acute ankle sprains.[30,32] Studies consistently report that topical diclofenac, compared with placebo, significantly

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reduced pain within 2 to 3 days of treatment ($P<.05$).[30,37,63,74] In a study of 233 patients, a reduction in pain on active mobilization was reported during the first 6 hours immediately after the first plaster application.[32] The tolerability profile of topical diclofenac was similar to that of placebo in the reviewed studies.[30,32,63,74] In each, the most common AEs were mild application site reactions, such as erythema or pruritus; no severe or systemic gastrointestinal AEs were observed during treatment with topical diclofenac.

A randomized, observer-blind trial involving 384 patients with acute soft tissue injuries reported that diclofenac gel was more effective than felbinac gel (another NSAID) on a variety of pain-related measures, including pain at rest, pain with movement or local pressure, swelling, mobility, bruising, and use of rescue analgesics.[91] Treatment differences were significant in favor of diclofenac for pain at rest ($P=.03$) and bruising on day 3 ($P=.03$) and for pain on pressure on day 7 ($P=.009$).

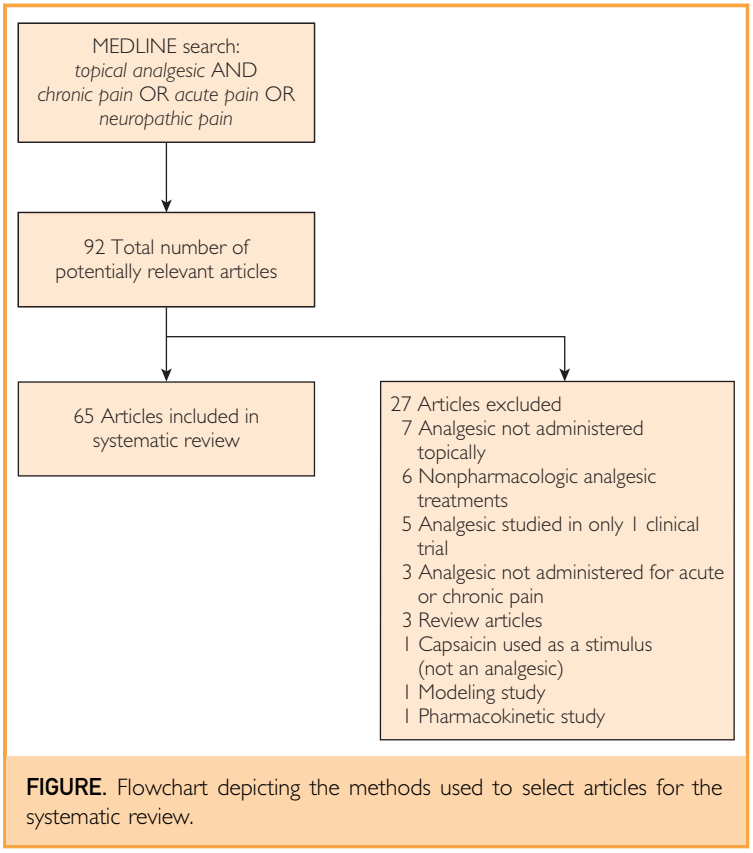

FIGURE. Flowchart depicting the methods used to select articles for the systematic review.

Arthritic Disorders. The efficacy of diclofenac sodium topical solution was investigated in a randomized, double-blind, vehicle-controlled trial involving 216 patients with osteoarthritis of the knee.[58] At 6 weeks, topical diclofenac produced significantly greater reductions than vehicle in Western Ontario and McMaster Universities pain scores (−5.2 vs −3.3; $P=.003$) and physical function (−13.4 vs −6.9; $P=.001$). Stiffness also was significantly reduced in patients receiving topical diclofenac, compared with the vehicle group (−1.8 vs −0.9; $P=.002$). The most common AE in both groups was skin dryness, which occurred in significantly more patients receiving topical diclofenac than those receiving vehicle (39% vs 21%; $P=.004$); however, only 4.7% of patients treated with diclofenac discontinued treatment because of skin reactions, suggesting that such reactions generally were well tolerated.

A randomized, double-blind, crossover study investigated the efficacy of 2% diclofenac sodium in a pluronic lecithin liposomal organogel formulation in 14 patients with chronic lateral epicondylitis.[80] Compared with placebo, diclofenac gel produced significant improvements in pain ($P=.007$) and wrist extension strength ($P=.03$). Only one patient developed a local rash during diclofenac gel treatment.

A gel containing 3% diclofenac in 2.5% sodium hyaluronate was more effective than placebo in relieving breakthrough pain in 119 patients with osteoarthritis who were receiving long-term NSAID therapy (≥1 month).[84] However, the effect was not statistically significant ($P=.057$).

Other Indications. A randomized, double-blind, placebo-controlled trial investigated the efficacy of the diclofenac sodium patch in 153 patients with myofascial pain involving the upper trapezius.[39] Treatment differences favoring diclofenac were seen at each time point during the 7-day treatment period; compared with placebo, diclofenac patch treatment produced significant improvement in pain, cervical range of motion, and measures of disability ($P<.05$), but it had no effect on the pressure pain threshold of the myofascial trigger point. Skin irritation was significantly less common with the diclofenac patch ($P<.05$).

A further study compared the efficacy of diclofenac sodium topical solution (16 mg/mL,

10 drops, 4 times daily) with that of oral diclofenac (50 mg, twice daily) in 36 patients with symptoms of temporomandibular joint dysfunction.[61] No significant group difference in pain relief was found after 2 weeks of treatment. However, 88.9% of patients receiving oral diclofenac reported epigastric symptoms, whereas no such symptoms were reported by patients receiving topical therapy. Few patients (16.7%) treated with diclofenac sodium topical solution reported mild and transient local irritation.

Ibuprofen

Chronic Knee Pain. Comparable efficacy of topical and oral ibuprofen was reported in a randomized, unblinded trial involving 20 patients with chronic knee pain.[31]

Chronic Leg Ulcers. In a pilot study conducted at a Canadian wound clinic and involving 24 patients with chronic leg ulcers, the use of an ibuprofen foam dressing produced a significantly greater reduction in wound pain ($P<.05$) when compared with local best practice in wound management (eg, moist healing dressings and antimicrobial or anti-inflammatory dressings).[51] The efficacy of the ibuprofen dressing was further confirmed in a randomized, double-blind trial of 122 patients.[52] In that study, pain during the first 5 days of treatment was significantly decreased in the ibuprofen group when compared with the control group (40% vs 30% decrease from baseline in pain intensity scores and 74% vs 58% of patients reporting pain relief; $P<.05$).

Soft Tissue Injuries. In a randomized, double-blind, double-dummy, parallel-group trial involving 100 patients with acute soft tissue injuries, ibuprofen gel was found to have efficacy comparable to that of oral ibuprofen.[71] The median time for the injury to be rated by patients as "completely better" (the primary end point) was 13.5 days with oral treatment and more than 14 days with topical therapy, with no significant group difference. Similarly, no significant differences were found between the treatment groups in swelling or in time to relief from pain at rest or with movement.

In a randomized, double-blind, placebo-controlled trial of 100 patients with acute ankle sprains, 5% ibuprofen cream produced a significant reduction in visual analog scale scores compared with placebo during the first 48 hours of treatment ($P<.05$).[85] However, no significant differences were found between the treatment groups in time to improvement of function or in use of rescue medication.

Other Studies. In a study of 10 healthy volunteers, 5% ibuprofen gel produced a significantly greater increase than oral treatment in pressure pain thresholds after exercise-induced jaw muscle soreness ($P<.05$).[79]

Ketoprofen

In a randomized, double-blind trial, 56 patients with acute soft tissue injuries were treated twice daily with 2.5% ketoprofen gel (total daily dose of 250 mg) or placebo for 7 days.[86] Treatment with ketoprofen gel resulted in a significant reduction in baseline pain scores at rest on days 3 and 7 of treatment ($P<.001$), whereas no significant change was found in baseline pain scores among placebo-treated patients. Ketoprofen gel also was associated with a greater improvement in function than placebo, but the between-group difference was not statistically significant. The incidence of local skin irritation was similar in the treatment and placebo groups (15% vs 17%).

In an open-label, randomized, multicenter trial of 1575 patients with acute soft tissue injuries, 2.5% ketoprofen gel compared favorably in efficacy to 1% diclofenac gel and was superior to 0.5% piroxicam gel in terms of improvements in mobility, pain on pressure or movement, and global pain assessments.[105] In a study of 30 patients with moderate or severe pain, 10% ketoprofen gel and 10% naproxen gel were found to be comparable in efficacy and tolerability, except for a greater reduction in pain with deep palpation in the naproxen group on day 3 of the 2-week study.[90]

The efficacy and tolerability of a ketoprofen transdermal delivery system patch and diclofenac gel were compared in a randomized, open-label trial of 223 patients with acute sports-related soft tissue injuries.[54] After 7 to 14 days of treatment, the ketoprofen patch was comparable (not inferior) to diclofenac gel in reduction of pain during daily activities (the primary end point). Both treatments were well tolerated.

Salicylates

In an open-label trial involving 45 patients with acute herpetic neuralgia (AHN) or postherpetic

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neuralgia (PHN), topical administration of a mixture of aspirin and diethyl ether produced effective pain relief, with most patients reporting "good to excellent" results.[87] A pilot double-blind, placebo-controlled, crossover trial involving 11 patients found that the topical aspirin and diethyl ether mixture was significantly more effective in relieving pain than placebo ($P<.05$), whereas topical mixtures of indomethacin or diclofenac in diethyl ether were not.[87] These initial findings were supported by a subsequent double-blind, placebo-controlled, crossover trial of 37 patients with AHN or PHN, in which the mean pain reduction was greater with the topical aspirin and diethyl ether mixture than with placebo (AHN, 66.7% vs 31.3%; PHN, 65.7% vs 34.1%), whereas topical mixtures of indomethacin or diclofenac had little effect.[82]

In a study of 19 patients with AHN or PHN, topical application of the aspirin and diethyl ether mixture (750 mg of aspirin) was associated with superior pain relief when compared with oral aspirin (500 mg; 82.6% vs 15.4% decrease in pain scores).[78] An additional study involving 30 patients with AHN reported significantly greater pain relief ($P<.001$) after administration of topical aspirin (75 mg/mL, 3 times daily) than after oral aspirin (375-750 mg, 3 times daily).[72]

Lidocaine

PHN and Diabetic Neuropathy. The efficacy of the 5% lidocaine medicated patch or plaster has consistently been reported to be superior to placebo and comparable or superior to oral pregabalin in patients with PHN pain or painful diabetic neuropathy.[36,40-42,83] A randomized, double-blind, placebo-controlled trial involving 71 patients with PHN found that 2 weeks of lidocaine plaster therapy was associated with improvements in pain, allodynia, quality of life, and sleep measures when compared with placebo.[41] However, a limitation of this study was the use of an enriched enrollment protocol in which patients who did not respond to lidocaine during an open-label, run-in period were excluded from the double-blind phase. Two further studies from the same group compared the efficacy of 5% lidocaine plasters and oral pregabalin in mixed groups of patients with PHN or painful diabetic neuropathy.[40,42] In both studies, the primary end point was the response rate at 4 weeks, which was defined as a change of 2 or more points from baseline or an absolute value of 4 or fewer points on an 11-point numerical rating scale of recalled mean pain intensity during the previous 3 days. Lidocaine plaster produced response rates of approximately 65% to 66% compared with 61% to 62% with oral pregabalin. In both studies, the response rates were higher with lidocaine plaster than with oral pregabalin among patients with PHN, whereas the 2 treatments produced comparable response rates among patients with diabetic neuropathy. Compared with oral pregabalin, lidocaine plaster also was associated with greater improvements in quality-of-life measures and a lower incidence of AEs.

Posttraumatic Neuropathy. In a pilot placebo-controlled study of 31 patients with posttraumatic peripheral neuropathy, 8% lidocaine pump spray was found to significantly reduce pain and tactile allodynia ($P<.01$) for a median of 5 hours (range, 2-60 hours) after application.[43] Treatment-associated AEs were limited to mild local irritation or flare and resolved within hours.

Other Indications. The efficacy of the 5% lidocaine patch was investigated in a randomized, placebo-controlled, crossover trial involving 40 patients with various focal neuropathic pain syndromes (principally PHN and postsurgical neuralgia).[65] Patches (up to 4560 cm^2 maximum) were applied for 12 hours daily for 1 week as an adjunct to concomitant oral pain medication (nonopioids such as NSAIDs, opioids, tricyclic antidepressants, or anticonvulsants). Compared with placebo, the lidocaine patch produced significant reductions in ongoing pain ($P=.017$) and allodynia ($P=.023$) during the first 8 hours after application, and efficacy was maintained for 7 days.

In a randomized, open-label trial of 41 patients, an emulsion containing 2.5% lidocaine and 2.5% prilocaine cream was found to be significantly more effective than inhalation of a nitrous oxide—oxygen mixture in relieving pain associated with debridement of leg ulcers ($P<.001$).[33]

Capsaicin

Neuropathic Pain. In a randomized, double-blind, placebo-controlled trial of 200 patients

with neuropathic pain (origin not reported), 0.025% capsaicin cream was significantly more effective in relieving pain than placebo ($P<.001$).[73] In the same study, a combination cream consisting of 0.025% capsaicin and 3.3% doxepin produced a similar reduction in pain when compared with 0.025% capsaicin or doxepin cream alone, but analgesia was achieved more quickly with the combination. Burning discomfort after application of the cream was reported by 81% of patients receiving 0.025% capsaicin alone and 61% of those receiving the capsaicin-doxepin combination. In contrast to the efficacy reported in this study, a randomized, double-blind trial of 26 patients with human immunodeficiency virus–associated peripheral neuropathy found that 0.075% capsaicin cream had no significant effect on neuropathic pain.[75]

Two randomized controlled trials of patients with PHN reported that a single 60-minute application of a high-concentration (8%) capsaicin patch produced significant pain relief ($P<.05$) when compared with a low-concentration (0.04%) patch, and this effect was sustained for up to 12 weeks.[29,38]

Migraine. A single small study of 23 patients reported that 0.1% capsaicin gel is effective in relieving mild or moderate pain in patients with acute migraine.[35]

Experimental Pain. In a study of 20 healthy volunteers, 0.075% capsaicin cream reduced facial sensitivity in response to mechanical, heat, or cold pain without affecting the response to nonpainful tactile stimuli.[53] In that study, capsaicin (40 μL, 6-mm strip) was applied 4 times daily for 2 weeks, and the burning sensations commonly induced by topical capsaicin decreased with repeated application.

Amitriptyline

Although the only approved use of amitriptyline is for the treatment of depression (amitriptyline hydrochloride, Qualitest Pharmaceuticals), amitriptyline is widely used off-label for a variety of conditions; in fact, the rate at which amitriptyline is used off-label is among the highest of all medications.[120] The off-label use primarily involves oral amitriptyline for the treatment of neuropathic pain,[121] although it also is prescribed for the treatment of headache and certain types of musculoskeletal pain.[122,123]

Neuropathic Pain. A number of placebo-controlled trials have examined the use of topical amitriptyline for the treatment of neuropathic pain.[47,59,67] These studies failed to show a significant benefit of topical amitriptyline at concentrations of 1% to 5% in patients with neuropathic pain of various causes.[47,59,67] However, the duration of the double-blind treatment in these studies was short, ranging from 2 days to 3 weeks. In a study of 20 patients with neuropathic pain, neither amitriptyline nor ketamine cream had a significant effect on pain when compared with placebo during 2 days of double-blind treatment; however, a significant decrease in pain was seen during subsequent open-label treatment with a combination cream consisting of 1% amitriptyline and 0.5% ketamine ($P<.05$).[67]

Experimental Pain. Studies in healthy volunteers demonstrated that topical amitriptyline at concentrations of 50 and 100 mmol/L produced a significant analgesic effect ($P<.05$) when compared with placebo[68] and was associated with transient increases in tactile and mechanical nociceptive thresholds.[45]

Glyceryl Trinitrate

A randomized, double-blind trial involving 154 patients with chronic lateral epicondylitis found a statistically significant analgesic effect ($P=.04$) at 8 weeks of treatment with topical glyceryl trinitrate (0.72 mg/d) when compared with placebo, but no significant differences were found between the 1.44-mg/d and 3.6-mg/d doses or between these 2 doses and placebo.[44] By contrast, in a follow-up study of 52 patients with chronic noninsertional Achilles tendinopathy, patients who had previously received topical glyceryl trinitrate for 6 months at a dose of 1.25 to 5 mg/d reported significantly less tendon tenderness ($P=.03$) and more improved function scores ($P=.04$) 3 years after the end of treatment when compared with patients who had received placebo.[48] In addition, 88% of patients receiving topical glyceryl trinitrate were asymptomatic after 3 years compared with 67% of patients treated with rehabilitation alone ($P=.03$). Finally, a study of 110 patients reported that topical glyceryl

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trinitrate (0.2%) treatment produced significantly faster wound healing after hemorrhoidectomy than placebo (P=.002).[69]

Opioids

A randomized, double-blind, placebo-controlled trial compared the analgesic efficacy of IntraSite gels (Smith and Nephew) containing morphine sulfate (10 mg/mL) or sterile water with that of conventional Jelonet dressings (Smith and Nephew) in 49 patients with superficial burns.[50] Patients receiving topical morphine had the greatest decrease in pain scores (>20 mm on a 100-mm scale) at 2 and 6 hours after application. However, patients receiving topical morphine used more supplementary analgesia than the other 2 groups and reported the least reduction in pain scores at 12 hours (the last assessment). Similarly, a study involving 24 patients with painful chronic skin ulcers found that topical morphine (10 mg in a gel formulation) had no analgesic efficacy when compared with placebo.[60]

Miscellaneous Agents

A number of miscellaneous agents have been reported to be effective in treating acute and chronic pain, including pimecrolimus 1% cream for the management of vulvar lichen sclerosus[28] and oral lichen planus,[49] topical menthol for chronic knee pain[62] and mechanical low back pain,[92] and topical phenytoin for superficial burns[66] and chronic leg ulcers.[70]

DISCUSSION

Topical formulations of a variety of analgesics have been studied for the treatment of diverse indications (Supplemental Table). However, many of the published studies were small, and studies involving patients with chronic pain were often of short duration. NSAIDs are among the most commonly prescribed drugs throughout the world,[124] and hence, it is not surprising that topical formulations of these agents have been studied more widely than topical formulations of other agents. The available evidence suggests that topical NSAIDs can be recommended for short-term pain relief in patients with acute soft tissue injuries or chronic joint-related conditions such as osteoarthritis.[17,22,23] Topical ibuprofen and topical diclofenac have been widely studied. Topical ibuprofen appears to be comparable in efficacy to oral ibuprofen in the treatment of chronic knee pain[31] or acute soft tissue injuries.[71] Topical diclofenac also has equivalent efficacy with oral diclofenac in the treatment of temporomandibular joint disorder.[61]

Topical lidocaine therapy can be recommended for use in patients with neuropathic pain, particularly PHN and diabetic neuropathy, and controlled trials have consistently found that such treatment can provide effective analgesia.[40-42,83]

Despite the widespread use of oral amitriptyline to relieve neuropathic pain, as well as the documented efficacy of oral amitriptyline in clinical trials,[121] few data exist to support the use of topical amitriptyline. Of interest, a recently published case report presented evidence of a dose-response relationship for neuropathic pain, with topical amitriptyline providing considerable analgesia at concentrations of 5% and 10%; in one of the 2 cases presented, however, the higher concentration was associated with systemic AEs, particularly drowsiness.[125]

Studies with topical capsaicin formulations have yielded varying results, depending on the dose used and the patient population studied. Furthermore, the burning sensation that follows the topical application of capsaicin may discourage the use of such treatment. Although no recommendations can be made at present for the use of topical capsaicin, topical capsaicin is approved for use in the treatment of pain associated with PHN (Qutenza [capsaicin] 8% patch, NeurogesX Inc).

The limited number of studies on topical morphine suggests that such therapy does not offer a significant advantage over oral morphine. Few data are available on the analgesic properties of other topical medications, such as indomethacin, niflumic acid, eltenac, naproxen, pimecrolimus, phenytoin, or menthol, and no recommendations can be made about the topical use of these agents in the treatment of acute or chronic pain.

Topical analgesics offer better tolerability than oral therapy. For example, studies comparing topical and oral NSAIDs have consistently reported more favorable tolerability profiles for topical agents.[31,61] In general, topical analgesics are devoid of systemic AEs, notably the gastrointestinal and cardiovascular events that often limit the usefulness of oral preparations of opioids, NSAIDs, and salicylates. Although application

site reactions are common with some topical preparations, these generally have been mild, transient, and well tolerated.

CONCLUSION

Topical analgesic therapy using NSAIDs or lidocaine has an important place in the management of acute and chronic pain conditions and warrants further study.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **AE** = adverse event; **AHN** = acute herpetic neuralgia; **NSAID** = nonsteroidal anti-inflammatory drug; **PHN** = postherpetic neuralgia

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