

TOPICAL USE OF NITRATES, CAPSAICIN, AND TRICYCLIC ANTIDEPRESSANTS FOR PAIN MANAGEMENT*

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ABSTRACT

Most physicians who treat pain recognize that it is a difficult and inexact area of medicine. Many patients seem to be resistant to conventionally available agents and, therefore, thinking "outside of the box" becomes a matter of clinical necessity. This necessity has prompted some investigators to test agents that may not be conventionally regarded as analgesics to determine evidence of their efficacy and value in pain management. This article provides a summary of existing medical evidence surrounding the topical use of nitrates, capsaicin, and tricyclic antidepressants for pain management.

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TOPICALLY APPLIED NITRATES

In the United Kingdom, topical nitrate patches are commonly used for angina treatment and have been reported anecdotally to have an analgesic effect. Surgeons have used topical nitrates to treat anal fissures, hypothesizing that the mode of action stems from smooth muscle relaxation.

The analgesic effects of nitrates have been investigated in a few small, controlled clinical trials that suggest these agents may be of some value in pain management. In a 1996 prospective double-blind study by Berrazueta et al,¹ 20 patients with shoulder pain syndrome caused by supraspinatus tendinitis were randomly assigned to either a transdermal nitrate patch or a placebo patch applied to the most painful area. At 24 hours, patients in the treatment group reported a significant decrease in intensity of pain as determined by a 0-10 visual analog scale (7.05 ± 0.4 to 4.5 ± 0.5); this was also true at 48 hours (2 ± 0.3 ; $P < .003$). Patients remained free of symptoms at 15 days. No changes were observed in the group with the placebo patch. These findings suggest that transdermal glyceryl trinitrate (GTN) may be of some use in treating tendon musculoskeletal disorders, and clinicians may wish to extrapolate from those findings to test GTN's efficacy in other common pain problems.

In an earlier double-blind study of 21 patients undergoing vein sclerotherapy in both legs,² transdermal GTN ointment was applied to the varicose vein in one leg and placebo was applied to the vein of the other leg used as control for thrombophlebitis signs. The investigators formulated a measure that encompassed not only a visual analog scale for pain, but also amount of redness, swelling, and inflammation. The application of nitrate significantly reduced inflammation following sclerotherapy (Figure 1). One hour after the application, 63% of cases in the transdermal GTN group showed signs of thrombophlebitis compared with 100% of cases in the placebo group ($P < .001$). Although inflammation naturally settled over time in all veins, those treated with GTN showed a more rapid reduction in the signs of inflammation. In fewer than 48 hours, all veins treated with GTN were free of signs of thrombophlebitis, compared with 65% of veins treated with placebo. Hypotheses surrounding modes

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of action suggest that organic nitrates are oxidized, causing activation of guanylate cyclase and increased intracellular cGMP, with a direct effect on the vein and the surrounding inflamed tissue.

A disadvantage reported with topical nitrate use is headache. Patients using GTN ointments risk applying too much, which can result in serious headache. The lowest dose available in patch formulations is 5 mg per 24 hours; even that dose can result in headache, so only 1 patch applied at a single site is therapeutically feasible. Some clinicians have taken the innovative approach of cutting 1 patch into smaller pieces and applying those pieces at several different sites simultaneously. Although no medical evidence supports this practice, anecdotal reports suggest some efficacy. Some conditions where nitrates may be of use include osteoarthritis, pathological fractures, or at the site of an operative wound, where an increase in perfusion running to the wound site is clinically advantageous. Potential disadvantages and advantages of use of topically applied nitrates for pain management are shown in Table 1.

CAPSAICIN

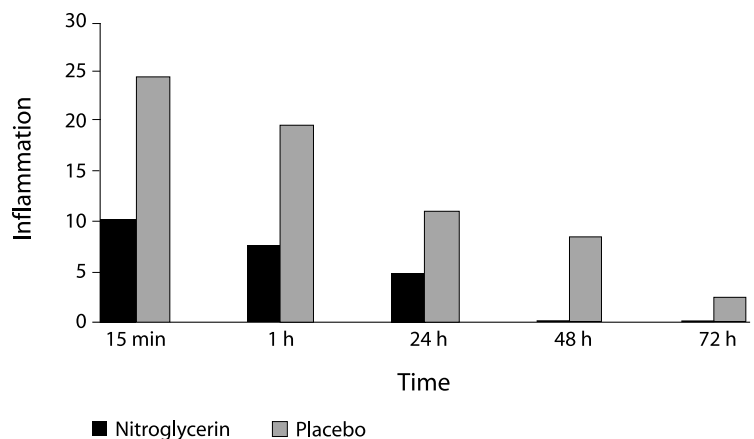
For nearly 150 years, the topical application of extracts of the capsicum pepper has been shown to produce pain relief.³ The active pain-relieving component of the chili pepper is capsaicin. When repeatedly applied topically in the appropriate concentration, capsaicin causes reversible depletion of the neuropeptide substance P from the sensory nerve endings, by activity at the vanilloid receptor,⁴ and possibly through a reversible decrease in the number of epidermal nerve fibers.⁵ Topical application of capsaicin has been shown to reduce the pain associated with a variety of conditions, including postherpetic neuralgia,⁶⁻⁸ painful diabetic neuropathy,⁹⁻¹¹ chronic distal painful polyneuropathy,¹² surgical neuropathy pain,¹³ postmastectomy syndrome,¹⁴ and osteoarthritis.¹⁵⁻¹⁷ Other clinical trials in rheumatoid arthritis and painful diabetic neuropathy have resulted in negative findings, and the results of placebo-controlled trials are confounded by the burning sensation that occurs with application of the active drug.¹⁸

Pain relief may take several weeks to occur with capsaicin. A major adverse effect is a burning discomfort, potentially leading to poor patient adherence. The addition of GTN to capsaicin can reduce the burning discomfort associated with application while producing enhanced analgesia and more rapid efficacy.^{19,20} As with GTN monotherapy, there is a risk of nitrate headaches, and transdermal nitrate patches may be applied only at a single site. Disadvantages and advantages to capsaicin therapy are summarized in Table 2.

TOPICAL TRICYCLIC ANTIDEPRESSANTS

Several years ago in the United Kingdom, a topical tricyclic antidepressant (TCA) containing doxepin was introduced for itch associated with eczema, although tricyclics are known to have a central mode of action. Anecdotal use of a topical TCA to treat a patient with supraorbital neuritis resulted in significant pain relief from the topical TCA. The topical cream was therefore used to treat several other patients, some of whom reported relief. These reports led to the initiation of a double-blind, placebo-controlled trial. Thirty patients

Figure 1. Inflammation Following Sclerotherapy for Bilateral Varicose Veins (N = 21)



Adapted from Berrazueta et al.²

with neuropathic pain were randomly assigned to receive either doxepin or placebo. After 4 weeks of treatment, baseline scores had increased slightly in the group taking placebo (from 6.49 to 6.91) but decreased noticeably in the group using the topical doxepin preparation (from 6.22 to 5.04; $P < .01$). In the study, 3 patients developed adverse effects normally associated with the use of oral TCAs.²¹ Subsequently, animal studies conducted by Sawynok et al showed that TCAs have a peripheral mode of action, suggesting an opportunity for additional clinical investigation.^{22,23}

A larger, randomized, double-blind, placebo-controlled study of 200 patients with chronic neuropathic pain was then initiated.²⁴ Patients applied a placebo, doxepin, capsaicin, or doxepin/capsaicin cream to the area of pain daily for 4 weeks. Baseline pain scores were taken 2 weeks before treatment. The combination of capsaicin and doxepin and the monotherapy of topical doxepin produced the same level of relief in study subjects (Figure 2). Patients did not experience the adverse effects of systemic TCAs, again suggesting a peripheral mode of action. In a subsequent study of patients using oral topical doxepin rinse to relieve oral mucosal pain due to cancer or cancer therapy, the rinse resulted in a reduction of pain intensity of more than 50%. Pain relief was extended for more than 3 hours, suggesting a peripheral mode of action that may be related to sodium channel blockade associated with TCAs.²⁵

As with all of the therapies described, topically applied TCAs are not effective or suitable for all patients. They are suitable only for small areas of application, as larger areas will result in significant systemic uptake. Maximum effect of the treatment is achieved in approximately 2 to 4 weeks. There are few adverse effects. This therapy may be useful in selected cases, such as in patients with a small patch of postherpetic neuralgia.

Pain management with topical analgesics will be effective in some but not all patients. In those patients who fail to respond to other pharmacologic therapy, a combination of oral and topical agent therapies should be considered. Nonpharmacologic treatment may also be considered, ranging from behavior modification and fostering of coping skills to the more major invasive medical techniques.

Table 1. Advantages and Disadvantages of Topical Nitrate Use

ADVANTAGES

- ▶ NSAID-like action without NSAID adverse effects
- ▶ Fast acting
- ▶ Increased local perfusion

DISADVANTAGES

- ▶ Associated with headache
- ▶ Can be used only at 1 site
- ▶ May result in tachyphylaxis
- ▶ Not all patients respond

Table 2. Advantages and Disadvantages of Topical Capsaicin Use

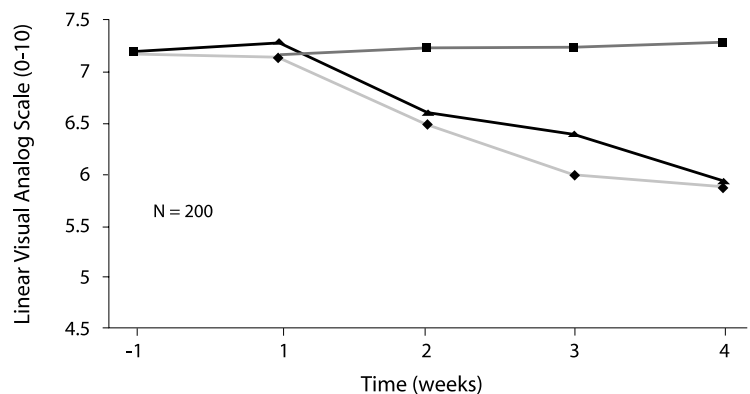
ADVANTAGES

- ▶ Lack of toxic effects
- ▶ Treats neuropathic and nonneuropathic pain
- ▶ Multiple sites of application possible
- ▶ Additive effects with other agents

DISADVANTAGES

- ▶ 2 to 4 weeks for maximum effect
- ▶ Discomfort with application
- ▶ Not all patients respond

Figure 2. Topical Doxepin vs Capsaicin for Neuropathic Pain



Adapted with permission from McCleane.²⁴

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