Topical Treatment of Neuropathic Pain: Applying the Evidence

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Topical treatment of neuropathic pain: applying the evidence.

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More than a million Canadians suffer from neuropathic pain (NeP).[1] Can topical agents help?

The International Association for the Study of Pain recently revised the definition of neuropathic pain (NeP) to be "pain caused by a lesion or disease of the somatosensory system".[2]NeP can arise from peripheral lesions or disease (trauma, diabetes, toxic exposures, infection),[3-5] as well as from spinal cord and central lesions (trauma, multiple sclerosis, infarcts, tumours).

Pain intensity is often measured using a visual-analogue scale (VAS) or numerical rating scale. A reduction in pain of ?30% is considered as moderate clinical benefit, and a reduction of ?50% is substantial clinical benefit.[36]

Chronic NeP can markedly diminish both quality of life and daily function. Pain reduction is the main goal of treatment, but improving sleep, daily function, and quality-of-life are also important.[1] First-line medications include oral amitriptyline, gabapentin and pregabalin. Duloxetine, venlafaxine, tramadol, and opioids are second- or third-line agents.[1,6-9] However, chronic NeP often persists after trials of all of these medications which can be frustrating for both the patient and the clinician.

Topical agents have the potential to deliver drugs locally without systemic toxicity.[10] They are often considered for the treatment of localised NeP pain when oral therapies have failed or have been stopped due to side effects. However, there is a lack of quality evidence for topical treatments in neuropathic pain and data is often conflicting. This may be due to varying responses of different forms of NeP, the location and surface area of application, and differences in formulations used.[14]

The following is the evidence from randomized controlled trials and systematic reviews regarding topical amitriptyline, ketamine, dimethyl sulfoxide (DMSO), lidocaine, and capsaicin.

Amitriptyline

Results from studies of topical amitriptyline cream in strengths from 1% to 5% are inconsistent.[15] Several RCTs did not show benefit with amitriptyline 5% in pluronic lecithin organogel gel,[16] amitriptyline 1%[17] or amitriptyline 2% cream[18] versus placebo. Case reports of higher strength amitriptyline (5% and 10%) have shown dose-related efficacy but also systemic adverse effects (slower cognition and difficulty concentrating).[15]

Amitriptyline is often used topically in combination with ketamine for NeP. One study showed significant relief from postherpetic neuralgia using amitriptyline 4% and ketamine 2%.[19] In some case reports, pain relief was rapid, with some patients experiencing pain reduction within 20 minutes of application.[15,20] Local redness was the most common adverse effect, but this may have been due to the vehicle.[15]

Ketamine

Ketamine, a general anaesthetic agent, decreases peripheral nociceptive signalling through non-competitive blockade of N-methyl-D-aspartate receptors on peripheral nerves.[21] In two short-term RCTs, neither ketamine 0.5% or 1% (with and without amitriptyline) were more effective than placebo for NeP.[17,18]

A RCT compared topical ketamine 5% cream (three times daily) to placebo in the treatment of painful diabetic neuropathy.[22] After one month, ketamine reduced some aspects of pain but change in pain intensity was no different than with placebo.[22] In patients with complex regional pain syndrome, a double-blind, placebo-controlled crossover trial (N=20) with topical ketamine 10% reported a reduction in allodynia, but not pain intensity.[21]

DMSO

DMSO increases the movement of drug through the skin in a concentration dependant manner.[23] It is an ingredient in topical diclofenac solutions, and may be used as a carrier in other compounded topical preparations. Skin dryness and irritation and possible systemic effects such as a garlic-like taste can occur with higher concentrations.[23-25]

DMSO has been used alone for NeP due to its probable modulation of afferent C-fibers[26] and free-radical scavenging.[25] A RCT (N=32) of CRPS patients with DMSO 50% in a fatty acid cream (to reduce skin dryness) reported pain reduction, but no difference compared to placebo.[25] A 2013 Cochrane review of CRPS treatments concluded that there is very low quality evidence that topical DMSO reduces pain or improves patients' self-ratings more than placebo.[27]

Lidocaine

A recent Cochrane review identified 12 studies (n=508) comparing topical lidocaine vs placebo or an active control.[28] The 5% medicated patch, gel and cream were used along with an 8% spray.[28] Lidocaine 5% may be effective in patients with localized peripheral neuralgia, including postherpetic neuralgia, for several weeks with a low risk of adverse reactions.[28]

Topical lidocaine is a first-line treatment in some guidelines for localized NeP, like postherpetic neuralgia with allodynia, but it is a second-line therapy in the Canadian Pain Society Guidelines.[1,7] The lidocaine 5% patch is not available in Canada, so preparations of 5%-10% must be compounded.[1]

Capsaicin

Capsaicin works by causing local desensitization after a period of initial irritation.[29] Topical capsaicin is available over-the-counter in concentrations of 0.025%-0.075%. Although an earlier systematic review of capsaicin in neuropathic pain found the number needed to treat (NNT) for a 50% reduction in pain to be 5.7 with capsaicin 0.075% applied 3-4 times per day,[31] a more recent Cochrane review found that there is insufficient data to draw conclusions regarding the its efficacy for neuropathic pain.[32] All studies reported local adverse skin reactions to capsaicin early in treatment, but these were reduced or disappeared after one to two weeks of treatment.[31]

A capsaicin 8% patch is approved in the U.S. for use in the treatment of pain associated with postherpetic neuralgia (Qutenza®, Acorda Therapeutics Inc.). The patch is applied by a physician for 30-60 minutes per treatment and may provide relief for up to 3 months.[30] A separate Cochrane review (4 studies of PHN and 2 of painful HIV-neuropathy) reported the

patch to be better than control (0.04% capsaicin for blinding).[33] The average NNT to feel "much" or "very much better" was 8.8 and 7.0, respectively, after 6 weeks.[33] Serious adverse effects were no different between the groups, but the safety of long term, repeated application of high-dose capsaicin is unknown. The patch is not available in Canada and future availability is uncertain.

Limitations

A wide variety of formulations, including creams, gels, and patches have been studied, and many are not commercially available in Canada or standardized. Extemporaneous compounding allows clinicians to individualize patient therapy, but specific formulation details are often not discussed in the literature, and some concerns have been raised over the variability of extemporaneous preparations.[13,34] Studies tended to be small and of short duration, and most studies have focused on specific conditions such as PHN or PDN; the extent to which results can be applied to other forms of NeP is unknown.[35] Thus there is uncertainty in extrapolating study results to other preparations and conditions.

Summary

Except for topical lidocaine and capsaicin 8%, there is little evidence for the efficacy of compounded topical therapies for peripheral NeP. However, because oral treatment is often ineffective, a trial of a topical analgesic may be worthwhile in patients with chronic neuropathic pain; even a small decrease in pain can dramatically increase their quality of life and the risk of significant adverse effects appears low.

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