Profile of the capsaicin 8% patch for the management of neuropathic pain associated with postherpetic neuralgia: safety, efficacy, and patient acceptability

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Abstract: Capsaicin is a naturally occurring irritant active ingredient found in hot peppers. It is a ligand for transient receptor potential channel vanilloid receptors, which are found in nociceptive nerve terminals in the skin. Initial exposure to topical capsaicin leads to excitation of these receptors, release of vasoactive mediators, erythema, intense burning, pain, and thereafter desensitization of sensory neurons resulting in inhibition of pain transmission. Capsaicin 8% has been licensed for the treatment of postherpetic neuralgia pain in recent years. A single application of high-concentration capsaicin for 60 minutes for postherpetic neuralgia has been robustly evaluated. Capsaicin 8% patches are applied to the most painful areas of healthy skin and allowed to remain for 60 minutes. Treatment can be repeated every 90 days if the pain persists or returns. The patches are usually applied in specialist pain clinics where patients can be pretreated and monitored. Health care staff need to take certain precautions before administering these patches to avoid unintentional contact. Common adverse effects of the capsaicin 8% patch are transient mild-to-moderate self-limiting application-site burning, pain, erythema, pruritus, papules, swelling, dryness, and hypertension. To manage local pain from capsaicin application, the skin is pretreated with a local anesthetic such as topical lidocaine or an oral analgesic such as oxycodone for up to 5 days. A transient increase in pain is usually seen within 48 hours of patch application before the pain-relieving effect starts. Systemic absorption is minimal and clinically insignificant. The nature of administration and relatively high cost of capsaicin patches can significantly limit their use to a small number of patients with severe refractory symptoms. This review highlights recent evidence related to the use and effectiveness of the 8% capsaicin patch for Postherpetic Neuralgia and discusses its safety and side-effect profiles.

Keywords: capsaicin, efficacy, safety, tolerability, high-dose patch, postherpetic neuralgia

Postherpetic neuralgia: definition, epidemiology, and pathogenesis

Pain originating from lesions of sensory nerves is described as neuropathic pain. It is typically associated with other symptoms such as hypersensitivity, burning, and numbness leading to a significant reduction in quality of life. Neuropathic pain can result from conditions such as diabetes, trigeminal neuralgia, HIV infection, herpes zoster, and trauma. Postherpetic neuralgia (PHN) is a common cause of neuropathic pain encountered in primary care. It is traditionally defined as persistence of pain beyond 1 month after healing of herpes zoster rash. However, other definitions of PHN based on time since appearance of rash do exist,¹ and consequently, its reported prevalence

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is considerably variable. The annual incidence of PHN in the UK is ~28 per 100,000 people.² A US 5-year retrospective cohort study showed that 10% of shingles patients may have pain persisting at least 90 days.³ Another study showed that 20% of herpes zoster patients older than 50 years will develop PHN even after commencing antiviral therapy.⁴ Older age and increased severity of initial zoster pain and rash are risk factors. The varicella zoster virus migrates up neural axons and remains dormant in dorsal root ganglia following primary infection. Reactivation of the virus leads to outbreaks of characteristic painful lesions that follow a dermatomal distribution. The underlying mechanisms for developing PHN still remain unknown. Some postulations include nervous system damage (degeneration of afferent fibers) leading to a sensitized hyperexcitability pain state, second-order neurons becoming responsive to A fibers originating from low-threshold mechanoreceptors, and central nervous system involvement in the form of loss of inhibitory interneurons.⁵ Suppressing viral replication in addition to multimodal analgesia aims to encourage healing and control pain. However, notwithstanding effective treatment of varicella zoster virus, PHN can still arise. The resulting pain remains very difficult to manage and has a major impact on patients' quality of life, functional status, and mental health. The oral analgesic medications currently available to treat PHN (tricyclic antidepressants [TCAs], pregabalin, gabapentin, and opioids) have the risk of serious systemic side effects. This has sparked a great deal of interest in topically applied agents. Topical therapy has the main benefits of delivering targeted therapy over the painful area and curbing the overall pill burden, which in turn encourages patient adherence.

Capsaicin: historical overview, mode of action, and formulations used for PHN

The discovery of the irritant medicinal properties of chilies in the West is thought to have originated from the Aztec civilization during which balms derived from chili peppers were used to treat painful conditions such as toothaches. Extracts derived from capsicum fruits appeared in the US Pharmacopeia as Oleoresin Capsaicin from 1860, and in Europe, another extract, Tinctura Capsici, was used as an anti-irritant analgesic remedy.^{6,7} It was not until the 19th century when capsaicin – the main active agent of hot peppers – was isolated. In the 1970s, scientists started to formally research capsaicin receptors and the concept of desensitization in response to repeated exposure to capsaicin.

The use of topical capsaicin for recalcitrant pain conditions such as PHN only started to appear in medical literature in the 1980s.

The International Union of Pure and Applied Chemistry name for capsaicin is (*E*)-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methylnon-6-enamide. It is a pungent ingredient naturally found in plants of the genus *Capsicum* and is an agonist at the transient receptor potential cation channel subfamily V member 1 (TRPV1) which was only formally realized in 1997 through modern DNA-cloning techniques.⁸ TRPV1 is a transmembrane tetrameric ion channel that has a significant preferential permeability to calcium. TRPV1 channels are mostly incorporated in nociceptive terminals of A δ and C fibers peripherally but can also be found centrally in dorsal root and trigeminal ganglia.⁹ They are activated by environmental stimuli (acidosis and high temperatures) and various endogenous compounds (eg, lipooxygenase derivatives, anandamide, and *N*-acyldopamines)¹⁰ leading to transient depolarization via sodium and calcium influx. However, the exposure of TRPV1-bearing nociceptors to the potent and highly selective agonist capsaicin results in a prolonged effect as the calcium:sodium permeability ratio of TRPV1 channels increases from 8:1 to 25:1.¹¹ Capsaicin can also induce calcium release from the endoplasmic reticulum as TRPV1 is found on intracellular organelles. Persistently high concentrations of intracellular calcium can activate protease enzymes leading to depolymerization of microtubules and cytoskeletal disruption.¹¹ In addition, high calcium influx is associated with chloride accumulation leading to osmotic swelling. Direct inhibition of mitochondrial respiration via interference with electron chain transport is a non-TRPV1-mediated effect that occurs with high concentrations of capsaicin. Through these well-recognized effects, the application of a single dose of high-concentration capsaicin or doses of lower concentrations continuously results in impaired local function of nociceptive nerve terminals expressing TRPV1.¹² The long-term local cellular and physiological modifications induced by capsaicin are collectively described as defunctionalization.¹²

The persistent analgesic effect of topical capsaicin can also be explained by causing reversible degeneration of epidermal neurons seen in skin biopsies of treated individuals.¹³ In one study, 3 weeks of topical capsaicin (0.075%) treatment resulted in ~80% epidermal denervation.¹³ Another study has shown that a single 60-minute application of capsaicin produces ~60% epidermal denervation.¹⁴ Degeneration of autonomic nerve fibers has been demonstrated after topical capsaicin application.¹⁵ This can lead to diminished

sympathetic and neurovascular function. Therefore, extra caution is required if topical capsaicin is to be used for patients with underlying sensory and autonomic dysfunction, for example, diabetes mellitus, due to the increased risk of skin ulceration.¹⁵ Depletion of neuropeptides such as Substance-P is also a result of repeated application of capsaicin. However, this is thought to be an association rather than a causative mechanism of action.^{9,11}

The commonly used topical capsaicin formulations can be classified into low-dose capsaicin (0.025%, 0.075%) and high-dose capsaicin (8%). The latter is commercially available as a cutaneous patch (Qutenza®) containing 179 mg of capsaicin per 280 cm². It is approved by the US Food and Drug Administration for the treatment of PHN and must be applied appropriately by trained personnel in specialist pain clinics. The patches are used as a single 60-minute application to the most painful areas of healthy skin, and can be cut into certain shapes before use. Treatment can be repeated every 90 days if the pain persists or returns. Common adverse effects of the capsaicin 8% patch are transient self-limiting application-site burning, pain, erythema, pruritus, papules, swelling, and dryness which are mild to moderate in severity but can lead to transient hypertension.⁹ Local pain from capsaicin application can be managed by skin pretreatment with a local anesthetic (eg, topical lidocaine) or an oral analgesic (eg, oxycodone) for up to 5 days.¹⁶ Current evidence-based guidelines for the treatment of PHN consider topical capsaicin 8% as a second- or third-line agent in patients who have failed at least one line of therapeutic options.¹⁷

Safety and patient tolerability of high-dose capsaicin patch

The safety profile and degree of patient tolerance to high-dose capsaicin patches has been investigated by several high-quality studies. Pretreatment with local anesthesia is integral in terms of ameliorating transient post-application pain. It was therefore important to assess whether the type of topical anesthetic impacted overall tolerability. A randomized prospective study compared three different local anesthetics (lidocaine 4% cream, topicalaine, betacaine) on 117 patients suffering from a variety of neuropathies including PHN. The average pain score at baseline and at 2–12 weeks was reported, and the differences in tolerability between the three local anesthetics were found to be negligible.¹⁸ Despite the absence of reported serious adverse effects, 50%–59% of patients reported local mild-to-moderate side effects, specifically, erythema, pain, papules, and pruritus, that generally resolved by day 2 of application.

A 60-minute patch application rather than 90 minutes is favored as the latter was associated with more local side effects and peri-treatment analgesic use, outweighing any additional analgesic effects.¹³

The analysis of 12 miscellaneous studies with different methodologies', and patients with various neuropathic pain conditions demonstrated that the highest increase in numeric pain-rating scale (NPRS) score was 2.3–2.8 and that treatment-related pain was the same regardless of the type of neuropathy.¹⁸

The pharmacokinetics of capsaicin 8% patches has been studied in patients treated for pain secondary to PHN, diabetes mellitus, and HIV-associated neuropathy. It was found that systemic absorption of capsaicin occurs through the skin in a concentration- and time-dependent manner. Plasma levels reach a peak (17.8 ng/mL) when patches are applied on the trunk. On the other hand, patches applied to the feet result in remarkably lower plasma concentrations. A twofold increase in plasma levels was observed by prolonging application time from 60 to 90 minutes. Capsaicin has an elimination half-life of 1.64 hours and is rapidly metabolized by hepatic cytochrome P450.¹⁹

In summary, although treatment with high-dose capsaicin patches is almost invariably associated with marked localized pain, this unpleasant side effect is relatively short lived, and most patients reach baseline scores within 48 hours without suffering from any severe reactions. These factors show why capsaicin 8% patches maintain a favorable safety profile and a good overall patient tolerance. Fortunately, the majority of studies related to capsaicin's efficacy were performed on patients suffering from PHN, building a strong case for its use to treat this painful condition.^{20,21}

Efficacy of high-dose capsaicin patches for treatment of PHN

The therapeutic efficacy of high-dose capsaicin patches is well established in medical literature as demonstrated by several reliable randomized controlled trials (RCTs). The emergence of such treatment leads to recognizing that it is not only important to achieve analgesic end points but also vital to prove that the benefit of long-term pain relief outweighs the post-application transient increase in pain and other local side effects. An important RCT showed that the treatment group (8% capsaicin patches) had a significant ($P=0.001$) 9.7% reduction in NPRS scores 2–8 weeks post-application when compared to the control group (0.04% patches). These results were applicable whether or not patients were already on concurrent medications for neuropathic pain.²²

Another randomized trial found that the 60-minute treatment duration was the minimum effective and the 90-minute treatment provided the largest decrease in pain intensity during weeks 2–8.²³ A report has implied that patients with PHN persisting beyond 6 months have a better analgesic therapeutic profile with capsaicin 8%.²⁴

A meta-analysis of high-dose capsaicin RCTs including PHN, painful diabetic neuropathy (PDN), and HIV-associated neuropathy has also shown a significant reduction in pain (30.7%) from baseline in the high-dose treatment groups as opposed to a 22.7% reduction in the low-dose patch control group during weeks 2–12. In all subgroups, a 30% reduction in pain scores was attained in 44% of high-dose patch versus 34% of low-dose patch (control). However, a limitation to this study was its short period (12 weeks) which meant that subgroups were not large enough to highlight their respective treatment benefits.^{25,26} A further meta-analysis with a larger group of PHN cases (1,313) treated with high-dose patches identified responders as those who had a 30% reduction in mean pain intensity scores. It demonstrated that a mean of 3.4 days was needed for the analgesic effect to start and 5 months was the duration of pain relief.²⁷ Five different responders (including full responders, partial responders, and nonresponders) were identified through the analysis of data from four RCTs. Treatment efficacies varied according to the response subgroup. Qutenza had 40% less nonresponders and 25% more full responders compared to low-dose (0.04%) capsaicin. This study also showed that Qutenza's efficacy had important predictors such as the efficacy of lidocaine pretreatment and larger pretreatment pain score variability.²⁸

In 2013, a Cochrane database systematic review of six randomized trials compared single application of high-dose (8%) capsaicin patch to low-dose (0.04%) patch in 2,073 adult patients with chronic neuropathic pain. Four of these trials involved 1,272 patients with PHN. At 8 and 12 weeks, capsaicin 8% patch therapy was associated with an increase in patients' reports of feeling much or very much better with numbers needed to treat of 8.8 and 7, respectively. Serious adverse effects were not more frequent with high-dose treatment than control. There was no difference in adverse event withdrawals, but "lack of efficacy withdrawals" were more common with control than active treatment. No deaths were judged to be attributed to the study treatment. The systematic review concludes that high-dose topical capsaicin treatment for PHN generates more participants with high levels of pain relief than control. However, the additional proportion who benefit is not large. For those who fully

respond, there are improvements in sleep, fatigue, depression, and quality of life.²⁹

A noninterventional study, Qutenza Safety and Effectiveness in Peripheral Neuropathic Pain (QUEPP), evaluated the effectiveness of a single application of capsaicin 8% in 1,044 patients (excluding diabetics) with peripheral neuropathic pain.³⁰ PHN was the commonest diagnosis (31.9%). A significant reduction in pain attacks as well as an improved sleep quality was reported. Responder rates of 30% and 50% were calculated for reduction of the mean NPRS score at all visits between days 7–14 and week 12 versus baseline of at least 30% and 50%, respectively. The $\geq 30\%$ responder rate was 42.7%, and the $\geq 50\%$ responder rate was 23.7%. A significant decrease in the use of opioids and anticonvulsants was also seen. The highest treatment response (mean relative change of the NPRS score on days 7–14 to week 12 versus baseline of -36.6%) was seen in patients with a history of pre-existing peripheral neuropathic pain of < 6 months, suggesting that early commencement of treatment may be beneficial.³⁰

The financial implication of using high-concentration capsaicin is a potential area for further research. Only one retrospective study has analyzed the cost-effectiveness of capsaicin 8% compared to other therapies for PHN. It calculated the proportion of patients achieving at least a 30% improvement in PHN pain. The outcome was cost per quality-adjusted life-year. The high-concentration capsaicin patch and topical lidocaine patch were significantly more effective than oral agents used to treat PHN. The incremental cost-effectiveness ratio for the 8% capsaicin patch overlapped with the topical lidocaine patch and was within the accepted threshold of cost per quality-adjusted life-year gained compared to TCAs, duloxetine, gabapentin, and pregabalin. However, there are no parallel studies available for comparison, and the authors acknowledge that the frequency of the 8% capsaicin patch retreatment could significantly impact its cost-effectiveness.³¹

Uses of topical capsaicin for other painful neuropathies

Between 18% and 24% of diabetic patients suffer from peripheral diabetic neuropathy which is difficult to manage given the limited choice of therapeutic agents (TCAs, gabapentinoids, topical lidocaine). No substantial evidence yet supports the use of high-dose capsaicin patch therapy as first line for PDN due to its lower response rate. However, some patients might experience a significant reduction in pain. A prospective observational study of 91 PDN patients treated with a single high-dose capsaicin patch showed a significant

reduction in pain that persisted by week 12 in 34% of the patients.³² HIV-associated distal symmetrical polyneuropathy (HIV-DSPN) is the commonest neurological complication of HIV-infected patients. HIV-DSPN pain can be unresponsive to traditional analgesic therapies. Unfortunately, high-dose capsaicin is not a first-line therapy for this condition due to the relatively higher numbers needed to treat to achieve modest analgesia. A study of 801 HIV-DSPN patients with foot pain showed modest pain relief with 41% of patients demonstrating a 30% reduction in symptoms and a 5-month mean response duration. Of those followed up for 12 months, 10% had complete resolution of pain.²⁵ Topical capsaicin has been evaluated for postsurgical pain in cancer patients via a controlled trial where a 0.075% cream was applied four times a day. Of the total number of patients, 53% (versus 17% of placebo control) experienced a significantly greater pain relief while using topical capsaicin.³³

Summary

In conclusion, the advent of high-concentration capsaicin has eliminated several drawbacks of its low-dose predecessor, which showed poor-to-moderate efficacy in treating PHN pain and required repeated applications resulting in poor tolerance to local irritant side effects and ultimately non-adherence to therapy. High-dose capsaicin patches appear to be safe and effective in treating PHN; the high-dose patch is however not without its disadvantages. Although it does not appear to have any serious systemic side effects, local pain and erythema still pose a challenge to its use in the field of pain medicine. Pretreatment with local anesthetics and oral analgesics can significantly ameliorate these side effects, improve tolerance, and optimize patient adherence. The long-term analgesic benefits of these patches can outweigh short-term painful effects of their application as shown by strong evidence that stemmed from a plethora of high-quality studies including randomized controlled double-blinded trials and systematic reviews. The availability of this novel therapeutic option is a significant development for PHN patients as a large subset are experiencing pain refractory to many oral medications as well as a cumbersome pill burden.

Disclosure

Dr G Baranidharan has consulted for Astellas on advisory Board in 2012. The authors report no other conflicts of interest in this work.

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