REVIEW ARTICLE

ANAESTHESIA, PAIN & INTENSIVE CARE
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Post-herpetic neuralgia in elderly: can topical capsaicin 8% patch be considered as first-line therapy?

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Received: 24 September 2018;
Reviewed: 15 November 2018, 01 January 2019;
Revised: 16 November 2018;
Re-reviewed: 16 November 2018, 26 January 2019;
Revised: 20 December 2018, 01 January 2019;
Accepted: 26 January 2019

ABSTRACT

Post-Herpetic Neuralgia (PHN) is a painful and debilitating complication of Herpes Zoster or Shingles (HZ). HZ is caused by reactivation of Varicella-Zoster Virus (VZV) and manifests as painful skin rash. Persistent pain for three or more months after the healing of HZ rash is termed as PHN. Elderly patients are more susceptible to develop HZ due to age related decline in immunity, a factor attributed to the reactivation of VZV residing in Dorsal Root Ganglion (DRG) after the first exposure. Older age, increased rash severity, severe pain, and female sex are some of the major risk factors for developing PHN following HZ. The risk of having PHN is five times higher in older adults of more than 80 years age while more than 50% of adults older than 70 years with HZ may develop PHN.

Treatment of PHN in elderly is a complex and challenging task. The risk of serious adverse events with oral medications is high due to factors such as polypharmacy for multi morbidity (drug interaction) and altered pharmacodynamic and pharmacokinetic profile (unexpected response, delayed clearance, etc.).

Topical Capsaicin 8% patch is a safe and effective therapy for PHN in elderly patients. It significantly reduces pain for months after single application for 60 minutes and well tolerated even on repeated applications. Capsaicin 8% minimally absorbed into systemic circulation and rapidly metabolized in the liver, therefore the risk of drug interaction is negligible. The pharmacokinetic and pharmacodynamic properties of Capsaicin 8% patch make it a suitable choice to be considered as first line therapy of PHN in elderly patients.

Key words: Neuropathic pain; Post-herpetic neuralgia; Elderly; Capsaicin 8%

Citation: Minhas MR, Aboalkhair A, Alghamdi HH. Post-herpetic neuralgia in elderly: can topical capsaicin 8% patch be considered as first-line. Anaesth. pain & intensive care 2019;23(1)225-230

INTRODUCTION

Post herpetic neuralgia (PHN), a chronic peripheral neuropathic pain condition, is a complication of herpes zoster rash (HZ; Shingles).[1] Herpes Zoster or Shingles are caused by varicella-zoster virus (VZV), a virus which belongs to herpes family, composed of double stranded deoxyribonucleic acid (DNA).[2] First exposure to VZV in early life causes an infection called Chicken Pox, during which, the VZV gains entry into dorsal root ganglion (DRG) and remains dormant for decades following the resolution of the infection. Reactivation of VZV can occur in later life after initial exposure results in HZ which is characterized by painful dermatomal rash.[3] HZ is thought to cause sensory neuronal damage in a manner that residual nerve fibres become hyper excitable and start to produce persistent and unpredictable neural signaling, causing a pain state that is often difficult to manage.[1] Almost 20% of individuals continue to experience pain after the healing of HZ rash. PHN is the term used when the pain persists three months or beyond the healing of herpes zoster rash".[1]

RISK FACTORS

Reactivation of VZV is thought to occur due to a decline in age related cell mediated immunity, therefore, ageing population is at higher risk of developing HZ and PHN. Severe pain during HZ, greater rash severity, severe neurosensory disturbance during acute zoster, a more pronounced zoster immune response, psychosocial distress, immunocompromised state, and female gender are the known risk factors for progression of HZ to PHN.[4,5] A recent study confirms acute zoster episode, prodromal pain (pain felt before lesion develop), severe rash, severe acute pain and ophthalmic involvement are major risk factors for PHN. The same study also confirms that increasing age is the established risk factor for PHN

PREVALENCE OF PHN IN ELDERLY POPULATION

The population of elderly people in the world is increasing at an unprecedented rate. It is estimated that by 2050, 30% of the world population will have adults older than 65 years of age.[7] A decline in cell mediated immunity with advancing age is attributed to a high incidence of HZ or Shingles in older adults, an overall population incidence of 3 per 1000 per year rising to 10 per 1000 per year by 80 years of age.[5] It is estimated that there is a 20% lifetime risk of developing HZ and the disease can affect 50% of people older than 85 years of age. As expected, this may also increase the incidence of PHN among elderly, which is confirmed in a study that 19·5% and 13·7% of patients developed PHN at least 1 and 3 months after HZ diagnosis.[8] Similarly, another study on epidemiology of PHN indicate the risk of having continued pain at 12 months is almost five times higher in adults who are 80 years of age as compared with those less than 80 years of age. Also, it is observed that almost 50% of adults older than 70 years of age reported pain lasting more than one year following the onset of HZ rash. [9]

TOPICAL 8% CAPSAICIN

Capsaicin is a highly selective and potent agonist of the transient receptor potential vanilloid receptor, subtype 1 (TRPV1) channel.[10] TRPV1 channels are highly expressed in the epidermal nociceptive sensory nerve fibres (C and A fibres) of the body area affected by HZ and PHN.[1] Topical administration of capsaicin directly stimulates TRPV1 expressing epidermal nociceptors, causing erythema, a burning sensation and enhanced sensitivity to stimuli.[10] Defunctionalization is thought to occur by multiple mechanisms such as influx of calcium and direct inhibition of electron-chain transport.[10] In a immunohistochemical study done on volunteers (n = 20), a single application of the capsaicin 8% patch for 60 or 120 min resulted in significantly ($p < 0.001$) lower mean ENF density at 7 days compared with a placebo patch resulting in reduced sensitivity to warmth without significant changes in cold sensation.[11] In a similar study (n = 36), a single 60-min application of the capsaicin 8% patch generated reduction in ENF density of almost 80% compared with untreated sites 1 week after exposure in volunteers.[12] Reduction of ENF density following capsaicin exposure is associated with impairment of heat-pain and sharp mechanical-pain sensations.[12] The clinical effect of capsaicin is reversible. It was reported that 24 weeks following capsaicin 8% application, almost full recovery (93%) of ENF density was observed.[12] On clinical examination, there were no significant "between-group differences" in tactile thresholds and sharp mechanical pain detection at weeks 12 and 24.[12]

Systemic absorption from the capsaicin 8% patch is very low. In a population pharmacokinetic analysis, it was noted that approximately 1% of capsaicin 8% dose was absorbed into the epidermal and dermal layers of the skin after a 60-min application and the mean maximum plasma concentration (Cmax) of capsaicin was 1.38 ng/mL after a mean application time of 1.46 h.[13] Capsaicin is metabolized rapidly in the liver by cytochrome P450 (CYP) enzymes resulting in a mean elimination half-life of 1.64 h.[13] No formal drug interaction studies have been performed with the capsaicin 8% patch. Given the low systemic absorption of capsaicin, it is unlikely that any clinically relevant drug interactions would occur or any dose adjustment is required for patients with renal or hepatic impairment.[14]

Role of 8% Capsaicin in PHN

The role of high concentration capsaicin patch (8% in an adhesive layer, NGX04010) is well established in the treatment of PHN. Capsaicin 8% has recently been approved in the EU for the treatment of peripheral neuropathic pain in adults.[15] The recommended dose is a single 60 minutes application of up to four patches. The treatment may be repeated every 90 days if the pain persists or reappears.

The efficacy of Capsaicin 8% patch in PHN has been confirmed in a number of randomized controlled trials and subsequent meta-analysis.

In controlled studies, the 8% capsaicin patch has been compared with an ultra-low-concentration patch (0.04%). In a multicenter, randomized controlled trial, 42% of PHN patients treated with capsaicin 8% patch reported a ≥30% reduction in Numerical Pain Rating Scale (NPRS) score compared with 32% in the active control group (Odds Ratio [OR] 1.56, 95% Confidence Interval [CI] 1.03 to 2.37; $p=0.03$).[16] In this same study, the mean percent change in NPRS score between baseline and weeks 2–12 was -29.9%

in the capsaicin 8% patch group versus -20.4% in the active control group. In another multicenter RCT in PHN, the mean percent change in NPRS score between baseline and weeks 2–8 was –32.0% in the capsaicin 8% patch group versus –24.4% in the active control group ($p=0.011$).[17] In the same study, a ≥30% reduction in NPRS score was achieved in 46% of capsaicin 8% patch-treated patients compared with 34% of active controls ($p=0.02$).

A meta-analysis of seven RCTs investigated the efficacy of capsaicin 8% patch in a number of peripheral neuropathic pain conditions containing 1,120 patients with PHN.[18] The percent change of NPRS score from baseline to weeks 2–12 was –30.7% in the capsaicin 8% patch and –22.7% in the control group, which yielded a group difference of 8.0% (95% CI 4.6, 11.5) ($p<0.001$); the proportion of patients achieving a 30% reduction in pain intensity was 44% for the capsaicin 8% patch-treated patients compared with 34% for control-treated patients.[18] In another meta-analysis of combined individual patient data (1,313 participants with PHN) from seven double-blind RCTs , 44% of patients had a ≥ 30% reduction in pain intensity, and 11% of patients achieved complete pain relief 2–12 weeks after capsaicin 8% patch treatment.[19] In those responding to treatment with capsaicin 8% patch, analgesia started within a few days of treatment and was sustained for an average of 5 months. In a Cochrane Database review of six studies involving 1,272 participants with PHN, it was concluded that capsaicin 8% patch treatment generated greater levels of pain relief than the active control [(20)]. Point estimates of the numbers needed to treat were 8.8 (95% CI 5.3–26) at 8 weeks and 7.0 (95% CI 4.6–15) at 12 weeks.

The highest treatment response, the mean relative change of the NPRS score on days 7–14 to week 12 versus baseline was −36.6% (4.6 SEM; n=105), was seen in patients with a history of pre-existing peripheral neuropathic pain of <6 months, suggesting that early initiation of treatment may be advantageous.[22] ELEVATE trial, a multicenter open label trial comprising of 24% PHN patients, reported Capsaicin 8% patch was non inferior to an optimized dose of oral pregabalin in managing moderate to severe neuropathic pain.[22] According to a specified subgroup analysis, the proportion of Capsaicin 8% patch recipients versus pregabalin recipients achieving a ≥30% decrease in the average NPRS score was 71.4 vs 76.7% (-5.3%; 95% CI -20.1 to 9.5) in patients with PHN. Capsaicin 8% was also associated with high satisfaction score in ELEVATE trial.

In the Qutenza Safety and Effectiveness in Peripheral neuropathic Pain (QUEPP) study, 31.9% PHN cases, mean relative pain intensity during weeks 1–12 decreased by 24.7% and significant reduction in pain attacks, increased sleep duration, and improved sleep quality were reported with Capsaicin 8% therapy.[23] Tolerability:

Overall, the clinical studies showed that the capsaicin 8% patch was generally safe and well-tolerated. The most commonly reported side effects were dermal irritation, erythema, and pain at the site of application. These effects were transient and mild to moderate in severity.

In the ELEVATE trial, treatment related adverse events were reported in 70.9% of capsaicin 8% patch recipients compared with 63.9% of pregabalin recipients. Application-site reactions were most common with the capsaicin 8% patch, while systemic adverse events, such as dizziness, headache, somnolence and nausea, were most common with pregabalin .[22]

An integrated analysis of tolerability indicates that nearly all tolerate NGX-4010 to ≥90% of the treatment duration; 54–64% used medications for application-related pain, and a similar incidence of medication use occurred with repeat applications (up to four times).[24] In the QUEPP study, 146 adverse drug reactions were reported in 106 of 1,063 patients of the safety population (10.0%); the most common among these were application site reactions, such as erythema and pain. NPRS score increases with patch application returned to baseline on average within 85 minutes following the treatment. Transient patch application-related pain was managed with local cooling or oral analgesics in nearly all cases. These findings indicated that patch application-related pain was not a barrier to use.

Cost:

In a cost-effective analysis that compared the Capsaicin 8% patch with existing PHN therapies showed that the cost of treatment with capsaicin 8% patch was comparable to the topical lidocaine patch, however, capsaicin 8% and topical lidocaine had significantly higher effectiveness rates than the oral agents used to treat PHN.[25]

Considerations related to Older Adults:

In general, management of pain in elderly patients is a complex and challenging task due to age related physiologic changes, which include altered drug absorption and decreased renal excretion, sensory and cognitive impairments, polypharmacy for multi morbidity, particularly chronic conditions such as disorders of gait and balance, kidney, lung, and cardiovascular diseases. Therefore, in the elderly patients, systemic treatment of pain usually requires lower dosing, slower titration, and more frequent monitoring for adverse effects than in younger patients.[26,27]

Available guidelines for the pharmacological

management of neuropathic pain suggest antidepressants (tricyclic antidepressants [TCAs], serotonin noradrenaline reuptake inhibitors (SNRI), gabapentinoids, anticonvulsants, opioids, and adjuvant analgesics. A Canadian Guidelines recommends antidepressants and gabapentinoids (TCAs, duloxetine, venlafaxine, gabapentin, pregabalin) as first-line therapies, while tramadol and other opioids as second-line options.[28] Recommendations specific to management of PHN made by European Federation of Neurological Societies (EFNS) are; TCA or gabapentin/pregabalin as first-line treatment in PHN, topical lidocaine may be considered as first line in the elderly, especially if there are concerns regarding the CNS side effects of oral medications, strong opioids and capsaicin cream are recommended as second choice.[29]

Despite the availability of several options, treatment of neuropathic pain in general population is not optimal, that is, less than 50% patients experience satisfactory pain relief and adverse effects are common limiting dose escalation and resulting in suboptimal dosing.[30] Recently, Zoster Quality Of Life (ZQOL) study, a cross-sectional study specifically done on older adults suffering from PHN, reported that almost 60% of the patients reported being in pain "most of the time" or "all of the time" with significant impact on Health-Related Quality of Life (HRQOL) and showed dissatisfaction with the treatment of PHN.[6] The mean age of participants in individual controlled trials for PHN ranges from 70 to 74 years, with a mean of 70.8 (standard deviation [SD] 11.7) years.[16,17] One integrated analysis considered age ranges, indicated that 75% of patients were aged ≥65 years, with 42% aged ≥75 years .[24] Results of these studies are clearly relevant to elderly populations.

As polypharmacy is common in the elderly, there is always a concern of drug interactions and adverse effects. However, due to minimal systemic absorption, topical capsaicin is devoid of such interaction. A reduction in oral medications consumption was observed when topical capsaicin was added to the treatment regimen.[31] In the QUEPP study, the use of opioids and anti-convulsants decreased significantly in capsaicin 8% patch treated patients.[31] Similar benefits were observed with topical lidocaine 5% patches, however, frequent application of patches (maximum 3 per day) for an extended period of time (3 to 4 years) resulted in poor compliance and discontinuation of therapy seen in almost 73% of patients.[32]

SUMMARY AND RECOMMENDATIONS

Treatment of PHN in elderly is complex and challenging due to the presence of co-morbidities and polypharmacy. Limited data available regarding Capsaicin 8% patch in the treatment of PHN in elderly population. Majority of the study subjects in controlled trails of capsaicin 8% patch were elderly patients. However, there is a lack of subgroup analysis on PHN in elderly patients. High quality evidence confirms that topical Capsaicin 8% produces no systemic side effects, has no drug interaction, and reduces the dosage of oral agents in adults. Given the unique pharmacological profile, topical analgesics appear to be an attractive choice to administer earlier in therapy of PHN in elderly patients.

Capsaicin 8% produces extended analgesia following single application. In contrast, multiple topical lidocaine 5% patches are required daily for years. It is recommended that topical Capsaicin 8% patches should be applied by a physician or health care professional at specialist care setting which makes it an expensive modality, almost equal to the cost of topical lidocaine 5% patch. However, with repeated use, experience and some training, Capsaicin 8% patch can be safely administered at primary care setting which may reduce the treatment cost significantly. Therefore, it is recommended that topical Capsaicin 8% be preferably administer as first-line agent in the management of PHN in elderly patients.

Conflict of Interest: None.

Authors contributions: All authors contributed equally in literature search and preparapion of this manuscript

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