Introduction

Post herpetic neuralgia (PHN), a chronic neuropathic pain persisting for more than 3 months after the rash of acute herpes zoster has healed, is debilitating and difficult to manage. It is the commonest complication of herpes zoster (shingles) occurring in 10 to 34% of patients. The increase in incidence and severity with age is a striking feature of PHN. The incidence varies depending on the definitions used to define post heretic neuralgia[1,2]. Globally precise figures on the incidence and prevalence of PHN are hard to obtain because of variable definitions and inadequate data. There is no published data from Sri Lanka on the incidence or prevalence of PHN or herpes zoster. However, herpes zoster and PHN are common conditions seen in primary and secondary health care settings with resistant PHN being referred to tertiary health care institutions.

Most experts agree that pain beyond 90-120 days after onset of rash is true chronic neuropathic pain[3,4]. The course of pain in herpes zoster has 3 phases: an acute herpetic pain that lasts approximately 30 days after onset of rash; a subacute phase that lasts 30-120 days after a rash; and PHN defined as pain that persists at least 120 days after the onset of rash[4,5]. Post herpetic neuralgia that continues six months after the onset of rash is more likely to be persistent for years[6]. PHN has an incidence of 10 to 20%[7]. The quality of life is affected by pain and associated symptoms such as fatigue and insomnia and decreased social activity[7,8].

Risk factors for PHN include older age, prodromal pain, extent and severity of rash and severity of acute herpes zoster pain[9]. Age older than 50 and a visual analogue scale over 5/10 are predictive of persistent pain at 3 months despite early treatment with antivirals[5].

In this update we have discussed different therapeutic options using number needed to treat (NNT) and number needed to harm (NNH). NNT is a measure of effectiveness of an intervention and is treatment specific and describes the difference between active treatment and control in achieving a particular clinical outcome. NNH is similar to NNT but describes adverse events.

Treatment of post-herpetic neuralgia

Post herpetic neuralgia is difficult to treat. There are a variety of treatment options. Randomised controlled clinical trials showed that 30 to 70% of patients with PHN do not achieve satisfactory relief[10]. No single treatment has been shown to be completely effective for all patients. Multimodal analgesic treatment strategy to balance efficacy and tolerability of medication regimen is often needed for the optimal management of post herpetic neuralgia.

Pain control is the mainstay of the treatment which depends on the type and nature of the pain. The nature of the neuropathic pain is variable and there are a variety of different pain mechanisms operating in different patients or in the same patient at different points of time. Therapeutic options could be drugs (oral or topical), nerve block / stimulation and prevention.

Antidepressants

Tricyclic antidepressants (TCAs) amitriptyline, nortriptyline and desipramine seem to be effective. They reduce the pain by inhibiting re-uptake of serotonin and norepinephrine at presynaptic nerve terminal and blocking calcium channels. According to clinical trials and meta-analysis the number needed to treat is 2.1 to 2.6[10]. Amitriptyline and nortriptyline are equally effective, with approximately 50% achieving a good response[11]. In a systematic review of studies in PHN patients minor adverse effects occured in 84% of the patients with a number need to harm (NNH) of 5.67 (3.34-18.58)[10]. Dizziness, sedation and anticholinergic effects were the most frequently reported adverse effects such as dry mouth, gastrointestinal discomfort, constipation, urinary retention, nausea, vomiting, blurred vision, confusion and orthostatic hypotension. Cardiac dysrhythmias such as QT prolongation, torsades de pointes and sudden cardiac death in patients with conduction abnormalities are also reported and review of baseline ECG especially in the elderly and those with a history of cardiovascular disease and hypokalaemia is recommended. These adverse effects are less pronounced at low doses. Starting at a low dose at bedtime and titrating gradually weekly to a target dose is recommended. Nortriptyline and desipramine are better tolerated compared to amitriptyline and considered a better option in the elderly[12]. Duloxetine and venlafaxine are selective serotonin and norepinephrine re-uptake inhibitors (SNRIs) and are used in acute herpes zoster pain and PHN. Clinically they are better tolerated than TCAs[13].

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Anticonvulsants

The exact mechanism of action of pregabalin and gabapentin are unknown. They act at the alpha 2 delta subunits of the voltage gated calcium channels with a consequent release of excitatory neurotransmitters including glutamate. These drugs are excreted unchanged in the urine thus, dose need to be adjusted according to renal function[10]. Studies have shown that the number needed to treat (NNT) is 2.8 for gabapentin for moderate improvement of PHN[14]. Two parallel group studies comparing different dose of gabapentin ranging from 1200mg/day to 3600mg/day showed that gabapentin was efficacious with no significant difference between groups. Pooled results for gabapentin gave a NNT of 4.39 (3.34-6.07). Gabapentin is usually prescribed in 3 or 4 divided dose and side effects include somnolence, dizziness, peripheral oedema and ataxia. These side effects are generally short lived but may require dose adjustment[10]. The analgesic efficacy of pregabalin was established in trials and the pooled NNT for a 50% pain reduction was 4.93 (3.66 - 7.58)[10]. Analgesic efficacy and adverse effect profiles are comparable to gabapentin but occur at a much lower dose. Pregabalin has a more predictable and linear pharmacokinetic profile compared to gabapentin. Titration of dose is rapid and usually prescribed in 2 divided doses[15].

Opioids

Studies have shown that opioids are effective in neuropathic pain including post herpetic neuralgia[10,16]. In a crossover randomised controlled trial, opioids and tricyclic antidepressants significantly reduced pain in post herpetic neuralgia compared to placebo (38.2%, 31.9% and 11.2% pain relief respectively). The number needed to treat was 2.8 for opioids and 3.7 for TCAs[17]. Pooled data from a quantitative systematic review of opioids yielded a NNT of 2.67[10]. Adverse effects of opioids include nausea, pruritus, dizziness, sedation and constipation. Most adverse events improved with time except constipation. Generally use of opioids is not encouraged due to the risk of addiction.

Tramadol

Tramadol, a synthetic 4-phenyl-piperidine analogue of codeine acts on the mu opioid receptor and is also a serotonin and norepinephrine reuptake inhibitor. Thus it has the properties of an opioid and a tricyclic antidepressant. In a randomised clinical trial tramadol (average dose 275mg/day) significantly improved quality of life in patients with PHN and the NNT was 4.8 (2.6-26.9)[10,18]. The wide 95% CI indicates that replication of this study is required before efficacy can be firmly stated. Adverse effects include nausea, dizziness, constipation, somnolence and headache. Concomitant use of SSRIs or selective monoamine oxidase inhibitors may lead to serotonin syndrome and seizures.

Topical lidocaine

A 5% lidocaine patch produces local analgesia without causing anaesthesia and also provides protection from mechanical irritation. Clinical trials in PHN showed that topical lidocaine produces significant reduction of pain and allodynia. Systemic adverse effects are minimal with topical lidocaine. Localised skin reactions have been reported in a small number. Efficacious and long term pain relief is possible within 2-3 weeks of initiation of lidocaine patch[20].

Topical capsaicin

Capsaicin is an alkaloid extracted from hot chilli peppers and acts on afferent nociceptor terminals. The repeated use of topical capsaicin causes depletion of substance P and other neuropeptides form nociceptive fibres (unmyelinated C fibers) resulting in analgesia. The use of capsaicin is limited due to local irritation and burning sensation, especially in PHN with allodynia. It is recommended to apply capsaicin following pretreatment with local anaesthetics[12]. Two parallel group studies compared capsaicin cream (0.075% cream) to placebo and the pooled NNT was 3.26 (2.26-5.85)[10].

Invasive treatments

Nerve block is less commonly used due to the need for expertise and risk of invasion related adverse effects. Epidural block, intrathecal analgesia and sympathetic nerve blocks have limited evidence for efficacy in PHN.

Nerve blocks

Epidural block with local anaesthetics and steroids is not effective in providing long term pain relief in patients with post-herpetic neuralgia[21]. In a systematic review intrathecal treatment was associated with an efficacy in 92% of the patients while efficacy was seen only in 17% of patients with epidural treatment.

However the intrathecal administration of steroids has beneficial effects[22] but increases risk of development of adhesive arachnoiditis. Pooled data in a systematic review showed that intrathecal therapy with lidocaine/methylprednisolone was effective with a NNT of 1.13 (1.05-1.22), but not with intrathecal lidocaine alone[10].

Sympathetic nerve block has beneficial effects in acute herpes zoster but does not provide long term pain relief[21]. There are some reports of long-term pain relief with peripheral nerve block using local anaesthetics but evidence is limited[23].

Spinal cord stimulation

Spinal cord stimulation is useful for chronic neuropathic pain and provides significant long term pain

relief in patients with PHN[24]. Spinal cord stimulation can be a treatment option for the management of intractable pain from PHN.

Vaccination against herpes zoster

Herpes zoster occurs as a result of decreased cell mediated immunity and is more common in elderly. The immunity can be enhanced by endogenous boosting. An episode of zoster boosts the immunity against varicella zoster virus (VZV) and recurrent herpes zoster is uncommon in immunocompetent adults. This is the rationale for developing a zoster vaccine to boost the immunity against VZV in previously exposed individuals. The zoster vaccine is a lyophilized preparation of a live attenuated VZV and is administered as a single subcutaneous injection.

The Shingles Prevention Study, the main efficacy trial[25] showed that vaccination caused significant reduction in the incidence of herpes zoster (51.3%) and PHN (66.5%). The burden of illness (measure of incidence, severity, duration of pain and discomfort) of herpes zoster was reduced by 61.1% and there was a 73% reduction in the number of cases of herpes zoster with severe and chronic pain.

The safety sub-study of the Shingles prevention study showed that few adverse reactions occurred; the most frequent one is the injection site reaction. There were no serious adverse events reported. The vaccine was efficacious over a 4 year follow-up period. Interim analysis of a 10 year follow-up study at 7 years showed that the vaccine significantly reduces the incidence of herpes zoster and the incidence of PHN and the burden of the disease[26].

The vaccine can be administered concomitantly with the influenza vaccine with no reported interactions,[27] however immunogenicity of the zoster vaccine is reduced when administered with pneumococcal vaccine and this combination should be avoided[28].

Conclusion

The incidence of herpes zoster and PHN increases with advancing age. Post-herpetic neuralgia is difficult to treat and may require multiple medications and referral to a pain specialist. Early diagnosis and appropriate pharmacological intervention of herpes zoster decreases the risk of PHN. Results of studies on vaccination against herpes zoster are promising. Sri Lankan demographics show an increased proportion of ageing which may increase the risk of incidence of herpes zoster and PHN. Preventive strategy with herpes zoster vaccination may be a cost effective option in the future.

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