Review Article

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Management of Painful Peripheral Diabetic Neuropathy

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Abstract
Diabetes Mellitus is an endocrine disorder which causes metabolic disturbance producing a state of hyperglycaemia. Hyperglycaemia adversely affects cardiovascular, renal, nervous and visual systems. The importance of good glycaemic control in these patients has been emphasised in literature to reduce the end organ damage. Diabetes can cause autonomic and peripheral neuropathy. The autonomic neuropathy can affect the cardiovascular, genitourinary and gastrointestinal systems. Peripheral neuropathy can cause acute and chronic sensorimotor neuropathy, which can cause significant morbidity in these patients affecting their daily activities and quality of life. It can be challenging to treat them because the pain can be resistant to the medication and the effective medication can be associated with adverse effects which the patients may find difficult to tolerate. It is very important to increase the dose of the drugs to their highest effective dose (within the therapeutic range of that drug) for each patient with a balance of the side effects caused by that drug in that patient. These patients often need more than one drug to provide adequate pain relief. There are guidelines and recommendations available to help the clinicians to use appropriate combination of available treatment options.

Epidemiology:

The WHO estimated that 171 million people had diabetes in the year 2000 and predicted this number to increase to 366 million in the year 2030. Given the increasing prevalence of obesity it is likely that these figures provide an underestimate of future diabetes prevalence[1]. Peripheral diabetic neuropathy (PDN) may be present in 60 to 65% diabetic patients, with 11% patients of diabetic neuropathy complaining of pain. The management of this condition can be particularly challenging as these patients may not get good response to the medications used for the treatment and the medications used are associated with side effects which the patients may find difficult to tolerate.

Pathophysiology:

Pathophysiology of PDN is complex and incompletely understood. Both peripheral and central processes contribute to the chronic neuropathic pain in diabetes. Peripherally at the molecular level due to hyperglycaemia, glycosylated end products are generated, which deposit around the nerve fibres causing demyelination, axonal degeneration and reduction in nerve conduction velocity. Deposition of glycosylated end products around the capillary basement membrane causes basement membrane thickening and capillary endothelial damage, which in association with a hypercoaguable state causes peripheral arterial disease. The peripheral arterial disease leads to neuronal ischemia which worsens nerve damage. There also occurs depletion of NADPH by activation of NADPH oxidase causing increased oxidative stress and generation of oxidative free radicals which aggravate the nerve damage. Calcium and sodium channel dysfunction, changes in receptor expression are the other peripheral processes which cause further neuronal tissue injury. The nerve damage can cause neuronal hyperexcitability. Neurotropic factors are required for nerve regeneration. In diabetes there occurs a low level of both nerve growth factors and insulin-like growth factors resulting in impaired neuronal regeneration. This can lead to peripheral hyperexcitability. Central sensitization is cause by increased excitability at the synapse, which recruits several sub-threshold inputs and amplifies noxious and non-noxious stimuli. Loss of inhibitory interneurons, growth of non-damaged touch fibres into the territory of damaged pain pathways, increased concentration of neurotransmitters and wind up caused by NMDA receptors are responsible for central sensitization at the level of dorsal horn in the spinal cord[2].

Clinical Presentation:

Chronic sensorimotor distal polyneuropathy is the most common type of diabetic neuropathy. Acute sensorimotor neuropathy is rare and is usually associated with diabetic ketoacidosis and acute neuritis caused by hyperglycaemia. Autonomic neuropathy is common and often under reported. It can affect cardiovascular, gastrointestinal and genitourinary system. The other presentations can be cranial neuropathies, thoraco-abdominal neuropathies or peripheral mononeuropathies involving median, ulnar, radial, femoral, lateral cutaneous nerve of the thigh or common peritoneal nerve.

The patients usually complain of one or more of the following symptoms. They can have a chronic continuous or intermittent pain described as burning, aching, crushing, cramping or gnawing pain. The pain can be associated with numbness. They

can have brief abnormal stimulus evoked pain like allodynia or hyperalgesia. Some patients also complain of brief lancinating pains described as electrical or lightening pains which can be spontaneous or evoked. The symptoms typically start in the toes and feet and ascend in the lower limb over years and are worse at night. Diabetic distal polyneuropathy is typically described in glove and stocking distribution but the upper limb involvement is rare. On examination there can be paradoxically reduced sensation to light touch and pin prick in the area of pain. Examination can also show features of allodynia (pain caused by a stimulus that does not normally cause pain), hyperalgesia (pain of abnormal severity in response to a stimulus that normally produces pain), hyperpathia (painful reaction to a repetitive stimulus associated with increased threshold to pain), dysaesthesia (unpleasant abnormal sensation as numbness, pins and needles or burning), paraesthesia (abnormal sensation which is not unpleasant) or evoke electric shock like pains. There can be features of peripheral autonomic neuropathy including vasomotor changes like colour changes of feet which can be red, pale or cyanotic and temperature changes like warm or cold feet. With autonomic neuropathy there can also occur trophic changes which includes dry skin, callouses in pressure areas and abnormal hair and nail growth and sudomotor changes involving swollen feet with increased or decreased sweating. Mechanical allodynia is the most common type of allodynia, but there can be thermal allodynia described as cold or warmth allodynia. Patient often describes cold allodynia as the pain getting worse in cold weather and warmth allodynia can make the patient keep the effected limb cool by using fan or ice bags. There can be reduced joint position sense, reduced vibration sense, reduced temperature sensation and reduced ankle jerks.

Diagnosis:

The diagnosis of PDN can be made by clinical tests using pinprick, temperature and vibration perception (using a 128-Hz tuning fork). The feet should be examined for ulcers, calluses and deformities. Combinations of more than one test have >87% sensitivity in detecting PDN. Other forms of neuropathy, including chronic inflammatory demyelinating polyneuropathy, B_{12} deficiency, hypothyroidism and uraemia, occur more frequently in diabetes and should be ruled out. If required these patients should be referred to a neurologist for specialized examination and testing[3].

Treatment Options:

US Food and Drug Administration has approved duloxetine in 2004 and pregabalin in 2005 for the treatment of painful DPN. Amitriptyline, nortriptyline and imipramine are not licenced for the treatment of neuropathic pain.

NICE clinical guidance on pharmacological management of neuropathic pain in adults in non-specialist settings as shown in Figure 1, recommends duloxetine as the first line treatment, which if contraindicated amitriptyline is suggested to be the first line. Second line treatment is amitriptyline or pregabalin. Pregabalin can be used alone or in combination with either amitriptyline or duloxetine, which if ineffective the patient should be referred to specialist pain services. While awaiting the referral tramadol can be started as the third line treatment. NICE also recommends that these patients should be reviewed to titrate the doses of the medication started, to assess the tolerability, adverse effects, pain reduction, improvement in daily activities, mood, quality of sleep and the overall improvement caused by the medication as reported by the patient[4].

The Mayo clinic recommends[5] the first tier of drugs for peripheral diabetic neuropathy are duloxetine, oxycodone CR, pregabalin and tricyclic antidepressants. The second tier of drugs iscarbamazepine, gabapentin, lamotrigine, tramadol and venlafaxine extended release. The topical agents suggested are capsaicin and lidocaine.

"Evidence Based guideline on treatment of Painful Diabetic Neuropathy", was formulated by American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. A systematic review of the literature between time period 1960 to 2008 was carried out. The review included the articles which looked at the efficacy of a given treatment either pharmacological or non-pharmacological to reduce pain and improve physical function and quality of life (QOL) in patients with PDN. They subsequently recommended that Pregabalin is established as effective and should be offered for relief of PDN (Level A). Venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release), and capsaicin are probably effective and should be considered for treatment of PDN (Level B). Other treatments have less robust evidence or the evidence is negative. Effective treatments for PDN are available, but many have side effects that limit their usefulness, and few studies have sufficient information on treatment effects on function and quality of life[6].

Non-pharmacological techniques:

Letícia et al. following their literature review on therapies used for PDN concluded that for non-pharmacological techniques like acupuncture, reiki, photic stimulation, electromagnetic stimulation of neural electrical stimulation, laser therapy, there is a lack of consensus about their effectiveness and there is scarce knowledge about them. They suggested new researches, including treatments for a longer period of time, with dosimetry control, and representative samples are necessary to discover the actual importance of these therapies for pain relief[7].Spinal Cord Stimulators have however been shown to be effective and safe in severe resistant cases[8,9].

Pharmacological Therapies:

Pregabalin: Pregabalin is a gamma aminobutyric acid analogue which binds to α2δ subunit of calcium channels and modulates them. Its starting dose is 150 mg/day with a maximum dose of 600 mg/day. As 98% of the drug is excreted unchanged in the urine, its dose is reduced in patients with renal impairment (creatinine clearance below 60 ml/min)[10]. A Cochrane Database Systematic Review in 2009 showed that Pregabalin was effective at daily doses of 300 mg, 450 mg and 600 mg, but a daily dose of 150 mg was generally ineffective. The NNT for at least 50% pain relief for 600 mg daily pregabalin dose compared with placebo was 5.0 (4.0 to 6.6) for PDN[11].

Duloxetine: Duloxetine reduces the reuptake of serotonin and noradrenaline at the level of spinal cord, thereby potentiating the descending inhibitory pain pathways to reduce pain. It is started at a dose of 30 mg/day and its dose can be increased to 120mg/day[10]. Sultan et al. in their systematic review found that pain relief achieved with daily dose of 60 mg Duloxetine was comparable with daily dose of 120 mg of Duloxetine. The number needed to treat (NNT) for at least 50% pain relief at 12 to 13 weeks with duloxetine 60 mg versus placebo was 5.8 as compared to NNT of 5.7 for daily dose of 120 mg of duloxetine. The side effects reported with Duloxetine were reduction in appetite, nausea, constipation and somnolence[12]. Systematic Reviews and cohort studies have shown that duloxetine provides overall savings in terms of better health outcomes and reduction in opioid use, in comparison to gabapentin and pregabalin, tricyclic antidepressants and venlafaxine, in pain caused by PDN[13, 14].

Gabapetin: Gabapentin is structurally related to gamma-aminobutyric acid (GABA) but acts by binding to the alpha2-delta subunit of voltage-gated calcium channels and thereby reducing the transmission of neuronal signals. Gabapentin bioavailability is non-linear and it tends to decrease with increasing dose. Gabapentin is not bound to plasma proteins and has a high volume of distribution. It is eliminated unchanged by the kidneys so in elderly patients and in patients with impaired renal function, its dose must be reduced. Gabapentin can be started froma daily dose of 300 to 900 mg and the dose can be increased to a maximum daily dose of 3600 mg over 3 weeks period[10]. Gabapentin provides good pain relief in about one third of patients when taken for neuropathic pain. Adverse events are frequent, but most of them are tolerable[15].

Tricyclic Antidepressants (TCA): Amitriptyline and nortriptyline are the commonly used TCA for PDN. They may be used if there is no benefit from pregabalin or gabapentin and duloxetine. They may be used alone or in combination with pregabalin or gabapentin. In small RCTs, amitriptyline has been found to relieve pain better than placebo in patients with diabetic neuropathy[10.] Amitriptyline is a tricyclic antidepressant with marked anticholinergic and sedative properties. It increases the synaptic concentration of noradrenaline and serotonin in the CNS by inhibiting their re-uptake by the pre-synaptic neuronal membrane. For neuropathic pain it is started at 10-25 mg orally once daily at bed time initially and increased according to response to a maximum of 150 mg/day.

TCA should be used with caution in patients with a history of epilepsy, cardiovascular disorders, deranged liver function, prostatic hypertrophy, history of urinary retention, blood dyscrasias, narrow-angle glaucoma or increased intra-ocular pressure. It's other side-effects are agitation, confusion and postural hypotension in elderly patients[10]. Amitriptyline is the most studied TCA for DPN and has been compared with placebo, imipramine, and desipramine. Amitriptyline, when compared with placebo, reduced pain to a significant degree. Pain relief was evident as early as the second week of therapy, with greater pain relief noted at higher doses (at a mean dose of 90 mg). A decrease in pain was not associated with improvement in mood. A systematic review of the TCAs, including fewer than 200 patients, found no difference in efficacy between the agents[16]. Nortriptyline is associated with fewer adverse events than amitriptyline and therefore it should be preferred in elderly patients.

Opioids: The use of opioids in chronic neuropathic pain has been a topic of debate because of uncertainty about their effectiveness, the concerns about addiction problems, the loss of efficacy with their long term use due to development of tolerance with their long term use and the development of hyperalgesia associated with their use. Cochrane review of twenty-three trials of opiates was carried out. The short-term studies showed equivocal evidence, while the intermediate-term studies showed significant efficacy of opioids over placebo, in reducing the intensity of neuropathic pain. Adverse events of opioids were reported to be common but were not life threatening. The authors recommended the need for further randomized controlled trials to establish long-term efficacy, safety (including addiction potential) and effects on quality of life[17]. In RCT Tramadol/Acetaminophen combination was shown to be associated with significantly greater improvement than placebo ($p < or = 0.05$) in reducing pain intensity, sleep interference and several measures of quality of life and mood[18]. In another RCT, controlled release (CR) oxycodone was compared with placebo, CR oxycodone resulted in significantly lower mean daily pain, steady pain, brief pain, skin pain, total pain and disability. In this study the number needed to treat to obtain one patient with at least 50% pain relief is 2.6[19]. Gabapentin and morphine combination in randomised controlled trial showed that the combination of the two drugs provided better analgesia at lower doses of each drug than either of the drugs used as a single agent[20].

Capsaicin: Capsaicin is the active component of chilli peppers. Capsaicin works by releasing the pro-inflammatory mediators like substance P from the peripheral sensory nerve endings and thereby causes its depletion from the peripheral nerve.

Pharmacological preparations of Capsaicin are available as 0.025% cream, 0.075% cream and 8% capsaicin patches[10]. Repeated application of a low dose (0.075%) cream, or a single application of a high dose (8%) patch has been shown to provide a degree of pain relief in some patients with painful neuropathy. Common side effect includes local skin irritation which causes burning and stinging. It is often mild and transient but sometimes severe and not tolerated by the patients leading to withdrawal from treatment. Capsaicin rarely causes systemic adverse effects. Capsaicin can be used either alone or in combination with other treatment to provide useful pain relief in individuals with neuropathic pain[21].

5% Lidocaine medicated plasters: A recent systematic review showed that 5% Lidocaine medicated plaster causes pain relief comparable to pain relief caused by amitriptyline, capsaicin, gabapentin and pregabalin in treatment of painful diabetic peripheral neuropathy. Lidocaine plaster being a topical agent may be associated with lesser clinically significant adverse events than the side effects of systemic agents. The need for further studies has been recommended by the reviewer as limited number and size of studies were included in the systematic review [22].

Conclusion:

The American Academy of Neurology, Mayo Clinic and NICE have both developed guidelines for treatment of peripheral diabetic neuropathic pain. There are several peripheral and central pathological mechanisms leading to the development of this condition and no single drug is available to target all these pathological mechanisms. Therefore often a combination of drugs is required for their management. Despite using a combination of medicines, managing these cases can be challenging. At the same time there is limited evidence on combination therapy in diabetic neuropathy and much work is required in this area. While using opioids for this condition the controversies over the use of opioids in non-malignant pain should be kept in mind and the advantages and disadvantages of using them should be discussed with the patients. Opioids should only be started with patient's consensus. The treatment should be modified from the guidelines on an individual basis to achieve the optimal pain relief.

Competing Interests
None
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