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NEUROPATHIC PAIN

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SUMMARY – Neuropathic pain refers to pain that originates from pathology of the nervous system. Common causes of neuropathic pain are diabetes mellitus, reactivation of herpes zoster, nerve compression or radiculopathy, alcohol, chemotherapy or abuse of some drugs, and trigeminal neuralgia. Specific symptoms of neuropathic pain are mechanical allodynia and cold hyperalgesia. Drugs to treat neuropathic pain can be divided into adjuvant analgesics (antidepressants and anticonvulsants), opioids and topical agents. The use of multiple drug therapies is common in practice. Despite considerable increase in the number of randomized placebo-controlled trials in neuropathic pain in the last few years, the medical treatment of neuropathic pain is still far from being satisfactory, with less than half of patients achieving significant benefit with any pharmacological drug.

Key words: *Neuralgia – drug therapy; Pain – treatment; Pain measurement; Analgesics – therapeutic use; Drug therapy – combination*

Introduction

Neuropathic pain is defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system'[1]. Neuropathic pain, in contrast to nociceptive pain, is described as 'burning', 'electric', 'tingling', and 'shooting' in nature. It can be continuous or paroxysmal in presentation. Whereas nociceptive pain is caused by the stimulation of peripheral of A-delta and C-polymodal pain receptors by algogenic substances (e.g., histamine bradykinin, substance P, etc.), neuropathic pain is produced by damage to, or pathologic changes in the peripheral or central nervous systems.

Examples of pathologic changes include prolonged peripheral or central neuronal sensitization, central sensitization related damage to the nervous system inhibitory functions, and abnormal interactions between the somatic and sympathetic nervous systems. The hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Allodynia is defined as pain resulting from a stimulus that ordinarily does not elicit a painful response (e.g., light touch). Hyperalgesia is defined as an increased sensitivity to normally painful stimuli. Primary hyperalgesia, caused by sensitization of C-fibers, occurs immediately within the area of the injury. Secondary hyperalgesia, caused by sensitization of dorsal horn neurons, occurs in the undamaged area surrounding the injury.

It can be a debilitating and difficult condition to treat and is often resistant to simple analgesics, requiring additional analgesic approaches[2]. It is not only devastating for patients but also places considerable demands on the society, including financial burdens relating to healthcare costs, workplace disruption, disability and benefits[3].

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Neuropathic Pain Mechanisms

Neuropathic pain is generated by electrical hyperactivity of neurons along the pain pathways. The sensory pathway consists of at least three neurons, and lesions anywhere along the pathway can lead to neuropathic pain. Changes in the expression of neuronal ion channels and receptors, synaptic connectivity, and anatomy all contribute to neuropathic pain (neural plasticity)[4,5]. Clinical investigations of pain mechanisms are labor intensive and require specialized equipment; thus, they are not yet practical for routine clinical use. Even in specialized pain research settings, it is difficult to identify specific neuropathic pain mechanisms. A simple focal peripheral nerve injury unleashes a range of peripheral and central nervous system processes that can all contribute to persistent pain and abnormal sensation[6].

Inflammation, reparatory mechanisms of neural tissues in response to injury, and the reaction of adjacent tissues to injury lead to a state of hyperexcitability in primary afferent nociceptors, a phenomenon termed peripheral sensitization. In turn, central neurons innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability termed central sensitization. Normally these sensitization phenomena extinguish themselves as the tissue heals and inflammation subsides. However, when primary afferent function is altered in an enduring way by injury or disease of the nervous system, these processes persist and may be highly resistant to treatment[7,8].

Injury or permanent loss of primary afferent fibers (deafferentation) differentiates peripheral neuropathic pain from other types of pain. Positive sensory phenomena (spontaneous pain, allodynia, and hyperalgesia) that are characteristic of patients with neuropathic pain are likely to have many underlying mechanisms, including ectopic generation of impulses as well as the *de novo* expression of neurotransmitters and their receptors and ion channels. Direct injury to central structures may permanently alter sensory processing, and in some patients it causes central neuropathic pain and dysesthesias. The mechanisms underlying central neuropathic pain, however, are still unclear[9-11].

Increased understanding of the underlying mechanisms has allowed for identification of new pharmacological targets and development of new neuropathic medications; however, so far it has not helped identify patients that are likely to respond to individual treatments.

Diagnosis of Neuropathic Pain

Neuropathic pain syndromes typically have both negative and positive sensory symptoms and signs[12]. Nonsensory neurologic symptoms and signs depend on the underlying cause and may independently contribute to pain and disability. Although neuropathic pain has been defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system", several investigators have recently argued that the inclusion of the term 'dysfunction' makes this definition vague and unacceptably broad[5]. The proposed solution is to define neuropathic pain as pain caused by a lesion of the peripheral or central nervous system (or both) manifesting with sensory symptoms and signs. Demonstrating a lesion of the nervous system compatible with particular symptoms and signs provides strong support for considering the pain to be neuropathic. However, when no lesion can be demonstrated, the limits of current diagnostic technology do not always allow for the possibility of neuropathic pain to be excluded. The diagnosis of neuropathic pain is based on medical history, review of systems, physical and neurologic examination, and appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging, and electrophysiologic studies[13]. In some instances, nerve or skin biopsy is necessary to visualize nerve fibers directly.

Our ability to translate pain complaints and sensory findings into specific pathophysiologic mechanisms that have treatment implications is in its infancy[7,14,15].

Treatment

Regardless of the cause, neuropathic pain affects multiple aspects of the patient's life. The management of neuropathic pain involves a multidisciplinary approach. Therapy for neuropathic pain includes the use of both non-interventional (pharmacological, psychological, and physical therapy) and interventional therapies.

Without due concern of the diagnosis, rehabilitation, and psychosocial issues, treatment has a limited chance of success. For peripheral nerve lesions, mobilization is needed to prevent trophic changes, disuse

atrophy, and joint ankylosis. Surgery may be needed to alleviate compression. Psychological factors should be constantly considered from the start of treatment. Anxiety and depression should be treated appropriately. When dysfunction is entrenched, patients may benefit from comprehensive approach provided by a pain clinic.

Pharmacotherapy

The best clinical approach to applied pharmacology currently incorporates empiric observation and identification of the possible mechanisms of neuropathic lesion and then uses the best available pharmacological information to match these potential disease mechanisms with putative drug mechanisms. Although monotherapy is the ideal approach, rational polypharmacy is often pragmatically used.

Several classes of drugs are moderately effective, but complete or near-complete relief is unlikely. Antidepressants and anticonvulsants are most commonly used. Evidence of efficacy is strong for several antidepressants and anticonvulsants.

Opioid analgesics can provide some relief but are less effective than for nociceptive pain; adverse effects may prevent adequate analgesia. Topical drugs and a lidocaine-containing patch may be effective for peripheral syndromes. Sympathetic blockade is usually ineffective except for some patients with complex regional pain syndrome[16,17].

Antidepressants

Tricyclic antidepressants (TCAs) are often regarded as first-line drugs for neuropathic pain. A recent systematic review of the literature, in which numbers needed to treat (NNTs) of treatments for different neuropathic pain syndromes were calculated, has found TCAs to be the most efficacious drugs for neuropathic pain (NNT 3.1; 95% confidence interval (CI) 2.7-3.7)[19,20]. This is based on the results from no less than 15 placebo-controlled designed trials, which uniformly demonstrated efficacy of amitriptyline, nortriptyline, desipramine, chlomipramine, imipramine and maprotiline, at a daily dose range of 30-200 mg, for post-herpetic neuropathy (PHN) and diabetic painful neuropathy (DPN)[21]. The main drawback of these trials is the small number of recruited patients in each of them. Yet, taken together, they provide a strong level of evidence for efficacy. Notably, two small trials found TCAs to be superior to placebo for central post-stroke pain and post-mastectomy neuropathic pain, whereas several others failed to demonstrate efficacy for spinal-cord injury pain, human immunodeficiency virus (HIV) neuropathy and phantom limb pain. Unfortunately, TCAs are associated with numerous adverse events and are not tolerated by many patients. When used, slow titration is required, especially in the elderly[22].

Two trials demonstrated efficacy of the selective serotonin reuptake inhibitors (SSRIs) citalopram and paroxetine (both at 40 mg/day) in DPN[23]. In another trial, fluoxetine was equal to placebo[24].

The selective serotonin and norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine are newer antidepressants that have shown efficacy for DPN at daily doses of 150- 225 mg and 60-120 mg, respectively. The NNTs of 4.6 (CI 2.9-10.6) for venlafaxine and 5.2 (CI 3.7-8.5) for duloxetine are superior to that of SSRIs but inferior to TCAs[6]. In two large randomized controlled trials (RCTs), duloxetine also significantly improved sleep and quality of life. Its most common adverse events are nausea, somnolence, dizziness and constipation, which all tend to decrease over time. The drug should not be used concomitantly with monoamine oxidase (MAO) inhibitors or in patients with impaired liver function. One notable advantage of the antidepressants (with the exception of venlafaxine) is that they can be administered once daily[25,26].

Side effects of tricyclic antidepressants

The most common side effects of TCAs are dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary hesitation. More selective TCAs such as nortriptyline are better tolerated than the non-selective ones, with less anticholinergic effects and sedation. A suspected association between TCA treatment and sudden cardiac death has raised concern; a recent epidemiological study found a slight increase in sudden cardiac death with TCA doses greater than 100 mg/day. Therefore, caution is recommended in older patients, particularly those with cardiovascular risk factors.

The SNRIs (duloxetine, venlafaxine) are safer to use than TCAs and are a better option in patients with cardiac disease. The relative risk of withdrawal due to side effects is weak and there is no need for drug level monitoring. The most frequently observed adverse events with duloxetine are nausea, vomiting, constipation, somnolence, dry mouth, hyperhidrosis, loss of appetite and weakness. Although immediate release of venlafaxine is associated with adverse central nervous system (CNS) and somatic symptoms such as agitation, diarrhea, increased liver enzymes, hypertension and hyponatremia, the extended release formulation seems to be by far more tolerable, the main side effects being gastrointestinal disturbances.

Anticonvulsants

In addition to antidepressants, selected anticonvulsants are often regarded as first line drugs for neuropathic pain. Randomized clinical trials (RCTs) have shown the efficacy of gabapentin, pregabalin, lamotrigine, carbamazepine and, to a lesser extent, some other anticonvulsants. Yet, with the exception of trigeminal neuralgia, the challenge of 50% pain relief in more than half of these patients is rarely met[26,27].

The most extensively studied drug in this class is pregabalin, which has shown efficacy for (PHN) and (DPN) in a large number of multicenter RCTs. The effective daily dose of 300-600 mg can reduce pain and improve sleep, functioning and quality of life. Pregabalin can be rapidly titrated. Unfortunately, the drug has not been studied in other types of neuropathic pain. The most commonly reported adverse events occurring during all controlled clinical trials were dizziness, somnolence, dry mouth and edema. Weight gain can also be a problem in some patients[28].

There is also strong evidence for the efficacy of gabapentin (900-3600 mg/day) for PHN and DPN. Although less broadly studied in other syndromes, gabapentin has shown efficacy in HIV-associated painful neuropathy, pain in Guillain-Barré's syndrome, phantom limb pain, cancer related neuropathic pain and complex regional pain syndrome type I[27]. RCTs have shown efficacy of lamotrigine for DPN, central post stroke pain, trigeminal neuralgia and mixed neuropathies, and of carbamazepine and oxcarbazepine for trigeminal neuralgia, DPN and mixed neuropathies. The need for a relatively slow titration and the adverse effect profile of these drugs make them a second line of antiepileptic treatment for these conditions, except for trigeminal neuralgia. Equivocal or negative (active therapy not superior to placebo) results were reported with lamotrigine for spinal cord injury pain, HIV-related neuropathy and mixed neuropathies, with topiramate for PDN, and with valproate for DPN and spinal cord injury pain[29].

Side effects of anticonvulsants

Carbamazepine entails frequent adverse events, which include sedation, dizziness, and gait abnormalities. Liver enzymes, blood cells, platelets and sodium levels should be monitored for at least one year because of the possible risk of hepatitis, anaplastic effects or hyponatremia. The induction of microsomal enzyme systems may influence the metabolism of several drugs. In contrast to carbamazepine, oxcarbazepine does not entail enzymatic induction and there is little risk of crossed cutaneous allergy. In the first months of treatment, sodium levels should be monitored because oxcarbazepine, like carbamazepine, induces hyponatremia, particularly in the elderly (6% in a cohort of 54 patients). As regards other side effects, although better tolerance has been claimed with oxcarbazepine as compared with carbamazepine, this notion lacks coxnsistent evidence from class I trials. In a recent trial in diabetic painful polyneuropathy, 27.5% of the oxcarbazepine group *versus* 8% of the placebo group discontinued treatment due to central or gastrointestinal side effects.

The most common side effects of gabapentin and pregabalin include dizziness, somnolence, peripheral edema, and dry mouth, with a similar frequency for both drugs. Whilst gabapentin is widely accepted as highly tolerable even at high dosages (>2400 mg), the reports on pregabalin change remarkably with the daily dose: with 150 to 300 mg there is almost no difference from placebo, whilst the withdrawal rate reaches 20% with 600 mg.

Lamotrigine is generally well tolerated. Side effects include dizziness, nausea, headache and fatigue. However, it may induce potentially severe allergic skin reactions. Lamotrigine should not be used in combination with valproate.

Opioids

Eight RCTs tested the efficacy of oral opioids for PDN, PHN, phantom pain and neuropathic pain of diverse etiologies. Four drugs were tested: morphine, oxycodone, methadone and levorphanol. All trials reported that opioids were efficacious in reducing spontaneous neuropathic pain by demonstrating either superiority to placebo or a dose-dependent analgesic response. Six of the eight studies were recently pooled to a meta-analysis, which found a mean pain intensity to be by 14 points lower in opioid-treated patients than in those treated with placebo (95% CI -18 to -10; $P<0.001$)[16,17]. The overall NNT of opioids for neuropathic pain is 2.5 (CI 2.0-3.2). Secondary outcome parameters such as physical and mental health, sleep and disability were measured in parts of these trials and yielded inconsistent results. Tramadol, which is not a typical opioid, yet has a weak affinity for opioid receptors, has been effective for DPN and PHN with NNT of 3.9 (CI 2.7-6.7)[5]. Common adverse events of opioids include nausea, constipation, dizziness and drowsiness.

Side effects

The most common side effects of opioids are constipation, sedation, nausea, dizziness and vomiting. The risk of cognitive impairment has been reported to be negligible, although morphine may impair attention at very high dosages. Tramadol has been reported to induce dizziness, dry mouth, nausea, constipation and somnolence with significantly more dropouts compared with placebo. There is an increased risk of seizures in patients with a history of epilepsy or receiving drugs which may reduce the seizure threshold. Serotonergic syndrome (various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, fever, nausea, diarrhea, flushing, and rarely, rhabdomyolysis and death) may occur if tramadol is used as an add-on treatment to other serotonergic medications (particularly selective serotonin reuptake inhibitors, SSRIs).

Topical Agents

Topical capsaicin cream has shown efficacy for DPN and PHN but its use is associated with burning, particularly during the first weeks of treatment. This can pose major problems, especially in patients primarily experiencing allodynia. Some studies report on patients that had seen an average of eight different physicians prior to referral to the pain clinic[30,31].

The application of topical lidocaine patches was found effective for PHN in three short-term RCTs and can also be used in patients with other focal peripheral neuropathies[32,33].

Drug Combinations

While combinations of drugs with different mechanisms of action are commonly used in clinical practice, only one trial tested the efficacy and safety of a combination of two drugs, and found that gabapentin plus morphine was more efficacious and safer than either drug alone[16]. This trial implies the possibility that polypharmacotherapy could enhance analgesia with fewer side effects.

Noninvasive Therapies

One of the simplest forms of noninvasive treatment for pain is transcutaneous electrical nerve stimulation (TENS). It has been used since the 1960s, following the development of the gate control theory of pain transmission by Melzack and Wall[8]. The technique is based on the interaction between small and large afferent fibers, which converge on the dorsal horn neurons before projecting to higher centers, and is a useful adjunctive treatment that is virtually free from adverse effects[34].

Invasive Therapies

The range of neurosurgical techniques used to treat neuropathic pain has increased over time and includes nerve modulation (e.g., dorsal column stimulation) and ablation[34]. Numerous ablative surgical techniques to destroy nerves have been described, including nerve avulsion or section, dorsal rhizotomy, spinal dorsal root entry zone lesions, spinothalamic tractotomies, thalamotomies, cingulotomy, frontal lobotomy, and even destruction of the primary sensory cortex. However, these treatments are generally not recommended as they cause more damage to the nervous system, which can intensify the neuropathic pain. Furthermore, none of these surgical techniques has been found to be uniformly successful in treating patients with neuropathic pain. Indeed, there are

many examples in the literature of patients who have undergone surgical therapies to treat pain (e.g., due to nerve injury, trigeminal neuralgia, amputation, or post-herpetic neuralgia), only to find that surgery has exacerbated their original pain.

An invasive treatment regimen that is supported by some clinical evidence, and a fairly convincing rationale, is spinal cord dorsal column stimulation. As with TENS, this technique attempts to modulate rostral nociceptive transmission in the spinal cord by stimulation of the large diameter nerve fibers. Success depends on patient selection, and it is generally accepted that patients also suffering some ischemic pain are particularly suited for this method of treatment[35]. The major advantage of this technique is that nerves are not deliberately damaged. Similarly, clinical evidence supports the use of microvascular decompression in providing relatively good long-term outcome for patients with trigeminal neuralgia[36]. Temporary nerve blocks achieved by injection of local anesthetic (e.g., lidocaine) are still sometimes used, although their efficacy is controversial and few placebo-controlled trials of this therapy have been performed[5].

The available data clearly indicate that approaches to the clinical management of neuropathic pain vary according to whether the patient is being treated by a pain specialist or by a non-specialist. While non-specialists tend to treat individual symptoms, pain specialists are more likely to select a drug therapy that is targeted towards the mechanisms that are presumed to be causing pain in an individual patient or the anti-neuralgic mechanisms of various drugs[6]. The available data clearly indicate that patients treated in specialized pain clinics are more likely to receive therapies with proven efficacy for the treatment of neuropathic pain than those treated in non-specialist clinics[37-40].

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Sažetak

NEUROPATSKA BOL

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Neuropatska bol nastaje kao posljedica disfunkcije perifernog ili središnjeg živčanog sustava. Najčešći uzroci neuropatske boli su dijabetes melitus, reaktivacija infekcije herpes zoster, kompresija živaca ili radikulopatija, pretjerana konzumacija alkohola, kemoterapija ili zlouporaba lijekova te neuralgija trigeminusa. Specifični simptomi neuropatske boli su mehanička alodinija i hladna hiperalgezija. U liječenju neuropatske boli rabi se nekoliko skupina lijekova. U prvu skupinu spadaju adjuvantni lijekovi, a to su antidepresivi i antiepileptici, opioidi i lokalna sredstva. U praksi se najčešće rabi kombinacija dviju ili više vrsta lijekova. Unatoč brojnim randomiziranim, placebom kontroliranim studijama na području neuropatske boli medikamentno liječenje neuropatske boli još uvijek nije zadovoljavajuće, te se zadovoljavajuća analgezija postiže u samo 50% bolesnika s neuropatskom boli.

Ključne riječi: *Neuralgija – terapija lijekovima; Bol – liječenje; Mjerenje boli; Analgetici – terapijska primjena; Terapija lijekovima – kombinirana*