Localized neuropathic pain

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Abstract

Localized neuropathic pain (LNP) is of peripheral origin and is characterized by circumscribed areas of pain with abnormal skin sensitivity or spontaneous symptoms that are characteristic of neuropathic pain, e.g., burning pain. It should be noted that LNP is confined to a specific area no larger than a letter size sheet of paper. LNP accounts for 60 % of neuropathic pain syndromes. There is no single etiology of LNP. The diagnostic approach is similar to that for other neuropathic pain conditions. General diagnostic tools are used to assess clinical features. So far, there are no specific guidelines for the management of LNP; for this reason, guidelines for general neuropathic pain are used. Topical treatments are included as part of second-line strategies in the Canadian Pain Society guidelines. Despite the lack of guidelines, 5 % lidocaine patches and 8 % capsaicin patches have been proven effective in LNP models.

KEY WORDS: Localized neuropathic pain. Pain topical treatment. Lidocaine patch. Capsaicin patches.

Dolor neuropático localizado

Resumen

El dolor neuropático localizado (DNL) es de origen periférico y se caracteriza por áreas circunscritas de dolor con sensibilidad anormal de la piel o síntomas espontáneos característicos de dolor neuropático, por ejemplo, dolor urente. Se debe resaltar que el DNL está confinado a un área específica no mayor a una hoja de papel tamaño carta. El DNL representa 60 % de las condiciones de dolor neuropático. No existe una única etiología. El abordaje diagnóstico es similar al de otros síndromes dolorosos neuropáticos. Se utilizan herramientas diagnósticas generales para evaluar las características clínicas. En la actualidad no existen guías específicas de manejo del DNL, por lo que se utilizan las guías para dolor neuropático en general. En las guías de la Sociedad Canadiense de Dolor se incluyen los tratamientos tópicos como parte de las estrategias de segunda línea. Pese a la falta de guías, los parches de lidocaína a 5 % y los parches de capsaicina a 8 % han demostrado ser efectivos en modelos de DNL.

PALABRAS CLAVE: Dolor neuropático localizado. Tratamiento tópico del dolor. Parche de lidocaína. Parches de capsaicina.

Introduction

Neuropathic pain is defined as pain that is secondary to a disease or lesion that affects the somatosensory system.¹⁻³ This type of pain has several presentation

forms: it can be continuous or recurrent episodic, and clinical features can refer to models of evoked or spontaneous pain. Neuropathic pain descriptors include burning, tingling, hyperalgesia, allodynia, electric shock sensation, pain to cold or heat, and numbness.¹ Both

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the expression of increased sensation to a stimulus that can cause pain (hyperalgesia) or pain response to an innocuous stimulus (allodynia) are objective descriptors that can accompany neuropathic pain.⁴

As for temporality, neuropathic pain can be acute or chronic; duration of the former is less than three months, and that of the latter, longer than that time.¹

According to the level of nervous system compromise, neuropathic pain is divided into central neuropathic pain, when there is spinal or supra-spinal cord compromise, and peripheral, when involvement is prior to spinal cord relay.^{5,6}

Localized neuropathic pain (LNP) is peripheral in origin and is characterized by circumscribed areas of pain with abnormal skin sensitivity or spontaneous symptoms, characteristic of neuropathic pain, e.g., burning pain. In addition, it should be noted that LNP is confined to a specific area not larger than a letter-size paper sheet.^{6,7}

The prevalence of peripheral neuropathic pain is approximately 2 % in the general population and 8 % in patients older than 55 years of age.⁸ Diabetic neuropathy is the leading cause of neuropathic pain in the world.^{9,10} LNP accounts for 60 % of neuropathic pain conditions.⁶

The main causes of LNP are associated with the following conditions:^{6,10,11}

- Infections (varicella zoster or human immunodeficiency virus).
- Metabolic diseases (diabetes mellitus, alcoholism, vitamin B₁₂ deficiency).
- Nutritional deficiency conditions.
- Toxic causes (ethanol, chemotherapy).
- Surgeries (thoracotomy or mastectomy, cesarean section, arthroscopy or arthroplasty, saphenectomy, inguinal surgery, cholecystectomy, among others).
- Nerve entrapments (Morton's neuroma, tarsal and carpal tunnel syndrome).
- Pathologies affecting nerve radicle (radiculopathy sequelae, low back pain, neuralgia, cervicobrachial syndrome).
- Complex regional pain syndrome type 1.

Neuropathic pain qualitative characteristics lead to the assumption of this disorder; however, recent development of diagnostic questionnaires has helped detecting clinical components of neuropathic origin in a simple, quick and specific way. These screening tools are the DN4 questionnaire, painDETECT, the Neuropathic Pain Symptom Inventory (NPSI) and the LANSS scale.⁵ For LNP clinical diagnosis there is also

a tool called the Diagnostic Tool.^{4,6,13,14} In general, neuropathic pain diagnosis is established through medical history, physical examination, and confirmatory tests.¹⁴

As for the management of LNP, three stages have been proposed:^{2,5}

1. Screening and diagnosis
2. Treatment
3. Follow-up model

Once clinical diagnosis has been established, neuropathic pain treatment is aimed at reducing the symptoms and improving patient functionality (Fig. 1).^{7,10,15}

There are different publications where reference is made to the pharmacological algorithm for the patient with neuropathic pain (Table 1).^{16,17}

It is important pointing out that if the patient presents with extreme hyperalgesia or uncontrollable symptoms despite appropriate treatment, referral to a specialist is recommended, regardless of the stage of treatment and care, for diagnostic reassessment.²

There are no specific guidelines or treatment recommendations for LNP, which is why those that exist for neuropathic pain in general are used.¹²

The European Federation of Neurological Societies and the International Association for the Study of Pain recommend the use of tricyclic antidepressants, anti-convulsants, and serotonin and norepinephrine reuptake inhibitors as the first option in the treatment of peripheral neuropathy; however, effectiveness occurs in approximately 30 to 40 % of patients, which is related to the adverse effects of these drugs, which decrease the quality of life.^{5,18,19,20}

The Canadian Pain Society guidelines refer that, for LNP, in addition to standard treatments, topical use of lidocaine is included as second-line treatment.¹⁷

It should be mentioned that non-steroidal anti-inflammatory drugs and paracetamol have not been shown useful in the treatment of neuropathic pain.⁵

The management of neuropathic pain is a clinical and therapeutic challenge, which sometimes does not show favorable results for months or even years. For this reason, different societies, including the Neuropathic Pain Special Interest Group (Neupsig, from the International Association for the Study of Pain), the European Pain Federation, and the Canadian Pain Society, have proposed stepwise treatments for the management of chronic neuropathic pain and their levels of evidence, which are described in Table 2.^{2,5,12,19,20,21}

In the particular case of LNP treatment, the use of topical agents is justified, unless there is any contraindication

Figure 1. Localized neuropathic pain detection tool. Modified from Mick G et al.: Is an easy and reliable diagnosis of localized neuropathic pain (LNP) possible in general practice? Development of a screening tool based on IASP criteria.¹⁰

Table 1. Neuropathic pain step by step pharmacological treatment

1. Evaluation and diagnosis establishment
– Establish and treat neuropathic pain cause
– Identify relevant comorbidities
– Explain the diagnosis, plan and treatment to the patient
2. Start symptom treatment with one or more of the following options:
– Selective serotonin and norepinephrine reuptake antidepressants
– α 2- δ calcium channel ligands
– Lidocaine 5 % patches
– Opioid analgesics or tramadol, in selected clinical circumstances
– Non-pharmacological treatments, after evaluation
3. Reassessment of pain and health-related quality of life
– If pain was substantially relieved and adverse side effects are tolerable, continue treatment
– If pain did partially improve, adjust initial dose of the drug or add another first-line agent
– If there is no adequate pain control, switch to other first-line drug
4. If first and second line pharmacological treatments fail, consider other first-line drugs or refer to pain specialist.

Source: Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations.¹⁶

such as lesion, atrophy or infection of the affected area of the body.^{16,30,31} This therapeutic model offers the following benefits:^{2,15,31,32}

- It decreases LNP and prevents adverse effects that might occur with oral treatment.¹⁶
- Doses are lower than orally-administered drugs total doses.²
- The risk of overdose and drug interactions is much lower than with orally administered drugs.²
- It reduces polypharmacy, especially in older adults.^{2,32}

In the treatment of LNP, anesthetics, muscle relaxants, anti-inflammatory drugs, antidepressants or a combination of these drugs have been used; however, some of them lack the level of evidence to support their use in this type of pain (Fig. 2).^{16,33}

Topical agents that are used in the treatment of LNP include:

- Lidocaine 2.5 % and prilocaine 2.5 % emulsion, which is the most widely used topical anesthetic in the management of LNP.²

Table 2. Neuropathic pain management, treatment lines and evidence

Treatment line	Drug	Mode of action	Dose	Indications	Adverse effects	Observations
First line	Immunomodulator					
	Pregabalin	Binding to voltage-gated calcium channel $\alpha 2\text{-}\delta$ subunit and NT release inhibition ^{16,22,23}	Initial dose 150 mg/day, with maximum dose of 600 mg/day (divided in doses every 12 or 8 hours) ^{15,16,24}	Post-herpetic neuralgia, neuropathic pain secondary to spinal cord injury, and diabetic neuropathy ^{16,25}	Somnolence, anxiety and dizziness ¹⁵	Level of evidence: high ^{15,24}
	Gabapentin		1200-3600 mg/day (divided in doses every 8 hours) ^{16,24,25}	Post-herpetic neuropathic pain, diabetic neuropathy, phantom limb pain, Guillain-Barré syndrome, neuropathic pain secondary to neoplastic process, and acute or chronic pain from spinal cord injury ^{16,25}	Somnolence, dyskinesia, transient dizziness and, to a lesser extent, peripheral edema, cognitive or gait impairment ^{15,16}	Level of evidence: high ^{15,24}
Second line	Tricyclic antidepressant					
	Amitriptyline	Serotonin and norepinephrine reuptake inhibitor, blocks NMDA and calcium channels ^{16,22}	Initial dose 10 to 25 mg/day up to a maximum dose of 150 mg/day ^{15,16}	Post-herpetic neuralgia and secondary to diabetic neuropathy	Anticholinergic symptoms (xerostomia, constipation, urinary retention), sedation, orthostatic hypotension or cardiotoxicity ^{7,9,15,22}	Level of evidence: high ¹⁵
	SNRI					
Second line	Duloxetine	Serotonin and norepinephrine reuptake inhibitors ^{16,22,23}	60-120 mg/day ^{16,24}	Pain secondary to diabetic neuropathy ^{16,22}	Nausea (there are no changes in blood pressure or electrocardiographic) ^{16,22}	Level of evidence: high ^{15,24}
	Venlafaxine		Initial dose 150 mg/day, up to a maximum dose of 225 mg/day ^{15,16,24}		Changes in electrocardiographic tracing ^{16,22}	Level of evidence: high ^{15,24}
	Tramadol	μ -opioid receptor agonist and serotonin and norepinephrine reuptake inhibitor ^{16,22}	Initial dose 50 mg every 6 hours, up to a maximum dose of 400 mg every 6 hours ^{16,24}	Post-herpetic neuropathic pain, post-amputation pain, and other polynuropathies ^{16,24}	Somnolence, dyskinesia, nausea, constipation, orthostatic hypotension ^{6,9,16}	Level of evidence: moderate ^{15,24}
Second line	Capsaicin	Binding to TRPV1 receptor, which favors Ca^{2+} permeability for receptor "de- functionalization" ¹⁶	Capsaicin 8 % patch (14 x 20 cm with 179 mg) ¹⁶	Localized neuropathic pain secondary to infection, post-herpetic neuropathic pain ^{*16,22,26,27}	Pain, erythema, itching, papules, dryness and transient burning of mild-moderate intensity in the area of application ¹⁶	Level of evidence: moderate ^{15,25}

(Continued)

Table 2. Neuropathic pain management, treatment lines and evidence (Continued)

Treatment line	Drug	Mode of action	Dose	Indications	Adverse effects	Observations
Third line	Strong opioids	Tapentadol	Tapentadol has been shown to be effective in the management of neuropathic pain; reduces approximately 30 % of pain intensity in nearly 50 % of patients. ²⁸			
	Botulinum toxin A injection	Botulinum toxin	Botulinum toxin is effective in patients with post-herpetic, post-traumatic or postsurgical neuralgia. ^{16,29}			
Fourth line	Interventional therapy ²⁸	<ul style="list-style-type: none"> Neural blockade and steroid injection Spinal stimulation (dorsal root ganglion or peripheral nerve) Cortical neurostimulation at the epidural or transcranial level Intrathecal therapy Physical/psychological/psychosocial therapy 				

*Pain reduction at the end of first day of use; however, there is a 30 % pain reduction towards the first week of treatment.²

SNRI = serotonin and noradrenaline reuptake inhibitors, Ca²⁺ = calcium, NT = neurotransmitters (glutamate, norepinephrine and substance P), NMDA = N-methyl-D-aspartate.

- lidocaine 5 % patch (10 to 14 cm in size, with 700 mg of lidocaine), a first-line topical drug that blocks sodium channels and stabilizes neuronal membranes (electrical threshold increase), thereby reducing ectopic discharges activity and improving pain transduction.^{2,8,34} The recommended dose, depending on the affected anatomical area, is one to three patches for 12 hours, whereby results are obtained in between two and four weeks.^{6,35} Their use is indicated in the treatment of post-herpetic neuralgia (with high efficacy), diabetic polyneuropathy, carpal tunnel syndrome, myofascial pain syndrome, pain secondary to osteoarthritis and chronic postoperative pain.^{36,37}

In several case reports of patients diagnosed with post-herpetic neuralgia, 60-70 % reduction of the area of pain was observed after three months of treatment with lidocaine 5 % patches.^{16,38}

Numerous patients have reported the use of topical lidocaine 5 % for more than eight years with no adverse effects.² Its adverse effects, which globally occur in less than 3 %, include mild erythema, itching, edema, or skin irritation at the site of application.²

Other topical anesthetics with bupivacaine or mepivacaine have been tested in animals; a reduction in hyperalgesia has been observed in comparison with lidocaine, although they continue on research protocols.¹⁶

Ketamine is a parenteral anesthetic that offers analgesia at suboptimal anesthetic doses;¹⁶ its mechanism of action involves a non-competitive blockade of NMDA (N-methyl-D-aspartate) receptors, which causes pain modulation by blocking glutamate synthesis.¹⁶ Application of ketamine 0.5-1 % gel in patients with post-herpetic neuropathy, diabetic polyneuropathy and pain secondary to trauma has not demonstrated efficacy; however, in patients with complex regional pain syndrome, a reduction in hyperalgesia and allodynia was observed after the application of 10 % ketamine.^{16,38}

Baclofen is a muscle relaxant, GABA_B receptor agonist, which reduces nerve impulse at the afferent pathways level through cellular hyperpolarization (intracellular potassium ions increase and calcium ions decrease).¹⁶ In human studies, topical baclofen 5 % as monotherapy in the management of neuropathic pain related to acromegaly and its combined use in the treatment of neuropathic pain secondary to lumbar spine dural herniation-associated radiculopathy has shown efficacy in pain reduction, with a high level of evidence.^{16,38}

Figure 2. Algorithm for diagnosis and treatment of localized neuropathic pain. Based on Likar R et al.: Treatment of localized neuropathic pain of different etiologies with the 5 % lidocaine medicated plaster - a case series.³³

As for topical non-steroidal anti-inflammatory drugs, diclofenac, which acts at the peripheral level, demonstrated good results in the treatment of orofacial neuropathic pain after topical administration of 5 % diclofenac, with a moderate level of evidence; application is safe, without dermatological adverse effects.^{16,39} The use of topical salicylates (aspirin and diethyl ether) have been proven excellent in the management of post-herpetic neuralgia, with moderate level of evidence.¹⁶

Regarding topical tricyclic antidepressants, amitriptyline is a serotonin and norepinephrine reuptake inhibitor by blocking voltage-gated sodium, potassium and calcium channels, as well as muscarinic, cholinergic, nicotinic, histaminergic, alpha-2 adrenergic receptors and NMDA receptors.^{16,23,38} Results have been ambiguous with amitriptyline at concentrations of 1-5 % in the treatment of post-herpetic pain and diabetic or post-traumatic neuropathy; in the management of pain due to idiopathic axonal polyneuropathy and post-traumatic neuropathy with amitriptyline at concentrations of 5-10

%, a low level of evidence was obtained.¹⁶ Concentrations higher than 10 % might turn out being effective in the management of pain; however, similar adverse effects to those systemically produced have been observed.^{13,16}

Ambroxol is a mucolytic agent with anesthetic effects through the block of voltage-gated sodium channels, 40 times more potent than lidocaine. Although a reduction of allodynia has been observed in LNP when topically applied, the results are inconclusive.^{16,39} In a report of cases, loperamide cream 5 % was effective for the management of intractable neuropathic pain.³⁹

Conclusions

Neuropathic pain syndromes are frequently observed in different clinical scenarios. LNP accounts for 60 % of neuropathic pain conditions⁶ and, undoubtedly, affects the quality of life of those who suffer from it.⁵

For this reason, it is important for medical personnel to identify neuropathic pain different scenarios, including LNP syndromes, for which other pharmacological modalities, such as topical treatments, can be offered, mainly in elderly people who already receive multiple drugs.^{2,3,5,9}

Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

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