Post-trauma and postoperative painful neuropathy

Neuropatia dolorosa pós-traumática e pós-operatória

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DOI 10.5935/1806-0013.20160050

ABSTRACT

BACKGROUND AND OBJECTIVES: Peripheral nerve injuries caused by accidental trauma, surgeries or diseases, may evolve to persistent, severe and refractory neuropathic pain, being a major economic and social problem because it often affects most productive population group causing sometimes devastating incapacities. In this brief review, aspects of the prevalence of neuropathic pain by trauma injury of peripheral nerves and its treatment will be evaluated.
CONTENTS: After evaluating neuropathic pain pathophysiology after peripheral nerve injury, the incidence of peripheral nerve trauma injury and of postoperative chronic pain, of predictive factors and of postoperative neuropathic pain prevention, pharmacological and non-pharmacological treatment of post-trauma and postoperative painful neuropathy are appreciated.
CONCLUSION: Literature has few studies evaluating neuropathic pain after trauma or surgical peripheral nerve injury and the expression "neuropathic pain" is not normally used to refer to pain after trauma nerve injury, which makes difficult to estimate the prevalence and incidence of post-trauma and postoperative painful neuropathy, although there is consensus that it is a severe worldwide problem, being considered a chronic disease with difficult and still inadequate treatment.

Keywords: Chronic pain, Neuropathic pain, Peripheral nerves injury, Postoperative pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As lesões de nervos periféricos causadas por traumas acidentais, cirurgias ou doenças, podem evoluir para dor neuropática persistente, grave, refratária ao tratamento, constituindo um importante problema econômico e social, pois frequentemente atinge a faixa etária mais produtiva da população, causando incapacidades muitas vezes devastadoras. Nesta breve revisão, serão analisados aspectos da prevalência da dor neuropática por lesão traumática de nervos periféricos e seu tratamento.
CONTEÚDO: Após analisar a fisiopatologia da dor neuropática após lesão de nervo periférico, da incidência da lesão traumática de nervos periféricos e da dor crônica pós-operatória, dos fatores preditivos e da prevenção da dor neuropática pós-operatória, é feita uma apreciação do tratamento farmacológico e não farmacológico da neuropatia dolorosa pós-traumática e pós-operatória.
CONCLUSÃO: A literatura apresenta poucos artigos que avaliaram a dor neuropática em pacientes após a lesão do nervo periférico traumático ou cirúrgica, e o termo dor neuropática não é normalmente usado para se referir a dor após uma lesão traumática do nervo, o que dificulta estimar a incidência e a prevalência da neuropatia dolorosa pós-traumática e pós-operatória, embora haja consenso que é um grave problema mundial, sendo considerada uma doença crônica cujo tratamento é difícil e ainda inadequado.

Descritores: Dor crônica, Dor neuropática, Dor pós-operatória, Traumatismos dos nervos periféricos.

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Conflict of interests: none – Sponsoring sources: none.

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INTRODUCTION

Peripheral nerve injuries, be them traumatic, surgical or associated to disease, may evolve to persistent, severe and refractory neuropathic pain (NP), the management of which is inadequate since less than half the patients report satisfactory pain relief with treatment[1].

TRAUMATIC PERIPHERAL NERVE INJURY

This is a severe world problem and may be considered important economic and social problem since it often affects most productive age groups and young populations, causing often devastating incapacities due to significant neurologic deficits with high percentage of persistent NP. Incidence varies according to peace and armed conflics periods and also according to the level of economic development. In general, injuries are caused by car and labor accidents, by cutting and penetrating objects, crushing, fractures, stretching and gunshot wound. Professional or amateur sportsmen injuries are also common[2,3].
Several professional or amateur sports activities are associated to peripheral nervous system (PNS) injuries. Although some of these injuries are specific for an individual sport, other peripheral nerve injuries occur in several sports activities. Most commonly sports associated to peripheral nerve injury are soccer, hockey and baseball, but many other sports have unique associations with peripheral nerve injury[3].
Literature has few articles evaluating NP in patients after peripheral nerve injury and the term NP is not normally used to refer to pain after traumatic nervous injury[4].
Traumatic nervous injuries may be devastating, leading to functional morbidity and psychological stress, and even in case of surgical treatment with motor function recovery, pain may induce defficiency and poor quality of life (QL), even preventing recovery and return to previous life, being difficult to foresee which patients shall develop persistent pain[5].
The incidence of traumatic peripheral nerve injury varies from 2.8 to 5% in the population, according to the type of survey[3,6].

CHRONIC POST-SURGICAL PAIN

In spite of the relative easiness to control pain during and immediately after surgery with local anesthetics, opioids, cyclo-oxygenase inhibitors and other drugs, pain persisting after surgical wound healing, persistent post-surgical pain, discomfort lasting more than 3 to 6 months after surgery, this is a major and not well known problem, and data suggest that an alarming number of patients develops chronic pain after routine surgeries. Chronic post-surgical pain is a major clinical problem[7].
Estimate incidence of chronic post-surgical pain varies depending on the type of surgery and surgical technique. Incidence after limb amputation is 50 to 85%; after thoracotomy 30 to 50%; after mastectomy 20 to 50%; after groin hernia repair 11.5 to 47%; after hysterectomy 32%; after hip arthroplasty 28%; after cholecystectomy 3 to 56%; after colectomy 28%; after vasectomy 15%; after Cesarean section 6 to 18% and after vaginal delivery 4 to 10%[8,9].
A recent review has shown that chronic post-surgical pain is experienced by 10-50% of individuals after classic surgeries, and may be severe in approximately 5 to 10% of these patients, being that 20% of patients look for a pain clinic due to chronic post-surgical pain. The incidence of NP is between 6% and 68%, depending on surgery type[10].
Another systematic database review evaluating 281 studies investigating persistent post-surgical pain after 11 types of surgeries, has concluded that the prevalence of probable or permanent NP was high in patients with persistent pain after thoracotomies (66%), mastectomy (68%), groin hernia repair (31%), hip and knee arthroplasty (6%). Results suggest that the

prevalence of NP among cases of persistent post-surgical pain differs according to the surgery, probably as a function of the probability of iatrogenic nervous injury[11].

A multicenter, prospective, observational study including 21 hospitals in 11 European countries has evaluated 3120 surgical patients. Evaluation via e-mail or telephone interview using the Brief Pain Inventory (BPI) and the Douleur Neuropathique *4* (DN4) has evaluated the incidence of moderate to severe chronic post-surgical pain. At 12 months, the incidence of moderate pain was 11.8% and of severe pain 2.2%. NP affected 35.4% of patients with moderate pain and 57.1% of patients with severe pain[12].

An Italian study collecting data via e-mail or telephone using BPI and DN4 and including 235 patients, has shown that the incidence of chronic post-surgical pain at 6 month was 45.2% for mild pain, 15.9% for moderate pain and 2.7% for severe pain, while the incidence of chronic post-surgical pain at 12 months was 35.9%, 11.8% and 2.5%, respectively for mild, moderate and severe pain. NP was present in 31.9% of respondents at 6 months and in 40.3% of respondents with chronic post-surgical pain at 12 months[13].

Chronic post-surgical pain seems to be consequence of the inflammatory process triggered by surgical aggression, but it is also manifestation of NP resulting from surgical injury of large peripheral nerves. Since the population of surgical patients is too large, the incidence of persistent post-surgical pain as compared to other classic forms of NP, such as post-herpetic neuralgia and other peripheral and central neuropathies, is high[14,15].

Pathophysiology of neuropathic pain after peripheral nerve injury

Aiming at helping and simplifying the understanding of the pathophysiology of this type of pain, some authors suggest that, in a summarized and schematic way, the following steps would be present in NP genesis after peripheral nerve injury:

1. Denervated Schwann cells and macrophages infiltrated distally to the nervous injury produce local and systemic cytokines which signal pain;
2. Neuron at injury site is a source of spontaneous ectopic excitability in sensory fibers;
3. Changes in expression of dorsal root ganglion genes alter sensitivity, responsiveness, transmission and survival of sensory neurons;
4. Spinal cord posterior horn is an area of altered activity and of genes expression producing central sensitization;
5. There is also inhibitory neurons loss and microglia activation. These events amplify sensory flow;
6. At brainstem level there is transmission modulation of impulses coming from the spinal cord;
7. Lymbic system and hypothalamus contribute by modulating mood, behavior and autonomic reflex;
8. Pain sensation is then generated in the cortex, where previous and cultural experiences, as well as expectations, converge to determine how patients feel;
9. There is also predisposition, genetic or not, of painful patients, which affects their reaction to treatment[16].

Several pathophysiological mechanisms have been suggested to explain these pain states, but the key-factor is the onset of spontaneous or ectopic activity in injured sensory neurons. Most part of this activity is developed within 20h after peripheral nerve injury, being especially detected in myelinated fibers type A. Ectopic discharge may originate in the injured area of the axonal segment of injured nerves, but most seem to originate in the body of sensory neurons found in dorsal root ganglion. Among multiple factors involved, ion channels are attractive targets due to their prominent role in neuronal excitability control, such as sodium channels, which seem to have revelant role in the persistence of NP behaviors and/or ectopic activity and potassium channels subtypes strongly regulated by traumatic injury, which could explain excitability changes of myelinated fibers and emergence of pain phenotypes[17-21].

Post-surgical NP appears after nervous or spinal cord and brain sensory transmitting systems injury, the major characteristic of which is the combination of sensory loss and paradoxical hypersensitivity. Nervous injury is the starting point for changes and leads to abnormal neural function, and sensory loss is the universal response to nervous injury, developing the so-called positive phenomena, such as spontaneous pain, dysesthesia, hypersensitivity and allodynia[15].

When nerves are injured during surgery, neuropathic pain component may develop originating chronic persistent post-surgical pain. Signs of neurologic injury with hypoesthesia have been reported after mastectomy, hernia repair and thoracotomy[22-24].

Predictive factors for post-surgical neuropathic pain

Among predictive factors for post-surgical NP there are psychologic and neurophysiologic aspects, genetic susceptibility, psychosocial factors such as pain expectation, fear, previous memories, social environment, work, physical activity levels, intraoperative manipulation of tissues and nerves, severe and long lasting pain before surgery and pain intensity in the immediate and late post-surgical period. Many surgical patiens have signs of painless neurological injuries, because just 10% of patients with nervous injury during jaw osteotomy develop clinically significant NP[24-28].

Psychosocial factors are also important for the development of chronic pain and should be treated as part of a holistic approach for perioperative care[29].

The association between acute post-surgical pain intensity and further development of chronic pain was observed after breast surgery, thoracotomy and groin hernia repair, however, whether this association is an indication of the extension of neuroplasticity changes induced by surgery, by lack of adequate analgesia or by preoperative predisposing factors is still not totally explained[30-32].

A European study has evidenced chronic pre-surgical pain, orthopedic surgery and percentage of time with severe pain in the first post-surgical day as risk factors for chronic post-surgical pain[12]. An Italian study has also evidenced that severe pain during the first 24 post-surgical hours seems to be predictor of chronic post-surgical pain[13].

A prospective study with 250 patients with painful degenerative lumbar radiculopathy treated with microdiscectomy has evidenced that 12% of patients had persistent post-surgical neuropathic pain, being observed strong predictive correlation with screening tests DN4 and Leeds Assessment of Neuropathic Symptoms and Signs, used for NP screening[33].

Since acute post-surgery pain intensity is related to the risk of chronic post-surgical pain, studies with preoperative nociceptive stimulation tests, stimulation with heat or chilled water proof before surgery may be useful to prevent chronic post-surgery pain[14,31,32,34-38]. Such tests have shown positive correlation between preoperative pain and immediate post-surgery pain.

Prevention of chronic post-surgery pain

Anesthesiologists play a critical role in decreasing the incidence of chronic post-surgery pain because they are involved in all surgical phases of patients, play a decisive role in surgery evaluation, and may develop strategies for prevention, detection and treatment of early and late post-surgery pain[10].

Since many surgeries producing persistent post-surgery pain are associated to nervous injury, techniques to prevent such injuries seem to be useful to prevent post-surgery NP, for example, laparoscopic hernia repair, which may decrease the risk of nervous injury as compared to open surgery, intercostobrachial nerve preservation in mastectomy, intracostal suture to avoid direct nerve compression after thoracotomy and minimally invasive techniques in other procedures, such as nephrectomy and sternotomy[14,34,39-42].

Post-thoracotomy pain syndrome is relatively common and is present in approximately 50% of patients after thoracotomy, and around 30% experience pain 4 to 5 years after surgery. In some patients, pain is severe and disabling. Exact mechanism of post-thoracotomy pain syndrome pathogenesis is not yet clear, but evidences suggest that this is a combination of NP and myofascial non-neuropathic pain. Intercostal nerve trauma during thoracotomy is the most probable cause.

Based on current evidences it is not possible to conclude which analgesic or surgical technique may prevent post-thoracotomy pain syndrome, avoiding intercostal nerve trauma and adopting an aggressive multimodal perioperative pain management regimen started before surgical incision. Patients should be cautioned in the preoperative period about the possibility of developing post-thoracotomy pain syndrome and how it may affect their post-surgery QL[43].

Chronic post-thoracotomy pain is a continuous dysesthesic burning pain in the incision site, which occurs in approximately 50% of patients after thoracotomy; however, pain is severe and disabling in 5%. Most probable cause is intercostal nerve injury although the exact mechanism for such is not totally understood[44].

The prevalence of neuropathic symptoms after thoracic surgery has varied from 35 to 83%. NP is associated to significantly more severe pain, higher

use of analgesics and further limitation in daily activities[45].
Intercostal nerve injury detected at surgery time is not associated to chronic pain intensity or altered skin sensation 3 months after surgery and it seems that there is a more significant cause for chronic pain in addition to intercostal nerve injury[46].
Extensive review after search in Medline, EMBASE, IME, IBECS and Cochrane Library databases has shown that different surgical techniques for thoracotomy are recommended, but common denominator is intercostal nerves preservation[47].

Pharmacological treatment of painful post-traumatic and post-surgery neuropathy

Treatment of post-traumatic and post-surgery NP patients should be done with drugs with consistent level of efficacy and safety based on randomized clinical trials available in the literature. Recommended first line treatments include tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors; α2-δ calcium channels inhibitors gabapentin and pregabalin. Opioid analgesics, especially tramadol and methadone are recommended as second line drugs which may be used as first line in selected cases.
Other drugs may be used as third line treatment, but which also may be used as second line treatment in some cases and include anticonvulsants, other antidepressants, mexiletine and NMDA (N-Methyl-Aspartate) receptor antagonists. Topical lidocaine and capasaicin are major drugs indicated to treat localized post-traumatic and post-surgery NP[48-57] (Table 1).

Table 1. Pharmacological treament of post-traumatic and post-surgery neuropathic pain.

Pharmacological treatment of post-traumatic and postoperative neuropathic pain		
First line	Second line	Third line
Tricyclinc antidepressants and dual norepinephrine/5 hydroxytryptamine reuptake inhibitors α2-δ calcium channels inhibitors, topic lidocaine	Tramadol Opioids	Anticonvulsants Other antidepressants NMDA antagonists Mexiletine Capsaicin Canabinoids
Pharmacological treatment of localized post-traumatic and postoperative neuropathic pain		
First line	Second line	Third line
Topic lidocaine	Topic Capsaicin	Topic amitriptyline

A randomized double-blind, cross-over and placebo-controlled study has evaluated NP of 15 patients,both in the arm and around breast scar, lasting 4 weeks. Dose was increased from 25mg until 100mg per day. Amitriptyline has significantly relieved NP, both in the arm and around breast scar, however, most patients have abandoned treatmet due to adverse effects[58].
A double-blind, randomized, cross-over study with venlaflaxin and inactive placebo, analyzing 13 patients with breast cancer NP has shown that mean daily pain intensity was not significantly decreased with venlafaxine as compared to placebo, however, mean pain relief and maximum pain intensity were significantly lower with venlafaxine as compared to placebo. Anxiety and depression were not affected, and intensity of adverse effects was not significantly different between both studied groups[59].
An Italian study evaluating 158 consecutive patients in a total of 211 traumatic neuropathies has shown that brachial plexus traumatic injury was more frequent with 36%, and radial, ulnar and fibular nerves with 15% of injuries. Pain was present in 66% of patients and NP in 50% of all patients. Traumatic neuropathies were more frequent in upper limbs and in young males after traffic accidents[60].
A double-blind, randomized, cross-over multicenter, placebo-controlled study was carried out to evaluate efficacy and safety of gabapentin to treat NP due to traumatic or post-surgery peripheral nerve injury using doses of up to 2400mg/day. The study included 6 centers and 120 randomized patients and has observed that gabapentin has promoted significantly better pain relief and quality of sleep as compared to placebo, and most common adverse effects were dizziness and tiredness[61].
An open study including 21 patients with peripheral NP due to traumatic or post-surgical peripheral nerve injury has treated them with 5% lidocaine patch for up to 12 weeks and had good reponse to quantitative sensory and temperature tests[56].
Plaster of 5% lidocaine was effective to treat localized post-surgery NP and post-traumatic pain. It was well tolerated and the risk of systemic adverse events and pharmacokinetic interactions with simultaneous drugs was minimal due to low systemic absorption[57].

Non-pharmacological treatment of painful post-traumatic and post-surgery neuropathy

Patients with persistent post-traumatic or post-surgery neuropathy refractory to pharmacological treatment should receive non-pharmacological, preferably noninvasive treatments, except in specific cases when NP is maintained by nervous compression or by the presence of neuroma in amputation stub.
A radiofrequência pulsada, não ablativa e/ou a neuroestimulação direta do nervo periférico ou da medula, podem ser opções em casos com muito sofrimento doloroso ou quando os efeitos adversos aos fármacos impedirem a continuidade do tratamento.
Non-ablative pulsed neurofrequency and/or direct peripheral nerve or spinal cord neurostimulation may be options in cases with severe pain or when drugs adverse events prevent the continuity of the treatment. Pulsed radiofrequency is a therapeutic modality with several potential applications in pain treatment, which as been used for having the advantage of controlling pain without destroying tissue. It has been applied to patients with persistent NP resistant to pharmacological treatment triggered after intercostal nerve injuries, thoracic surgeries or mastectomies[62-64].
Patients with persistent peripheral NP after peripheral nerve injury, refractory to invasive interventions or drugs, may benefit from transcutaneus magnetic stimulation administered during 6 to 8 weeks, which is a noninvasive treatment option[65].
Another technique is peripheral nerve stimulation with implanted nerve stimulator applied to the axillary cavity directly in the involved nerve branch, which is effective to control severe NP by post-traumatic nervous injuries in upper limbs[66]; and motor cortex stimulation between 1 and 3 months after surgery has shown real efficacy for chronic peripheral NP refractory to pharmacological treatment[67].

CONCLUSION

Since there are few studies in the literature evaluating NP in patients after traumatic or surgical peripheral nerve injury, and the term NP is not normally used to refer to pain after traumatic nervous injury, it is very difficult to estimate the incidence and prevalence of post-traumatic and post-surgery painful neuropathy, although there is consensus that it is a severe world problem being considered a chronic disease the management of which is still inadequate.

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