LUCAS MARTINS DE EXEL NUNES

Uso de eletrodo plano concêntrico para avaliação de pacientes com dor em membros inferiores e características neuropáticas

Use of concentric planar electrode for evaluation of patients with lower limbs pain and neuropathic characteristics

Versão original

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo, para obtenção do título de Doutor em Ciências.

Pragrama de Neurologia
Orientação: Prof. Dr. Daniel Ciampi de Andrade

São Paulo
2022

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DEDICATION

To my wife Andressa, for her love and support in everything in my life, no different with this thesis

To my parents Alcyr and Marta, for their love for me, their life example and for their values which shaped my character and made me believe in my dreams.

To my son Henrique, for making it all make sense.

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I feel very privileged having worked with other faculty members and members of the Pain Center of Division of Neurology and the Institute of Physical Medicine and Rehabilitation, placed at the Clinics Hospital of the Faculty of Medicine of the State of São Paulo. I would like to thank all my patients, for understanding the relevance of this thesis and participation in its execution.

Lastly, I would like to thank my family for their love and support throughout this journey.

Standards adopted:

This thesis is in accordance with the following rules at the time of its publication:

References: adapted from the International Committee of Medical Journals Editors (Vancouver).

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Abbreviations of journal titles according to the List of Journals Indexed in Index Medicus.

RESUMO

Nunes LME. Uso de eletrodo plano concêntrico para avaliação de pacientes com dor em membros inferiores e características neuropáticas [tese]. São Paulo: Universidade de São Paulo, Faculdade de Medicina; 2022.

A dor neuropática é definida como uma condição associada a uma lesão ou doença que afeta o sistema somatosensorial (SSS). A lesão do SSS é frequentemente determinada por estudos eletrodiagnósticos convencionais (EDX) em casos de dor neuropática periférica. No entanto, o EDX não pode detectar neuropatia de pequenas fibras, que podem ser a causa de lesões do SSS em alguns pacientes. Realizamos um estudo prospectivo avaliando o ganho na faixa diagnóstica provocado pelo uso de dois testes neurofisiológicos adicionais: potenciais evocados relacionados a dor obtidos por um eletrodo concêntrico (CN-PREP) e o reflexo nociceptivo de flexão (NFR) quando adicionado ao EDX.

Foram incluídos pacientes com histórico de dor crônica nos membros inferiores e um escore positivo do questionário Douleur Neuropathique (DN4), encaminhados para EDX de rotina. Além do EDX, os pacientes foram submetidos ao CN-PREP e medições do NFR.

Foram incluídos 100 pacientes (54 mulheres , 57± 12 anos) com suspeita de (provável) dor neuropática. O EDX foi alterado em 47% dos pacientes, enquanto a adição do CN-PREP aumentou a faixa diagnóstica para 69%. A adição de NFR ao EDX e CN-PREP aumentou a positividade para 72,0%, enquanto o restante dos pacientes tiveram resultados normais para os três testes. Considerando o EDX como teste de referência, a sensibilidade do CN-PREP foi de 85,1% e a especificidade 58,5%. O CN-PREP mostrou-se tolerável para os pacientes, enquanto o NFR foi associado a um maior desconforto.

Mostramos que os CN-PREPs podem ser adicionados à avaliação neurofisiológica de rotina de pacientes com suspeita de dor neuropática, o que aumenta a positividade diagnóstica. Resta saber qual é a sensibilidade real e a especificidade dos CN-PREPs neste cenário quando comparados aos padrões de ouro de avaliação de fibras de pequeno porte, como a densidade de fibra nervosa intraepidérmica e potenciais evocados a laser, para que a taxa de falsa positividade de tal estratégia possa ser determinada.

Palavras-Chave: Dor neuropática. Dor Crônica. Avaliação eletrofisiológica. Potencial Evocado de fibras finas relacionado a dor.

ABSTRACT

Nunes LME. Use of concentric planar electrode for evaluation of patients with lower limbs pain and neuropathic characteristics [thesis]. São Paulo: Universidade de São Paulo, Faculdade de Medicina; 2022.

Neuropathic pain is defined as a condition associated with an injury or disease that affects the somatosensory system (SSS). SSS lesion is frequently determined by conventional electrodiagnostic studies (EDX) in cases of peripheral neuropathic pain. However, EDX cannot detect small fiber neuropathy, which may be cause of SSS lesions in some patients. We have conducted a prospective study assessing the gain in diagnostic range brought about by the use of two additional neurophysiological tests: pain related evoked potentials obtained by a concentric electrode (CN-PREP), and the nociceptive flexion reflex (NFR) when added to EDX.

We included patients with a history of chronic pain in the lower limbs and a positive Douleur Neuropathique questionnaire score addressed for routine EDX. In addition to EDX, patients underwent evoked potential with concentric electrode (CN-PREP) and measurements of nociceptive flexion reflexes.

100 patients (54 female , 57±12 years) were included with suspected (probable) neuropathic pain. EDX was altered in 47% of patients, while the addition of CN-PREP increases diagnostic range to 69%. The addition of NFR to EDX and CN-PREP increased positivity to 72.0%, while the remaining had normal results for the three tests. Considering EDX as the reference test, CN-PREP sensitivity was 85.1% and specificity 58.5%. The CN-PREP proved to be tolerable for patients, while NFR was associated with more discomfort.

We have shown that CN-PREPs can be added to the routine neurophysiological assessment of patients with suspected neuropathic pain, which increases diagnostic positivity. It remains to be determined the actual sensitivity and specificity of CN-PREPs in this scenario when compared to gold standards of small fiber assessment such as intraepidermal nerve fiber density and laser-evoked potentials, so that the false positive rate of such a strategy can be determined.

Keywords: Neuropatic pain. Chronic Pain. Electrophysiological evaluation. Pain Related Evoked Potentials.

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LIST OF ABBREVIATIONS AND ACRONYMS

American Association of Neuromuscular and Electrodiagnosis Medicine (AANEM).

BPI (Brief Pain Inventory)

Compound Muscle Action Potential (CMAP)

DN4 (Douleur Neuropathique in 4 Questions)

Conventional electrodiagnostic studies (EDX)

Evoked Potential with Planar Concentric Electrode (CN-PREP)

Institute of Physical Medicine and Rehabilitation (IMREA)

International Association for the Study of Pain (IASP)

Intraepidermal Electrical Stimulation Evoked Potentials (IEEPs)

McGill Pain Questionnaire (MPQ)

Needle Electromyograph (EMG)

Negative Predictive Value – NPV

Nerve Conduction Studies (NCS)

Nociceptive flexion reflex (NFR)

Pain-related evoked potentials (PREPs)

Positive Predictive Value (PPV)

Quantitative Sensory Testing (QST)

Somatosensory system (SSS)

Special Interest Group on Neuropathic Pain (NeuPSIG)

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1 INTRODUCTION

The definition of neuropathic pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”, suggested by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) in 2008, has been widely accepted. In contrast, the proposed grading system of possible, probable, and definite neuropathic pain from 2008 has been used to a lesser extent (Finnerup, 2016), mainly due to practical difficulties in fulfilling all the criteria.

Neuropathic pain is defined as a condition associated with an injury or disease that affects the somatosensory system and is characterized by positive and negative sensory phenomena and pain of neuropathic descriptors (Treede et al, 2008; Reicher, 2018). Some studies have shown the prevalence of neuropathic pain in about 2% of the general population, reaching 8% in adults (Martyn, Hughes, 1997). However, due to its difficult diagnosis, there is still not enough evidence to specify prevalence of neuropathic pain (Haanpää et al., 2011), which may underestimate the number of patients (Torrance et al., 2006; Bouhassira et al., 2008).

Chronic pain has an undeniable impact on the quality of life of patients, with direct financial consequences for themselves and for individuals who are committed to take care of them (Meyer-Rosberg et al., 2001). But caring for people with chronic pain can also lead to indirect high costs both to health systems and the labor market (Henschke, Kamper, Maher, 2015; Castro et al., 2019; Dydyk, Grandhe, 2022).

In the UK, for example, a study has shown that a teenager with chronic pain costs 8,000 euros a year to public funds (Sleed et al, 2005). Individuals with moderate and severe chronic pain lose a mean of eight working days every six months, representing impactful indirect costs related to this disease. In Australia, a country of 22.7 million people, the total annual cost of chronic pain treatment in 2007 was $34.3 billion, or $10.847,000 per person (MBF Foundation, 2007). The total cost across Europe was estimated at about 1.5% to 3% of continental GDP (Reid et al., 2011).

In 2008, about 100 million adults in the United States were affected by chronic pain, which represented a cost of US$560 billion to US$635 billion to public funds in 2010. This cost is higher than those related to heart disease (US$309 billion), cancer (US$243 billion) and diabetes (US$188 billion) (Phillips, 2006).

Brazil, in turn, is a poor country that is still struggling to overcome long-standing social challenges, such as the lack of basic sanitation. In addition to these problems, overcome by

developed nations, the country still must deal with modern health problems, such as chronic pain, which generates an even more relevant economic impact.

Neuropathic pain implies the confirmation of injury in the somatosensory system which is composed of fine fibers (Haanpää et al., 2011). The presence of peripheral nerve injury is necessary, however, alone, insufficient for the occurrence of pain. Diagnosis should be based on history, physical examination, specific questionnaires, and laboratory tests that use quantitative instruments to measure objective responses, as well as electrophysiological studies.

Access to nerve damage requires specific diagnostic tools to prove its presence. Isolated clinical examination is less sensitive than several complementary tests in the diagnosis of somatosensory pathway lesions (England, Asbury, 2004). In this context, electrophysiological studies intend to fill the gap regarding the functional evaluation of fine fibers in this specific system (DiStefano, 2017).

Conventional electrodiagnostic studies (EDX) are probably the most frequently used complementary tests for the diagnosis of all types of neuropathies (Barraza-Sandoval, Casanova-Mollà, Valls-Solé, 2012; Ross, 2012). Physicians use those tools to diagnose diseases of the peripheral nerves, neuromuscular junction, and muscles. These tests are considered an extension of clinical history and examination, and their results should always be interpreted considering the clinical context (Choi, Di Maria, 2021). Peripheral neuropathy, also known as peripheral polyneuropathy, is a general term for a broad range of disorders that cause damage and dysfunction on the nerves of the peripheral nervous system in several different patterns. EDX testing can not only identify whether a peripheral neuropathy may be present, but also provide information the clinician may use to determine the etiology, the severity, and the prognosis of the disorder (Novello, 2022). However, because they predominantly evaluate thick fibers (A-β), they present important limitations (Table 1).

Fine fiber neuropathies involve a-∂ and C fibers, which are not accessed by conventional electrophysiological studies (EDX). Alternatively, electrophysiological studies that analyze the involvement of fine fibers (A-∂ and C) in the evaluation of neuropathic pain have been presented. For almost a decade, reviews on neuropathic pain have referred to evoked potentials as important diagnostic tool and called pain related evoked potentials (PREP) (Cruccu, 2004, 2008).

Clinical neurophysiologic investigation of pain pathways in humans is based on specific techniques and approaches since conventional methods of nerve conduction studies and somatosensory evoked potentials do not explore these pathways. The proposed techniques use various types of painful stimuli (thermal, laser, mechanical, or electrical) and different types of

assessments (measurement of sensory thresholds, study of nerve fiber excitability, or recording of electromyographic reflexes or cortical potentials).

Table 1 - Morphological and functional characterization of neuropathies of nerve fibers

Type of nerve fiber	Myelin	Diameter (μm)	Driving speed (m/s)	Sensory information	Electrophysiological evaluation (EDX)
A-α	Myebellized	13-20	8-120	Proprioception	Yes (H reflection)
A-β	Myebellized	6-12	30-70	Touch and vibration	Yes (sensory neuroconduction)
A-∂[a]	Little myebellized	1-5	5-40	Feeling cold and pain	No
C.A.	Unmyelinic	0.3-1.5	0.5-2	Feeling of warmth and pain	No

Source Adapted from Sène (2018)

The two main tests used in clinical practice are quantitative sensory testing and pain-related evoked potentials (PREPs). PREPs offer the possibility of an objective assessment of nociceptive pathways. Three types of PREPs can be distinguished depending on the type of stimulation used to evoke pain: laser-evoked potentials, contact heat evoked potentials, and intraepidermal electrical stimulation evoked potentials (IEEPs). These three techniques investigate both small-diameter peripheral nociceptive afferents (mainly Aδ nerve fibers) and spinothalamic tracts without theoretically being able to differentiate the level of lesion in the case of abnormal results. In routine clinical practice, PREP recording is a reliable method of investigation for objectifying the existence of a peripheral or central lesion or loss of function concerning the nociceptive pathways, but not the existence of pain. Other methods, such as nerve fiber excitability studies using microneurography, more directly reflect the activities of nociceptive axons in response to provoked pain, but without detecting or quantifying the presence of spontaneous pain. These methods are more often used in research or experimental study design. Thus, it should be kept in mind that most of the results of neurophysiologic investigation performed in clinical practice assess small fiber or spinothalamic tract lesions rather than the neuronal mechanisms directly at the origin of pain and they do not provide objective quantification of pain (Lefaucheur, 2019).

Currently, the use of laser stimulus evoked potentials has been recommended for evaluation of fine fibers in patients with neuropathic pain with evidence level (A) (Haanpää et al., 2011). However, the laser used to obtain evoked potentials has a series of restrictions, among which we highlight the induction of skin lesions and/or the worsening of pre-existing lesions (Treede, Lorenz, Baumgärtner, 2003). In addition, the high costs of the equipment make it difficult to use in clinical practice (Haanpää et al., 2011). Thus, studies that enable a method of evaluation of fine fibers with lower cost and side effects are necessary. The evaluation of fine fibers by intraepidermal electrical stimulation was proposed in the 1980s (Bromm, Meier, 1984), with subsequent innovations (Inui et al., 2002; Oh, 2015).

Lefaucher et al. (2012) have demonstrated the usefulness of the study of fine fibers by electrical evoked potentials with the use of a concentric needle (CN-PREP) compared with the CO2 laser method (LEP). In this work, in addition to values comparable to laser potentials, those with electrical stimuli presented fewer undesirable effects.

Another form of electrophysiological evaluation of the somatosensory pathways is the recording of the nociceptive flexion reflexes described by Sherrington in 1910. Several studies have shown that the nociceptive flexion reflex and the nociceptive flexion reflex responses obtained correspond to pathways conducted by A-β and A-∂ fibers, mediated by spinal and supra spinal segments, respectively (Le Masson, 2005: Sandrini, 2005). Corroborating this, some studies have shown that painful conditions such as fibromyalgia and other pain-related conditions can modify these responses (Üçeyler, 2013; Obermann et al., 2008)

In clinical practice, currently, the use of scales for pain assessment is more frequent than any complementary examination. Neuropathic *Pain Symptom Inventory* (NPSI) is the only tool for assessing neuropathic pain of both central and peripheral origin, and has been validated in Brazil (de Andrade et al, 2011) (APPENDIX A). Other scales frequently used in pain assessment are: DN4 (*Douleur Neuropathique in 4 Questions*) (APPENDIX B), BPI *(Brief Pain Inventory)* (APPENDIX C) and McGill Pain Questionnaire (MPQ) (APPENDIX D) (Haanpää et al., 2011, Martinez, Grassi, Marques, 2011).

There are several approaches for the evaluation of neuropathic pain. However, there is still no clinical and electrophysiological routine for the correct diagnosis that meets the criteria described above.

Thus, the objective of this study was to compare the degree of contribution brought by evoked potentials related to pain obtained by electrical stimulation and concentric planar electrode in the diagnosis of peripheral neuropathies associated with neuropathic pain. The aim of the present study is to assess the gain in diagnostic range of adding two neurophysiologic

tests (CN-PREP and nociceptive flexion reflexes) to the usual EDX of patients with neuropathic pain in the lower limbs.

2 METHODS

2.1 Study design

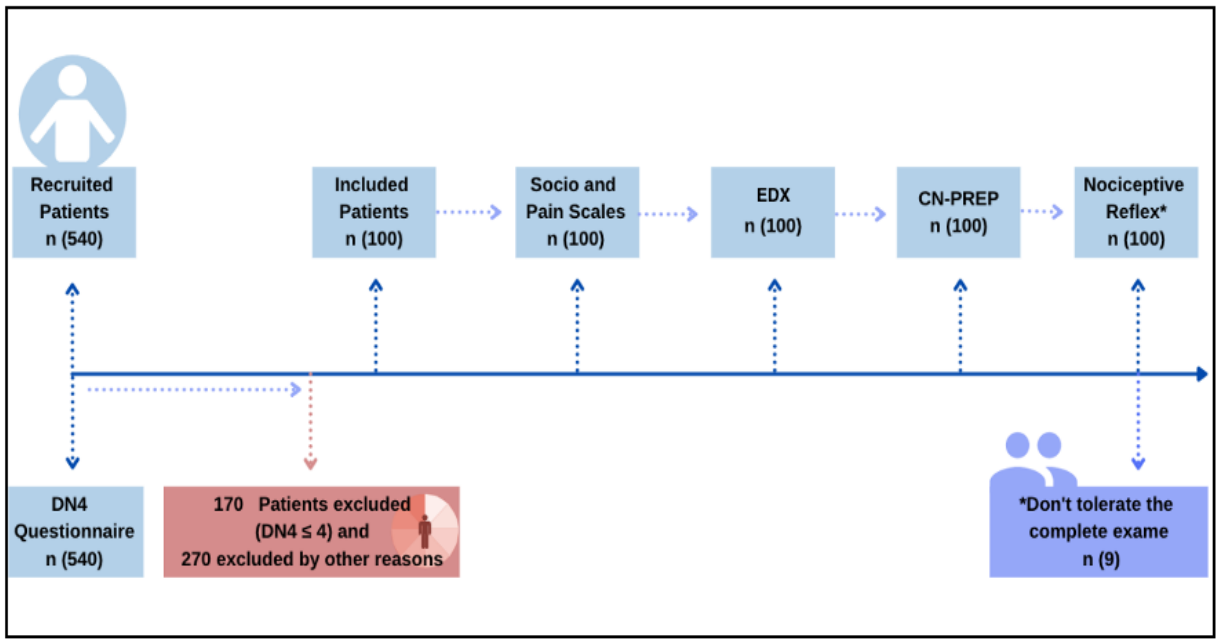
We included patients over 18 years old, with a history of chronic pain in the lower limbs and DN4 test ≥ 4 (indicative of pain with neuropathic characteristic) and referred from the Institute of Physical Medicine and Rehabilitation (IMREA), placed at the Clinics Hospital of the Faculty of Medicine of the State of São Paulo, to perform EDX (Raja et al., 2020). The DN4 questionnaire is a clinician-administered screening tool that comprises various clinical items, including allodynia, and indicates neuropathic pain when the score is ≥4.

Exclusion criteria were physical and intellectual incapacity to answer the applied questionnaires, physical or psychological inability to undergo electrophysiological tests, clinical contraindications to electrophysiological tests, or the volunteer decision to leave the project or no longer participate.

All patients underwent clinical examination using bed-side tools. Patients were grouped according to the clinically documented presence or absence of neuropathic pain, as assessed by the DN4 questionnaire. They were also evaluated by the NPSI, BPI and MPQ scales, instruments that assess intensity, correlated aspects, and various pain characteristics.

In addition to this clinical evaluation, these patients were submitted to electrophysiological studies with conventional electrodiagnosis studies (EDX), evoked potential with planar concentric electrode (CN-PREP) and record of the nociceptive flexion reflexes (Flowchart 1). Two staff members examined the patients clinically, and the others did neurophysiological testing, with those recording EDX being blinded to CN-PREP data and vice versa. The research was approved by the Institutional Review Board (CAPPesq: 36978214.1.0000.0068). Enrollment occurred between 2018 and 2019, and patients gave their informed consent (APPENDIX E).

Flowchart 1 – Care, inclusion and exclusion of patients, and application of pain scales and electrophysiological tests.



Source: Prepared by the author himself.

2.2 Neurophysiological tests

The assessments were performed in a single session, with the EDX being performed first, the exam for which they had been referred, and later, we added the concentric needle pain related evoked potential (CN-PREP) and the nociceptive flexion reflexes tests randomly. All tests are performed with the patient lying down, the room is heated between 21ºC and 23ºC, the temperature of the patient's extremities is maintained above 34ºC, and the impedance of all tests bellow 5Ω, as recommended in the scientific literature (Weber, Turk, 2008; Carneiro Filho et al. 2008). The doctor performing an examination was blind to the other tests. We used the Four-Channel (Photograph 1), registered at ANVISA 10263610036 to perform the EDX, and Two-Channel NeuroMep Micro (Photograph 2), registered at ANVISA to the CN-PREP and nociceptive flexion reflexes. To evaluate the reliability of the equipment and the parameters chosen, tests have also been performed in individuals without complaints of neuropathic pain and without comorbidities.

Photograph 1 – Nihon-Koden Neuropack

Source: Available at https://mfimedical.com/en-de/products/nihon-kohden-neuropack-s1-meb-9400-emg-ep

Photograph 2 – NeuroMep Mic

Source: Available at https://kandel.com.br/equipamentos/emg/neuro-mep-micro/

2.2.1 Conventional electrodiagnostic studies (EDX)

Electrodiagnosis (EDX) consists of two components: nerve conduction studies (NCS) and needle electromyograph (EMG) studies. These tests can assess the pattern and degree of nerve involvement and underlying nerve and muscle pathology. Electrodiagnosis is thus well suited to contribute to fully characterize peripheral nerve disorders (Brownell, A, 2010).

NCS are an essential tool in the evaluation of the peripheral nervous system. The sensory nerve action potential (SNAP) provides information on the sensory nerve axon and its pathway from the distal receptors in the skin to the dorsal root ganglia, while the compound muscle action potential (CMAP) is an assessment of the motor nerve fibers from their origins in the anterior horn cell to their termination along muscle fibers. Various parameters of the SNAP and CMAP waveforms are used to determine the number of functioning nerve fibers and the speed of conduction (Tavee, 2019). The stimulus of NCS is totally tolerable, causing no damage. Our examination routine included sensory and motor evaluation of superficial and deep fibular nerves, sural and tibial nerves in the lower limbs. The examination was always bilateral, and the normative values followed those of the American Association of Neuromuscular Electrodiagnostic Medicine (AANEM), American Academy of Physical Medicine and Rehabilitation (AAPMR), American Academy of Neurology (AAN) (AANEM, 1992; AANEM, AAPMR, AAN, 1999; AANEM, AAPMR, 1999; AANEM, AAN, AAPMR, 2002; Brownell, Bromberg, 2010).

In the second stage (EMG), the asepsis was first performed at the site of the bites. Our examination routine included proximal and distal muscles in the lower limbs. The electrical

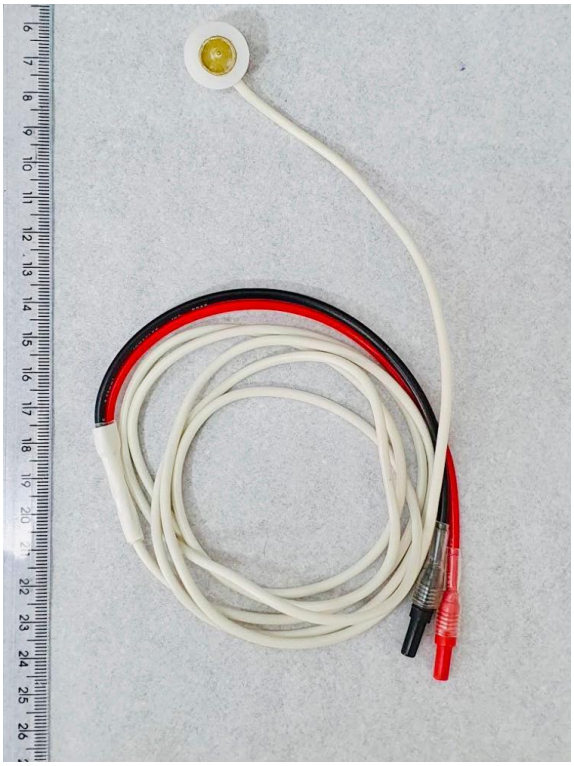
muscular activity at rest, with the collaboration of the patient, and in contraction, which allowed the detection of possible motor axon damage, were analyzed.

Based on the NCS and EMG findings, following AANEM criteria and England et al. (2005) and Patel et al., (2005), the tests were categorized into four types: (1) normal; (2) polyneuropathy; (3) neuropathy; and (4) radiculopathy.

2.2.2. Concentric needle pain related evoked potential (CN-PREP)

Electrical stimulation was performed with a concentric plane electrode (Photograph 3) designed to excite nociceptive fibers in the surface layer of the dermis. The electrode was identical to that described in previous studies (Katsarava, 2006a; Lefoucheur, 2012). Each stimulus consisted of a three-pulse train (pulse duration: 0.5 ms, pulse interval: 5ms).

Photograph 3 – Concentric planar electrode developed and patented in Brazil by the pain group of the Department of Neurology and Neurosurgery – Hospital das Clínicas, USP-São Paulo and used in this study to perform CN-PREP



Source: Prepared by the author himself

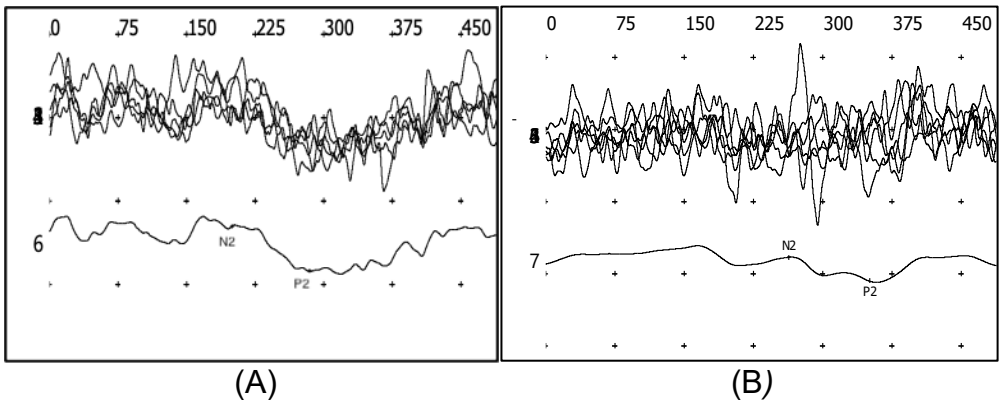
We standardized the stimuli in the back of the hands, back of the feet and the place of pain reported by the patient. The electrode was moved slightly during the collection of curves to avoid habituation of responses. The potential obtained consists of negative and positive complex, with peaks called N2 and P2 (Graphic 1). Peak-to-peak distance is used to calculate amplitude. The N2-P2 component was evaluated, captured in standard assemblies following system 10-20 (Kaube et al., 2000; Lefaucher, 2012; Oh, 2015) using subcutaneous needle electrodes placed in Cz-A1(Oh, 2015; Katsarava et al., 2006a). A bracelet strapped around the left forearm was used as a ground electrode. Two blocks of 10 to 15 trials were performed with NRS 60-70 reported by the patient. We used filters in the range between 0.5 and 30Hz. The mean of the CN-PREP was obtained in at least ten trials. The individual pain threshold was determined by stimulating the area of interest twice with increasing and decreasing current intensities until the subject reported a pin-prick sensation. The mean value was taken as the individual pain threshold. The researcher was the one who conducted the study-measured amplitudes (peak to peak) and latencies.

Abnormal PREPs can be observed in the following situations: (i) a peripheral loss of nociceptive afferents or an altered function or excitability of these afferents; (ii) a central lesion of the spinothalamic tracts (or pain integration brain centers) or an altered function or excitability of these tracts (or centers); and (iii) a disturbance of the attention paid to the stimulation. To limit the latter phenomenon, the patient should be asked to report (or even quantify) all perceived stimuli delivered during the test (Lefaucheur, 2019).

As performed in other studies, we analyzed the values of N2 latency and amplitude N2/P2 (Obermann et al., 2008). The classification of the results obtained in the evoked potentials followed criteria established by the authors of this study, based on other studies (Nutti, 2016; Obermann et al., 2008).

Criteria: latency or amplitude of the amended CN-PREP in at least one evaluated limb or comparative evaluation between sides when the pain was unilateral. N2 values were considered abnormal when latency was above 212ms and or amplitude below 8.8 μV. In case the N2/P2 amplitude to stimulation of the affected side was depressed by at least 30% or latency responses was delayed by at least 30ms, compared to the normal side, we also considered abnormal (Beydoun et al., 1993; Garcia-Larrea et al., 2010). The evaluation was restricted to the area of pain reported by the patient. The tests using this criterion were classified as normal or altered.

Graphic 1 – CN-PREP potentials on the foot of an individual without (A) and with (B) neuropathic pain and peripheral neuropathy.



Source:Prepared by the author himself

2.2.3 Nociceptive flexion reflex-RIII

Following the first studies carried out by Willer (1977) and later by Garcia Larrea (Garcia-Larrea et al., 1993; Garcia-Larrea, Sindou, Mauguière, 1989), the potentials were obtained by regular electrical stimulation of the sural nerve in the ankle, behind the lateral malleolus. Trains of five consecutive shocks of duration of 1ms, delivered at 500 Hz, were applied on the sural nerve at intensities ranging from 0 to 50 mA. Flexor reflexes recorded by surface bipolar electrodes were applied to the skin that covers the short head of the ipsilateral femoral biceps. The responses were analyzed within a 50-250ms window and amplified with a passing band of 30-1500 Hz. Responses were abolished if absent by two stimuli consecutive to 50mA or patient intolerance. A flexion response was considered a nociceptive flexion reflex based on the latency and morphology criteria: to be accepted as a nociceptive flexion reflex the recorded reflexes had to present a polyphasic form and early latency between 80 and 130ms (Hugon, 1973; Willer, 1977) compatible with the latency of A delta fibers. In normal individuals, this response is accompanied by a subjective sensation of pin prick and/or short-term pain in the sural territory.

Special care was adopted to avoid interference with other non-nociceptive flexion reflexes, such as nociceptive flexion reflex, which has shorter latencies (<70ms post-stimulus) and usually presents a biphasic form, never being associated with a subjective sensation of pain (Hugon, 1973; Willer, 1977). The nociceptive flexion reflex was classified as present or absent

in the lower limbs and called RIII response. The tests using this criterion were classified as normal or altered.

2.3 Pain assessment scales

2.3.1 Brief pain inventory (BPI)

It is a questionnaire that includes a pain severity index (mean of questions 3-6, with a numerical rating scale that ranged from 0 to 10, such that the lower the score was, the lower the pain level was) and measurement of the interference of pain with daily activities (mean of the 7 items, with an intensity numerical rating scale ranging from 0 to 10, where zero meant no interference and 10 for maximal interference imaginable) (Ferreira, 2011). In addition, this questionnaire provided information on pain medications and dosing. The study's primary outcome was the worst pain level over the last 24 hours, ranging from 0 to 10 on numerical rating scale.

2.3.2 McGill pain questionnaire – short form (MPQ)

It has 14 descriptors of pain referring 3 aspects and qualities of pain: sensory–discriminative, affective–emotional, and cognitive–evaluative (Ferreira, Andrade, Teixeira, 2013).

2.3.3 Douleur neuropathique 4 questionnaire (DN-4)

This is a 10-item questionnaire used to screening tool for neuropathic pain, which presents questions for interview and clinical signs testing. The score was measured for each positive item, assigning zero for each negative item. The total score is ten points. A result equal to four or more suggests neuropathic pain (Santos, 2009). It is positive when scores ≥ 4.

2.3.4 Neuropathic pain symptom inventory (NPSI)

It is composed of 10 items that are presented as numerical rating scales with a range from 0 to 10, each referring to a specific feature: superficial spontaneous pain (question 1), deep spontaneous pain (mean of questions 2 and 3), paroxysmal pain (mean of question 5 and 6), evoked pain (mean of questions 8, 9, and 10) and paresthesia/dysesthesia (mean of questions

11 and 12) (de Andrade et al., 2011). The total score possible is 100. The temporal aspects of continuous and paroxysmal pain are assessed in question 4 (duration of spontaneous pain over the last 24 hours) and question 7 (number of pain attacks over the last 24 hours). Neuropathic pain symptom inventory was also used here to evaluate nonparoxysmal pain: scores of 4 or higher than the mean in the first domain (superficial spontaneous pain) and second domain (deep spontaneous pain) were considered to represent continuous pain.

2.4 Statistical analyses

Descriptive analysis included calculation of mean and standard deviation (SD) for continuous variables, and absolute and relative frequencies for categorical variables. The questionnaires' reliability was investigated using the Cronbach's Alpha coefficient. Histograms and quantile-quantile graphs and the Shapiro-Wilk test were performed to check the adherence of the quantitative variables score to a normal distribution.

The evaluation of the neurophysiological studies was performed in three stages. Initially, a descriptive analysis was performed, presenting the possible combinations of results between exams. Then, the accuracy of CN-PREP and RIII was evaluated, taking the EDX as the reference test. Sensitivity, specificity, positive predictive value – PPV and negative predictive value – NPV were calculated.

Finally, the existence of associations between the assessments of neuropathic pain scales and the results of the CN-PREP and the EDX was verified.

To analyse associations between qualitative variables, the chi-square test was used.

To compare the means of quantitative non-parametric variables according to dichotomous variables, the Mann-Whitney U test was used. The Bonferroni correction was performed to confirm statistically significant differences. The significance level was set to $p < 0.050$. The Shapiro-Wilk test was performed to verify the adherence of quantitative variables to the normal distribution, determining types of statistical tests to be used later.

Finally, the hypothesis of associations between subjective assessments of neuropathic pain (Neuropathic pain symptoms inventory - NPSI) and CN-PREP latency and amplitude results was tested. For this, correlations between quantitative variables were analyzed using spearman's correlation coefficient. With a statistically significant correlation, Bonferroni correction was performed. The descriptive level $p<0.050$ was adopted.

In the latency variables, for cases with absent electrical potential, the value 500 was imputed. In the amplitude variables, for cases with absent electrical potential, the value 0 (zero) was imputed. Analyses were performed with inclusion of patients with absent potential and then replicas were performed with the exclusion of these patients.

Data analyses were performed using the IBM SPSS Statistics version 20 software, and data were exported to the Excel program to verify consistency. For recoding, calculation of scores and statistical analysis, STATA software version 14 was used.

3 RESULTS

3.1 Patients and clinical features

Were included 100 patients with neuropathic characteristic (54 women and 46 men), age ranging from 30 to 92 years (57 ±12.21). Most participants were women (54.0%), over 50 years old (76.0%) (Table 2).

Table 2 - Descriptive statistics of sociodemographic qualitative variables of patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Variable	n	%
Sex		
Male	46	46,0
Female	54	54,0
Age group (in years)		
30 to 49	24	24,0
50 to 56	21	21,0
57 to 67	29	29,0
68 to 92	26	26,0
Naturalness		
Alagoas	2	2,0
Amazon	1	1,0
Bahia	14	14,0
Ceará	4	4,0
Holy Spirit	1	1,0
Maranhao	1	1,0
Minas Gerais	6	6,0
Paraiba	1	1,0
Pernambuco	6	6,0
Piaui	1	1,0
Paraná	3	3,0

Sergipe	1	1,0
Sao Paulo	57	57,0
Not informed	2	2,0
Marital status		
Single	18	18,0
Married	59	59,0
Consensual union	4	4,0
Separate	5	5,0
Divorced	9	9,0
Widow(er)	5	5,0
Religion		
Atheist	2	2,0
Evangelical	19	19,0
Catholic	55	55,0
Spiritist	10	10,0
Other	14	14,0
Practitioner in religion		
No	37	37,0
Yes	63	63,0
Ethnicity		
White	60	60,0
Brown	21	21,0
Black	14	14,0
Yellow	5	5,0
Schooling		
Illiterate	1	1,0
Elementary School	23	23,0
Middle school	47	47,0
Superior	25	25,0
Postgraduate studies	4	4,0
Work situation		
Employee	22	22,0
Unemployed	12	12,0
Retired	35	35,0
Housewife	12	12,0
Autonomous	9	9,0
Student	0	0,0
Health license	8	8,0
Informal work	2	2,0
Total	**100**	**100,0**

Source: Prepared by the author himself. More details see Appendix F.

Among participants, 30.0% reported general health status as poor or very bad and 48.0% as neither bad nor good, 22.0% reported alcohol consumption, 16.0% smoking, 38.0% were overweight and 30.0% were obese. The largest share of the participants was right-handed (98.0%). The most frequent self-reported diseases were systemic arterial hypertension (55.0%), diabetes (34.0%) and peripheral vascular disease (7.0%), and 34.0% of participants reported

having another disease than those questioned (Table 3).

Table 3 - Descriptive statistics of qualitative variables related to self-reported health and disease of patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Variable	n	%
Self-assessment of general health status		
Very bad	4	4,0
Bad	26	26,0
Neither bad nor good	48	48,0
Good	18	18,0
Very good	4	4,0
Consumption of alcoholic beverages		
No	78	78,0
Yes	22	22,0
Smoking		
No	84	84,0
Yes	16	16,0
Nutritional status		
Malnutrition	2	2,0
Eutrophy	30	30,0
Overweight	38	38,0
Grade I obesity	23	23,0
Grade II obesity	6	6,0
Grade III obesity	1	1,0
Preferential use of the hand		
Righty	98	98,0
Left-handed	2	2,0
Diabetes		
No	66	66,0
Yes	34	34,0
Cerebrovascular disease		
No	98	98,0
Yes	2	2,0
Systemic arterial hypertension		
No	45	45,0
Yes	55	55,0
Peripheral vascular disease		
No	93	93,0
Yes	7	7,0
Chronic kidney disease		
No	99	99,0
Yes	1	1,0
Malignancy		
No	99	99,0
Yes	1	1,0
Cardiocirculatory disease		
No	98	98,0
Yes	2	2,0

Liver disease		
No	99	99,0
Yes	1	1,0
Depression		
No	99	99,0
Yes	1	1,0
Gastrointestinal tract disease		
No	98	98,0
Yes	2	2,0
Autoimmune disease		
No	98	98,0
Yes	2	2,0
Other disease(s)		
No	66	66,0
Yes	34	34,0
Total	**100**	**100,0**

Source: Prepared by the author himself

3.2 Electrophysiological tests

Data shows that 47.0% of patients had altered EDX, and the most frequent alteration was polyneuropathy, followed by neuropathy and radiculopathy. CN-PREP were abnormal in 62% of the sample (Table 4). The nociceptive flexion reflex was abnormal in 15.0%, including cases that did not support the end of the test (Table 4).

Table 4 - Descriptive statistics of electrophysiological test results among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Examination or evaluation	n	%
CN-PREP*		
General alteration		
Alteration	62	62,0
EDX**		
Normal	53	53,0
Neuropathy	11	11,0
Polyneuropathy	26	26,0
Radiculopathy	10	10,0
RIII***		
Right foot and/or left foot		
Normal	85	85,0
Altered	15	15,0
Total	**100**	**100,0**

Source: Prepared by the author himself
*CN-PREP (evoked potential of concentric needle electrodes).
** EDX - Conventional electrodiagnostic studies
***Component RIII of Nociceptive Flexion Reflex

In all CN-PREP latency measurements, the mean latency was higher among altered patients (347,65ms; SD 146,18 p<0,001) than normal ones (187,95ms SD 22,7 p<0,001). (Table 5).

There was also a statistically significant association between amplitude score and the CN-PREP results (p<0.001), confirmed by the Bonferroni test (p<0.001). Amplitude had a higher mean among people with normal CN-PREP (37.42μV; SD=14.39) than among those with altered results (10.87 μV; SD=14.01) (Table 5).

Pain assessment using analog scales obtained a mean of 5.14 points (SD=1.18 points) during the CN-PREP and 8.88 points (SD=1.69) during RIII (Table 5).

Table 5 - Descriptive statistics of the scores of electrophysiological test results among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Evaluation	n	Mean (±SD)	p
CN-PREP - latency			
Normal	38	187.95±22.77	p<0.001
Altered	62	347.65±146.18	
CN-PREP - amplitude			
Normal	38	37.42±14.39	p<0.001
Altered	62	10.87±14.01	
CN-PREP – pain*			
VAS	100	5.14±1.18	
RIII- pain			
VAS	100	8.88±1.69	

Source: Prepared by the author himself

*Pain: VAS - evaluation with visual analog scale ranging from 0.000 to 10.00 points.

Table 6 presents the characteristics of the latency and amplitude variables of the CN-PREP in various contexts. In the evaluation of latency with inclusion of cases with absent potential, it was observed that the highest value was the latency of the left foot in the valley, with a mean of 355.9 milliseconds (SD=96.7), ranging from 232.0 to 500.0 milliseconds, with a median of 313.5 milliseconds. The lowest value was the latency of the right foot at the peak, with a mean of 268.4 milliseconds (SD=120.5), ranging from 149.0 to 500.0 milliseconds, with

a median of 220.5 milliseconds.

When patients with no electrical potential detected in latency assessments were excluded, the highest value was right foot latency in the valley, with a mean of 307.1 milliseconds (SD=36.3), ranging from 216.0 to 382.0 milliseconds, with a median of 309.0 milliseconds. The lowest value was left foot latency at peak, with a mean of 199.9 milliseconds (SD=31.6), ranging from 133.0 to 305.0 milliseconds, with a median of 197.0 milliseconds.

In the evaluation of the amplitude with inclusion of cases with absent potential, it was observed that the amplitude of the right foot had a mean of 23.9 microvolts (SD=18.3), ranging from 0.0 to 90.0 microvolts, with a median of 21.9 microvolts. The amplitude of the left foot had a mean of 21.0 microvolts (SD=19.1), ranging from 0.0 to 88.2 microvolts, with a median of 19.7 microvolts.

When patients without electrical potential detected in the amplitude assessments were excluded, the right foot had a mean of 29.2 microvolts (SD=15.9), ranging from 6.7 to 90.0 microvolts, with a median of 26.6 microvolts. The left foot had a mean of 29.1 microvolts (SD=16.4), ranging from 4.0 to 88.2 microvolts, with a median of 27.6 microvolts.

Table 6 - Descriptive statistics of latency and amplitude measurements of CN-PREP among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Parameter	n	Mean	Median	Standard deviation	Minim	Maxim
Latency with inclusion of cases with missing potential						
Right foot latency at peak	100	268,4	220,5	120,5	149,0	500,0
Latency right foot in the valley	100	345,7	322,0	84,1	216,0	500,0
Left foot latency at peak	100	287,0	213,0	139,4	133,0	500,0
Latency left foot in the valley	100	355,9	313,5	96,7	232,0	500,0
Right foot amplitude	100	23,9	21,9	18,3	0,0	90,0
Amplitude left foot	100	21,0	19,7	19,1	0,0	88,2
Exclusion values for cases with missing potential*						
Right foot latency at peak	80	210,4	203,0	34,7	149,0	315,0
Latency right foot in the valley	80	307,1	309,0	36,3	216,0	382,0
Left foot latency at peak	71	199,9	197,0	31,6	133,0	305,0
Latency left foot in the valley	71	297,1	295,0	33,5	232,0	425,0
Right foot amplitude	80	29,2	26,6	15,9	6,7	90,0
Amplitude left foot	71	29,1	27,6	16,4	4,0	88,2

Source: Prepared by the author himself

* According to CN-PREP criteria (evoked potential of concentric needle electrodes), the potential was absent in 20 cases of the right foot and 29 cases of the left foot

For latency analyses with inclusion of cases with absent potential, the value of 500 milliseconds was imputed. For the analyses excluding these cases, they were taken from the sample. For amplitude analyses with inclusion of cases with absent potential, the value 0.0 microvolts were imputed. For analyses excluding these cases, they were taken from the sample.

3.2.1 Evaluation of the combined tests

When considering the combined results of the 3 tests of the protocol, it is observed that, among patients evaluated, 28.0% had no positive diagnosis - i.e., the three tests had normal results -, and 72.0% had a positive diagnosis with at least one of the 3 tests indicating alteration. It is also noted that 8.0% had the 3 tests concomitantly indicating the presence of neuropathic pain (Table 7).

Table 7 - Distribution of patients with pain in the lower limbs according to concordant/discordant evaluations of EDX, CN-PREP and RIII, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Evaluation*	n	%
Normal EDX, normal PREP and normal RIII	28	28,0
Normal EDX, normal PREP and altered RIII	3	3,0
Normal EDX, altered PREP and normal RIII	18	18,0
Normal EDX, altered PREP and altered RIII	4	4,0
EDX altered, PREP normal and RIII normal	7	7,0
EDX altered, PREP altered and RIII normal	32	32,0
EDX altered, PREP altered and RIII normal	0	0,0
EDX altered, PREP altered and RIII altered	8	8,0
Total	**100**	**100,0**

Source: Prepared by the author himself
* EDX = Conventional electrodiagnostic studies, CN-PREP = Evoked potential of concentric needle electrodes, RIII = RIII Component of Nociceptive Flexion Reflex

Previous results have shown that the positive diagnosis was made in less than half of the patients (47.0%) when performing only EDX, which is the reference test, and the CN-PREP complementary examination offers a higher percentage of positive results (62.0%). The crossing results of EDX and CN-PREP showed that 31.0% of the patients presented both tests with normal results, 40.0% with both altered tests and 29.0% with divergent results. In addition, the crossing between EDX and RIII showed that 46.0% of the participants presented both tests with normal results, 8.0% with both altered exams and 46.0% with divergent results. Crossing CN-PREP and RIII, 35.0% of the participants presented both tests with normal results, 12.0% with both altered exams and 53.0% with divergent results (Table7).

Considering the best performance of CN-PREP, if this test is taken as a reference test, the performance of the EDX would bring an increase in positive diagnosis in 7.0% of the patients, and the subsequent increase of RIII would contribute with a further 3.0% of positive results (Table 8). In this routine proposed with three tests, in our series, 72% of patients would have an altered diagnosis, against 47% performing only EDX in this sample.

Table 8 - Distribution of improvement in the diagnosis of pain in the lower limbs according to inclusion of exams, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Evaluation*	**n**	**%**
CN-PREP only	62	62,0
CN-PREP + EDX	69	69,0
CN-PREP + EDX + RIII	72	72,0
No diagnosis**	28	28,0
Total***	**100**	**100,0**

Source: Prepared by the author himself
* EDX = Conventional electrodiagnostic studies, CN-PREP = Evoked potential of concentric needle electrodes, RIII = RIII Component of Nociceptive Flexion Reflex
**Patients without confirmed diagnosis of MMII neuropathy in none of the three tests
*** Total patients evaluated

3.2.2 CN-PREP and RIII accuracy taking EDX as the reference test

The use of CN-PREP alone presented the best performance, and its association with the RIII did not provide relevant improvements. The sensitivity of CN-PREP was 85.1% (95%CI : 71.7% to 93.8%), specificity was 58.5% (95% CI: 44.1% to 71.9. The PPV was 64.5% (95%CI: 51.3% to 76.3%), NPV was 81.6% (95% CI: 65.7% to 92.3%). It is noteworthy that specificity was higher when considering patients with positive diagnosis in CN-PREP and RIII (92.5%; CI95%: 81.8% to 97.9%) (Table 9).

Table 9 - Analysis of the accuracy of CN-PREP* and RIII* compared to EDX* for diagnosis of neuropathy among patients with pain in the lower limbs, Hospital das Clínicas,

FMUSP, São Paulo, 2016 to 2019.

Parameters	Sensitivity - % (IC95%)	Specificity - % (IC95%)	PPV - % (IC95%)	NPV - % (IC95%)
CN-PREP	85,1 (71,7 - 93,8)	58,5 (44,1 - 71,9)	64,5 (51,3 - 76,3)	81,6 (65,7 - 92,3)
RIII	17,0 (7,6 - 30,8)	86,8 (44,1 - 71,9)	53,3(26,6 - 78,7)	54,1(43,0 - 65,0)
CN-PREP or RIII altered**	85,1 (71,7 - 93,8)	52,8 (38,6 - 66,7)	61,5(48,6 - 73,3)	80,0(63,1 - 91,6)
CN-PREP and RIII altered***	17,0 (7,6 - 30,8)	92,5 (81,8 - 97,9)	66,7(34,9 - 90,1)	55,7(44,7 - 66,3)

Source: Prepared by the author himself

* EDX = Conventional electrodiagnostic studies, CN-PREP = Evoked potential of concentric needle electrodes, RIII = RIII Component of Nociceptive Flexion Reflex

** Considering how patients with a positive diagnosis in CN-PREP or RIII are patients with

Considering as patients with positive diagnosis in CN-PREP and RIII

PPV=Positive predictive value, NPV=Negative predictive value

3.3 Pain assessment

The screening of neuropathic pain through DN-4 identified that the mean was 5.97 (SD=1.74). The evaluation by means of the NPSI had a 31.45 score (SD=23.56), and the dimensions with the most intense pain were superficial spontaneous pain (mean=4.08; SD=3.88) and paraesthesthesia/dyssesthesia (mean=4.50; SD=3.00). Regarding the evaluation of chronic pain through the Brief McGill, the overall score presented a mean of 10.11 (SD=3.53 points), and the dimension with the highest intensity of chronic pain was sensory pain (mean=5.47; SD=2.29). The pain inventory through the BPI showed that the intensity/severity of pain had a mean of 5.58 points (SD=2.49) and pain interference had a mean of 6.01 (SD=2.81). The dimensions with the highest intensity were the worst pain the participant felt in the last 24 hours (mean=7.00; SD=2.64), interferences in walking ability (mean=6.63; SD=3.04), at work (mean=6.59, SD=3.01) and in general activity (mean=6.52; SD=2.99) (Table 10).

The symptoms indicative of neuropathic pain reported more frequently by patients were: other pain different from these everyday kinds of pain (99.0%), troublesome pain (95.0%), tingling at the site of (91.0%), numbness at the site of pain(89.0%), sore/ aching (85.0%), nagging (84.0%), tiring-exhausting (82.0%), sickening (74.0%), pain spreading (73.0%), tugging pain (72.0%), touch hypoesthesia (72.0%) and burning (70.0%) (Graphic 2).

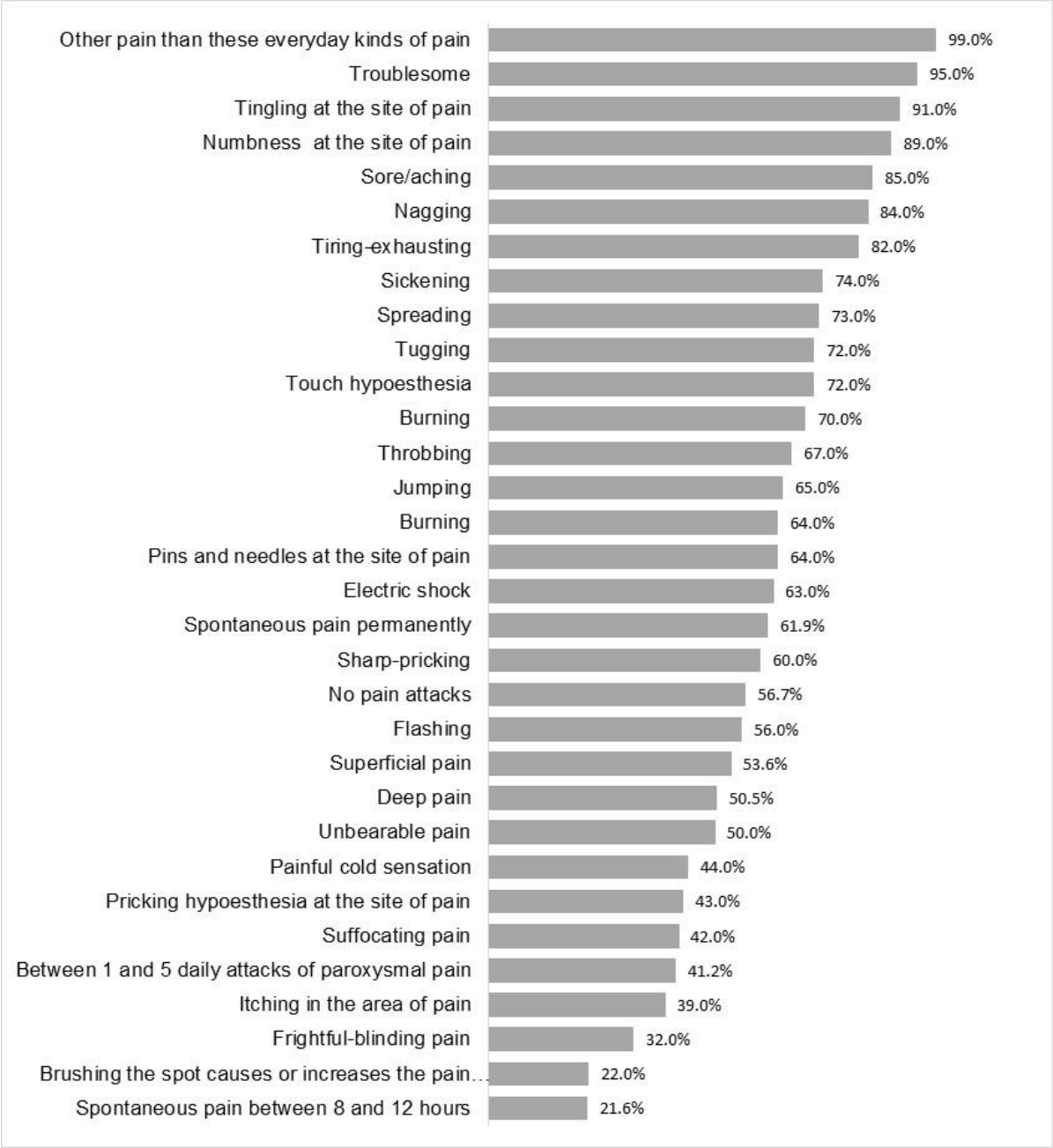
Table 10 - Descriptive statistics of neuropathic pain assessment scores according to the questionnaire used among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Neuropathic Pain Screening Questionnaire - DN4*		
DN4 overall score (0.00-10.00)	*100*	*5.97±1.74*
Neuropathic Pain Inventory - NPSI		
NPSI Overall score (0.0-100.0)	*97*	*31.45±23.56*
Superficial spontaneous pain (0.0-10.0)	97	4.08±3.88
Deep spontaneous pain (0.0-10.0)	97	3.55±3.27
Paroxysthet pain (0.0-10.0)	97	2.33±3.03
Evoked pain (0.0-10.0)	97	2.51±2.61
Paraesthesia / dyssesthesia (0.0-10.0)	97	4.52±3.00
McGill Brief Questionnaire for Chronic Pain Assessment		
McGill Overall Score (0.0-15.0)	*99*	*10.11±3.53*
Sensory (0.0-8.0)	99	5.47±2.29
Affective (0.0-5.0)	99	3.17±1.40
Evaluative (0.0-2.0)	99	1.46±0.58
Brief Pain Inventory - BPI		
BPI Intensity/Severity of Pain (0-10)	*99*	*5.58±2.49*
Worst pain you've felt in the last 24 hours (0-10)	99	7.00±2.64
Pain weaker than you've felt in the last 24 hours (0-10)	99	4.44±2.95
Average pain you feel (0-10)	99	5.99±2.46
Pain you are feeling at this point (0-10)	99	4.87±3.15
BPI Pain Interference (0-10)	*100*	*6.01±2.81*
General activity (0-10)	100	6.52±2.99
Mood (0-10)	100	5.94±3.32
Walking ability (0-10)	100	6.63±3.04
Work (0-10)	100	6.59±3.01
Relationship with other people (0-10)	100	5.60±3.37
Sleep (0-10)	100	5.93±3.47
Ability to enjoy life (0-10)	100	4.87±3.52

Source:Prepared by the author himself

* Inclusion criteria in the study: score ≥ 4 points

Graphic 2 - Distribution (%) of symptoms indicative of neuropathic pain among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019



Source: Prepared by the author himself

3.3.1 Correlation analyses

There was no statistically significant association (p<0.050) between any of the pain assessments and CN-PREP results. The pain measurements associated with the results of the EDX were the scores of DN-4, paroxysmal pain of the NPSI and evoked pain of the NPSI. The mean DN-4 was higher among people with altered EDX (6.36; SD = 1.87) than among those with normal EDX (5.62; SD = 1.56) (p=0.05; Bonferroni=0.034). The mean evoked pain was higher among participants with altered EDX (3.26; SD=3.05) than among those with normal result (1.86; SD=1.95) (p=0.031; Bonferroni=0.008). Paroxysmal pain had a higher mean among participants with altered EDX (2.99; SD=3.44) than among those with normal result (1.76; SD=2.53), without association with the Mann-Whitney test (p=0.088), but the Bonferroni test identified a statistically significant association (p=0.046). (Table 11, Graphic 3 and Graphic 4)

Table 11 - Descriptive statistics of neuropathic pain assessment scores according to cn-prep and EDX* results among patients with pain in lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Descriptor, dimension or score**	Normal CN-PREP		CN-PREP altered		p§	NORMAL EDX		EDX altered		p§
	n	Mean±dp	n	Mean±dp		n	Mean±dp	n	Mean±dp	
Neuropathic Pain Screening Questionnaire - DN4* **										
DN4 overall score (0.00-10.00)	*38*	*5.95 ± 1.74*	*62*	*5.98 ± 1.76*	*0,914*	*53*	*5.62 ± 1.56*	*47*	*6.36 ± 1.87*	**0.050a**
Neuropathic Pain Inventory - NPSI										
NPSI Overall score (0.0-100.0)	*36*	*34.94±22.27*	*61*	*29.39±24.23*	*0,166*	*52*	*27.29±19.26*	*45*	*36.27±27.14*	*0,153*
Superficial spontaneous pain (0.0-10.0)	36	4.67 ± 3.62	61	3.74 ± 4.01	0,368	52	4.25 ± 3.71	45	3.89 ± 4.09	0,768
Deep spontaneous pain (0.0-10.0)	36	3.99 ± 2.98	61	3.29 ± 3.42	0,243	52	3.50 ± 3.10	45	3.60 ± 3.48	0,926
Paroxysthet pain (0.0-10.0)	36	2.96 ± 3.26	61	1.96 ± 2.85	0,110	52	1.76 ± 2.53	45	2.99 ± 3.44	**0.088b**
Evoked pain (0.0-10.0)	36	2.48 ± 2.29	61	2.52 ± 2.79	0,764	52	1.86 ± 1.95	45	3.26 ± 3.05	**0.031c**
Paraesthesia / dyssesthesia (0.0-10.0)	36	5.10 ± 2.69	61	4.18 ± 3.15	0,135	52	4.36 ± 2.70	45	4.71 ± 3.34	0,629
McGill Brief Questionnaire for Chronic Pain Assessment										
McGill Overall Score (0.0-15.0)	*37*	*10.59 ± 3.31*	*62*	*9.82 ± 3.65*	*0,269*	*52*	*9.85 ± 3.45*	*47*	*10.40 ± 3.63*	*0,396*
Sensory (0.0-8.0)	37	5.92 ± 2.13	62	5.21 ± 2.36	0,140	52	5.37 ± 2.33	47	5.60 ± 2.26	0,613
Affective (0.0-5.0)	37	3.24 ± 1.28	62	3.13 ± 1.48	0,705	52	3.02 ± 1.39	47	3.34 ± 1.40	0,254
Evaluative (0.0-2.0)	37	1.43 ± 0.55	62	1.48 ± 0.59	0,676	52	1.46 ± 0.54	47	1.47 ± 0.62	0,793
Brief Pain Inventory - BPI										
BPI Intensity/Severity of Pain (0-10)	*37*	*5.74 ± 2.30*	*62*	*5.48 ± 2.61*	*0,605*	*52*	*5.6 ± 2.32*	*47*	*5.55 ± 2.69*	*0,966*
Worst pain you've felt in the last 24 hours (0-10)	37	7.22 ± 2.42	62	6.87 ± 2.78	0,639	52	7.06 ± 2.53	47	6.94 ± 2.79	0,946
Pain weaker than you've felt in the last 24 hours (0-10)	37	4.46 ± 2.97	62	4.44 ± 2.96	0,933	52	4.37 ± 3.04	47	4.53 ± 2.88	0,785
Average pain you feel (0-10)	37	5.92 ± 2.20	62	6.03 ± 2.61	0,630	52	5.96 ± 2.29	47	6.02 ± 2.65	0,774

Pain you are feeling at this point (0-10)	37	5.35 ± 2.71	62	4.58 ± 3.38	0,246	52	5.02 ± 2.67	47	4.70 ± 3.64	0,654
BPI Pain Interference (0-10)	*38*	*6.16 ± 2.65*	*62*	*5.92 ± 2.92*	*0,842*	*53*	*5.65 ± 2.91*	*47*	*6.42 ± 2.66*	*0,161*
General activity (0-10)	38	6.53 ± 2.91	62	6.52 ± 3.06	0,855	53	6.19 ± 3.01	47	6.89 ± 2.95	0,176
Mood (0-10)	38	6.50 ± 2.83	62	5.56 ± 3.57	0,360	53	5.57 ± 3.30	47	6.36 ± 3.34	0,151
Walking ability (0-10)	38	6.76 ± 2.94	62	6.55 ± 3.12	0,963	53	6.28 ± 3.19	47	7.02 ± 2.84	0,190
Work (0-10)	38	6.50 ± 2.81	62	6.65 ± 3.15	0,466	53	6.25 ± 3.00	47	6.98 ± 3.01	0,096
Relationship with other people (0-10)	38	5.92 ± 3.25	62	5.40 ± 3.46	0,459	53	5.19 ± 3.50	47	6.06 ± 3.19	0,226
Sleep (0-10)	38	5.63 ± 3.29	62	6.11 ± 3.59	0,278	53	5.66 ± 3.34	47	6.23 ± 3.62	0,211
Ability to enjoy life (0-10)	38	5.29 ± 3.34	62	4.61 ± 3.63	0,416	53	4.42 ± 3.62	47	5.38 ± 3.37	0,194

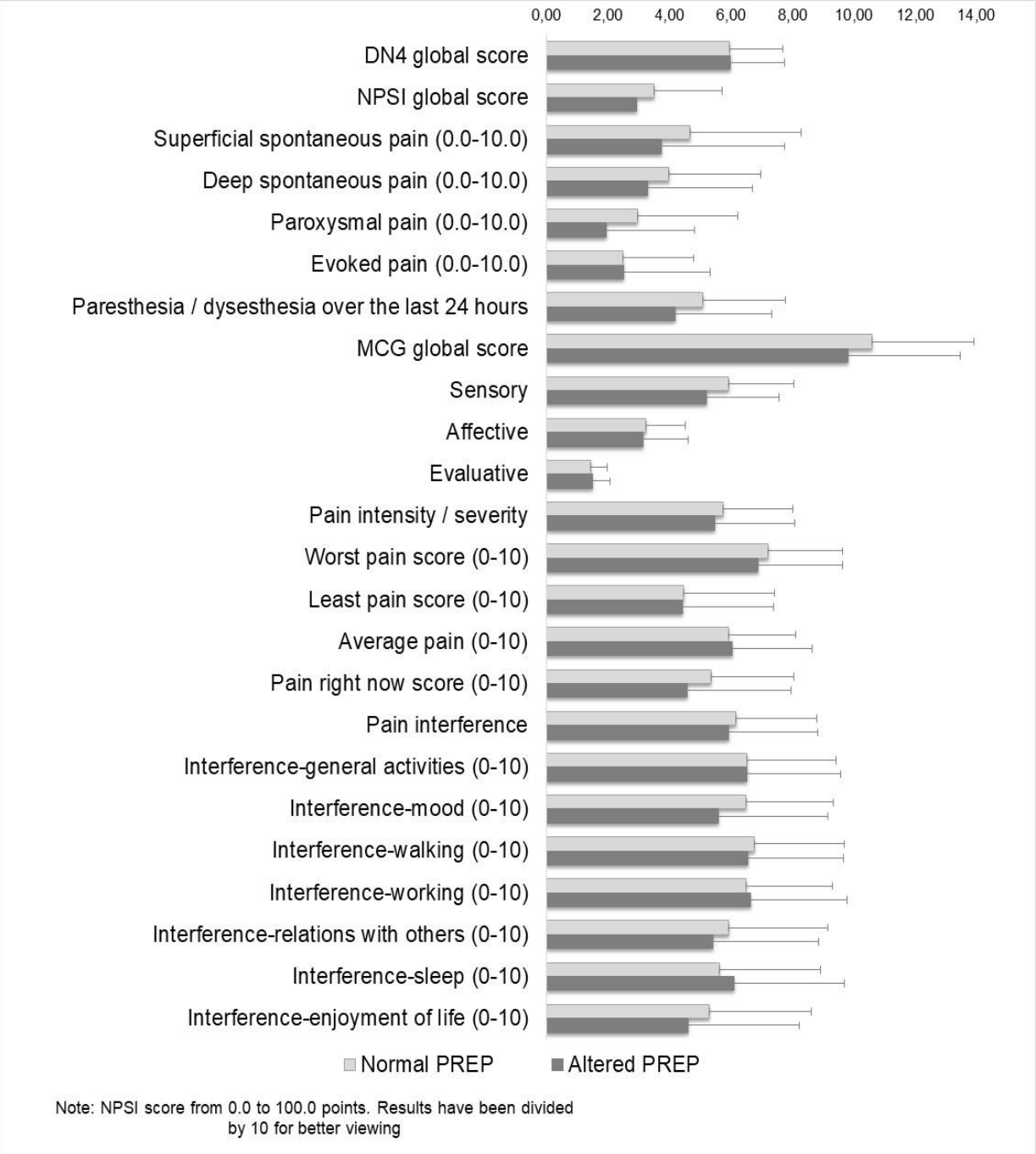
Source: Prepared by the author himself

*CN-PREP = Evoked potential of concentric needle electrodes **The higher the score, the higher the indication of presence/intensity of pain

***Inclusion criteria in the study: score ≥ 4 points

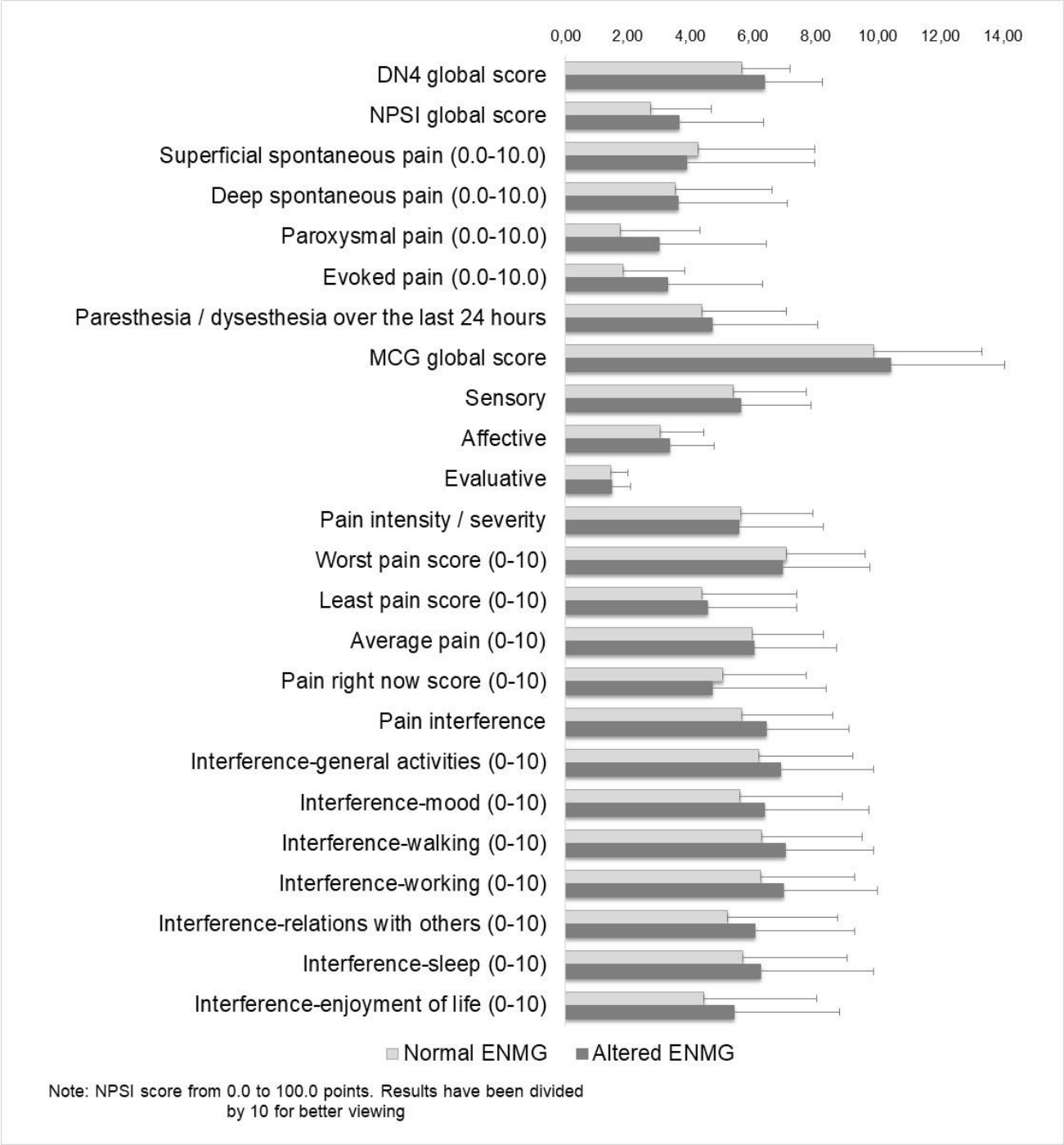
§ Mann-Whitney Bonferroni correction test: a: p=0.034; b: p=0.046; c: p=0.008

Graphic 3 - Mean score of neuropathic pain assessment scores according to CN-PREP results among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.



Source: Prepared by the author himself

Graphic 4 - Mean score of neuropathic pain assessment scores according to EDX results among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.



Source: Prepared by the author himself

ENMG=EDX

Table 12 presents the characteristics of the latency and amplitude variables of the CN-PREP and the NPSI measurements.

In the evaluation of latency with inclusion of cases with absent potential, it was observed that the highest value was the latency of the left foot in the valley, with a mean of 355.9 milliseconds (SD=96.7), ranging from 232.0 to 500.0 milliseconds, with a median of 313.5 milliseconds. The lowest value was the latency of the right foot at the peak, with a mean of 268.4 milliseconds (SD=120.5), ranging from 149.0 to 500.0 milliseconds, with a median of 220.5 milliseconds.

When patients with no electrical potential detected in latency assessments were excluded, the highest value was right foot latency in the valley, with a mean of 307.1 milliseconds (SD=36.3), ranging from 216.0 to 382.0 milliseconds, with a median of 309.0 milliseconds. The lowest value was left foot latency at peak, with a mean of 199.9 milliseconds (SD=31.6), ranging from 133.0 to 305.0 milliseconds, with a median of 197.0 milliseconds.

In the evaluation of the amplitude with inclusion of cases with absent potential, it was observed that the amplitude of the right foot had a mean of 23.9 microvolts (SD=18.3), ranging from 0.0 to 90.0 microvolts, with a median of 21.9 microvolts. The amplitude of the left foot had a mean of 21.0 microvolts (SD=19.1), ranging from 0.0 to 88.2 microvolts, with a median of 19.7 microvolts.

When patients without electrical potential detected in the amplitude assessments were excluded, the right foot had a mean of 29.2 microvolts (SD=15.9), ranging from 6.7 to 90.0 microvolts, with a median of 26.6 microvolts. The left foot had a mean of 29.1 microvolts (SD=16.4), ranging from 4.0 to 88.2 microvolts, with a median of 27.6 microvolts.

Table 12 also presents the results of the overall neuropathic pain score and the results of the dimensions that make up the NPSI. The overall score, based on an increasing intensity score from 0.0 to 100.0. had a mean of 31.5 points (SD=23.6 points), ranging from 0.0 to 92.0, with a median of 25.0 points. In scales ranging from 0.0 to 10.0 points of increasing intensity, the dimensions that make up the overall score that presented the highest scores were parathesthesia /dyssesthesia (mean=4.5 points; SD=3.0) and superficial spontaneous pain (mean=4.1 points; SD=3.9).

Table 12 - Descriptive statistics of latency and amplitude measurements of CN-PREP* and neuropathic pain inventory - NPSI measurements among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Parameter	n	Mean	Median	Standard deviation	Minim	Maxim
Latency with inclusion of cases with missing potential						
Right foot latency at peak	100	268,4	220,5	120,5	149,0	500,0
Latency right foot in the valley	100	345,7	322,0	84,1	216,0	500,0
Left foot latency at peak	100	287,0	213,0	139,4	133,0	500,0
Latency left foot in the valley	100	355,9	313,5	96,7	232,0	500,0
Right foot amplitude	100	23,9	21,9	18,3	0,0	90,0
Amplitude left foot	100	21,0	19,7	19,1	0,0	88,2
Exclusion values for cases with missing potential						
Right foot latency at peak	80	210,4	203,0	34,7	149,0	315,0
Latency right foot in the valley	80	307,1	309,0	36,3	216,0	382,0
Left foot latency at peak	71	199,9	197,0	31,6	133,0	305,0
Latency left foot in the valley	71	297,1	295,0	33,5	232,0	425,0
Right foot amplitude	80	29,2	26,6	15,9	6,7	90,0
Amplitude left foot	71	29,1	27,6	16,4	4,0	88,2
Neuropathic Pain Inventory - NPSI						
Overall score (0.0-100.0)	97	31,5	25,0	23,6	0,0	92,0
Superficial spontaneous pain (0.0-10.0)	97	4,1	5,0	3,9	0,0	10,0
Deep spontaneous pain (0.0-10.0)	97	3,5	4,0	3,3	0,0	10,0
Paroxysmal pain (0.0-10.0)	97	2,3	0,0	3,0	0,0	10,0
Evoked pain (0.0-10.0)	97	2,5	1,7	2,6	0,0	9,3
Paraesthesia / dyssesthesia (0.0-10.0)	97	4,5	4,5	3,0	0,0	10,0

Source: Prepared by the author himself

* According to cn-prep criteria (evoked potential of concentric needle electrodes), the potential was absent in 20 cases of the right foot and 29 cases of the left foot

For latency analyses with inclusion of cases with absent potential, the value of 500 milliseconds was imputed. For the analyses excluding these cases, they were taken from the sample.

For amplitude analyses with inclusion of cases with absent potential, the value 0.0 microvolts was imputed. For analyses excluding these cases, they were taken from the sample

The analyses of the correlations between latency and amplitude parameters and pain assessments through NPSI are presented in Table 13 e 14.

In the comparison of latency measures with inclusion of cases with absent potential and NPSI parameters, there was an inverse and statistically significant correlation between right foot latency at peak and paraesthesthesia/dyssesthesia (r=-0.222; p=0.029 after Bonferroni correction). No statistically significant correlations were observed in any of the other parameters.

In the comparison of latency measures with exclusion of cases with absent potential

and NPSI parameters, no statistically significant correlations were observed. Initially, associations of right foot latency at the peak with the overall NPSI score and the dimensions of superficial continuous spontaneous pain, deep continuous spontaneous pain, paroxysmal spontaneous pain and paresthesia/dyssesthesia were identified, but the Bonferroni test ruled out these associations.

The measurements of right foot and left foot amplitude, both with inclusion and excluding cases with absent potential, did not present statistically significant correlations with any of the NPSI parameters.

Table 13 - Analysis of correlations between CN-PREP* latency and amplitude measurements and neuropathic pain inventory - NPSI** measurements among patients with pain in the lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Parameter	Overall score	Superficial continuous spontaneous pain - burning	Deep continuous spontaneous pain - grip and pressure	Paroxysthet spontaneous pain	Evoked pain (allodin / hyperalgesia)	Paraesthesia / dyssesthesia
Latency (in milliseconds) with inclusion of cases with missing potential						
Right foot latency at peak						
n	97	97	97	97	97	97
r§	-0,164	-0,154	-0,152	-0,129	-0,088	-0,222
p	0,108	0,132	0,138	0,208	0,393	**0,029** $
Latency right foot in the valley						
n	97	97	97	97	97	97
r§	-0,066	-0,038	-0,087	-0,011	-0,006	-0,119
p	0,519	0,711	0,397	0,915	0,954	0,248
Left foot latency at peak						
n	97	97	97	97	97	97
r§	-0,134	-0,049	-0,114	-0,103	-0,074	-0,132
p	0,193	0,636	0,266	0,316	0,473	0,198
Latency left foot in the valley						
n	97	97	97	97	97	97
r§	-0,095	-0,001	-0,082	-0,100	-0,023	-0,099
p	0,354	0,989	0,426	0,329	0,827	0,333
Latency (in milliseconds) excluding cases with missing potential						
Right foot latency at peak						
n	77	77	77	77	77	77
r*	-0,259	-0,273	-0,277	-0,259	-0,158	-0,309
p	0,481 $	0,342 $	0,313 $	0,486 $	0,171	0,131 $
Latency right foot in the valley						
n	77	77	77	77	77	77

r*	-0,094	-0,086	-0,168	-0,069	-0,027	-0,138
p	0,416	0,456	0,144	0,552	0,815	0,230
Left foot latency at peak						
n	68	68	68	68	68	68
r§	-0,110	0,038	-0,054	-0,109	-0,058	-0,162
p	0,374	0,757	0,663	0,375	0,639	0,188
Latency left foot in the valley						
n	68	68	68	68	68	68
r§	-0,038	0,126	0,013	-0,101	0,042	-0,090
p	0,756	0,305	0,916	0,414	0,734	0,464
Amplitude (in microvolts) with inclusion of those with potential absent cases						
Right foot amplitude						
n	97	97	97	97	97	97
r§	0,081	0,049	0,064	0,078	0,040	0,088
p	0,433	0,632	0,536	0,447	0,697	0,393
Amplitude left foot						
n	97	97	97	97	97	97
r§	0,086	0,028	0,071	0,045	0,039	0,086
p	0,401	0,785	0,490	0,663	0,701	0,402
Amplitude (in microvolts) excluding cases with missing potential						
Right foot amplitude						
n	79	79	79	79	79	79
r§	0,052	0,038	0,053	0,110	0,004	0,100
p	0,647	0,741	0,646	0,333	0,976	0,380
Amplitude left foot						
n	69	69	69	69	69	69
r§	-0,012	-0,031	0,008	0,026	-0,062	0,004
p	0,923	0,799	0,948	0,831	0,614	0,973

Source: Prepared by the author himself

* According to cn-prep criteria (evoked potential of concentric needle electrodes), the potential was absent in 20 cases of the right foot and 29 cases of the left foot

For latency analyses with inclusion of cases with absent potential, the value of 500 milliseconds was imputed. For the analyses excluding these cases, they

were taken from the sample.
For amplitude analyses with inclusion of cases with absent potential, the value 0.0 microvolts was imputed. For analyses excluding these cases, they were taken from the sample
** Overall score from 0 to 100 points and dimensions with scores from 0 to 10 points
§ Spearman correlation coefficient $ Bonferroni correction

Table 14 - Analysis of correlations[§] between CN-PREP* latency and amplitude measurements and neuropathic pain inventory - NPSI** among patients with pain in lower limbs, Hospital das Clínicas, FMUSP, São Paulo, 2016 to 2019.

Parameter	Overall score	Superficial continuous spontaneous pain - burning	Deep continuous spontaneous pain - grip and pressure	Paroxysthet spontaneous pain	Evoked pain (allodin / hyperalgesia)	Paraesthesia / dyssesthesia
Latency (in milliseconds) with inclusion of cases with missing potential						
Right foot latency at peak	-0,164	-0,154	-0,152	-0,129	-0,088	**-0.222** [1, 2]
Latency right foot in the valley	-0,066	-0,038	-0,087	-0,011	-0,006	-0,119
Left foot latency at peak	-0,134	-0,049	-0,114	-0,103	-0,074	-0,132
Latency left foot in the valley	-0,095	-0,001	-0,082	-0,100	-0,023	-0,099
Latency (in milliseconds) with inclusion of cases with missing potential						
Right foot latency at peak	0.481 [1, 3]	0.342 [1, 3]	0.313 [1, 3]	0.486 [1, 3]	0,171	0.131 [1, 3]
Latency right foot in the valley	-0,094	-0,086	-0,168	-0,069	-0,027	-0,138
Left foot latency at peak	-0,110	0,038	-0,054	-0,109	-0,058	-0,162
Latency left foot in the valley	-0,038	0,126	0,013	-0,101	0,042	-0,090
Amplitude (in microvolts) with inclusion of cases with absent potential						
Right foot amplitude	0,081	0,049	0,064	0,078	0,040	0,088
Amplitude left foot	0,086	0,028	0,071	0,045	0,039	0,086
Amplitude (in microvolts) excluding cases with missing potential						
Right foot amplitude	0,052	0,038	0,053	0,110	0,004	0,100
Amplitude left foot	-0,012	-0,031	0,008	0,026	-0,062	0,004

Source: Prepared by the author himself

[$] Spearman correlation coefficient [1] $p<0.05$ [2] Bonferroni correction $p<0.05$ [3] Bonferroni correction $p>0.05$

* According to cn-prep criteria (evoked potential of concentric needle electrodes), the potential was absent in 20 cases of the right foot and 29 cases of the left foot

For latency analyses with inclusion of cases with absent potential, the value of 500 milliseconds was imputed. For the analyses excluding these cases, they were taken from the sample.

For amplitude analyses with inclusion of cases with absent potential, the value 0.0 microvolts was imputed. For analyses excluding these cases, they were taken from the sample

** Overall score from 0 to 100 points and dimensions with scores from 0 to 10 points

4 DISCUSSION

In this sample, a datum that draws attention consists in the superior diagnostic sensitivity of CN-PREP compared to EDX. Although EDX is the most accessible electrophysiological peripheral nerve assessment test worldwide, in our study it demonstrated lower sensitivity to CN-PREP (Table 08). Considering EDX as the reference test, CN-PREP sensitivity was 85.1% and specificity 58.5%, making CN-PREP possibly a good test for diagnostic screening. In addition, the CN-PREP proved to be a tolerable examination by the patients, evidenced by the analysis of the analog pain scale (VAS) applied during the examination and by the absence of give-ups during the examination.

As already described in other studies (Lefaucheur, 2012), we can also consider CN-PREP an easy-performing exam and no side effects. When we analyzed the routine using EDX and PREP jointly, the positivity was 69%. Nociceptive flexion reflex would add 3% diagnostic sensitivity to the tests. However, the low tolerance that patients referred to in this last test based on VAS responses casts doubt on its applicability. The analysis of the association of pain scales with electrophysiological tests revealed increased values in the DN4 and NPSI scales with statistical significance in individuals who presented altered EDX, indicating that this exam alterations are possibly related to pain complaints, as also observed in clinical practice. In the evaluation of CN-PREP latency measures with the inclusion of cases with absent potential and NPSI parameters, there was an inverse and statistically significant correlation between latency and paraesthesia/dyssesthesia. This means that by the findings, the higher the latency score, the lower the perception of paraesthesia/dysthesthesia. This may indicate that the CN-PREP considered more altered are related to the decrease in pain perception, with negative symptoms and with alterations in the somatosensory pathway.

In fine fiber pathologies, there is also an inverse correlation between the severity of symptoms and the density of fibers evaluated in skin biopsy (Zhou, 2019). A rarefaction of these structures in the most severe cases may also be the cause of the alteration evidenced in the electrophysiological tests.

Important is that neurophysiological techniques used to investigate patients with pain in routine clinical practice, such as Quantitative Sensory Testing (QST) - if limited to thermal detection thresholds - and PREPs, are highly sensitive to demonstrate lesions and deficits that affect pain pathways, much more than giving evidence for peripheral or central sensitization phenomena.

As discussed earlier, according to IASP guidelines there is no established protocol for the diagnosis of defined neuropathic pain and neither the ones that exist are feasible into practice outside university. Although clinical evaluation and laser evoked potential form the gold standard for this type of evaluation, practical restrictions limit these tests. Several studies have demonstrated the usefulness of the study of fine fibers with evoked potential using concentric planar electrode and its practical advantages (Lefaucheur, 2012, 2019). Some applied this evaluation in controlled pathological contexts but restricted to a few pathologies or only healthy volunteers (Üçeyler et al, 2013; Mark Obermann et al., 2007; Treede, Lorenz, Baumgärtner, 2003; Oh, 2015). No or few studies, however, have applied this evaluation in an outpatient context, with a great diversity of pathologies, having as a common point the complaint of neuropathic pain.

This study aimed at analyzing whether superficial electrical stimulation of the skin, using a concentric plane electrode (CN-PREP), can serve as armed propaedeutics in the diagnosis of neuropathic pain. The use of PREPs in electrodiagnosis remains undeveloped, partly due to the cost of laser equipment. Therefore, the development of less complicated and less expensive stimulation techniques for PREPs is welcome and the concentric planar electrode is particularly attractive (Lefaucheur, 2012).

The present study reports results that support the use of surface and focal electrical appliances to stimulate and evaluate small diameter sensory afferences. This remains to be determined whether the PREPs obtained with this type of stimulation are convenient in the daily practice of the neurophysiologic clinic, to assess the integrity of the spinothalamic tract. Further studies to address this problem are necessary (Lefaucheur, 2012). The concentric planar electrode has been used in several clinical studies (Katsarava et al., 2006b; Mueller et al., 2010; Obermann et al., 2007, 2008; Yoon, 2011), associated or not with other fine fiber evaluation tools (Hansen et al., 2015, Üçeyler, 2013; Obermann et al., 2007) but no work has previously made a correlation with the most widespread electrophysiological examination worldwide, electroneuromyography (EDX).

The studies mentioned above used, in addition to CN-PREP, skin biopsy, QST, LEP, etc., all methods of nociception assessment that are basically used in the university environment and in research, either for cost or for the operational complexity of the method. CN-PREP is an easy-to-use, inexpensive tool that can be coupled to any electroneuromyography device. All these things make CN-PREP, like electroneuromyography for the evaluation of thick fibers, become a universalized tool for fine fiber evaluation, increasing in clinical practice the expec-

tation of evaluation of clinical neurophysiologists. The aim of this study was to verify the degree of contribution of the evoked potential with concentric planar electrode for the diagnosis of defined neuropathic pain, analyzed in isolation and in conjunction with other electrophysiological tests, in different pathological contexts. We also sought correlations of these tests with pain assessment scales, used in the management of patients with neuropathic pain. All these characteristics make it an unprecedented study.

The patients were recruited from an outpatient clinic of EDX where mostly patients who with chronic conditions are treated. They were referred from the rehabilitation service of the Hospital da Clinicas de São Paulo. The final sample was balanced between genders, ages and pathologies as well as the evaluation scales, evidenced by the cronbach's alpha coefficient used for this analysis.

It is noteworthy that the results refer to a small sample: patients who were already stratified by its clinical referral or clinical complaint and matched the inclusion criteria. Results showed that we were possibly accurate in the selection of patients with neuropathic pain. Among the limitations of our study, we highlight the use of normality values based on other deferential populations of ours because there are no national studies standardizing these tests. Even in places with a greater tradition in carrying out these evaluations, there is still no consensus on how to interpret the findings and what to value (Nutti, 2016; Lefaucheur, 2012; Lefaucheur, 2019; Oh 2015).

Our study found that patients with altered CN-PREP had potentials with lower amplitude. This ratifies other studies that also reported this finding (Lefaucheur, 2019). As described above, there is still a difficulty in classifying abnormal responses, perhaps the evaluation of amplitudes is an important parameter, and we value this in our evaluation. In the literature, PREP amplitude also can be used as an objective biomarker of provoked pain, useful for pharmacologic studies of analgesics or for assessing the effects of brain stimulation procedures on pain (Schaffler et al., 1987, 2004, 2005, 2017; Truini et al., 2010; Bradley et al., 2016; Pommier et al., 2016; Kirimoto et al., 2018).

Although our work cannot be considered completely double blind, we took care to separate the physicians who performed the EDX from the physicians who performed the other electrophysiological tests. This can be considered a factor for better reliability of the results. Despite a low percentage of illiterate patients included in the study, the characterization of pain based on assessment scales has often proved difficult to understand for our patients. We opted for exploratory work; thus, limitations were already expected.

The pathophysiology of nociceptive fibers includes two different aspects: fiber loss or

reduced function on the one hand and hyperactivity of fibers or hyperexcitability, on the other. The first alteration is at the origin of negative symptoms (deficit of thermoalgesic sensation), while the last one is at the origin of positive symptoms (pain). The main problem in relation to neurophysiological investigations of pain in a clinical context is that the most used techniques, such as the measurement of thermal detection thresholds (using QST) or the registration of PREPs (using radiant or contact heating), are sensitive to nociceptive function, but less specific in relation to aspects related to directness with pain complaint. The same conclusion applies to skin biopsy, which is considered the gold standard for the diagnosis of painful neuropathy of small fibers, but only demonstrates the loss of small intraepidermal nerve fiber terminations (Lefaucheur, 2019)

In conclusion and as explained in the introduction, neuropathic pain is defined as "resulting from a direct consequence of an injury or disease affecting the somatosensory system" or "caused by an injury or disease of the somatosensory nervous system" , and includes a variety of physiosiopathological mechanisms with secondary neuroplastic alterations that occur in the nociceptive system (Colloca et al., 2017). Many questions are raised about the adequacy of confirmatory tests to affirm a possible, probable or definitive note of neuropathic pain. Therefore, it will always be necessary to be careful with the interpretations that can be extracted from neurophysiological tests in clinical practice to investigate pain.

5 CONCLUSION

We have shown that CN-PREPs can be added to the routine neurophysiological assessment of patients with suspected neuropathic pain, which increases diagnostic positivity. It remains to be determined the actual sensitivity and specificity of CN-PREPs in this scenario when compared to gold standards of small fiber assessment such as intraepidermal nerve fiber density and laser-evoked potentials, so that the false positive rate of such a strategy can be determined.

6 SUGGESTIONS FOR FUTURE WORK

As previously stated, despite the limitations of the sample, normality parameters and the absence of statistically significant correlations, the findings encourage us to continue in this line of research. Difficulties for diagnosis and, consequently, treatment of neuropathic pain still persist and new studies adding answers to this problem are necessary. We consider that the

encouragement of future studies following the same line, correcting the limitations of the present study, constitute an important contribution in the academic scenario.

7 CONFLICT OF INTEREST STATEMENT

The author have no conflict of interest to declare.

8 FUNDING

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10 APPENDIX

APPENDIX A – Neuropathic pain symptom inventory (NPSI)

NPSI – Versão brasileira (de Andrade, *et al.*, 2011)

INVENTÁRIO DE SINTOMAS DE DOR NEUROPÁTICA

Data:
Nome: Apelido:
Sexo:
Idade:

Você tem sofrido de dor devido a lesões ou doença do sistema nervoso. Essa dor pode ser de diversos tipos. Você pode ter dor espontânea, ex.: dor na ausência de qualquer estímulo, que pode ser duradoura ou ocorrer em ataques breves. Você pode também ter dor provocada ou aumentada por leve toque, pressão ou contato com o frio na área dolorosa. Você pode sentir um ou mais tipos de dor. Este questionário foi desenvolvido para ajudar seu médico a melhor avaliar e tratar diferentes tipos de dor que possa sentir.

Nós queremos saber se você sente dor espontânea, sem qualquer estímulo. Para cada das seguintes questões, por favor, selecione o número que melhor descreve a sua gravidade média da dor espontânea durante as últimas 24 horas. Selecione o número 0 se você não sente tal dor (circule um número apenas).

Q1. Sua dor dá a sensação de queimaduras?

Não queima	0	1	2	3	4	5	6	7	8	9	10	A pior queimadura imaginável

Q2. Sua dor dá a sensação de apertar?

Não aperta	0	1	2	3	4	5	6	7	8	9	10	Aperta o pior imaginável

Q3. Sua dor dá a sensação de pressão?

Sem pressão	0	1	2	3	4	5	6	7	8	9	10	A pior pressão imaginável

Q4. **Durante as últimas 24 horas**, a sua dor espontânea tem estado presente:
Selecione a resposta que melhor descreve o seu caso.

- Permanente ☐
- Entre 8 e 12 horas ☐
- Entre 4 e 7 horas ☐
- Entre 1 e 3 horas ☐
- Menos que 1 hora ☐

Nós queremos saber se você teve ataques breves de dor. Para cada uma das seguintes questões, por favor, selecione o número que melhor descreve a gravidade média dos seus ataques de dor durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q5. Sua dor dá a sensação de choque elétrico?

Sem choque elétrico	0	1	2	3	4	5	6	7	8	9	10	O pior choque elétrico imaginável

Q6. Sua dor dá a sensação de apunhalar?

Sem apunhalada	0	1	2	3	4	5	6	7	8	9	10	A pior apunhalada imaginável

Q7. Durante as últimas 24 horas, quantos destes ataques de dor você teve? Selecione a resposta que melhor descreve o seu caso.

- Mais de 20 ☐
- Entre 11 e 20 ☐
- Entre 6 e 10 ☐
- Entre 1 e 5 ☐
- Sem ataque de dor ☐

Nós queremos saber se você sente dor provocada ou aumentada por leve toque, pressão, contato com o frio na área onde dói. Para cada das seguintes questões, por favor, selecione o número que melhor descreve a gravidade da dor provocada durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q8. Sua dor é provocada, ou aumentada, por um leve toque na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável

Q9. Sua dor é provocada, ou aumentada, por pressão na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável

Q10. Sua dor é provocada, ou aumentada, por contato com algo frio na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10	A pior dor imaginável

Nós queremos saber se você sente sensações anormais na zona onde dói. Para cada das seguintes questões, por favor, selecione o número que melhor descreve a gravidade média das sensações anormais durante as últimas 24 horas. Selecione o número 0 se você não sentiu tal dor (circule um número apenas).

Q11. Sente alfinetes e agulhas?

Sem alfinetes nem agulha	0	1	2	3	4	5	6	7	8	9	10	Os piores alfinetes e agulhas imagináveis

Q12. Sente dormente?

Sem dormência	0	1	2	3	4	5	6	7	8	9	10	O mais dormente imaginável

APPENDIX B – Questionnaire for the diagnosis of neuropathic pain (DN4)

Questionário Para diagnóstico De Dor Neuropática – DN4

QUESTIONÁRIO PARA DIAGNÓSTICO DE DOR NEUROPÁTICA – DN4

Por favor, nas quatro perguntas abaixo, complete o questionário marcando uma resposta para cada número:

ENTREVISTA DO PACIENTE

Questão 1: A sua dor tem uma ou mais das seguintes características?

	Sim	Não
1- Queimação		
2- Sensação de frio dolorosa		
3- Choque elétrico		

Questão 2: Há presença de um ou mais dos seguintes sintomas na mesma área da sua dor?

	Sim	Não
4- Formigamento		
5- Alfinetada e agulhada		
6- Adormecimento		
7- Coceira		

EXAME DO PACIENTE

Questão 3: A dor está localizada numa área onde o exame físico pode revelar uma ou mais das seguintes características?

	Sim	Não
8- Hipoestesia ao toque		
9- Hipoestesia a picada de agulha		

Questão 4: Na área dolorosa a dor pode ser causada ou aumentada por:

	Sim	Não
10- Escovação		

ESCORE

0 – Para cada item negativo 1 – Para cada item positivo

Dor Neuropática: Escore total a partir de 4/10.

( ) Dor Nociceptiva ( ) Dor Neuropática

APPENDIX C – Brief Pain Inventory

INVENTÁRIO BREVE DE DOR

1) Durante a vida, a maioria das pessoas apresenta dor de vez em quando (dor de cabeça, dor de dente, etc.). Você teve hoje, dor diferente dessas?

1.Sim 2.Não

2) Marque sobre o diagrama, com um X, as áreas onde você sente dor, e onde a dor é mais intensa.

3)Circule o número que melhor descreve a pior dor que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

4) Circule o número que melhor descreve a dor mais fraca que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

5) Circule o número que melhor descreve a média da sua dor.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

6) Circule o número que mostra quanta dor você está sentindo agora (neste momento).

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

· Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of Brief Pain Inventory to Brazilian patients with pain. Support Care Cancer. 2010 Mar 10. [Epud ahead of print].

7) Quais tratamentos ou medicações você está recebendo para dor?

Nome	**Dose/ Freqüência**	**Data de Início**

8) Nas últimas 24 horas, qual a intensidade da melhora proporcionada pelos tratamentos ou medicações que você está usando?
Circule o percentual que melhor representa o alívio que você obteve.

Sem alívio 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% alívio completo

9) Circule o número que melhor descreve como, nas últimas 24 horas, a dor interferiu na sua:

Atividade geral

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Humor

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Habilidade de caminhar

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Trabalho

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Relacionamento com outras pessoas

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Sono

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu completamente

Habilidade para apreciar a vida

O 1 2 3 4 5 6 7 8 9 10

Não interferiu interferiu

· Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of Brief Pain Inventory to Brazilian patients with pain. Support Care Cancer. 2010 Mar 10. [Epud ahead of print].

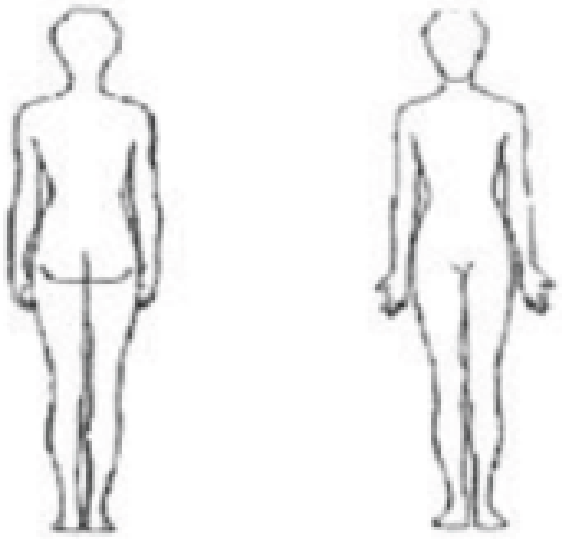
APPENDIX D –McGill Form

McGill forma breve

Marcar com "X" a presença ou ausência de cada característica da dor

Dimensão Sensitiva	Presente	Ausente
Latejante		
Pontada		
Choque		
Fina/agulhada		
Fisgada		
Queimação		
Espalha		
Dolorida		
Dimensão Afetiva		
Cansativa		
Enjoada		
Sufocante		
Apavorante		
Aborrecida		
Dimensão Avaliativa		
Que incomoda		
Insuportável		

Intensidade da dor



Localização da dor (marcar a localização)

APPENDIC E – Free and informed consent form

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .:.....

..... DOCUMENTO DE IDENTIDADE Nº :

..... SEXO : .M ☐ F ☐

DATA NASCIMENTO: ...../...../.....

ENDEREÇO ..... Nº ..... APTO: ..... BAIRRO: ..... CIDADE ..... CEP:.....

TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....

..... NATUREZA (grau de parentesco, tutor, curador etc.) ..... DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐

DATA NASCIMENTO.: ...../...../.....

ENDEREÇO: ..... Nº ..... APTO: ..... BAIRRO: ..... CIDADE: .....

CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA: **Uso de eletródio planar concêntrico para avaliação de pacientes com dores em membros inferiores e características neuropáticas.**

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____

.....

PESQUISADOR : .Prof. Daniel Ciampi de

Andrade..... CARGO/FUNÇÃO:

Coordenador do Centro de Dor do Departamento de Neurologia

HC/FMUSP..... INSCRIÇÃO CONSELHO REGIONAL Nº **108.232** .....

UNIDADE DO HCFMUSP: Instituto de Medicina Física e Reabilitação

.....

3. AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MÍNIMO **X** RISCO MÉDIO ☐

RISCO BAIXO ☐ RISCO MAIOR ☐

4.DURAÇÃO DA PESQUISA : .36 meses.....

1– A dor neuropática é definida como um quadro associado a uma lesão ou doença acometendo o sistema nervoso. A pessoa que tem essa doença pode apresentar como principais sintomas uma dor que tem como caraterística parecer um formigamento, choque ou queimação. O seu diagnóstico é estabelecido através de uma avaliação clínica e alguns exames, dentre eles o Potencial Evocado, a Eletroneuromiografia e o teste do reflexo nociceptivo de retirada, que tem como finalidade avaliar a função dos nervos do seu corpo. Dessa maneira consegue-se fazer o diagnóstico correto e assim realizar o tratamento adequado. Essas informações estão sendo fornecidas para a sua participação voluntária neste estudo, cujo objetivo é promover o diagnóstico correto da sua doença (Dor Neuropática) e assim proporcionar ao médico que encaminhou o Sr./Sra. para o nosso serviço, condições de aliviar os seus sintomas e fazer um tratamento eficaz.

2– Os procedimentos de coleta de dados serão:

a) Aplicação de questionário envolvendo informações sobre a idade, ocupação profissional, doenças associadas, histórico de trauma ou cirurgia em membro superior ou região cervical e medicamentos utilizados.

b) Aplicação de questionários que avaliarão o tempo dos sintomas e a suas características.

c) Realização de um exame físico que avalia a sensibilidade e força das pernas.

3– Serão realizados de maneira separada 3 exames: Eletroneuromiografia, Potencial Evocado e teste do reflexo de retirada, cuja finalidade é avaliar a função dos nervos das suas pernas através de um estudo com uma pequena agulha e leves choques. Esse procedimento é seguro e tolerável pelos pacientes e poderá diagnosticar a alteração responsável pelos seus sintomas e assim dar condições para a implementação do tratamento correto.

4– Os prováveis riscos do procedimento, mesmo sendo incomuns, são: vermelhidão, dor no local da picada da agulha e formação de pequenos hematomas.

5– Benefícios para o participante: através desse estudo, poderemos diagnosticar de uma forma correta a sua doença (Dor Neuropática) e assim proporcionaremos condições ao médico que o encaminhou, de lhe oferecer o melhor tratamento e assim aliviar os seus sintomas.

6– Para a participação neste estudo é fundamental que você tenha mais de 18 anos, dor há mais de 2 meses, consiga ler e entender os questionários.

7– A coleta dos dados e procedimentos serão feitos no Instituto de Medicina Física e Reabilitação (IMREA) do Hospital das Clínicas da FMUSP - Unidade Clínicas.

8– Garantia de acesso: em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. A principal investigadora é a Dr Daniel Ciampi de Andrade que pode ser encontrado no endereço: Rua Dr. Ovídio Pires de Campos, portaria 3 do InRAD - Cerqueira César – São Paulo, SP – CEP 05403-010. Telefone:(11) 2661-7557. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5ºandar – tel: 3069-6442 ramais 16, 17, 18 ou 20 – e-mail: cappesq@hcnet.usp.br

9– É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

10– Direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente;

11– Direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

12– Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa.

13 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo: "**Uso de eletródio planar concêntrico para avaliação de pacientes com dores em membros inferiores e características neuropáticas".**

Eu discuti com o Dr. Daniel Ciampi de Andrade sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO- HCFMUSP

_____ _____/_____/_____
Assinatura do paciente/representante legal Data

_____ _____/_____/_____
Assinatura da Testemunha Data

Para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual. *(Somente para o responsável do projeto)*

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

_____ _____/_____/_____
Assinatura do responsável pelo estudo Data

APPENDIX F - Sociodemographic questionnaire

I.DADOS SÓCIODEMOGRAFICOS		
SEXO	IDADE	DATA DE NASCIMENTO
1.masculino ( ) 2.feminino ( )	_____ anos	/ /
NÍVEL EDUCACIONAL:		
1.Analfabeto( ) 2. Ensino médio ( ) 3. Ensino fundamental ( ) 4.Superior ( ) 5.pós-graduação ( )		
ESTADO CIVIL:		
1.solteiro( ) 2.casado( ) 3.união consensual( ) 4.separado( ) 5.divorciado( ) 6.viúvo( )		
SITUAÇÃO CONJUGAL: 1.Com companheiro( ) 2.sem companheiro( )		
RELIGIÃO:		
1.ateu( ) 2.evangélico( ) 3.católico( ) 4.espírito( ) 5.Outro_____		
PRATICANTE:	SITUAÇÃO DE TRABALHO:	
0. não( ) 1. sim ( )	1.empregado( ) 2.desempregado( ) 3.aposentado( ) 4.dona de casa( ) 5.autônomo( ) 6.estudante( ) 7.Licença saúde( ) 8.informal( )	
Você está trabalhando atualmente? 0.não ( ) 1.sim ( )		
RENDA:		
I.individual(mensal):R$		
II.Suficiente para suprir necessidades? 0.não ( ) 1.sim ( )		
III.familiar (mensal): R$	IV.Nº de pessoas que vivem com esta renda:	
VI.Você é o principal responsável pelo sustento de sua família? 0.não ( ) 1.sim ( )		
CASO VOCÊ NÃO TENHA RENDA PRÓPRIA		
I. Como você se mantém?		
1. ajuda da família ( ) 2. ajuda de instituição ( ) qual?_____ 3. ajuda de vizinhos ou amigos ( ) 4. ajuda de pessoas estranhas ( )		
COMO AVALIA A SUA SAÚDE DE FORMA GERAL		
1.muito ruim( ) 2.ruim( ) 3. nem ruim nem boa( ) 4. Boa( ) 5. muito boa ( )		
2.Você tem alguma das seguintes doenças:	Rubrica do sujeito de pesquisa ou responsável_____ Rubrica do pesquisador_____	

	Não 0	Sim1
1. Diabetes Mellitus		
2. Cerebrovascular		
3. Hipertensão arterial		
4. Doenças vascular periférica		
5. Doença renal crônica		
6. Neoplasia maligna		
7. Doença cardiocirculatória		
8. Doença hepática		
9.Depressão		
10. Doença do trato gastrointestinal		
11. Doença autoimune		
12.Outras:_____		

III.

ANTECEDENTES MÉDICOS PESSOAIS: 31 – Tratou-se de alguma destas doenças:

()Artrite reumatóide ()Asma ()Bronquite ()Hepatite ()Amigdalite ()Derrame (AVC)

()Fibromialgia ()Sinusite ()Pressão alta (HAS) ()Diabete ()Úlcera ()Gastrite

()Rinite alérgica ()Coração ()Doença renal (rins) ()Depressão ()Infecções ()Enxaqueca

()Herpes zoster (cobreiro) ()Parkison ()Outra:

_____

Bebe?

Fuma?

Destro/ canhoto?

Usa contraceptivo oral?

Rubrica do sujeito de pesquisa ou responsável_____

Raça

Rubrica do pesquisador_____

Altura
peso

– Está em tratamento médico atual? ( )N ( )S Doenças que tem e remédios que usa:_____

tem dor em alguma parte do corpo? se sim onde?

Observações

Nacionalidade

Naturalidade:_____

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____