The contribution of concentric electrode-evoked potentials and nociceptive withdrawal reflex to the routine neurophysiological assessment of neuropathic pain: cross-sectional study

A contribuição dos potenciais evocados por eletrodo concêntrico e reflexo de retirada nociceptiva para a avaliação neurofisiológica de rotina da dor neuropática: estudo observacional transversal

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DOI 10.5935/2595-0118.20230067-en

ABSTRACT

BACKGROUND AND OBJECTIVES: Conventional electrodiagnostic studies (EDX) are frequently used to support the diagnosis of peripheral neuropathic pain. However, routine EDX has poor diagnostic yield for identifying small fiber neuropathy, which may be cause of neuropathic pain in some patients. This study aimed to assess the gain in diagnostic yield brought by adding pain-related evoked potentials with concentric electrode (CN-PREP) and nociceptive withdrawal reflex (NWR) assessments to EDX.

METHODS: Transversal observational accuracy study which included patients referred to routine EDX in a tertiary-care hospital who reported chronic neuropathic pain in their lower limbs. Besides routine EDX, subjects underwent CN-PREP and NWR assessments. Diagnostic yield and tolerability were examined and compared between test studies.

RESULTS: The study enrolled 100 patients (54% female), with 57 ± 12 years. EDX was altered in 47% of all patients. The addition of CN-PREP alone, and NWR combined with CN-PREP increased diagnostic yield to 69% and 72%, respectively. CN-PREP proved to be well tolerable, while NWR was associated with higher test-related pain intensity and discontinuation rate (9% vs. 0%). Considering EDX as the reference test, CN-PREP sensitivity was 85.1% and specificity 58.5%.

CONCLUSION: Combining CN-PREP with the routine EDX for patients with neuropathic pain is feasible and results in increased diagnostic yield. Conversely, the addition of NWR to the aforementioned tests provides little improvement to this yield and is less tolerable to the patient. Further studies are needed to determine the actual sensitivity and specificity of CN-PREP when compared to the gold-standard for small fiber neuropathy diagnosis, i.e. intraepidermal nerve fiber density assessment.

Keywords: Chronic pain, Electrodes, Neuralgia, Polyneuropathies, Somatosensory evoked potentials.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Estudos convencionais de eletrodiagnóstico (EDX) são frequentemente usados para apoiar o diagnóstico de dor neuropática periférica. No entanto, o EDX de rotina tem baixo rendimento diagnóstico para identificar neuropatia de pequenas fibras. O objetivo deste estudo foi avaliar o ganho no rendimento diagnóstico pela adição de avaliações de potenciais evocados relacionados à dor com eletrodo concêntrico (CN-PREP) e reflexo de retirada nociceptiva (NWR) ao EDX.

MÉTODOS: Estudo de precisão observacional transversal que incluiu pacientes encaminhados para EDX de rotina com dor neuropática crônica em membros inferiores. Além do EDX de rotina, os indivíduos foram submetidos às avaliações CN-PREP e NWR. O rendimento diagnóstico e a tolerabilidade foram examinados e comparados entre os estudos de teste.

RESULTADOS: O estudo envolveu 100 pacientes (54% mulheres), com 57 ± 12 anos. O EDX estava alterado em 47%. A adição de CN-PREP sozinho e NWR combinado com CN-PREP aumentou o rendimento diagnóstico para 69% e 72%, respectivamente. O CN-PREP provou ser bem tolerável, enquanto o NWR foi associado a maior intensidade de dor relacionada ao

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Submitted on January 25, 2023.
Accepted for publication on July 29, 2023.
Conflict of interests: none – Sponsoring sources: This work was supported by the HC-FMUSP Pain Center, CNPq (scientific production scholarship MJT, DCA), by the Center for Neuroplasticity and Pain (CNAP), and by the Danish National Research Foundation (DNRF121, Novo Nordisk Grant NNF21OC0072828).

HIGHLIGHTS

- Pain-related evoked potentials with concentric electrode testing are feasible and well tolerated for the routine neurophysiologic assessment of peripheral neuropathic pain in a real-world setting.
- The addition of pain-related evoked potentials with concentric electrode testing to routine electrodiagnostic studies may increase the diagnostic yield of neurophysiologic evaluation for peripheral neuropathic pain.
- Combining nociceptive withdrawal reflex evaluation to pain-related evoked potentials with concentric electrode and routine electrodiagnostic studies adds little to the diagnostic yield and is less tolerable to patients.

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teste e taxa de descontinuação (9% vs. 0%). Considerando o EDX como teste de referência, a sensibilidade do CN-PREP foi de 85,1% e a especificidade de 58,5%.
CONCLUSÃO: A combinação do CN-PREP com o EDX de rotina para pacientes com dor neuropática é viável e resulta em maior rendimento diagnóstico. Já a adição de NWR aos testes mencionados fornece pouca melhora nesse rendimento e é menos tolerável para o paciente. Mais estudos são necessários para determinar a real sensibilidade e especificidade do CN-PREP quando comparado ao padrão-ouro para diagnóstico de neuropatia de pequenas fibras, ou seja, a avaliação da densidade de fibras nervosas intraepidérmicas.
Descritores: Dor crônica, Eletrodos, Neuralgia, Polineuropatias, Potenciais evocados.

INTRODUCTION

Chronic pain affects 16% to 28% of the general population[1,2] and has an undeniable impact on their quality of life, as well as direct financial consequences[3]. On the other hand, 7% of the general population suffer from neuropathic pain (NP), which also results in a heavy burden to patients and their families. According to the International Association for the Study of Pain (IASP), NP is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (SSS), and its specific localization within the nervous system".
Its diagnosis should be based on history, physical examination, specific questionnaires, and complementary tests that may support the identification of the lesion to the SSS and its specific localization within the nervous system. Electrophysiological testing is frequently used for this purpose in instances of peripheral neuropathic pain[4,5]. In fact, conventional electrodiagnostic studies (EDX) are the most frequently used complementary tests for the diagnosis of peripheral neuropathies[6,7]. EDX provide valuable data that may help determine the etiology, severity, and prognosis of these conditions[8].
However, because these tests predominantly evaluate large, myelinated fibers (A-β), their sensitivity is significantly hindered when assessing patients with small fiber neuropathy, or in cases where both small and large fiber involvement are present.
Thus, the objective of this study was to investigate the feasibility and contribution of adding to routine EDX two neurophysiological tests, able to assess small nerve fiber function, namely: concentric electrode pain-related potentials (CN-PREP) and nociceptive withdrawal flexion reflexes (NWR), in terms of improving the yield of the diagnosis of SSS lesion among patients with probable NP in their lower limbs.

METHODS

A transversal observational accuracy study with convenience sample, approved by the local Ethics Review Board (#36978214.1.0000.0068). The consecutive sample was formed by adult patients (>18 years old) referred by their physicians to the Institute of Physical Medicine and Rehabilitation (*Instituto de Medicina Física e Reabilitação* - IMREA) to perform EDX. The patients were included according to the following criteria: i. reported chronic pain in their lower limbs; ii. scored ≥ 4 in the *Douleur Neuropathique 4* questionnaire (DN4); iii. presented physical examination findings that allowed for fulfilling current IASP criteria for probable neuropathic pain[9].
Exclusion criteria were: physical and intellectual inability to answer the questionnaires; physical or psychological inability to undergo electrophysiological tests; clinical contraindications to the study's tests; or unwillingness to participate. Enrollment occurred between January 2018 and December 2019. All included subjects provided their written Free Informed Consent Term (FICT) before they were enrolled. This work followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting cross-sectional studies.
All enrolled subjects were assessed with a structured interview and questionnaires, which investigated general demographic data, clinical features, and burden of their chronic pain. In addition to this clinical evaluation, these patients underwent electrophysiological studies with conventional EDX, CN-PREP and recording of NWR (Figure 1).

Pain scales and questionnaires

In clinical practice, currently, the use of scales for pain assessment is more frequent than any complementary examination.
The following questionnaires were used to assess the patients' chronic pain characteristics and burden:
(a) Verbal Numeric Rating Scale (v-NRS): self-reported 11-point scale that measures pain intensity from zero (no pain) to 10 (highest possible).
(b) Short-form McGill Pain Questionnaire (SF-MPQ): examines pain descriptors divided into three dimensions: sensory (eight

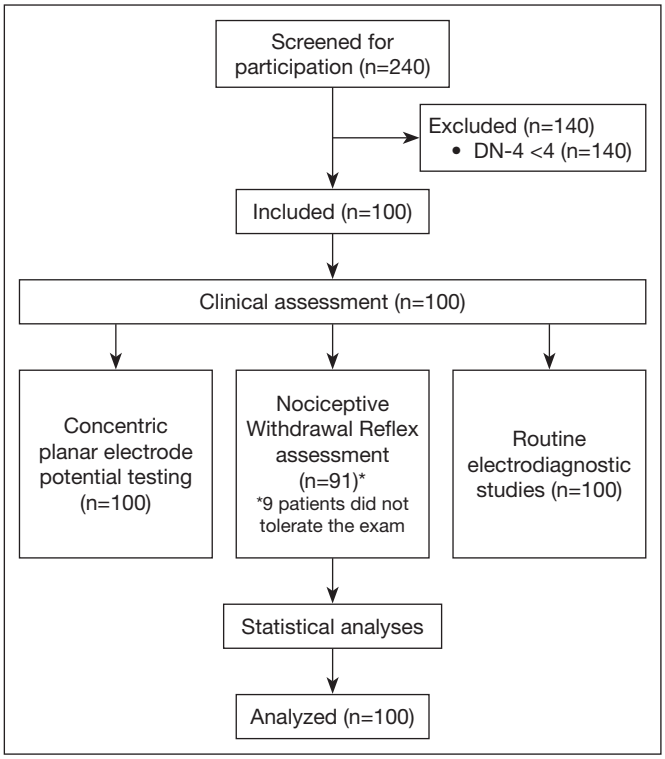

Figure 1. Flowchart of patients' selection and assessment

items), affective (five items) and evaluative (two items)[10]. The total and dimension-specific scores are obtained by counting the words chosen by the patient[10,11].

(c) Brief Pain Inventory (BPI): Measures least, average and worst pain intensity in the last 24 hours as well as current pain intensity with a v-NRS. It also measures pain interference on general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life. Total interference score ranges from zero to 70, and higher scores mean higher inference of pain[12,13].

(d) Douleur Neuropathique Questionnaire-4 (DN-4): A screening test for NP composed of ten items. It ranges from 0 to 10 and is considered positive when ≥4[14,15].

(e) Neuropathic Pain Symptoms Inventory (NPSI): A qualitative and quantitative inventory of NP symptoms that enables the identification of different clinical pain phenotypes through discrimination and quantification of five distinct relevant dimensions of NP: burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia. Its total score ranges from zero to 100, and each dimension's score ranges from zero to 10 with higher scores indicating more intense symptoms[16].

Neurophysiological tests

The assessments were performed in a single session. All tests were performed with the patient in horizontal decubitus, at a room temperature between 21ºC and 23ºC. The temperature of the patient's extremities was maintained above 34ºC, and the impedance of all tests bellow 5Ω, as recommended in the literature[17,18]. The doctor performing the examination was blind to the results of other tests. A four-channel Neuropack device (ANVISA registry number 10263610036) was used to perform the EDX, and a two-channel NeuroMep Micro (ANVISA registry number 80969869005) for testing CN-PREP and NWR.

Conventional electrodiagnostic studies (EDX)

EDX consisted of two components: nerve conduction (NCS) and needle electromyograph (EMG) studies. 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 were used to determine the number of functioning nerve fibers and the speed of conduction. In the second stage (EMG), the asepsis was first performed at the site of the bites.

The 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.

These tests can assess the pattern and degree of nerve involvement, underlying nerve and muscle disease as well as contribute to characterize peripheral nerve disorders[19].

Concentric needle pain related evoked potential (CN-PREP)

Pain related potentials were tested with electrical stimulation induced by a concentric planar electrode (Figure 2). This electrode was designed to excite nociceptive fibers in the surface layer of the dermis and was identical to that described in previous studies[20,21]. Each stimulus consisted of a three-pulse train (pulse duration: 0.5 ms, pulse interval: 5ms).

The stimuli were applied on the dorsal region of the hands and feet, and the site of the pain reported by the patient. The electrode was moved slightly during the registration of curves to avoid habituation. The potential obtained consists of negative and positive wave complex, with peaks named N2 and P2 (Figure 3A and 3B). Peak-to-peak distance was used to calculate the potential's amplitude. The N2-P2 component was recorded through electrodes assembled following the 10-20 international system[21-23], with subcutaneous needle electrodes placed in Cz-A[22,24].

Nociceptive withdrawal reflex

According to previously published studies[21,25,26], NWR was assessed with regular electrical stimulation of the sural nerve in

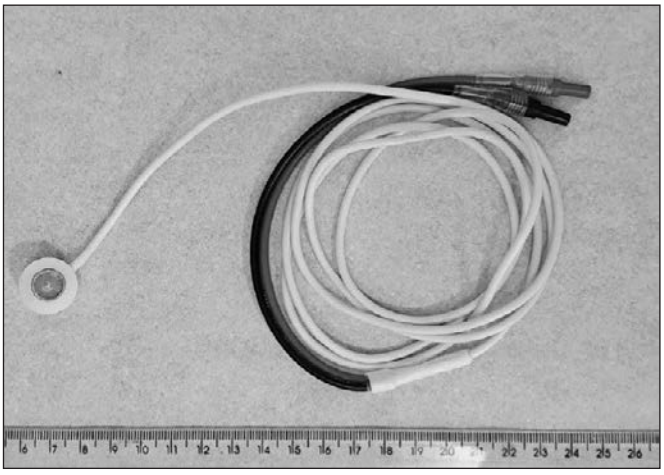

Figure 2. Concentric planar electrode developed and patented in Brazil by the Pain Center of the Department of Neurology of the University of São Paulo Teaching Hospital

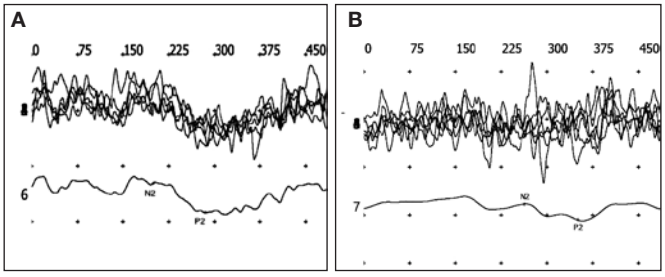

Figure 3. CN-PREP on the foot of individuals with and without neuropathic pain and peripheral neuropathy.

This figure presents the readings of scalp electrodes, positioned at the Cz and A1 regions of the international 10-20 system, after stimulation of the foot with a concentric planar electrode, in a healthy subject (A) and a patient with neuropathic pain and peripheral neuropathy (B). The N2-P2 potentials are indicated in each image, and can be seen to be larger in A than in B. Amplitude is presented in a 40μV scale, and time in a 75 ms scale.

the ankle. Trains of five consecutive stimuli (duration of 1ms, frequency 500 Hz) were applied in the sural nerve, at intensities ranging from zero to 50 mA. Flexor reflexes were recorded by surface electrodes applied at the ipsilateral femoral biceps muscle. The responses were analyzed within a 50-250 ms window and amplified with a passing band of 30-1500 Hz. Responses were considered abolished if absent after two consecutive 50 mA stimuli. Nociceptive withdrawal flexion reflexes were identified based on established latency and morphology criteria: polyphasic form and early latency between 80 and 130 ms[21,27].

Statistical analyses

Continuous variables were described as mean and standard deviation (SD), and the categorical ones as absolute and relative frequencies. Visual inspection through histograms and quantile-quantile graphs and the Shapiro-Wilk test were performed to assess whether continuous variables followed a normal distribution.

The accuracy of CN-PREP and NWR tests was evaluated taking the EDX as reference. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The existence of associations between the assessments of NP scales and the results of the CN-PREP and the EDX was verified. To analyze 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 case the assessed electrical potential was considered abolished, the value 500 was imputed for the latency, and the value zero for the amplitude variables. Data analyses were performed using the IBM SPSS Statistics software for Windows, Version 20.0 (Armonk, New York).

RESULTS

The research included 100 patients with neuropathic characteristics (54 women and 46 men), age ranging from 30 to 92 years (57 ± 12.21). Most participants were women (54.0%) and over 50 years old (76.0%). Their general demographic features are presented in table 1.

Pain assessment

Chronic pain intensity was 5.99 ± 2.46 on average, and 4.87 ± 3.15 at the moment of the assessment. Results showed an overall moderate interference (6.01 ± 2.81) to the subjects' functionality. Interference was more severe for the following dimensions: walking ability (6.63 ± 3.04), work (6.59 ± 3.01) and general activity (6.52 ± 2.99) (Table 2). Mean DN-4 and NPSI scores were 5.97 ± 1.74 and 31.45 ± 23.56, respectively. The NPSI dimensions with higher mean scores were "superficial spontaneous pain" (4.08±3.88) and "paresthesia/dysesthesia" (4.50 ± 3.00, table 2). The most common NP descriptors were tingling (91%), numbness (89%) and burning (70%).

The overall mean SF-MPQ score was 10.11 ± 3.53, and 5.47 ± 2.29 for sensory, 3.17 ± 1.40 for affective and 1.46 ± 0.58

Table 1. Descriptive statistics of electrophysiological tests results among patients with probable neuropathic pain in the lower limbs

Results	n	%
EDX		
Normal	53	53.0
Neuropathy	11	11.0
Polyneuropathy	26	26.0
Radiculopathy	10	10.0
CN-PREP		
Normal	38	38.0
Altered	62	62.0
NWR		
Present	85	85.0
Abolished	15	15.0
Total	100	100.0

EDX = conventional electrodiagnostic studies; CN-PREP = Evoked potential of concentric needle electrodes; NWR = nociceptive withdrawal reflex, the RIII component was taken into account and measured. CN-PREP was considered abnormal when latency was above 212 ms and/or amplitude below 8.8 μV and/or N2/P2 amplitude was depressed by at least 30% and/or latency responses was delayed by at least 30 ms, compared to the normal side.

Table 2. Descriptive statistics of the electrophysiological test results and test-related pain among patients with neuropathic pain in the lower limbs

Evaluation	n	Mean (±SD)	p-value
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			
v-NRS	100	5.14 ± 1.18	
NWR- pain			
v-NRS	100	8.88 ± 1.69	

EDX = conventional electrodiagnostic studies; CN-PREP = Evoked potential of concentric needle electrodes; NWR = nociceptive withdrawal reflex, the RIII component was considered and measured; v-NRS = verbal numeric rating scale; CN-PREP-pain = pain reported during CN-PREP assessment; NWR-pain = pain reported during NWR assessment.

for evaluative dimensions. The most frequently reported pain descriptors were troublesome (95.0%), sore/aching (85.0%), nagging (84.0%), tiring-exhausting (82.0%), sickening (74.0%), spreading (73.0%), and tugging (73.0%).

Electrophysiological tests

Forty-seven percent of patients had altered EDX, and the most common diagnosis was polyneuropathy, followed by truncal nerve neuropathy and radiculopathy. CN-PREP were abnormal in 62% of the sample (Table 1). Comparing individuals with normal and altered CN-PREP results, the mean latency to the N2P2 response was higher (187,95 ± 22,77 ms vs 347,65 ± 146,18 ms p<0.001) while amplitudes were lower (37.42 ± 14.39 μV vs 10.87 ± 14,01 μV p<0.001) in the latter group (Table 2).

CN-PREP and NWR contribution to EDX

Routine EDX was altered among 47% subjects with probable NP. When combined with CN-PREP, the diagnostic yield increased to 69%. However, by adding NWR testing, the rate of positive diagnosis only improved to 72% (Table 3). On the other hand, reported pain intensity during testing was higher during NWR than CN-PREP assessment (8.88 ± 1.69 vs. 5.14 ± 1.18). Moreover, while nove (9%) individuals did not tolerate the former and discontinued testing, CN-PREP was well tolerated by all. Tests not completed due to patient intolerance were considered non-existent or abolished because the researchers reached very high intensities and did not find response.

Taking the EDX as reference, the sensitivity of CN-PREP alone was 85.1% (95% CI 71.7% to 93.8%) and its specificity 58.5% (95% CI 44.1% to 71.9). The PPV was 64.5% (95% CI 51.3% to 76.3%) and the NPV was 81.6% (95% CI 65.7% to 92.3%). While adding NWR to CN-PREP (i.e. considering a positive diagnosis when either the former or the latter were altered) did not improve sensitivity nor specificity significantly, when both NWR and CN-PREP were altered, the specificity rose to 92.5% (95% CI 81.8% to 97.9%, table 4).

Pain scales and electrophysiological tests associations

DN4 scores tended to be higher among patients with altered EDX (p=0.05). Furthermore, NPSI scores for the dimensions "paroxysmal pain" (0=0.046) and "evoked pain" (p=0.031) where significantly higher among those with altered in EDX. No other statistically significant association was observed between pain scale and neurophysiologic testing results (Table 3).

Table 3. Diagnostic yield of pain-related evoked potential with concentric needle electrodes, conventional electrodiagnostic studies and nociceptive withdrawal reflex assessment of patients with suspected neuropathic pain in the lower limbs

Tests	n	%
PREP only	62	62.0
PREP + EDX	69	69.0
PREP + EDX + NWR	72	72.0
All tests normal	28	28.0
Total	100	100.0

EDX = conventional electrodiagnostic studies; CN-PREP = Pain-related evoked potential with concentric needle electrodes; NWR = Nociceptive withdrawal reflex.
Normal exams = Patients without confirmed diagnosis of lower limbs neuropathy in none of the three tests.

DISCUSSION

The present study found that the addition of CN-PREP to current EDX routine tests, when examining subjects with probable neuropathic pain in a real-world setting, provided higher percentage of altered results compared to EDX alone. The further addition of the NWR slightly increased the diagnostic yield, but at the cost of almost 10% of patients not tolerating the exam. CN-PREP assessment proved to be feasible and tolerable[22].

Although skin biopsy with intraepidermal nerve fiber density determination and laser evoked potentials are currently the gold standards for small nerve fiber assessment in peripheral neuropathic pain, practical restrictions may limit these tests, especially in economically restricted environments. On the other hand, previously published studies have demonstrated the usefulness of examining evoked potentials with concentric planar electrode for investigating the function of small nerve fibers, and its practical advantages for a range of diseases[22,28]. Most of these researches applied this evaluation in controlled disease contexts, restricted to a few diseases or only healthy volunteers[24,29-31]. Few studies, however, have conducted this evaluation in an outpatient context with a great diversity of diseases having as a common point the presence of neuropathic pain.

CN-PREP is an easy-to-use, inexpensive tool that can be coupled to any electroneuromyography device. These features make CN-PREP a potentially valuable addition to routine EDX, increasing its contribution to the clinical assessment of patients suspected neuropathic pain. The concentric pla-

Table 4. Pain-related evoked potential with concentric needle electrodes and nociceptive withdrawal reflex accuracy taking the conventional electrodiagnostic studies as a reference in the assessment of patients with suspected neuropathic pain.

Parameters	Sensitivity % (95% CI)	Specificity % (95% CI)	VPP % (95% CI)	VPN % (95% CI)
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)
NWR	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 NWR	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 NWR	17.0 (7.6 - 30.8)	92.5 (81.8 - 97.9)	66.7(34.9 - 90.1)	55.7(44.7 - 66.3)

EDX = conventional electrodiagnostic studies; CN-PREP = Pain-related evoked potential with concentric needle electrodes; NWR = nociceptive withdrawal reflex, the RIII component was taken into account and measured; PPV = Positive predictive value; NPV = Negative predictive value.

nar electrode has been used in several clinical studies[30,32-35] associated or not with other small nerve fiber evaluation tools[28,36,37], but to the best of the present authors' knowledge no work yet has compared it with the most widespread electrophysiological examination worldwide, electroneuromyography (EDX). It 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 possibility are necessary[22].

It must, however, be acknowledged that the present study had some limitations. Reference normative values and diagnostic cut-off determination procedures that have been previously reported but were not yet fully validated were used. Similarly to laser-evoked potentials, CN-PREPs do not benefit form extensive and widely accepted normative data such as those available for EDX[22,24,28,38]. The sample was a convenience one, since no data available in the literature would allow the authors to formally calculate sample size in the real-world scenario of patient enrollment that the latter were willing to entertain. Nonetheless, the present's study data will be valuable to allow for better estimations of sample size requirements in future studies assessing CN-PREPs in real-world settings. Although the present work cannot be considered as double blinded, the authors took care to separate the researchers who performed the EDX from those who performed the other electrophysiological tests. This may have contributed to the reliability and internal validity of the results.

CONCLUSION

The study has shown that the addition of CN-PREPs to routine EDX studies in the clinical assessment of patients with suspected neuropathic pain is feasible and may increase the diagnostic yield of routine neurophysiological assessments in a real-world scenario. However, the use of NWR in this context does not seem to provide substantial benefit and may be less feasible due to poor tolerability. The actual sensitivity and specificity gain by combining CN-PREP with EDX remain to be determined, since direct comparisons of this approach to gold standard methods used to assess small fibers in this specific scenario have not been performed yet in large patient samples.

ACKNOWLEDGMENTS

The authors would like to thank the patients, the University of São Paulo Teaching Hospital employees and the IMREA, especially Prof. Dr Linamara Rizzo Batisttella, for their invaluable support in the development of this research.

AUTHORS' CONTRIBUTIONS

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Writing - Review and Editing, Visualization

Tae Mo Chung
Research, Visualization

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