The Validity and Reliability of a New Modified Persian Version of DN4 to Discriminate Non-neuropathic from Neuropathic

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Abstract

Introduction: One of the popular questionnaires for screening neuropathic pain is the DN4 (Douleur Neuropathique 4) which has been translated into many languages and validated in different populations. So, we wanted to determine the Persian version of this questionnaire's reliability and validity to differentiate neuropathic pain from other painful non-neuropathic conditions.

Methods: This cross-sectional study was conducted on 120 patients who suffered from chronic pain referred to the Physical Medicine and Rehabilitation Department at the three great referral hospitals in Tehran, Iran in 2016. In this study, a modified version of DN4 was used to validate adding a question related to the appearance of pain in an especial joint and adding visual analogue scaling (VAS) score in each item.

Results: The modified DN4 questionnaire had high reliability for assessing neuropathic pain with the Cronbach's alpha coefficient of 0.874. The correlation coefficients obtained by the retest intra-class correlation test ranged from 0.650 to 0.941. Also, the internal consistency of Spearman's R coefficients ranged from 0.482 to 0.904. Test-retest reliability analysis also showed a higher intraclass correlation (ICC) value in the neuropathic than non-neuropathic pain group (0.85 vs 0.73). The modified DN4 questionnaire could effectively discriminate neuropathic pain from non-neuropathic pain with the area under the curve (ROC) of 0.989 (95% CI: 971–1000, $P < 0.001$). The best cutoff value for the modified DN4 questionnaire to diagnose neuropathic pain was 5, yielding a sensitivity of 98.3% and a specificity of 90.3%.

Conclusion: Applying the new modified Persian version of DN4 achieved by adding a VAS score and a new question related to the appearance of pain in an especial joint led to high reliability and validity for this tool to discriminate neuropathic from non-neuropathic pain.

Keywords: DN4, Neuropathic pain, Persian version, Questionnaire, Reliability, Validity

Introduction

Neuropathic pain is a complex problematic condition characterized by chronic pain accompanied by injury and dysfunction of the nerve fibers especially the somatosensory system.¹ Etiologically, several causes including diabetes mellitus, alcoholism, musculoskeletal disorders, nerve injuries, multiple sclerosis, parkinsonism, chemotherapy-induced neuropathy, tumor infiltration, spinal surgical interventions, shingles, HIV infection or post-herpetic neuralgia have been suggested.²⁻⁴ Neuropathic pain is usually described as a burning or shooting pain with numbness and tingling. In

this regard, this pain diagnosis is based on interviews and accurate physical examination to discover the primary source of pain and its-related triggering.⁵ Unfortunately, no gold standard tool has been introduced for the final diagnosis of neuropathic pain. However, a combination of physical assessment and neurological tests is employed to achieve the final diagnosis.⁶ According to "The European Federation of Neurological Sciences guidelines", describing disease symptoms by the patients, along with stimulus-evoked pains induced by a mechanical, chemical, or thermal stimulus, can be potentially diagnostic.⁷ Besides diagnostic tools, some

screening instruments and questionnaires have been developed to screen the neuropathic pain and differentiate it from other painful conditions such as nociceptive pain. One of the most used questionnaires for screening neuropathic pain is the DN4 (Douleur Neuropathique 4) which was primarily structured in French version.⁸ This tool has some items about how the patient feels the pain. Also, it has items requiring professional assessment of reduced or increased sensation (hypoaesthesia vs allodynia).⁹ The DN4 has been translated into different languages and validated in diverse populations. The present study aimed to determine the modified Persian version of this questionnaire's reliability and validity to identify neuropathic pain from other painful non-neuropathic conditions.

Materials and Methods

Study Population

This cross-sectional study was conducted on 120 consecutive patients who suffered from chronic pain referred to the Physical Medicine and Rehabilitation Department at three great referral hospitals in Tehran (Firoozgar hospital, Shafa yahyaieian hospital, Rasol Akram hospital), Iran, in 2016.

The eligible subjects for entering the study include patients aged higher than 18 years suffering chronic pain within the last three months, regardless of its neuropathic or non-neuropathic nature. The severity of pain was initially determined according to the visual analogue scaling (VAS) method ranged from 0 to 110. Exclusion criteria were any syndromes with unknown origin, pain induced by malignancies, complex regional pain syndrome, headache, visceral pains, severe depression, history of using alcohol or substances abuse.

The primary diagnosis was based on the interview and physical examination done by a physical medicine expert. Two physicians physically examined the patients at two times within 24 to 48 hours and fulfilled the questionnaires. Ethically, the Declaration of Helsinki principles were respected. Entering the study was subject to the prior written consent of the patients. The principal researcher had adequately explained the objectives and methodology, and informed consent was signed before recruiting the patient.

Tool Description

In this study, a modified version of DN4 was used to validate adding a question and adding a VAS score in each question. The questionnaire's first three items were related to the quality of pain, including tingling, painful cold or electric shock sensation. The other four questions described abnormal feelings of pain, such as tingling, numbness, and itching.

Three items of the questionnaire were physical assessment and had been performed by the physician. The

added question in our tool was about pain in an especial joint. For each item, "1" was the score for "yes" and "0" for "no." The patient is defined to have neuropathic pain by a total score of 4 or more.

The Method of Validation

To assess the modified DN4 questionnaire's reliability and internal consistency, reliability analysis (by calculating the Cronbach's alpha coefficient) and the Spearman correlation test (by calculating correlation coefficient) were used.

The Kappa value was also determined to assess agreement between the two experts who completed the questionnaires.

Statistical Analysis

Statistical analyses were performed in SPSS 22 (SPSS Inc., Chicago, IL). Mean $\pm$ standard deviation (SD) was used to describe quantitative data, and percentages and frequencies were applied for categorical variables. The Kolmogorov-Smirnov test was used to assess normality. The statistical tests of chi-square test or Fisher exact test were used to investigate the relationship between categorical variables. Also, the student *t* test (for normally distributed) or Mann-Whitney U test (for non-normally distributed) were used to compare means between groups. The correlation between the study parameters was assessed using the Pearson's correlation test. The area under the curve (ROC), and the best cutoff point for the DN4 total score to achieve optimal sensitivity and specificity for diagnosing neuropathic pain were also determined.

For the statistical analysis, the statistical software SPSS version 22.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In total, 120 patients (78 women and 42 men) were entered. Neuropathic pain was diagnosed in 61 patients (41 women and 20 men), and thus 59 patients (37 women and 22 men) suffered from non-neuropathic pain with no difference between the two genders ($P=0.7$). The average age of participants was 49.99 ± 16.27 years (ranged from 20 to 89 years). No difference was revealed in mean age between the patients with neuropathic (50.96 ± 15.92 years) and non-

neuropathic pain (48.98 ± 16.71 years) ($P=0.7$). Regarding occupational status, in total, 75 patients (62.5%) were employed that the rate of employment in neuropathic pain and non-neuropathic pain groups was 65.6% and 59.4%, respectively ($P=0.57$). Regarding educational level, an academic degree was revealed in 32.8% of patients with neuropathic pain and 18.6% of those with non-neuropathic pain with no difference

($P=0.09$). 65.6% of patients with neuropathic pain use analgesic drugs, which is significantly higher than those who suffered non-neuropathic pain (40.7%) ($P=0.01$). The mean body mass index (BMI) in the neuropathic pain group was 19.40 ± 38.10 kg/m², and in the non-neuropathic pain group was 16.20 ± 36.20 kg/m² ($P<0.01$). Regarding the severity of pain based on the VAS scoring system, the mean VAS score in the neuropathic pain group was 73.81 ± 4.63 and in the non-neuropathic pain group 68.68 ± 3.61 revealing more severe pain in the former group ($P<0.001$). The mean DN4 score for patients with neuropathic pain was 7.11 ± 1.30 that was significantly higher when compared to those with non-neuropathic pain (1.02 ± 1.01) ($P<0.001$). Also, the mean score reported by the two interviewers was 3.97 and 4.11, indicating no difference.

As shown in Table 1, the modified DN4 questionnaire had high reliability for assessing neuropathic pain with the Cronbach's alpha coefficient of 0.874). The correlation coefficients obtained by the retest intra-class correlation

test ranged from 0.650 to 0.941. Also, Spearman's r coefficients ranged from 0.482 to 0.904 indicating high internal consistency reliability for the questionnaire.

The kappa agreement test showed a high agreement value between the two questioners (kappa value of 0.520). Test-retest reliability analysis (Table 2) also showed higher intraclass correlation (ICC) value in the neuropathic pain group (0.85) than in the non-neuropathic pain group (0.73).

Using the ROC curve analysis, the DN4 system could effectively discriminate neuropathic pain group from non-neuropathic pain with the area under the ROC of 0.989 (95% CI: 971–1000, $P<0.001$) (Figure 1). The diagnostic performance of different cutoff points for DN4 is described in Table 3.

The best cutoff value for DN4 to diagnose neuropathic pain was 5 yielding a sensitivity of 98.3% and a specificity of 90.3%. In a sub-analysis based on the pain severity, the value of DN4 for predicting neuropathic pain was significantly higher in those with VAS ≥ 70 than in patients

Table 1. Reliability of DN4 by Considering Each Item of the Tool

Items	Internal-Rater Agreement Kappa Cohen's	Test-Retest ICC	Reliability Cronbach Alpha Coefficient	Internal Consistency Spearman's r Coefficient
Burning	0.833 SEM: 0.050	0.879		0.783
Painful cold	0.777 SEM: 0.064	0.851	0.455	0.742
Electric shocks	0.520 SEM: 0.105	0.650		0.482
Tingling	0.850 SEM: 0.048	0.920		0.851
Pins and needles	0.883 SEM: 0.043	0.941		0.889
Numbness	0.881 SEM: 0.044	0.938	0.693	0.884
Itching	0.635 SEM: 0.100	0.783		0.652
Hypoesthesia to touch	0.850 SEM: 0.048	0.921		0.853
Hypoesthesia to prick	0.882 SEM: 0.043	0.938	0.808	0.884
Brushing	0.769 SEM: 0.078	0.869	-	0.769
Joint pain	0.899 SEM: 0.040	0.949	-	0.904
Total		0.979	0.874	

Table 2. Test-Retest Reliability in Both Neuropathic and Non-neuropathic Pain Groups

	Test-Retest Reliability		
	First Assessment Mean (SD)	Second Assessment Mean (SD)	ICC (95% CI)
Total	3.97 (3.25)	4.11 (3.27)	0.975 (0.96 – 0.98)
Neuropathic pain group	6.86 (1.37)	7.11 (1.31)	0.85 (0.75 – 0.91)
Non-neuropathic pain group	0.97 (1.32)	1.01 (1.02)	0.73 (0.54 – 0.84)

Figure 1. Area Under the ROC Analysis to Determine the Value of DN4 for Predicting Neuropathic Pain (AUC=0.989, Sensitivity=98.36, Specificity=98.31, 95% CI = 0.971-1.000).

with lower pain severity (AUC: 0.999 versus 0.988).

We also assessed the value of DN4 to diagnose mixed pains. Overall, 15 patients with mixed pain (8 women and 7 men, mean age 51 years) were assessed. The mean BMI in those patients was 25.86 kg/m², and the mean duration of pain was also 26.38 months. The Receiver operating characteristic (ROTC) analysis showed a high value for DN4 for discrimination of neuropathic pain group from non-neuropathic pain in the mixed subgroup (AUC: 0.977). The best cutoff point for DN4 to predict neuropathic pain in the mixed pain group was ≥ 5 , with a sensitivity of 88.9% and 100% specificity.

Discussion

According to our study, the Persian version of DN4 questionnaire was a valid and reliable tool for assessing neuropathic pain among our population. By modifying the structure of the original version of DN4 (for the first time) and achieving a new modified format (mainly by adding the VAS as a new arm), the modified version could more effectively differentiate non-neuropathic

from neuropathic pain. In the study population, those suspected of having neuropathic pain, the modified DN4 questionnaire's assessment can effectively discriminate neuropathic pain from other non-neuropathic sources of pain.

We also highlighted the discriminative value of the modified DN4 concerning the baseline pain duration and severity, emphasizing the importance of adding some items related to the quality and duration of pain in the original format of DN4 as performed in our survey.

In a similar survey in the Iranian population, the sensitivity, specificity, and Youden Index in cutoff point ≥ 4 were 90%, 95%, and 0.85, respectively, with a Cronbach's alpha coefficient of 0.852 for the whole scale and the inter-rater agreement and test-retest reliability of 0.957 and 0.918, respectively,¹⁰ which were very close to our observations. In a study by Chatila et al¹¹ in 2017 using a new Arabic version of the DN4, internal consistency for the whole DN4 questionnaire was 0.86, and the intra-class correlation coefficient was also 0.99. The test-retest reliability kappa coefficient for each item ranged from 0.92 to 1.00. Furthermore, the AUCs of 0.97 and 0.94 were reported for the 10-item DN4 and the 7-item DN4, respectively.

A specificity of 82.3% and sensitivity of 97% were obtained for the 7-item DN4 at the threshold score of 3. On the other hand, the specificity of 95.8% and sensitivity of 93.0% were seen for the 10-item DN4 at the cutoff point of 5, which were similar to our study. It was first shown that the Arabic version of this tool is also valid for assessing neuropathic pain. Also, the best cutoff point for the DN4 scale can be similar to that obtained in our population. In a similar survey on the Greek version of DN4,¹² the AUC was 0.92. At the threshold of >4 , a 93% sensitivity and a specificity of 78% were achieved for the DN4 scale for discerning non-neuropathic from neuropathic pain.

In a similar experience on the Spanish version of the DN4,¹³ the questionnaire was reliable with the Cronbach's alpha coefficient of 0.71, inter-rater agreement coefficient of 0.80 and test-retest intra-class correlation coefficient of that was very similar to our study. They also indicated its high validity with obtaining a cut-off value >4 points, which was the best value to discriminate

Table 3. Diagnostic Performance of DN4 at Different Cutoff Points

Cut-off	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Predictive Value	Negative Predictive Value
3 $\leq$	98.36 (CI:91-99)	86.44 (CI:75-93)	7.25 (CI:75-93)	0.02 (CI:0-0.13)	88.24 (CI:79-93)	98.08 (CI:87-99)
4 $\leq$	98.36 (CI:91-99)	96.6 (CI:88-99)	29.02 (CI:7.4-113.3)	0.02 (CI:0-0.13)	96.77 (CI:88-99)	98.28 (CI:88-99)
5 $\leq$	98.36 (CI:91-99)	98.31 (CI:90-99)	58.03 (CI:8.5-405)	0.02 (CI:0-0.12)	98.36 (CI:89-99)	98.31 (CI:89-99)
6 $\leq$	96.72 (CI:88-99)	98.31 (CI:90-99)	57.07 (CI:8-398)	0.03 (CI:0.01-0.13)	98.33 (CI:89-99)	96.67 (CI:88-99)

neuropathic from non-neuropathic pains. In total, reviewing the literature shows that various versions of DN4¹⁴ tested in different populations are reliable and valid to predict neuropathic pain. Also, the best cutoff value of DN4 to differentiate neuropathic from non-neuropathic pain is in the range of 4 to 5, achieving acceptable sensitivity and specificity.

Conclusion

In our study, applying the new modified Persian version of DN4 achieved by adding a VAS score and a new question related to the appearance of pain in an especial joint led to high reliability and validity for this tool to discriminate neuropathic from non-neuropathic pain.

Authors' contributions

SPM: designing the study, reading and approving the final version of the manuscript; KM and SA: data collection; SE: data analysis. All authors equally contributed to writing the manuscript.

Ethical Approval

Declaration of Helsinki principles were respected. Entering the study was subject to the prior written consent of the patients. The principal researcher had adequately explained the objectives and methodology, and informed consent was signed before recruiting the patient.

Competing Interests

None to be declared.

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