Subgrouping of Peripheral Neuropathic Pain Patients According to Sensory Symptom Profile Using the Korean Version of the PainDETECT Questionnaire

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ABSTRACT

Background: A culturally validated Korean version of the PainDETECT Questionnaire (PD-Q) was used to identify neuropathic pain components (NeP) in patients suffering from chronic pain. The purpose of this study was to determine if the Korean PD-Q can be used to subgroup patients with peripheral NeP according to sensory symptom profiles.

Methods: This study included 400 Korean patients with peripheral neuropathic pain diagnosed as probable or definite NeP. The total scores and subscores for each item in PD-Q were transformed into a Z-score for standardization. Hierarchical cluster analysis was performed to identify clusters of subjects by PD-Q scores.

Results: The mean total PD-Q score of the study participants was 14.57 ± 6.46. A hierarchical cluster analysis identified 5 clusters with distinct pain characteristic profiles. Cluster 1 had relatively severe burning and tingling sensations. The mean total PD-Q score for cluster 2 was the lowest of the 5 clusters. Cluster 3 tended to be vulnerable to pain in response to cold/heat stimulation. Cluster 4 showed relatively severe pain induced by physical stimuli, such as light touch or slight pressure. Cluster 5 had high scores for all NeP symptoms.

Conclusion: This study demonstrates the ability of patients to cluster by symptoms using the Korean PD-Q. Subgrouping of peripheral neuropathic pain by sensory symptom profile may be useful in making effective drug treatment decisions.

Keywords: Peripheral Nervous System Diseases; Polyneuropathies; Mononeuropathies; Postherpetic; Pain; Cluster Analysis
INTRODUCTION

Neuropathic pain (NeP) is caused by lesions or disorders of the somatosensory nervous system. NeP pathophysiology is a complex process that includes sensitization, alterations in brain connectivity, and ectopic nerve activity.\(^1\) Although NeP can be caused by various etiologies, the symptoms and characteristics of pain are influenced by each pathophysiological mechanism rather than the etiology.\(^1,2\) This has important therapeutic implications that affect personalized treatment of neuropathic pain.

Sensory phenotypes in NeP patients can be measured using quantitative sensory testing (QST); however, this method is limited because it is time-consuming and requires a skilled examiner. For this reason, several self-assessment methods, termed patient-reported outcomes (PROs), have been developed for immediate use in various environments. PROs include the Leeds assessment of neuropathic symptoms and signs, the NeP symptom inventory, and PainDETECT. The PainDETECT Questionnaire (PD-Q) was validated to identify NeP components in patients suffering from chronic pain.\(^3\) Pain descriptors in the PD-Q correlate with QST items related to pain thresholds in patients with radiculopathy.\(^4\)

All PROs are based on surveys. Thus, linguistic characteristics heavily influence PROs. The original German and English versions and the culturally validated Spanish, Dutch, Turkish, Japanese, and Korean versions have been widely used.\(^5-9\)

A previous study demonstrated successful subgrouping of sensory profiles in patients with NeP using the PD-Q.\(^10\) However, using a PRO in Korean to develop sensory profiles and subgrouping in patients with peripheral NeP has not been demonstrated. The purpose of this study is to examine whether subgrouping of Korean peripheral neuropathic pain patients according to sensory symptom profiles is possible using the Korean PD-Q.

METHODS

Study participants and design

A cross-sectional observational study was performed at five tertiary medical centers. For inclusion of this study, all enrolled Korean participants should have been diagnosed with ‘probable’ or ‘definite’ NeP by NeP diagnostic criteria. The diagnosis was based on the updated grading system for neuropathic pain suggested by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) in 2016.\(^11\)

Participants confirmed their history, neuroanatomically relevant neurological lesions, sensory signs, and outcomes of confirmatory tests by researchers according to the IASP NeuPSIG criteria.\(^11\) Patients were excluded from the study if pain expression was limited due to mental illness or poor ability to speak Korean. In addition, the study excluded patients under 20 years of age and patients with other types of pain in addition to peripheral neuropathic pain. Subjects continued to receive medications for controlling NeP, after being enrolled in the study.

Clinical assessment

Data on patients’ age, gender, height, weight, past medical history, etiology of peripheral neuropathic pain, prescribed medications for treating NeP, and duration of illness were collected. Patients with NeP freely described their symptoms in Korean and filled out the PD-Q in the presence of a researcher. The PD-Q consists of 9 descriptors, including 7 Likert
scales related to different pain symptoms, one question on the pattern of pain course, and one question on the presence of radiating pain. Data were collected in a single visit from October 2018 to June 2020.

Statistical analyses
For standardization, Z-score transformations of the totals and subscores from the Korean PD-Q were analyzed. A hierarchical cluster analysis (HCA) was performed to identify clusters using PD-Q scored and presented as a dendrogram. Cubic Clustering Criterion (CCC) and Pseudo-F Statistic (PFS) and Pseudo-T2 (PST2) was used to determine the optimal number of clusters. We used the Euclidian distance metric combined with the Ward linkage method to optimize the agglomerative coefficient. Data was analyzed without imputation for missing data because data was collected in a single visit.

For evaluating the NeP components of chronic pain, two cut-off values in the total score were suggested in the original study. A score of ≤ 12 indicated that NeP was unlikely to be present, and ≥ 19 indicated that NeP was highly likely. Scores between 12 and 19 indicated an unclear outcome. However, NeP could not be ruled out. These categories are presented as the number of subjects, frequency, and percentage and used for analyzing the subgrouping clusters. All statistical analyses were conducted using SAS software (version 9.4).

Ethics statement
The study was reviewed and approved by the Institutional Review Board of Ajou University Hospital (approval No. MED-0BS-18-204), Konkuk University Medical Center (approval No. KUH11170178), Nowon Eulji Medical Center (approval No. 2018-06-013), Chungnam National University Hospital (approval No. 2018-07-034) and Kangbuk Samsung Hospital (approval No. 2018-06-050). Informed consent was obtained from all participants. Participants also had the right to refuse study participation.

RESULTS
Of the 401 patients screened in this clinical study, 400 were included in this study. One patient withdrew from participation. The mean age of the patients was 61.59 ± 11.94 years, with a median value of 62 years. More than half of the patients were over 60 years old; 167 (41.8%) patients were males, and 233 (58.2%) were females (Table 1). The etiologies of neuropathy included polyneuropathy in 325 (81.3%) patients, mononeuropathy in 49 (12.2%) patients, and postherpetic neuralgia in 26 (6.5%) patients. Metabolic causes were the most common culprits for polyneuropathy, and diabetes was the most common metabolic cause (Table 1). The mean duration of neuropathy was 1.75 ± 2.74 years. Ninety-two (23%) patients were diagnosed with neuropathy at the time of enrollment in this study; the remaining 308 (76%) patients were previously diagnosed with neuropathy. Among the previously diagnosed patients, 287 (71.3%) patients took prescribed medication to alleviate NeP, and all patients reported their medications. Out of 680 responses, the most administered drugs were gabapentinoids (69.4%), followed by opioids (15%) and antidepressants (10.7%, Table 2).

The mean PD-Q total scores of the 400 participants were 14.57 ± 6.46; 169 patients scored 12 or less, 116 patients scored between 13 to 18, and 115 patients scored 19 or higher (Table 3). The severity of each sensory symptom was measured, and the most common response was “no” for “burning sensation” (43.00%), “pain by light touch” (54.00%), “electric shock-like
“pain” (40.50%), “pain on cold/heat stimulation” (39.50%), and “pain by slight pressure” (54.00%, Table 3). For “tingling sensation” and “numbness,” the most frequently indicated severity was “strongly” (Table 3).

As a result of HCA analysis, the local maximum could not be found because the value continued to increase in the PFS method. However, the local maximum of CCC method and the local minimum of PST2 method showed the same five clusters. The HCA used the Korean PD-Q to identify five clusters with distinct peripheral neuropathic pain characteristics (Fig. 1, Table 4). Cluster 1 (72 patients) showed relatively severe burning and tingling sensation compared to the other items. In cluster 2 (123 patients), 79.67% had a total score of ≤ 12, and the mean total PD-Q score was the lowest of the 5 clusters. Patients in cluster 2 mainly complained of tingling sensation and numbness, and few patients reported other symptoms. Cluster 3 (58 patients) had a relatively low burning sensation score but tended to be vulnerable to pain stimulated by cold/heat. Cluster 4 (102 patients) showed relatively severe pain induced by physical stimuli, such as light touch or slight pressure. In cluster 5 (45 patients), the proportion of patients with PD-Q of ≥ 19 was 93.33%, and the mean total score was the highest. None of the patients in cluster 5 had a PD-Q score of ≤ 12. Patients in this cluster were characterized by having high scores for all NeP symptoms.

**DISCUSSION**

The variability of pain-related sensory abnormalities in patients with NeP impedes diagnosis and pharmacotherapy. Thus, various PROs have been developed as convenient screening tools in the clinical field. Despite the invention of diagnostic instruments, the management
of NeP is often ineffective. A primary cause of the ineffective management of NeP is the lack of effective patient subgrouping, making the application of effective drugs difficult. NeP medications have different effects depending on the mechanisms of pain. Therefore, NeP management can be effectively improved when drugs are appropriate for the pain mechanism. In addition, drugs that showed encouraging results in preclinical trials often showed negative results in clinical trials, impeding future development. However, when
looking closely at the results of these clinical studies, effects were not shown in the entire patient cohort but were shown in specific groups of patients with similar symptoms. Traditional etiological grouping did not fully elucidate the different characteristics of the symptoms for individual NeP patients, but grouping was possible according to their pain phenotype. Thus, if NeP patients are grouped appropriately according to their symptoms, effective tailored treatment can be applied to each group.

Subgrouping of NeP by sensory profile may indicate individual pathophysiological mechanisms of pain generation and may be useful in developing effective drug treatments. Applying this perspective to the patients in this study, patients in cluster 1 mainly complained of burning pain and tingling sense. The main pathophysiologic mechanism of NeP is afferent neuron sensitization due to activation of receptors and channel proteins, such as TRPV1. Capsaicin cream and high concentration patches desensitize TRPV1-containing sensory axons via depolarization of TRPV1 ligand-gated channels on nociceptive fibers. Therefore, the use of capsaicin can be considered for patients in cluster 1. Cluster 3 exhibited severe thermal allodynia, which is likely due to central sensitization. Thus, the use of drugs such as pregabalin and gabapentin, that attenuate peripheral or central sensitization may be considered beneficial. For effective pain treatment, some patients require the use of multidrugs that control various mechanisms from an early stage; patients with severe sensory symptoms in all categories, such as cluster 5, corresponding to this group.

In most cases, pain must be estimated based on the patient’s expression of pain, and the language used by the patient is important. Each language has a different origin, and Korean and/or Eastern cultures have different and unique perspectives on “pain.” Therefore, the PRO must be in the appropriate language. The PD-Q can be used in various etiologies and clinical situations, and the questionnaire has been validated in various languages. However, subgrouping patients by sensory symptoms is quite different from using PRO as a diagnostic tool. This study is significant in that it demonstrates patients’ ability to cluster by symptoms using the Korean PD-Q.

There are several limitations to this study. First, most participants were polyneuropathy patients. A similar number of patients with other etiologies, such as mononeuropathy and postherpetic neuralgia, was not analyzed. The clinical application would have been more widespread if the patient group was more diverse. Second, for humanitarian reasons, most subjects in this study were being treated for NeP while participating in this study. Thus, more than 1/3 of the participants were measured to have PD-Q scores of ≤12. However, since NeP has clear diagnostic criteria, and the PD-Q is an instrument that detects NeP elements of chronic pain early to select an appropriate treatment, this study’s results are acceptable.
Classifying PD-Q using cut-off values of 12 and 19 points was helpful for cluster formation and understanding the clusters. Third, the previous study in which patients were clustered using the PD-Q was also organized into five groups. However, the detailed characteristics of the clusters were quite different from this study. The different cluster characteristics may be due to differences in language, patient etiology, duration of illness, and/or the influence of drugs on each study. While the previous studies tended to be clustered according to each pain symptom, in the results of Korean patients, the intensity of pain was an important clustering point, which may be a result of reflecting cultural differences. If NeP patients are grouped in similar sensory symptom profiles in any country and any condition, the application of PRO would be much easier to use without the need for cultural validation. However, such a comprehensive application is not possible. If follow-up studies complement these limitations, a more uniform grouping of NeP patients would be possible, and applying PROs in clinical research or clinical settings can be reviewed.

The process of grouping using sensory symptom profiles and confirming the effect of treatment on grouped patients will be expanded. This grouping of patients will be helpful in the validation of new treatments in the future. In setting the treatment group and measuring the effects of treatment, effective measurement methods will be explored according to the language and culture used in each region. These changes will eventually contribute to precision pain treatment, so continuous attention is needed.

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