

FACTORS INFLUENCING THE SEVERITY OF PAIN IN PATIENTS WITH PERIPHERAL DIABETIC NEUROPATHY

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Received: 17 May 2017, Revised and Accepted: 04 July 2017

ABSTRACT

Objective: The principal aim of this study was to identify factors influencing the severity of peripheral diabetic neuropathy pain (PDNP), a symptom of the common neurological complication of diabetes mellitus, and peripheral diabetic neuropathy.

Methods: A cross-sectional study was performed using two self-administered questionnaires among subjects recruited from outpatient clinics at Hospital Tengku Ampuan Afzan, Kuantan, Malaysia. The Neuropathic Pain-4 tool was used to evaluate the presence of PDNP, and the Short-Form McGill Pain Questionnaire (MPQ) was used to characterize and determine the severity of PDNP. Sociodemographic and clinical data were collected from the patients.

Results: The MPQ indicated that most patients reported experiencing mild pain for all sensory pain descriptors other than throbbing and aching (mostly reported to be moderate) and hot-burning (mostly reported to be no pain). The severity of pain was found to be significantly related to the length of time for which the patients had suffered from diabetes in those patients who had been diagnosed over 10 years previously ($p=0.04$). Indian patients reported a higher severity of pain overall ($p=0.04$). No significant relationship was found between pain severity and any of the following factors: Type of diabetes (I or II), gender, smoking status, alcohol consumption, obesity, medication taken, or presence of other diseases.

Conclusion: In this study, most patients with PDNP reported the severity of the pain to be "mild." The pain severity may be influenced by a patient's ethnicity and the length of time for which they have suffered from diabetes.

Keywords: Factors, Severity of pain, Peripheral diabetic neuropathy.

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INTRODUCTION

Peripheral diabetic neuropathy pain (PDNP) is a complication of diabetes mellitus affecting many patients with that condition [1]. A neurological disorder, PDNP is defined as pain directly resulting from peripheral somatosensory system abnormalities in diabetic people; it is among the principal causes of increased mortality and morbidity [2]. As described in Tesfaye and Selvarajah [3], the foremost clinical indicators of PDNP are insensitivity (a consequence of which is an increased risk of injury and ulceration of the foot) and painful neuropathic symptoms. In comparison to painless diabetic neuropathy, painful diabetic neuropathy has a deleterious effect on patients' mental and physical quality of life [4]. The presence of chronic painful peripheral neuropathy over an extended period can be a cause of great distress to patients and may even lead to anxiety or depression. On the other hand, this type of complication lower the scale of quality of life of patients as the ratio of morbidity and mortality increased, whereas society undergo in extreme burden due to health-care cost [5].

One-fifth of patients with diabetes and one-third of patients with diabetic peripheral neuropathy experience painful symptoms [6]. The severity of the pain varies greatly, manifesting as, for example, aching, paresthesia (a tingling or pricking ["pins and needles"]), burning, a shooting pain, similar to an electric shock, or a lancing (or "stabbing") pain. However, the exact symptoms cannot be considered to be reliable indicators of nerve damage. Patients with little sensory deficit – and so little nerve damage – can experience the symptoms of severe pain; those

with no pain can have exhibit evidence of nerve damage in the form of complete numbness of the foot, which is associated with a greatly elevated risk of ulceration [7]. In Malaysia, there is sparse information regarding PDNP incidence and severity.

PDNP pathogenesis remains a matter of some uncertainty although a number of theories have been proposed. One such theory involves autoimmune and metabolic disorders in combinations with glial cell activation and changes in the expression of calcium and sodium channels; another involves alterations to the blood vessels that supply the peripheral nerves [8]. Research has demonstrated a small number of drugs to be of benefit in pain reduction for PDNP. The use of combination therapy as a means of optimizing clinical outcomes has been investigated [9], but there has been insufficient research into the epidemiology of PDNP despite the high associated comorbidity [10].

METHODS

Study design and participants

This cross-sectional study to both evaluate and measure the intensity of pain of patients suffering from PDNP was performed using two self-administered questionnaires, the Short-Form McGill Pain Questionnaire (MPQ) and the Neuropathic Pain-4 (DN4) tool.

The inclusion criteria for the subject were as follows:

- Age greater than 18 years
- Diagnosis of diabetic neuropathy for at least 12 months

- No mental disability (for example, dementia, mental disorder, or Alzheimer's disease)
- Neuropathic pain attributed to diabetic neuropathy by the presence of four or more of the following symptoms contained on the DN4 assessment form:
 - Painful: Electric shock, painfully cold, burning
 - Non-painful: Tingling, itching, numbness, "pins and needles."
- No neuropathy pain due to other diseases
- Able to read and write in either English or Malay.

The subjects were recruited patients attending the clinics of the Medical Outpatient Department of a single Malaysian Hospital – the Hospital Tengku Ampuan Afzan (HTAA) in Kuantan, Pahang. Patients were given the questionnaire, written in both English and Malay, and the study information sheet. Those patients who agreed to participate in the study consented to their participation by signing an informed consent form (ICF) and any questions the patients had were answered. Patients were instructed by the researcher to complete the questionnaire by themselves and were given as much time as they required to do so. Subjects were then interviewed before their appointment in the clinic. Further to the collection of the MPQ and DN4, the information collated was fundamental sociodemographic details, details of their diabetes (type and duration), medications, alcohol consumption, smoking status, and other diseases.

Ethical considerations

The objective of the study was clearly explained to all participants. The ICF was attached to the questionnaire and signed by the subject before participation in the study. Subjects were assured that all information provided on the questionnaires would remain confidential. The collected data were used for academic purposes and exclusively for this study.

Ethical approval for the study was obtained from the HTAA Director, the Head of Department of the MOPD in the HTAA, the International Islamic University of Malaysia Research Ethics Committee (IREC-471) and the Ministry of Health Malaysia (NMRR-15-1998-28435).

Measurement tools

DN4 (*Douleur Neuropathique-4*, or '*Neuropathic Pain-4*')

The DN4 tool is a screening tool used to determine the presence of neuropathic pain through the identification of the presence or otherwise of a number of forms of pain or associated sensations. It comprises 10 items; a positive item (indicating presence) is assigned a score of 1, while a negative item (indicating absence) is assigned 0. A diagnosis of neuropathic pain is indicated by a total of at least 4 when the scores are summed across all 10 items [11].

About 7 of the 10 items relate to the description of the pain and the associated, abnormal, sensations. The pain descriptors are painful cold, burning and electric shocks. The sensations are numbness, itching, tingling, and "pins and needles." The remaining three items, tactile dynamic allodynia (using a soft brush), pinprick hypoesthesia (using a toothpick), and touch hypoesthesia (using a soft brush) are evaluated in the painful area [11].

Short-form MPQ

Characterizing pain qualities, as shown in Fig. 1, on a four-point scale, the MPQ has become one of the most widely-used research and clinical tools in assessing pain since its introduction in 1987 [12]. 11 of the characteristics are seen as sensory pain descriptors – these are 1-11 in Fig. 1; the remaining four are viewed as affective terms associated with experiencing pain [13]. The ordinal scale used to score the 15 terms comprises four levels [14]: 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain).

Sample size

The required sample size was calculated according to the following formula:

S. No.	Type of Pain	None (0)	Mild (1)	Moderate (2)	Severe (3)
1	Throbbing	○	○	○	○
2	Shooting	○	○	○	○
3	Stabbing	○	○	○	○
4	Sharp	○	○	○	○
5	Cramping	○	○	○	○
6	Gnawing	○	○	○	○
7	Hot-burning	○	○	○	○
8	Aching	○	○	○	○
9	Heavy	○	○	○	○
10	Tender	○	○	○	○
11	Splitting	○	○	○	○
12	Tiring-exhausting	○	○	○	○
13	Sickening	○	○	○	○
14	Fearful	○	○	○	○
15	Punishing-cruel	○	○	○	○

Fig. 1: The McGill pain questionnaire used in this study

Table 1: Subjects' sociodemographic and clinical characteristics

Variables	n=102 (%)
Gender	
Female	54 (52.9)
Male	48 (47.1)
Age groups, years	
<50	19 (18.6)
50-59	42 (41.2)
≥60	41 (40.2)
Race	
Malay	66 (64.7)
Chinese	21 (20.6)
Indian	15 (14.7)
Duration of diabetes	
1-5 years	33 (32.4)
6-10 years	52 (51.0)
>10 years	17 (16.7)
Types of diabetes	
I	12 (11.8)
II	90 (88.2)
Obesity	
Normal	7 (6.9)
Overweight	61 (59.8)
Obese	34 (33.3)
Type of medications	
Insulin only	9 (8.8)
Biguanide	66 (64.7)
Sulfonylurea	18 (17.6)
Insulin and biguanide	3 (2.9)
Sulfonylurea and biguanide	6 (5.9)
Smoking	
Smoker	38 (37.3)
Non-smoker	64 (62.7)
Alcohol consumption	
Alcoholics	15 (14.7)
Non-alcoholics	87 (85.3)
Other diseases	
None	22 (21.6)
Hypertension	44 (43.1)
Hyperlipidemia	25 (24.5)
Metabolic syndrome (DHC)	11 (10.8)

DHC: Diabetes, hyperlipidemia and cardiovascular diseases

$$n = \frac{Z^2 \times P(1-P)}{e^2}$$

Where the value of Z was taken from the standard normal distribution corresponding to the desired confidence level (1.96 for a 95% confidence interval [CI]), P is the expected exact proportion and e is the desired precision (one-half the desired CI width). To account for

Table 2: Responses to the McGill questionnaire

S.No.	Type of pain	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
1	Throbbing	-	18 (17.6)	75 (73.5)	9 (8.8)
2	Shooting	6 (5.9)	58 (56.9)	36 (35.3)	2 (2)
3	Stabbing	8 (7.8)	70 (68.6)	21 (20.6)	3 (2.9)
4	Sharp	15 (14.7)	65 (63.7)	20 (19.6)	2 (2)
5	Cramping	34 (33.3)	60 (58.8)	7 (6.9)	1 (1)
6	Gnawing	35 (34.3)	60 (58.8)	6 (5.9)	1 (1)
7	Hot-burning	80 (78.4)	22 (21.6)	-	-
8	Aching	-	3 (2.9)	58 (56.9)	41 (40.2)
9	Heavy	3 (2.9)	60 (58.8)	36 (35.3)	3 (2.9)
10	Tender	9 (8.8)	72 (70.6)	18 (17.6)	3 (2.9)
11	Splitting	40 (39.2)	51 (50.0)	11 (10.8)	-
12	Tiring – exhausting	-	13 (12.7)	81 (79.4)	8 (7.8)
13	Sickening	1 (1.0)	13 (12.7)	72 (70.6)	16 (15.7)
14	Fearful	-	25 (24.5)	47 (46.1)	30 (29.4)
15	Punishing – cruel	4 (3.9)	53 (52.0)	38 (37.3)	7 (6.9)

the possibility of incomplete questionnaires being returned, 10% was added to the total sample size. This yielded a sample size for the study of $n = (92 + 10) = 102$ [15].

Statistical analysis

Results for continuous variables were expressed as the mean and standard deviations, while those for the categorical variables were expressed as percentages and frequencies. The differences in the overall Short-Form McGill Pain Score with regard to clinical characteristics and demographic variables were analyzed using one-way analysis of variance and independent samples t-tests. All data analysis was performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA). Results were considered significant at a $p < 0.05$.

RESULTS

Subjects' demographic characteristics

Table 1 summarizes the sociodemographic and clinical characteristics of the 102 subjects. Of these diabetic patients experiencing PDNP, two-thirds were Malay, approximately half were female and 95% were overweight or obese. Approximately, one-seventh of the patients were alcoholics and over one-third (37%) were smokers. 88% of patients had been diagnosed with Type II diabetes, while 51% received their diagnosis between 6 and 10 years before completing the questionnaire (17% were diagnosed earlier than this). Only 9% of the subjects were treating their diabetes with insulin alone with a further 9% receiving combination therapy. 18% were treated with sulfonylurea, while 65% were treated with biguanide. In terms of other diseases, 25% subjects were suffering from hyperlipidemia, 11% from metabolic disease and 43% from hypertension.

DN4 tool and MPQ

The results of the neurological assessment performed through the DN4 questionnaire provided a score for all respondents of at least 4 out of 10, indicating the presence of diabetic neuropathy pain.

Table 2 shows the number of patients experiencing each intensity of pain for each of the terms on the MPQ. As can be seen in the table, the majority of patients reported "mild" intensity for all of the sensory descriptors, with three exceptions. The majority of patients reported no hot-burning pain, while "throbbing" pain and "aching" pain were both described as "moderate" by most patients. Severe pain was, in general, reported relatively infrequently, although over 40% of patients reported experiencing severe aching pain. Most of the affective descriptors caused moderate pain to most patients, the exception being "punishing-cruel," which 53 patients (52%) described as "mild" pain.

Table 3 shows the influence of the sociodemographic and clinical factors on pain severity. The duration of diabetes was found to be associated

Table 3: Influence of sociodemographic and clinical characteristics on pain severity

Variables	Mean±SD	p value
Gender		
Female	19.91±4.33	0.266
Male	20.79±3.64	
Age groups, years		
<50	19.79±4.63	0.712
50-59	20.21±3.83	
≥60	20.68±3.99	
Race		
Malay	19.97±4.14	0.040
Chinese	19.71±3.48	
Indian	22.73±3.59*	
Duration of diabetes		
1-5 years	19.15±4.14	0.038
6-10 years	20.46±3.86	
>10 years	22.18±3.72*	
Types of diabetes		
I	21.33±3.44	0.308
II	20.19±4.10	
Obesity		
Normal	20.43±3.82	0.596
Overweight	20.00±4.07	
Obese	20.88±4.04	
Type of medications		
Insulin only	20.67±3.20	0.305
Biguanide	19.71±4.07	
Sulfonylurea	21.56±3.66	
Insulin and biguanide	22.33±5.68	
Sulfonylurea and biguanide	21.83±4.62	
Smoking		
Smoker	20.97±3.68	0.196
Non-smoker	19.94±4.20	
Alcohol consumption		
Alcoholics	19.67±3.59	0.462
Non-alcoholics	20.44±4.10	
Other diseases		
No diseases	20.68±3.78	0.655
Hypertension	20.07±3.75	
Hyperlipidemia	20.92±4.83	
Metabolic syndrome (DHC)	19.27±3.84	

* $p < 0.05$. DHC: Diabetes, hyperlipidemia and cardiovascular diseases, SD: Standard deviation

with pain severity, subjects who had been diagnosed over 10 years ago having significantly higher MPQ scores ($p = 0.04$). A significantly higher MPQ score was also reported among Indian patients ($p = 0.04$). No significance associations were found between gender, medication, smoking status, alcohol consumption, obesity, diabetes type or other diseases, and severity of pain.

DISCUSSION

In this study, the neuropathy symptom score was utilized to determine the PDNP. It was found that all patients' overall MPQ scores were in the range 19.15±4.14 to 22.83±4.62. This corresponds to the majority of patients experiencing mild to moderate pain. A study in the United Kingdom [6] reported that 80% of patients with PDNP described their pain as either moderate or severe. It is well-established that while a certain proportion of diabetic patients with peripheral neuropathy will present with associated numbness or pain, a large number will be asymptomatic on presentation. As a result, it is essential that medical staff identify patients at risk of developing complications when and have the means of doing so [16].

The results of this study indicated that, among the ethnicities included in the study, Indian patients were more likely to experience greater neuropathy pain. This is consistent with existing research in the literature reporting Indians to be the ethnic group most affected by diabetic foot problems and other complications from diabetes. This is, in itself, corroborated to some extent by the finding of the National Health and Morbidity Survey, NHMS III [17], that the ethnic group in Malaysia exhibiting the highest rate of amputations of the lower limb was Indian. The results of this study show that the length of time for which a patient has suffered from diabetes can be a significant indicator of the severity of pain among patients having the disease for more than 10 years. This finding, that suffering from diabetes for a long time contributes to the intensity of PDNP, is consistent with a recent study in India [18], in which most patients with longstanding diabetes reported either severe or moderate pain levels.

CONCLUSION

Most patients with PDNP reported the severity of the pain to be "mild." The pain severity may be influenced by a patient's ethnicity and the length of time for which they have suffered from diabetes.

ACKNOWLEDGMENT

This study was supported by International Islamic University Malaysia (RIGS 16-286-0450).

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