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Assessment of Diabetic Peripheral Neuropathy Using Current Perception Threshold

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The aim of this study was to compare the current perception threshold (CPT) with a nerve conduction study (NCS) to evaluate the usefulness of CPT in the diagnosis of diabetic Peripheral Neuropathy (DPN). CPT measurement is quantitative method for assessment of peripheral sensory nerve function using electrical impulse. Enrolled in this study were 142 patients with type 2 diabetes who underwent both CPT testing and NCS between January 2013 and April 2016. DPN was diagnosed by NCS. CPT was performed on the right index finger and great toe of each patient. Patients with burning, tingling sensation and with longer history of diabetes tended to have a higher prevalence of DPN. In all frequencies tested (2000, 250, 5 Hz), CPT values of the DPN group were higher than the normal group. After classification in either the normoesthesia or hypoesthesia group according to CPT, the DPN group had a significantly higher prevalence of hypoesthesia than normal group. The receiver operating characteristics curve analysis showed that CPT had a high area under curve value for predicting the presence of DPN. In conclusion, CPT measurement is clinically valuable in detecting nerve dysfunction in patients with type 2 diabetes.

Keywords: Current perception threshold, Diabetic neuropathy, Nerve conduction study

Introduction

Along with nephropathy and retinopathy, diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, affecting more than 50% of patients [1]. More than 80% of DPN patients have a distal symmetrical sign or symptom like tingling, burning pain or numbness which is prominent in the lower limbs.

These lower limb sensory abnormalities put the patient at risk for injury. For that reason, DPN has a major role in the development of foot ulceration and subsequent lower limb amputation. These complications reduce quality of life, decreases daily living activities and, finally, increases mortality rate. Early diagnosis of DPN is really important to slowing the progression of complications. In practice, DPN diagnosis is based on patient history, symptoms and physical examination. In general, neurological examination findings show 60-90% of patients have DPN. However, neurological examination has many limitations because up to 50% of DPN patients are asymptomatic [2]. There are many screening tests for DPN, such as 128 Hz tuning fork, Semmes-Weinstein 10 g monofilament, and the ankle reflex measurement. Nerve conduction study (NCS) has been known as the most specific test for diagnosing DPN. However, NCS is time consuming and painful for patients. Moreover, small diameter nerve fibers, usually damaged in early stage of DPN, are difficult to detect by NCS. Current perception threshold (CPT) testing is also known as reliable technique for assessing DPN [3-5]. It evaluates the functional status of three distinct nerve fibers (large size myelinated Aβ fibres, medium size myelinated Aδ fibres and unmyelinated C fibers) at frequencies of 2,000, 250 and 5 Hz, respectively. A few studies that assessed the relationship between CPT and NCS have been published, but the parameters of each test were not considered in detail [6,7]. This study investigates the clinical characteristics of the study population and compares the multiple parameters of CPT with NCS to evaluate the usefulness of CPT for DPN diagnosis.

Materials and Methods

Materials

1. Subjects

Patients with type 2 diabetes mellitus (T2DM) who underwent both CPT testing and NCS between January 2013 and April 2016 were retrospectively enrolled in the study at Keimyung University Dongsan Medical Center. T2DM was diagnosed according to the American Diabetes Association criteria (2013) and all patients received general diabetes care in our department of internal medicine. Subjects with 1) other peripheral neuropathy, such as carpal tunnel syndrome and radiculopathy; 2) diabetic foot ulcer; 3) history of stroke; and 4) other causes of cognitive impairment, such as Alzheimer disease and Parkinson's disease, were excluded. We retrospectively reviewed the medical records of enrolled patients. All data, including age, sex, body mass index, HbA1c, duration of diabetes, presence of diabetic complication and symptoms, were documented.

Methods

1. Nerve Conduction Study

NCS was performed by rehabilitation physicians using a Medelec Synergy EMG machine (VIASYS Healthcare, Surrey, UK). NCS protocol is as follows: (1) Sural, peroneal, median and ulnar sensory nerve conductions are performed on the right upper and lower limbs; (2) Peroneal, tibial, median and ulnar motor nerve conductions are performed same as above; and, (3) If a study is untestable on the right limb at any of the nerves (sensory or motor), the study is performed on the left limb.

2. Diagnosis of DPN and NCS Parameters

Compound muscle action potential (CMAP) amplitude, sensory nerve action potential (SNAP) amplitude, motor conduction velocities (MCV) and distal latencies were individually assessed in each of the five nerves (sural, peroneal, median, ulnar, tibial) mentioned previously. Diagnostic confirmation of DPN was based on abnormality of any nerve conduction study in two separate nerves; one of them must be the sural nerve [8]. SNAP at the median and sural nerves and MCV at the median and tibial nerves were used to compare with CPT results.

3. Measurement of Current Perception Threshold

CPT using the Neurometer® (Neurotron Inc, Baltimore, Maryland, USA) generates a constant alternating current stimulus. In this study, CPT was applied to the right index finger in upper extremity and the right great toe in lower extremity. If a study is untestable on the right limb, it was performed on the left limb. Testing was performed using the following protocol: (1) With the patient lying in a supine position, two electrodes coated with conductive gel were positioned at the test site and held in place with tape; (2) At each stimulus frequency (2,000, 250 and 5 Hz), the current was increased slowly (0 to a maximum 999 ㎂) until the subject began to feel any sensation at the site where the electrodes were attached; and, (3) The test was repeated 3 times to reduce technical error and increase test accuracy. Patients were classified as normoesthesia or hypoesthesia and placed into subgroups accordingly. Hypoesthesia was defined as having a CPT value above the normal range as indicated in the manufacturer's instruction manual [9].

4. Statistical Analysis

SPSS version 21 software (IBM Corp, Chicago, IL) was used to analyze data. Independent t-tests and chi-square tests were performed to assess differences in mean values and prevalence between groups, respectively. Due to abnormal distribution of the CPT, a Mann-Whitney U test was used to compare mean values of CPT between patients with or without neuropathy. Correlation between NCS and CPT was evaluated by spearman's rank correlation test. A receiver operating characteristic (ROC) curve analysis was used to determine predictive values of CPT for diagnosis of DPN at each frequency. $P < 0.05$ was considered statistically significant.

Results

Out of a total of 293 patients who underwent NCS and CPT testing, 142 patients (men = 67, women = 75) were included in our final analysis. During data collection, 151 patients were excluded due to the presence of other diseases (stroke = 39, DM foot ulcer = 43, chemotherapy induced peripheral neuropathy = 40, and other peripheral neuropathy = 39). The prevalence of

Table 1. Clinical characteristics of the subjects

Characteristics	Value
Number	142
Male: Female, n (%)	67 (47) : 75 (53)
Age, years	55.9 ± 14.3
Duration of diabetes, yr	7.9 ± 8.7
Complications[a], n (%)	12 (8.5)
Symptoms[b], n (%)	64 (45.1)
BMI, kg/m²	24.9 ± 3.4
HbA1c, %	9.6 ± 2.6

Values are presented as number (%) or mean ± standard deviation. [a]diabetic retinopathy and diabetic nephropathy. [b]tingling, burning sensation and numbness. BMI: body mass index, HbA1c: hemoglobin A1c.

Table 2. Characteristics of patients according to NCS

	NCS		*P*-value
	Normal	DPN	
Number	98	44	0.057
Age, years	54 ± 13	59 ± 14	0.026
Duration of diabetes			
Mean duration, years	5.8 ± 7.3	12.5 ± 9.9	< 0.001
< 10 years (n)	81	23	< 0.001
> 10 years (n)	17	21	< 0.001
Complications[a], n (%)	6 (6)	6 (16)	0.190
Symptoms[b], n (%)	33 (33)	31 (72)	< 0.001
BMI, kg/m²	25.4 ± 3.1	23.9 ± 3.7	0.023
HbA1c, %	9.7 ± 2.8	9.5 ± 2.3	0.961

[a]Diabetic retinopathy and diabetic nephropathy. [b]Tingling, burning sensation and numbness. NCS: nerve conduction study, BMI: body mass index, HbA1c: hemoglobin A1c, *P*-value from comparisons between the patients with and without DPN.

complications, such as diabetic retinopathy and diabetic nephropathy, was 8.5%, while the prevalence of symptoms including tingling, burning sensation and numbness was 45.1% (Table1). Patients with a longer history of diabetes (≥ 10 years) and symptoms tended to show a higher prevalence of DPN ($p < 0.001$). However, the presence of complications was not related to DPN. Old age and lower BMI was associated with DPN ($p < 0.05$). However, there was no significant difference in mean HbA1c and gender between the normal and DPN group (Table 2).

1. Association between CPT and DPN

Mean CPT values at each frequency in both the normal and DPN groups are summarized in Table 3. In all frequencies, CPT values in the DPN group were higher than the normal group, but the difference was not statistically significant at frequencies of 250 Hz and 5 Hz in the upper limbs

Table 3. Mean CPT value according to NCS

	NCS		*P*-value
	Normal	DPN	
CPT values			
2,000 Hz in 2nd finger	256 ± 68	344 ± 144	< 0.001
250 Hz in 2nd finger	130 ± 70	166 ± 149	0.135
5 Hz in 2nd finger	87 ± 89	116 ± 149	0.084
2,000 Hz in Great toe	361 ± 114	631 ± 283	< 0.001
250 Hz in Great toe	153 ± 100	351 ± 243	< 0.001
5 Hz in Great toe	107 ± 102	250 ± 202	< 0.001

Values are presented as mean ± standard deviation. *P*-value from comparisons between the patients with and without DPN. CPT: current perception threshold, NCS: nerve conduction study.

Table 4. Prevalence of hypoesthesia in CPT and NCS

CPT frequency	Subgroup	NCS		*P*-value
		Normal n (%)	DPN n (%)	
2nd finger				
2,000 Hz	Normoesthesia	96 (98)	29 (65.9)	< 0.001
	Hypoesthesia	2 (2)	15 (34.1)	
250 Hz	Normoesthesia	92 (93.9)	30 (68.2)	< 0.001
	Hypoesthesia	6 (6.1)	14 (31.8)	
5 Hz	Normoesthesia	90 (91.8)	32 (72.7)	< 0.001
	Hypoesthesia	8 (8.2)	12 (27.3)	
Great toe				
2,000 Hz	Normoesthesia	95 (96.9)	19 (43.2)	< 0.001
	Hypoesthesia	3 (3.1)	25 (56.8)	
250 Hz	Normoesthesia	91 (92.9)	14 (31.8)	< 0.001
	Hypoesthesia	7 (7.1)	30 (68.2)	
5 Hz	Normoesthesia	92 (93.9)	22 (50.0)	< 0.001
	Hypoesthesia	6 (6.1)	22 (50.0)	

Values are presented as number (%). *P*-value from comparisons between the patients with normoesthesia and hypoesthesia using chi-square test. CPT: current perception threshold, NCS: nerve conduction study.

Table 5. Correlation between CPT and NCS

CPT frequency	Site	Marker	ρ	*P*-value
2,000 Hz	2nd finger	median SNAP	-0.442	< 0.001
	2nd finger	median MCV	-0.015	0.861
	Great toe	sural SNAP	-0.381	< 0.001
	Great toe	tibial MCV	-0.196	0.019
250 Hz	2nd finger	median SNAP	-0.308	< 0.001
	2nd finger	median MCV	-0.096	0.255
	Great toe	sural SNAP	-0.430	< 0.001
	Great toe	tibial MCV	-0.317	< 0.001
5 Hz	2nd finger	median SNAP	-0.277	0.001
	2nd finger	median MCV	0.047	0.581
	Great toe	sural SNAP	-0.373	< 0.001
	Great toe	tibial MCV	-0.269	0.001

Spearman's rank correlation analysis. *P*-value from comparisons between the CPT and NCS. CPT: current perception threshold, NCS: nerve conduction study, CV: conduction velocity, SNAP: sensory nerve action potential, ρ, correlation coefficient.

(Table 3). After classification in either the normoesthesia or hypoesthesia group, according to the normal range of CPT, the DPN group had a significantly higher prevalence of hypoesthesia than the normal group in all frequencies in the upper and lower limbs ($p < 0.001$) (Table 4).

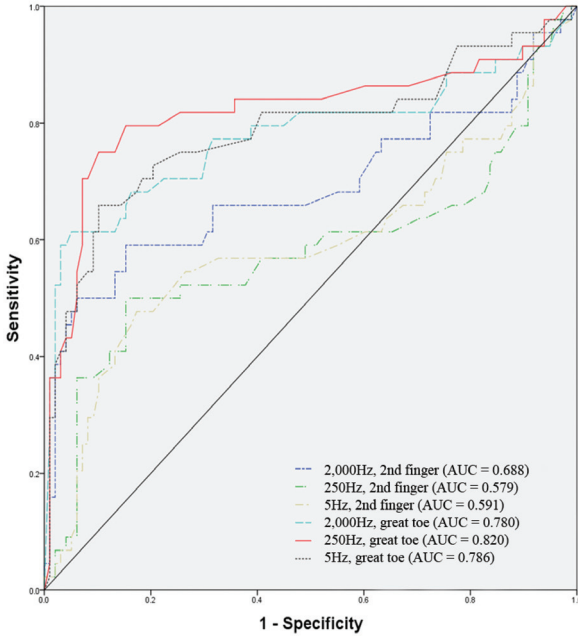

Fig. 1. ROC curve of the CPT for predicting neuropathy. CPT, current perception threshold; AUC, area under curve.

Spearman's rank correlation analysis was also used to evaluate the correlation between CPT values at each frequency and various markers of nerve conduction study. The CPT values in all frequencies were closely correlated with median SNAP amplitude, sural SNAP amplitude, and tibial CV. CPT values of 2000 Hz at the index finger showed significant negative correlations with median SNAP (ρ = -0.442) and CPT values of 250 Hz at the great toe showed significant negative correlations with sural SNAP (ρ = -0.430) (Table 5). The ROC analysis showed that CPT at 2000, 250, and 5 Hz in the lower limbs showed a high predictive value of DPN; AUC (areas under the curve) were 0.780, 0.820 and 0.786, respectively (p < 0.001) (Fig. 1). AUC in the upper limbs were not shown to have sufficient predictive value.

Discussion

In T2DM patients, DPN is a common complication. Although its pathophysiology is not well identified, a combination of metabolic and vascular factors is postulated to be involved. In its neurologic component, DPN manifests as segmental demyelination and axonal degeneration, which result in nerve dysfunction [3]. A typical sensory nerve is classified by its diameter. The smallest unmyelinated C fibers transmit dull pain and temperature, and have important function in the peripheral autonomic system. Medium-sized small myelinated Aδ fibers transmit sharp pain, temperature and pressure sensation. The largest myelinated Aβ fibers transmit touch and pressure sensation [5].

In this study, the DPN group tended to show longer history of diabetes and presence of symptoms. The difference of HbA1c values and the presence of complications were not statistically significant between groups. These results showed that DPN has a time dependent component of poor glycemic state.

CPT was significantly associated with DPN. The CPT values in all frequencies were higher in the DPN group when compared with the normal group, but the differences were not statistically significant at 250, 5 Hz in the upper limbs. In the subgroup analysis, the prevalence of hypoesthesia in CPT and the DPN in NCS was compared. In all frequencies, the DPN group had a significantly higher prevalence of the hypoesthetic CPT than the normal group. However, the prevalence of abnormal CPT in the DPN group was relatively low, especially in the upper limbs below 50%. This result suggests that CPT has a low correlation value in patients with symptoms in their upper limbs. The results of our study are also consistent to those found previously by Koo [7].

In comparison between CPT frequencies and each NCS parameter, correlation coefficients at 2000, 250 Hz were higher than at 5 Hz. Masson *et al.* [11] reported similar trends in their results that high frequency detection thresholds correlated best with large fiber function. Furthermore, the correlation coefficient was higher for sensory nerve parameters (median SNAP and sural SNAP amplitude) than for motor nerve parameters (median MCV and tibial MCV) in all CPT frequencies, which is consistent with a previous study [6]. It is suggested by this result that CPT shows some selectivity for sensory nerve function rather than motor nerve function.

The ROC curve analysis showed that the AUC of all CPT frequencies in lower limbs were 0.7~0.9, which showed relatively high predictive values for diagnosis of DPN. However, AUC in upper limbs were not shown to have sufficient predictive performance.

Cristian et al. regarded DPN as a small fiber neuropathy [10]. Since NCS can only examine large myelinated nerve fibers, diagnosis of early stages of DPN, which has damage in small diameter nerve fibers, has been limited [3]. However, CPT testing using Neurometer® can evaluate the functional status of three distinct nerve fiber types. It is able to test three different types of nerve fibers (Aβ, Aδ, C) at frequencies of 2000, 250, and 5 Hz, respectively [6]. For this reason, CPT was recommended by the American Association of Clinical Endocrinologists (AACE) as an early screening method for DPN in 2009. The results of this study show a good correlation between CPT and NCS in both upper and lower limbs at all frequencies. It also provides verification that CPT in the lower limbs has high predictive value compared to the upper limbs at the frequencies of 250 Hz and 5 Hz.

This study has some limitations. First, autonomic neuropathy with diabetes was not considered. An association between CPT at 5 Hz and autonomic dysfunction has been reported in a few studies [7]. Second, in the diagnosis of DPN, symptom related diagnostic tools such as NTSS-6 (neuropathy total symptom score-6) or 10 g monofilament were not used. Clinical validity of these tests has been confirmed previously [12]. However, because NCS was performed for all patients to make a diagnosis of DPN using an electrophysiological method, objectivity of this study was higher than previous studies. Third, CPT is a relatively subjective test which relies on the subject's sensory response and may be influenced by other factors, such as skin resistance, amount of contact pressure of electrode to the skin, subject's ability to focus on minimal changes in stimulus intensity.

Summary

This study showed that CPT is significantly correlated with myelinated sensory nerve fibers in detecting abnormalities in T2DM patients. Although it is subjective and has low sensitivity, CPT has a high predictive value, especially in the lower limbs at 250 and 5 Hz stimulation frequency. In conclusion, CPT measurement with the Neurometer® is clinically valuable in the assessment of unmyelinated nerve fibers and detecting nerve dysfunction in patients with T2DM. However, diagnostic confirmation of DPN must be done with other diagnostic tools. Further study is needed to establish more accurate values of CPT.

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