Original Article

Inter-trial Variation in the Sensitivity of Thermal Threshold Testing for the Diagnosis of Neuropathy in Type 2 Diabetes Mellitus

Abstract

Background: Thermal threshold testing (TTT) is a simple non-invasive approach for diagnosing diabetic neuropathy earlier. Conventionally the TTT is done in all four limbs and at least 6 trials are done to obtain the mean threshold, which is time consuming. **Aim:** We propose to assess the validity and reliability of reduced number of trials of TTT in the lower limbs. **Materials and Methods:** After obtaining ethics approval from the Institute Ethics Committee, 100 patients with type 2 Diabetes Mellitus of both gender between the ages of 35 to 65 years attending medicine OPD were recruited. Neuropathy assessment was done using Temperature threshold testing. At least 6 trials were performed for each site and the mean threshold obtained. The mean of 5 trials, 4 trials and 3 trials were noted for the comparison. **Results:** On comparing hot tests of 3 trials with 6 trials had a sensitivity and specificity of 88.7% and 96.6 %. In cold threshold testing, 4 trials and 3 trials showed similar results of sensitivity of 77.8%, specificity of 98.8%. The measures of agreement between the hot trials 6 vs 5 had Kappa value of 0.953, 6vs 4 showed a Kappa value of 0.862 and 6 vs 3 showed Kappa value of 0.819. **Conclusion:** Hot threshold tests of lower limb are more sensitive than cold thresholds. The 4 trial test is a reliable test and can be performed over 6 trial tests. When time is a factor, three trials are sufficient to diagnose small fibre neuropathy.

Keywords: *Diabetic neuropathy, sensitivity, temperature threshold testing, trials, validity*

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Introduction

Diabetic neuropathy is one of the devastating complications of diabetes that affects autonomic, peripheral, and cranial nerves. Only 20%–30% of diabetes mellitus (DM) patients with peripheral neuropathy experience symptoms such as pain in the early stages of the disease.[1,2]

Diagnosis of diabetic neuropathy has become difficult nowadays as most patients come at later stages of the disease where they end up with amputation or more debilitating disease. Diabetic neuropathy is diagnosed by signs, symptoms, nerve conduction study, quantitative sensory testing, and autonomic testing; two of these five are suggested for clinical diagnosis.[3] Nevertheless, these tests aid in diagnosing only large fiber neuropathy.

Thermal threshold testing (TTT) is a simple noninvasive approach for diagnosing the condition early as small fibers are compromised earlier in diabetic neuropathy.[4] Vibration perception threshold (VPT) is a simple noninvasive bedside approach that has been used in a few studies to assess diabetic peripheral neuropathy and it is also considered the gold standard for determining diabetic neuropathy.[5] However, VPT also like other tests assesses the large fibers only.

Conventionally, the TTT is done in all four limbs, and at least 6 trials are done to get the mean threshold for each site,[4,6] which is time-consuming and often leads to delay in diagnosis. Hence, we propose a study to assess the validity and reliability of a reduced number of trials of TTT in the lower limbs. We have considered the lower limb thresholds alone as diabetic peripheral neuropathy affects the lower limb nerves earlier.[7]

Methods

After receiving ethics approval from the Institute Ethics Committee, the study was carried out at AIIMS, Bibinagar (AIIMS/BBN/IEC/APR/2021/32/10.5.2021). One hundred patients with Type 2 diabetes of both

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genders, aged 35–65, and who were enrolled in the Medical Outpatient Department at AIIMS, Bibinagar, were included in the study. Exclusion criteria included people having a history of endocrine disorders, neurological issues, B12 deficiency, alcoholism, stroke, leprosy, any neurological disorder, cancer, and unwillingness to participate in the study.

We recorded the patient's name, age, gender, employment status, and level of education. A thorough medical history was obtained, covering the duration of diabetes and medication use. A comprehensive physical examination encompassed measurements of height, weight, and blood pressure. Five milliliters of blood was drawn to measure the glycated hemoglobin (HbA1C), postprandial blood sugar (PPBS), and fasting blood sugar (FBS) levels. Neuropathy assessment was done using temperature threshold testing following the below protocol.

Temperature threshold testing

The digital thermal aesthesiometer (VJ instruments v. 4.8.0) was used to evaluate the cold and hot thresholds of each study participant on both sides of their foot's toes. The testing was done in a temperature-controlled room at 25°C. The site tested is placed on the probe and the reference temperature is set at 32°C and the temperature is increased or decreased at 1°C/s for hot or cold testing, respectively. The temperature rises for hot threshold testing and declines for cold threshold testing from the reference. Every time the subjects started to feel warm or cold, they had to hit the button. At least 6 trials were performed for each site and the average of the trials was considered the mean threshold. The mean of 5 trials, 4 trials, and 3 trials were noted for the comparison.

Data were expressed as mean ± standard deviation and analyzed statistically using the Statistical Package for Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA). The thresholds were compared between 6 trials, 5 trials, 4 trials, and 3 trials to assess the sensitivity and specificity of the tests. The measures of agreement between the 6 trials, 5 trials, 4 trials, and 3 trials were also noted.

Results

We have considered 100 Type 2 DM patients, but due to loss of data, only 94 patient's data were analyzed. This study compares the mean of hot and cold threshold measurements which is the resultant of 6 trials, 5 trials, 4 trials, or 3 trials. The study was done to assess whether the lesser number of trials in assessing the average thresholds is as good as 6 trials.

The mean age of patients was 51.38 years with a duration of DM of 6.41 years on average. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 129.96 and 82.93 mm of Hg, respectively. The mean body mass index (BMI) was 25.65 kg/m^2. The FBS and PPBS values were 173.87 and 296.83 mg/dl. The mean HbA1c value was 9.49. The hot thresholds for the lower limb in 6, 5, 4, and 3 trials were 47.25°C ± 3.42°C, 47.17°C ± 3.41°C, 47.07°C ± 3.5°C, and 46.97°C ± 3.5°C, respectively. The cold thresholds for the lower limb in 6, 5, 4, and 3 trials were 22.53°C ± 4.31°C, 22.5°C ± 4.28°C, 22.5°C ± 4.27°C, and 22.43°C ± 4.23°C, respectively [Table 1].

Table 1: General characteristics of the study population

Parameters	*n*=94, mean±SD
Age (years)	51.38±10.76
Duration of DM (years)	6.41±6.18
SBP (mm of Hg)	129.96±17.96
DBP (mm of Hg)	82.93±12.21
BMI (kg/m^2)	25.65±6.78
FBS	173.87±74.82
PPBS	296.83±123.58
HbA1c	9.49±2.63
Hot 6 trials	47.25±3.42
Hot 5 trials	47.17±3.41
Hot 4 trials	47.07±3.5
Hot 3 trials	46.97±3.5
Cold 6 trials	22.53±4.31
Cold 5 trials	22.5±4.28
Cold 4 trials	22.5±4.27
Cold 3 trials	22.43±4.23

DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; HbA1c: Glycated hemoglobin; SD: Standard deviation

On comparing hot test, 5 trials with 6 trials sensitivity was 98.4% and specificity was 96.9% with similar positive predictive value and negative predictive value. The hot tests with 4 trials showed a sensitivity of 91.9 and specificity of 96.9%, a positive predictive value of 98.3, and a negative predictive value of 86.1, whereas on comparing hot tests with 3 trials 6 trials had a sensitivity and specificity of 88.7% and 96.6%, a positive predictive value of 98.2%, and a negative predictive value of 81.6% [Table 2].

The cold thresholds when compared with 6 trials, the 5 trials tests had a sensitivity of 88.9%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 98.8%. The 4 trials and 3 trials showed similar results of sensitivity of 77.8%, specificity of 98.8%, positive predictive value of 87.5%, and negative predictive value of 97.7% [Table 3].

The measures of agreement between the different trial numbers when assessed in comparison with 6 trials, the hot trials 6 versus 5 had a $\kappa = 0.953$, 6 versus 4 showed a $\kappa = 0.862$, and 6 versus 3 showed a $\kappa = 0.819$, all significantly associated. The cold trials 6 versus 5 had a $\kappa = 0.935$, 6 versus 4 had a $\kappa = 0.806$, and 6 versus 3 had a $\kappa = 0.806$ [Table 4].

Discussion

This study was designed to assess the validity of 3 trials of temperature threshold testing over the 6 trials testing.

Table 2: Comparison of the results of hot threshold tests of 5 trials, 4 trials, and 3 trials with the 6 trials results

Parameters	Hot 6 trials positive	Hot 6 trials negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive (%)
Hot 5 trials positive	61	1	98.4	96.9	98.4	96.9
Hot 5 trials negative	1	31				
Hot 4 trials positive	57	1	91.9	96.9	98.3	86.1
Hot 4 trials negative	5	31				
Hot 3 trials positive	55	1	88.7	96.9	98.2	81.6
Hot 3 trials negative	7	31				

Table 3: Comparison of the results of cold threshold tests of 5 trials, 4 trials, and 3 trials with the 6 trials results

Parameters	Cold 6 trials positive	Cold 6 trials negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive (%)
Cold 5 trials positive	8	-	88.9	100	100	98.8
Cold 5 trials negative	1	85				
Cold 4 trials positive	7	1	77.8	98.8	87.5	97.7
Cold 4 trials negative	2	84				
Cold 3 trials positive	7	1	77.8	98.8	87.5	97.7
Cold 3 trials negative	2	84				

Table 4: Measures of agreement between the various trials with the 6 trials

Measures of agreement	κ	*P*
Hot trials 6 versus 5	0.953	<0.001
Hot trials 6 versus 4	0.862	<0.001
Hot trials 6 versus 3	0.819	<0.001
Cold trial 6 versus 5	0.935	<0.001
Cold trial 6 versus 4	0.806	<0.001
Cold trial 6 versus 3	0.806	<0.001

The temperature threshold testing assesses small fiber neuropathy by assessing the thresholds for hot and cold in the specified sites on the upper limb and lower limb. However, in this study, we have considered lower limb temperature thresholds only as diabetic neuropathy is length-dependent, and hence lower limbs are affected first. We selected 94 Type 2 diabetic patients attending the medicine outpatient department and assessed the neuropathy by temperature threshold testing in the lower limbs for both hot and cold tests. The tests were averaged for 6 trials and the mean threshold is used for assessing neuropathy. With a cutoff value of 47°C for hot thresholds and 16°C for cold thresholds, the neuropathy was confirmed.[4]

The mean age of patients was 51.38 years with nearly 6 years of DM on average. This shows that most patients were in the middle age with varying years of DM. The age of patients in the study group also suggests that Type 2 DM which was earlier considered a disease of old is now common in the middle age group and more recently in the younger age group which is in concurrence with other studies.[8,9] The duration of the disease varied from 1 to 12 years across the study group. The prevalence of neuropathy in the study participants was 63% based on 6 trials (data not shown), suggesting that more than half the participants were suffering from neuropathy. The 6-year duration of DM is observed time to develop neuropathy according to Kebede *et al*.[10]

The mean SBP and DBP were 129.96 and 82.93 mm of Hg, respectively. Our patients were not hypertensive considering the mean values, however, hypertension is a common phenomenon seen in Type 2 DM patients.[11] It has been postulated that insulin resistance is the main culprit for vascular remodeling which contributes to increased peripheral resistance and hence hypertension.[12] The mean BMI of these patients was 25.65 kg/m^2 which falls under the obese category as per the Asian classification similar to another study.[13] The incidence of complications increases as the BMI increases.[14] In a follow-up study, higher BMI in adolescents was linked to a higher chance of Type 2 diabetes being identified at an earlier age.[15]

The glycemic profile of our patients was in the diabetes range with a mean HbA1c of 9.49. These patients were on anti-diabetic drugs but the values suggest that they were not particularly adherent to therapy or were not on proper control of diet. It is important to do dynamic monitoring of HbA1c in patients to choose better hypoglycemic drugs to create more effective glucose-controlling strategies.[16] An individualized HbA1c optimization and patient education regarding HbA1c give better glycemic control.[17]

The thresholds for hot in the lower limbs in 6 trials, 5 trials, 4 trials, and 3 trials did not differ much. Similar results were seen for the cold thresholds. The hot thresholds are assessed by asking the subject to press the button whenever he starts to feel warn, and cold thresholds were also determined similarly. The hot sensation is carried by the C fibers which are unmyelinated thin fibers constituting the small fibers and thus they assess the small fiber neuropathy.

There are different opinions about using thermal thresholds as a diagnostic tool as the distal–proximal and contralateral homologous thermal thresholds had wide normal limits.[18] Another study pointed to a large interperson variability over time.[19] These differences in these studies may be due to the small sample size they used. A recent study has proved the diagnostic utility in diagnosing neuropathy in sarcoidosis-related small fiber neuropathy.[6] Yet another study demonstrated its reliability and validity for evaluating pain.[20] Hence, if we are comparing the values of a particular site or limb, then it is of great value in detecting small fiber neuropathy.

The mean of the 6 trials is usually taken to assess the neuropathy. When we compared the 6 trials over 5 trials, the sensitivity and specificity were 98.4% and 96.9%, respectively. 6 trials versus 4 trials also had a reasonably good sensitivity and specificity compared to 6 trials. Whereas on comparing 3 trials with the 6 trials, the sensitivity reduced to 88.7, however, the specificity remained the same. Similarly, comparing the cold thresholds of 6 trials versus the 5 trials, tests had a sensitivity of 88.9% and specificity of 100%. The 4 and 3 trials showed similar sensitivity and specificity. This proves that 4 trials and 3 trials give the same results in the case of cold tests. The cold sensation is carried by the Aδ fibers which are relatively thicker than the C fibers and also we can observe that the sensitivity and specificity of hot thresholds are much better than the cold thresholds. Hence, we can say that on comparing hot and cold thresholds, the hot threshold test is more sensitive and specific than the cold threshold test. Similar results have been observed earlier.[4] In another study, height had a significant positive correlation with hot thresholds suggesting its good sensitivity to changes in the length of the fiber.[21]

The kappa value (measure of agreement) was measured between the different trials in comparison with 6 trials. The hot trials 6 versus 5 had a $\kappa = 0.953$, 6 versus 4 showed a $\kappa = 0.862$ whereas 6 versus 3 showed a $\kappa = 0.819$, all significantly associated. The cold trials 6 versus 5, 4, and 3 have a $\kappa = 0.935$, 0.806, and 0.806, respectively. On observing the measures of agreement, it seems that 4 trials and 3 trials are good enough when there are time constraints. On comparing 4 versus 3 for sensitivity, 4 trials seem to be better. Although the sensitivity of 3 trials is a little <4 trials, still the 3 trials test is valid and reliable. Hence, we conclude by saying that 4 trials are good enough to diagnose small fiber neuropathy instead of 6 trials as the test is time-consuming, however, 3 trials also can be performed when there are more number of patients and less time.

Conclusion

Thermal thresholds can be used to diagnose small fiber neuropathy. Hot threshold tests of the lower limb are more sensitive than cold thresholds. The 4-trial test is the reliable test and can be performed over 6 trial tests. When time is a factor, three trials are sufficient to diagnose small fiber neuropathy although three trial tests demonstrate good agreement with six trials.

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Ethical statement

The study was approved by Institute Ethics Committee of AIIMS, Bibinagar with approval No. AIIMS/BBN/IEC/APR/2021/32 dated 10.5.2021.

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Conflicts of interest

There are no conflicts of interest.

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