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REPORTS OF ORIGINAL INVESTIGATIONS

Reproducibility of current perception threshold with the Neurometer® *vs* the Stimpod NMS450 peripheral nerve stimulator in healthy volunteers: an observational study

Reproductibilité du seuil de perception du courant avec les stimulateurs des nerfs périphériques Neurometer® *vs*. Stimpod NMS450 chez des volontaires sains: une étude observationnelle

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Abstract

Purpose *Current methods of assessing nerve blocks, such as loss of perception to cold sensation, are subjective at best. Transcutaneous nerve stimulation is an alternative method that has previously been used to measure the current perception threshold (CPT) in individuals with neuropathic conditions, and various devices to measure CPT are commercially available. Nevertheless, the device must provide reproducible results to be used as an objective tool for assessing nerve blocks.*

Methods *We recruited ten healthy volunteers to examine CPT reproducibility using the Neurometer® and the Stimpod NMS450 peripheral nerve stimulator. Each subject's CPT was determined for the median (second digit) and ulnar (fifth digit) nerve sensory distributions on both hands – with the Neurometer at 5 Hz, 250 Hz, and 2000 Hz and with the Stimpod at pulse widths of 0.1 msec, 0.3 msec, 0.5 msec, and 1.0 msec, both at 5 Hz and 2 Hz. Intraclass correlation coefficients (ICC) were also calculated to assess reproducibility; acceptable ICCs were defined as* $\geq$ *0.4.*

Results *The ICC values for the Stimpod ranged from 0.425-0.79, depending on pulse width, digit, and stimulation; ICCs for the Neurometer were 0.615 and 0.735 at 250 and 2,000 Hz, respectively. These values were considered acceptable; however, the Neurometer performed less efficiently at 5 Hz (ICCs for the second and fifth digits were 0.292 and 0.318, respectively).*

Conclusion *Overall, the Stimpod device displayed good to excellent reproducibility in measuring CPT in healthy volunteers. The Neurometer displayed poor reproducibility at low frequency (5 Hz). These results suggest that peripheral nerve stimulators may be potential devices for measuring CPT to assess nerve blocks.*

Résumé

Objectif *Dans le meilleur des cas, les méthodes actuelles pour évaluer les blocs nerveux, telles que la perte de perception de la sensation de froid, sont subjectives. La stimulation nerveuse transcutanée est une autre méthode, qui a été utilisée par le passé pour mesurer le seuil de perception du courant (CPT en anglais) chez les personnes atteintes de neuropathies. Il existe plusieurs dispositifs pour mesurer le CPT. Toutefois, le dispositif doit être en mesure de fournir des résultats reproductibles si l'on veut pouvoir l'utiliser comme outil objectif d'évaluation de la curarisation.*

Méthode *Nous avons recruté dix volontaires sains pour étudier la reproductibilité du CPT lors de l'utilisation des stimulateurs des nerfs périphériques Neurometer® et*

Author contributions *Ban Tsui* made substantial contributions to study conception and design. *Ban Tsui, Danika Leung,* and *Gareth Corry* contributed to the acquisition of data. *Ban Tsui, Timothy Shakespeare, Danika Leung*, *Jeremy Tsui,* and *Gareth Corry* contributed to the analysis and interpretation of data. *Ban Tsui, Timothy Shakespeare,* and *Gareth Corry* made substantial contributions to drafting the article and revising it critically for important intellectual content. *Jeremy Tsui* contributed to statistical analysis.

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Stimpod NMS450. Le CPT de chaque participant a été déterminé dans les territoires sensitifs des nerfs médian (deuxième doigt) et ulnaire (cinquième doigt) de chaque main, en réglant le Neurometer à 5 Hz, 250 Hz et 2000 Hz et le Stimpod à des durées d'impulsion de 0,1 msec, 0,3 msec, 0,5 msec et 1,0 msec, à 5 Hz et 2 Hz. Les coefficients de corrélation intraclasse (CCI) ont également été calculés afin d'évaluer la reproductibilité; les CCI ont été définis comme étant acceptables à $\geq$ *0,4.*

Résultats *Les valeurs CCI pour le Stimpod se situaient entre 0,425 et 0,79, selon la durée d'impulsion, le doigt et la stimulation; les CCI pour le Neurometer étaient de 0,615 et 0,735 à 250 et 2000 Hz, respectivement. Ces valeurs ont été considérées comme acceptables; toutefois, le Neurometer était moins efficace à 5 Hz (les valeurs de CCI pour le deuxième et le cinquième doigt étaient de 0,292 et 0,318, respectivement).*

Conclusion *Globalement, le Stimpod a affiché une reproductibilité bonne à excellente pour mesurer le CPT chez des volontaires sains. Le Neurometer a montré une reproductibilité médiocre à basse fréquence (5 Hz). Ces résultats suggèrent que les stimulateurs de nerfs périphériques pourraient constituer des dispositifs potentiels de mesure du CPT pour évaluer les blocs nerveux.*

External electrical currents can be applied by various commercially available devices for electrodiagnostic sensory nerve testing, allowing determination of the sensory nerve Current Perception Threshold (CPT), defined as the lowest current that can be detected. The Neurometer® (Neurotron, Inc., Baltimore, MD, USA) is an example of such a device; it has been used clinically to detect peripheral neuropathy in diabetic individuals.[1-7] By measuring CPT and CPT trends, transcutaneous nerve stimulation has been suggested as an effective tool in diagnosing and monitoring conditions associated with worsening peripheral neuropathy (i.e., increasing CPT values), such as diabetes mellitus or vibration-induced neuropathy.[2]

Current standard techniques for determining nerve block effectiveness are limited by the inherent subjectivity of patient self-reporting (e.g., cold test, pinprick tests). Commonly used assessment methods, including loss of cold sensation and, to a lesser extent, motor function impairment, are useful for assessing neurologic function following a block. Nevertheless, these methods essentially provide an "all or none" response and are difficult to quantify when predicting the block trend. Nerve stimulation therefore presents a practical method for evaluating block effectiveness or trend of onset after performing the regional block.

Several groups have reported the application of transcutaneous nerve stimulation with the Neurometer to assess different local anesthetic regimens used in regional anesthesia by comparing CPT before and after application of the anesthetic.[8-10] Also, stimulation of the sural nerve with an electric current has been used to assess epidural fentanyl injection.[11] Peripheral nerve stimulators, which are commonly used for locating nerve structures, can also facilitate transcutaneous stimulation via adhesive gel pads or a percutaneous electrode guidance probe,[12] but these devices have not been well studied for measuring CPT. Furthermore, to be clinically useful, the CPT results obtained by transcutaneous nerve stimulation devices must be reproducible. We hypothesized that the CPT values obtained with the peripheral nerve stimulator would show acceptable reproducibility. Here, we examined a common peripheral nerve stimulator, Stimpod NMS450, *vs* the Neurometer to determine whether transcutaneous nerve stimulation can provide reliable reproducible CPT measurements in our study population of healthy volunteers. The primary outcome of this study was reproducibility of CPT measurements using the peripheral nerve stimulator. Intraclass correlation coefficients were calculated to examine reproducibility between two separate trials with each of the devices.

Methods

Study population

Following approval from our institutional Research Ethics Board on July 4, 2012 and written consent from participants, we rerecruited ten volunteers for our pilot study. Participants were healthy adults (> 18 yr of age) with no implanted electrical devices (e.g., pacemaker, spinal cord or peripheral nerve stimulator) or history of neuropathic lesions or polyneuropathic conditions. The study was performed in August 2012 at the University of Alberta Hospital, Edmonton, Alberta, Canada.

Study design

While in a seated or supine position, each volunteer had paired adhesive pediatric electrodes (Neotrode II, ConMed Corp., Utica, NY, USA) attached to the medial and lateral borders of the distal phalanges of the second (median nerve distribution) and fifth (ulnar nerve distribution) digits of one hand. The electrodes were connected to the Neurometer or a Stimpod NMS450 nerve stimulator (Xavant Technology, Pretoria, South Africa). The study team used a switch box to select between the two devices and to deliver current to the second or fifth digit or to deliver no current at all (neutral position). Neotrodes® were used instead of the gold-plated electrodes typically used with the Neurometer because the Neurometer electrodes are built with a connector that did

not fit into the Stimpod. This way, we were also able to connect to both devices (via the switch box) without the need to change electrodes when measuring with one device or the other. The setup is shown in Fig. 1.

Once the electrodes were attached, an escalating current was delivered from the Neurometer (accuracy up to 0.001 mA) to the second digit of the first hand at frequencies of 2,000 Hz, 250 Hz, and 5 Hz, in that order. The member of the research team performing the experiment was responsible for manually controlling the current. The subjects were asked to report when they felt an "electrical" sensation in their finger. To correct for a possible delayed response in a subject's perception of the stimulus and also to gain a more precise CPT reading, the current was reduced gradually until the subject could not detect it and then the current was increased gradually until the stimulus was perceptible. This last reading was defined as the CPT.

Next, a ground electrode (Red Dot, 3 M Health Care, St Paul, MN, USA) was placed on the subject and connected to the Stimpod, and the subject's second digit was stimulated with current (accuracy ± 5%) at a frequency of 5 Hz and pulse widths of 0.1 msec, 0.3 msec, 0.5 msec, and 1.0 msec, in that order, followed by stimulation at 2 Hz and the same order of pulse duration. Again, a member of the research team increased the current manually until the subject could detect an "electrical" sensation, which was recorded as the CPT. This sequence was repeated for the fifth digit of the same hand.

For all volunteers, a duplicate set of data was collected for both hands using both devices in the same order and sequence as the first set of recordings. A new pair of electrodes was used for each digit. There was no rest period between measurements apart from changing the electrodes prior to obtaining the duplicate set of data. Data were entered into a Microsoft® Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet by a member of the research team.

Statistical analysis

Mean and standard deviation values were calculated in Microsoft Excel. One-way random intraclass correlation coefficients (ICCs) were calculated to assess reproducibility between trials. Briefly, CPT values were determined for each device at each setting for each digit for each volunteer. The values at each site were then averaged among the ten volunteers. The values of the right and left digit were then averaged to obtain the mean ICC for that digit. Upper and lower confidence interval (CI) values were determined in a similar fashion. For sample size calculation, the lowest ICCs we would accept were 0.4 (considered borderline "good" according to Fleiss),[13] and the expected ICCs of the devices were assumed to be 0.8 ("excellent"). We assumed that the current threshold for both hands was similar in healthy volunteers. Based on a β value of 0.2 and α value of 0.05 for two measurements for each of the left and right hands for the second digit (total $n = 4$), the estimates of sample size (K) for the intraclass correlation would be 8.0 using the method described by Walter *et al.*[14] The same parameters were used for measurements of the fifth digit ($n = 4$). Intraclass correlation coefficients and 95% CIs were calculated using SPSS® version 20 (IBM Corp., Armonk, NY, USA).

Results

Six male and four female volunteers were recruited for the study. Mean age (range) was 29 (18-49) yr, their height was 170 (150-189) cm and their weight was 71 (46-105) kg. All subjects completed the testing; a complete data set was obtained for all subjects, and no subject withdrew due to test discomfort. During the study, most volunteers reported sensory perception with the Neurometer as

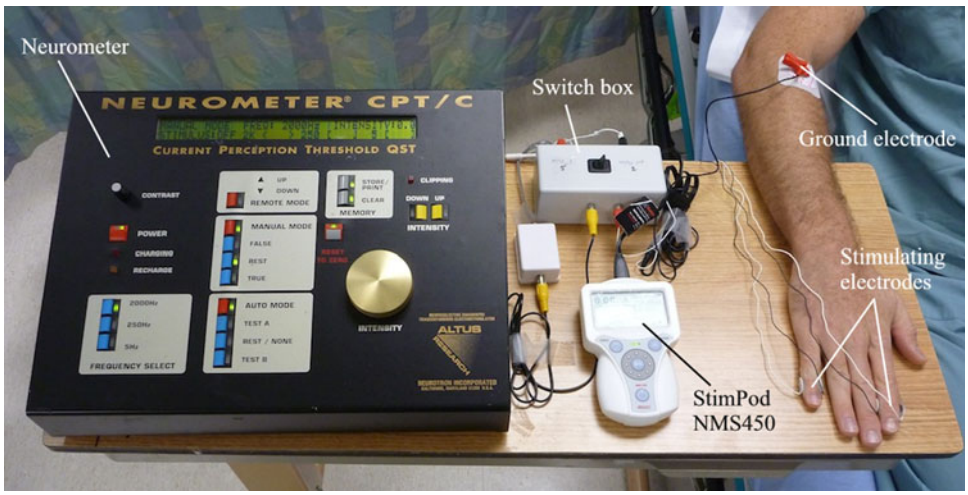

Fig. 1 Setup of current perception threshold testing equipment. Shown are the Neurometer, Stimpod NMS450, switch box, and subject with stimulating and ground electrodes attached

"tingling", while they reported stimulus with the Stimpod as "tapping". The bipartite graph in Fig. 2 shows a comparison of CPT values between the first and second tests for the Neurometer and Stimpod at each setting for the second digit of the right hand. Similar results were obtained for the second digit of the left hand as well as for the fifth digit of both hands (data not shown). The Table shows CPT readings for the Neurometer at each frequency and for the Stimpod at each frequency/pulse width stimulus. Compared with the Neurometer, we observed a reduction in CPT at all sites at both 2 Hz and 5 Hz with the Stimpod as the stimulating pulse duration increased from 0.1 msec to 1 msec. All of the ICC values fell within the good (0.4-0.75) and excellent ($\geq$ 0.75) ranges for reproducibility except those of the Neurometer at 5 Hz (second digit, 0.292; fifth digit, 0.318) (Fig. 3).

Discussion

The data generated by our study show that the CPT obtained using the Stimpod can be reliably reproduced. Importantly, this reproducibility is consistent for both the second and fifth digits of both hands and most frequency/pulse duration combinations.

Intraclass correlation (ICC) can be used to evaluate strength of association.[15] Intraclass coefficient values range from one to zero, indicating 100% and no reproducibility, respectively. In this study, the ICC values of the Neurometer at 5 Hz fell outside the range of acceptable reproducibility for both the second and fifth digits, whereas all the other ICCs were in the "good" or "excellent" range. Even so, these conclusions are based on the results and analysis presented here, and they are applicable to the devices and settings tested in this study.

The Neurometer uses a transcutaneous electrical current for CPT measurement. The device has previously been tested successfully for CPT reproducibility in various study populations;[3,16-18] therefore, we decided to utilize the Neurometer as a benchmark device to compare with a peripheral nerve stimulator. At low frequency (5 Hz), the Neurometer showed poor reproducibility according to ICC calculations. On the other hand, our data show that the Stimpod possesses an acceptable level of reproducibility at similar frequencies (5 Hz or less), suggesting that it could potentially be an alternative tool for assessing nerve blocks if there is a significant magnitude of change in CPT before and after a block.[19,20] The fact that the Neurometer did not provide reproducible results at a low frequency in our study is not surprising because such poor reproducibility has been reported previously.[21] In fact, most of the information supporting Neurometer reproducibility comes mainly from the manufacturer. In contrast, a published review of the literature regarding the Neurometer found "…little published information about reliability of test results between operators and the replicability of results between testing times".[22] The analyses presented here show that Neurometer CPT measurements at 5 Hz fell into the poor or unacceptable range of reproducibility for the purposes of this study when compared with the Stimpod at similar frequencies.

In terms of practicality, the Neurometer is expensive and cumbersome and does not lend itself to portability in its current form (Fig. 1). Moreover, it is not readily available in regional block areas of hospitals or operating theatres. In contrast, peripheral nerve stimulators are portable and relatively inexpensive, and they are routinely available in anesthetizing locations within hospitals. Since these devices are also used for nerve localization and testing,[12,23] anesthesiologists are already familiar with their functions and use. Peripheral nerve stimulators deliver time-adjustable pulsed direct current and current-controlled and frequency-adjustable stimuli. It has been suggested that the pulse duration used in direct current peripheral nerve stimulators has some bearing on whether motor or sensory nerves are stimulated. In particular, a pulse duration of $\leq$ 0.1 msec is suggested to stimulate motor neurons more selectively without undue sensory discomfort,[24] whereas a pulse duration of $\geq$ 0.3 msec is considered to be more selective for sensory nerves,[12] although this distinction remains unclear in clinical practice.[25] The ICCs of the Stimpod at a frequency of 2 Hz and a pulse width of 0.3 msec fell within the "good" and "excellent" ranges of reproducibility for the second and fifth digits, respectively, potentially making this a useful combination of settings for CPT testing.

Regarding limitations, since we performed our study by systematically testing the Neurometer prior to testing the Stimpod, it is possible that a non-random difference in mean scores across trials may have been introduced. This could introduce a learning effect that could be enhanced by lack of training or lack of a period of familiarization. In order to examine this possibility, we created bipartite graphs for CPT values for each device/setting/digit showing each volunteer's CPT readings for the first and second tests (Fig. 2). In our view, based on these graphs, no obvious learning effect was introduced between the first and second tests in our study, as we cannot detect any trend to suggest that testing the Neurometer first had any positive effect on perception of the Stimpod stimulus.

This work is also limited because the optimal frequency and pulse duration for stimulating peripheral sensory nerves has yet to be established, although we consider our study to be a reasonable and valid starting point towards determining this value. Another factor that may influence our results is the positioning of our volunteers

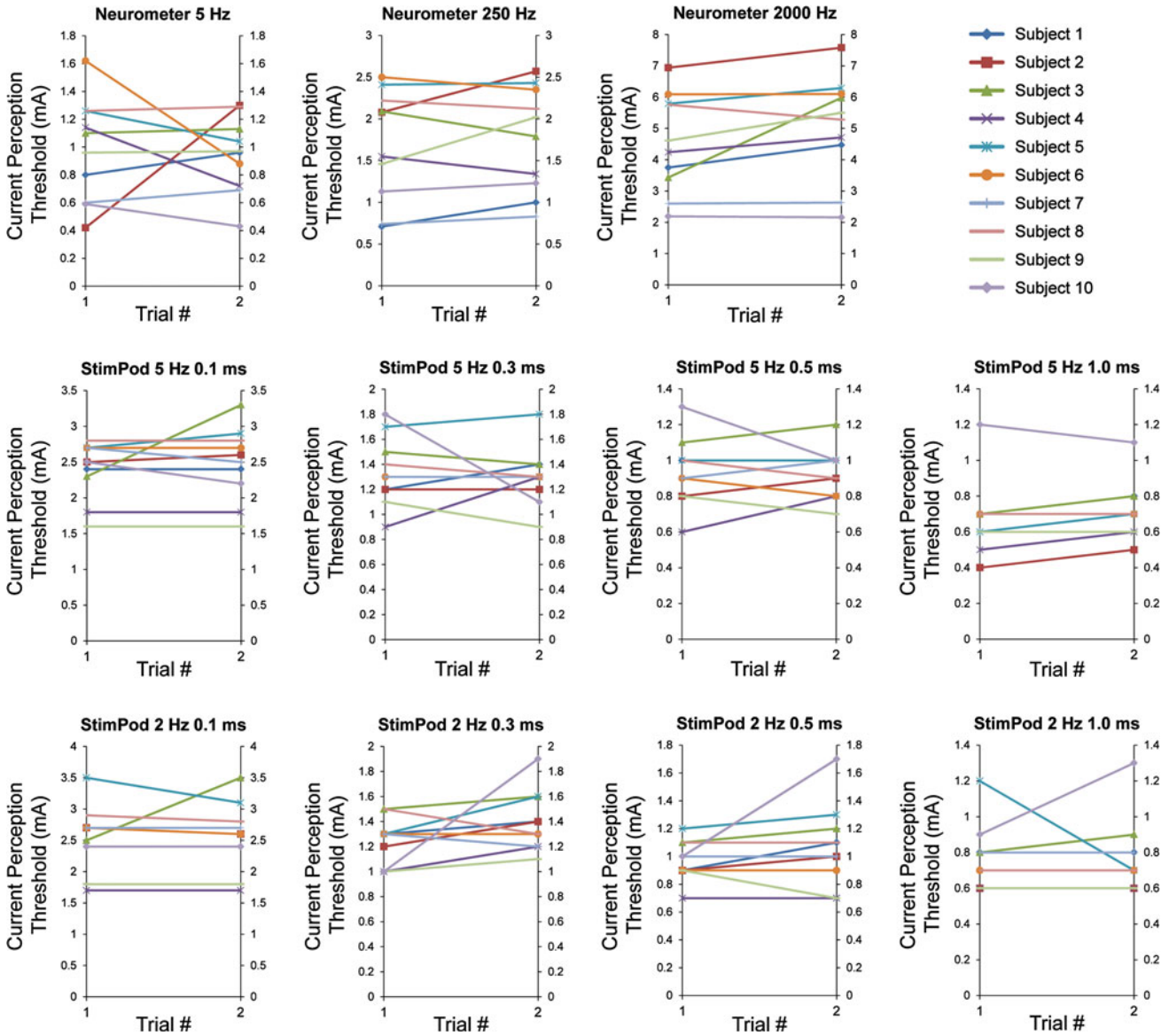

Fig. 2 Current perception threshold (CPT) reported for the Neurometer and Stimpod at each setting for the second digit of the right hand. The values are shown for the first (left) and second (right) trial on each panel

Table Current perception threshold values for each device and setting

Device	Neurometer			Stimpod 5 Hz				Stimpod 2 Hz			
Settings	5 Hz	250 Hz	2,000 Hz	0.1 msec	0.3 msec	0.5 msec	1.0 msec	0.1 msec	0.3 msec	0.5 msec	1.0 msec
Second digit	0.99	1.65	4.63	2.44	1.26	0.93	0.68	2.53	1.30	1.01	0.74
Mean (SD) (mA)[†]	(0.37)	(0.54)	(1.47)	(0.52)	(0.27)	(0.20)	(0.18)	(0.59)	(0.27)	(0.24)	(0.20)
Fifth digit	0.86	1.40	3.90	2.41	1.20	0.93	0.69	2.48	1.27	0.96	0.73
Mean (SD) (mA)[†]	(0.32)	(0.45)	(1.1)	(0.59)	(0.29)	(0.24)	(0.20)	(0.62)	(0.34)	(0.27)	(0.22)

[†] Values are averaged from both trials and both hands. SD = standard deviation

while CPT values were being recorded. A variance in CPT values has been shown between subjects in a horizontal position *vs* a tilt-up position,[26] although the clinical significance of this finding remains unclear.[27]

From a technical standpoint, the electrical output of the Neurometer is bipolar stimulation with a sinusoidal wave, while that of the peripheral nerve stimulator is monopolar stimulation with a monophasic pulse (Fig. 4). Fig. 4 also

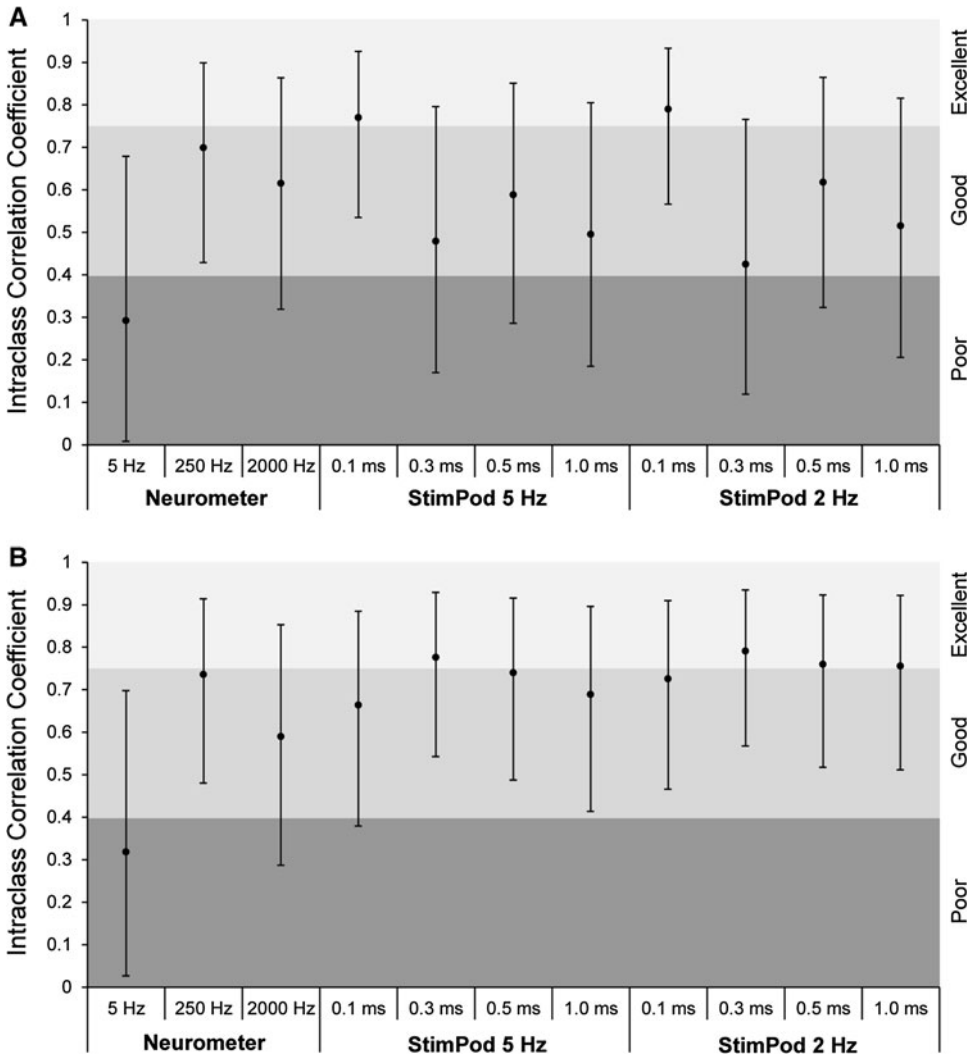

Fig. 3 Reproducibility of the Neurometer and Stimpod at each setting for the second digit (A) and fifth digit (B). Reproducibility is represented by intraclass correlation coefficients (ICC; filled circles). As shown, ICC < 0.4 denotes poor reproducibility; ICC 0.4-0.75 denotes good reproducibility; ICC ≥ 0.75 denotes excellent reproducibility.[13] Bars indicate 95% confidence intervals

shows that the calculated impedance of the peripheral nerve stimulator is lower than that of the Neurometer despite the same stimulation frequency at the same location. The implications of this difference remain largely unknown but may suggest that the electrical pulses delivered by the peripheral nerve stimulator may be more effective in overcoming the skin's impedance. Although the complex biophysics behind each method of transcutaneous stimulation is beyond the scope of this discussion, it is worth pointing out that our volunteers describe the sensory perception with the Stimpod as "tapping", while the Neurometer stimulus was interpreted as "tingling". This variation suggests that the tapping sensation experienced with the Stimpod could originate from a different sensory modality or from nerve fibres distinct from those involved in the tingling sensation experienced with the Neurometer. Although the underlying mechanism of this phenomenon is unknown, one possible explanation for the variation in perception may be partly due to the nature of the different stimulation waveforms of the individual devices. Nevertheless, the subjects in our study indicated that the pulsatile nature of the stimulus provided by the Stimpod and the more discrete stepwise changes in current were easier to perceive compared with the continuously increasing current delivered by the Neurometer. This may also have contributed to the poorer reproducibility shown at the 5 Hz frequency (Fig. 3). For CPT testing to be an acceptable method for monitoring the progression of nerve blocks, the test must be tolerable and acceptable to patients, and it must be easy to perform in a timely manner. In our study, none of the subjects withdrew due to discomfort, and none viewed the testing as unacceptably unpleasant, particularly when using the peripheral nerve stimulator. Nevertheless, it is important to point out that both devices will elicit not only "tingling" but also pain at high current settings. In our experience, CPT measurements can be obtained readily and in a rapid manner with the peripheral nerve stimulator.

Further studies are required to determine if CPT, as measured by a peripheral nerve stimulator, would be clinically reproducible and clinically useful to monitor the

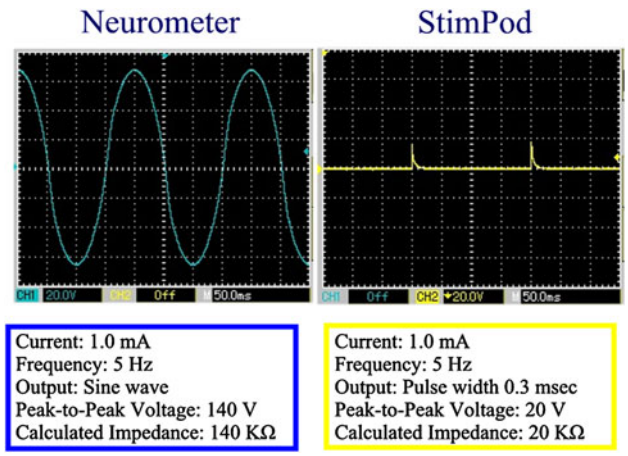

Fig. 4 Voltage display from measurement of transcutaneous stimulation on a volunteer with the Neurometer (*left*) and Stimpod (*right*) at the same location (left second digit). Output curves were obtained with an oscilloscope (UNI-T 2035C, UNI-Trend, Hong Kong, China)

progression of sensory neural blockade after a peripheral nerve block. Measurement of CPT may be used in addition to, or in place of, applying ice to monitor for loss of cold sensation. This is especially relevant, as C fibres are presumed to respond optimally to both low frequency (5 Hz) electrical current and cold stimuli.[9] Furthermore, it may be possible through further study to determine a percent increase in CPT that correlates with loss of cold sensation. The results presented here suggest that a peripheral nerve stimulator can be used at low frequency to obtain CPT with acceptable reproducibility; however, since most commercially available peripheral nerve stimulators can be set to a frequency of 1 Hz or 2 Hz (but not 5 Hz), it is likely to be more clinically relevant to consider using these frequencies when planning future studies.

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Conflicts of interest None declared.

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