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New diagnostic measures of oxaliplatin-induced peripheral sensory neuropathy

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A B S T R A C T

Objective: Oxaliplatin-induced peripheral neuropathy (OIPN) is an unwanted side effect of oxaliplatin chemotherapy treatment. OIPN manifests in an acute phase that lasts a few days after injection and a persistent phase that may become chronic. Currently, there is no consensus about a clinically applicable, quantitative, and objective measure of OIPN.

Methods: Seventeen patients treated with oxaliplatin containing adjuvant chemotherapy for stage III colon cancer, but otherwise healthy, were tested with six quantitative sensory tests (QST) and five large fibre perception threshold tracking (PTT) measures (quantified by, e.g., rheobase and electrotonus threshold) one hour before each of the 12 chemotherapy cycles given at two weeks' intervals. These measures were repeated at 3, 6, and 12-month follow-ups. The temporal development of OIPN assessed by the Common Terminology Criteria for Adverse Events (CTCAE) scale, QST, and PTT measures was calculated by linear regression.

Results: The CTCAE score showed a tri-phasic increase during the treatment and remained increased during the follow-up. The vibration threshold ($R = 0.25$, $p<0.001$), the cold pain threshold ($R = 0.17$, $p = 0.02$), and the rheobase ($R = 0.28$, $p < 0.001$) increased during treatment, whereas the cold detection threshold ($R=-0.16$, $p = 0.002$) decreased. The cold pain threshold and the rheobase remained increased, and the cold detection and heat pain threshold remained decreased during follow-up.

Conclusions: Increased cold pain sensitivity and decreased large fibre sensitivity (increased rheobase) correlate to the persistent OIPN, whereas the CTCAE score assesses both acute and persistent OIPN. Furthermore, the novel PTT method assessed the nerve excitability changes caused by the oxaliplatin.

Introduction

Oxaliplatin in combination with 5-fluorouracil (FOLFOX) has increased survival substantially in stage III colorectal cancer (CRC) [1, 2, 41, 47] and prolonged life in stage IV patients, but its use is severely compromised by neurotoxic side effects [16]. In addition, a resent retrospective study indicated that the effect of oxaliplatin may be limited [20]. Therefore, it is important to weigh the risk of neurotoxicity against treatment effect.

Oxaliplatin-induced peripheral neuropathy (OIPN) manifests as two types of sensory neuropathy; an acute type that is mainly affecting the hands and the perioral area and is believed to resolve within days [27, 43], and a persistent and possibly chronic type that affects both hands and feet [29, 46].

Acute OIPN is experienced by nearly all patients and its symptoms are often triggered by cold stimulation [5, 17, 27]. Acute symptoms peak at day 3 of each FOLFOX cycle, but they do not always resolve between treatment cycles [29]. The underlying mechanisms are believed to differ between the two types of OIPN, but the severity of the acute OIPN may predict the severity of persistent OIPN [29].

To date, there is no consensus about clinically applicable quantitative measures for identifying patients at risk of developing persistent OIPN. Therefore, the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) score is used to assess OIPN, and the decision to reduce or discontinue oxaliplatin is based on the results obtained with this subjective scale. The prevalence of OIPN varies substantially between studies; from 0.6% to 46% of patients at one-year follow-up, mainly due to the subjective nature of the CTCAE grading [7,

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38]. More objective and quantitative methods are needed to both predict and monitor the development of OIPN with the aim to still optimize the treatment but minimize the neurotoxic effects and hence the sensory implications (see e.g., [26]).

Several quantitative sensory tests (QSTs), such as vibration, pinprick, warmth and cold detection, and pain thresholds, have been shown to be related to OIPN and are eligible for use in OIPN studies as part of a QST monitoring battery [24]. QST techniques can be selected to specifically assess perceptions related to Ab (vibration) and Ad and C fibre activation (thermal and pin-prick thresholds). These methods are dependant on patient participation but can be used to supplement other objective methods such as nerve conduction studies although they assess the integrity of the large nerve fibres and not the small fibres predominantly involved in the symptomatology of OIPN. OIPN has been shown to cause declined sensory nerve action potential amplitudes of the sural nerve after the 8th or 9th cycle of oxaliplatin treatment, but these abnormalities have not been observed at earlier cycles [25, 30] due to the sensitivity and specificity of this gross large nerve fibre assessment.

Threshold tracking is an alternative method used to assess more specifically the excitability of peripheral nerve fibres via the stimulation of large nerve fibres and the recording of the compound action potential of the sensory nerve or the muscle electromyogram [10]. Oxaliplatin has been shown to alter the sensory nerve fibre excitability that may be related to changes in voltage gated sodium (Nav) channel activation (A. V [22].). These changes result in hyper-excitability alterations in the median nerve by the fourth cycle of oxaliplatin, indicating that excitability changes may be predictive of persistent OIPN [30]. Therefore, measuring altered nerve fibre excitability may provide the needed quantitative and clinically applicable method for assessing OIPN during treatment targeting the underlying neurobiological mechanisms of OIPN.

While threshold tracking assesses the membrane properties of nerve trunks, it appears that symptoms of OIPN affect the most distal parts of the nerve reaching hands and feet [17, 29]. Perception threshold tracking (PTT) has recently been proposed as an easy-to-use bedside method for assessing the excitability of distal cutaneous nerve fibre endings [19, 33]. Through this method, strength-duration relations and the threshold electrotonus can be assessed [19]. PTT has not previously been used for assessing the underlying neurobiological mechanisms of oxaliplatin-induced neurotoxic effects.

The present study was designed to assess 1) large and small fibre QST changes and 2) the PTT changes during and up to 1 year after adjuvant oxaliplatin treatment of colon cancer patients. Further, the purpose was to describe the QST and PTT measurements in relation to the CTCAE grading.

Materials and methods

Ethical conduct of the study

All patients provided written informed consent for the procedures which were conducted in accordance with the Helsinki Declaration of 1975 and approved by the Local Ethics Committee (approval number: N-20,140,024).

Patients

From April 1, 2014, to September 30, 2015, 83 patients newly diagnosed with and operated for colon cancer and referred to the Department of Oncology, Aalborg University Hospital, to receive adjuvant chemotherapy were screened according to the inclusion criteria of the protocol. Twenty-three patients with stage IV colon cancer were excluded. A total of 60 patients with stage III colon cancer were screened for the study. The exclusion criteria were symptomatic sensory and/or motor neuropathy, diabetes mellitus, HIV, alcohol abuse, having received neurotoxic chemotherapy prior to the study, not able to speak or understand Danish, or unable to provide informed consent. Twenty-three patients who underwent radical surgery for histopathologically confirmed stage III colon cancer were included. These patients were eligible for the actual standard adjuvant combination chemotherapy with modified FOLFOX 6 (mFOLFOX6): folinic acid, fluorouracil, and oxaliplatin. All patients were over 18 years old and presented no signs of peripheral neuropathy (i.e., CTCAE grade = 0) at the baseline visit. Three patients withdrew their consent at the beginning of the study. As neurotoxicity was the primary outcome, three patients who had the oxaliplatin dose reduced during the first six cycles due to haematologic toxicity were excluded; thus, a total of 17 patients remained in the study and were included in the data analysis.

Treatment

The following regime was used: 400 mg/m^2 bolus of fluorouracil, 2400 mg/m^2 infusion of fluorouracil over 46 h, 85 mg/m^2 infusion of oxaliplatin over two hours, and 400 mg/m^2 infusion of folinic acid over two hours for six months (12 biweekly cycles) of mFOLFOX6 [13].

CTCAE grades of peripheral sensory neuropathy and dose modifications

The patients were assessed for OIPN according to the CTCAE v. 4.0 scale prior to each treatment cycle using the following grades: grade 1 (Asymptomatic; loss of deep tendon reflexes or paraesthesia); grade 2 (Moderate symptoms; limiting instrumental ADL); grade 3 (Severe symptoms, limiting selfcare ADL); grade 4 (Life-threatening consequences - urgent intervention indicated).

According to the department's clinical guidelines, the dose of oxaliplatin was reduced by 25% if a grade ≥2 CTCAE score was present at any time between cycles. In the event of a recurrent grade ≥2 CTCAE score or persistent OIPN, oxaliplatin was discontinued.

Experimental setup

Patients participating in the study were examined one hour before each chemotherapy cycle. During this time, a clinical examination and a series of six QSTs and six PTTs tests were conducted. Follow-up tests were performed at 3, 6 and 12 months after completed chemotherapy (Fig. 1). All data were noted in the patient files separately for each treatment cycle and were then transferred to Excel files saved on a server in the Clinical Research Unit.

Assessment of oxaliplatin-related peripheral neuropathy

All tests were performed in a designated room by the principal investigator or by a physician trained by the principal investigator.

The QSTs consisted of vibration threshold, warmth detection threshold, cold detection threshold, heat pain threshold, cold pain threshold, and pain ratings of pinprick stimulation. The tests were conducted in this order and as recommended in the German Research Network on Neuropathic Pain standards [36]. The pinprick stimulation was performed by applying 12.8 g and 60.0 g weighted pins (Custom made at Aalborg University) with a diameter of 0.2 mm for approximately 1 second to the dorsum of the right hand. The patient was asked to indicate the perceived pain intensity on a visual analogue scale (VAS) from 0 (no pain) to 10 (worst imaginable pain). The vibration threshold test was performed by placing a 100 Hz vibrometer (Vibrameter, Somedic, Sweden) on the third metacarpal bone of the left hand and continuously increasing the vibration intensity until the patient indicated the sensation of vibrations. The thermal thresholds were assessed with a 9 cm^2 contact thermode (TSAII, Medoc, Ramat-Yishai, Israel). The thermode was placed on the inner side of the wrist and set to a baseline temperature of 32 °C. To assess warmth and cold detection thresholds, the temperature was increased/decreased by 1 °C/s until the patient indicated the perception of a temperature change by pushing a

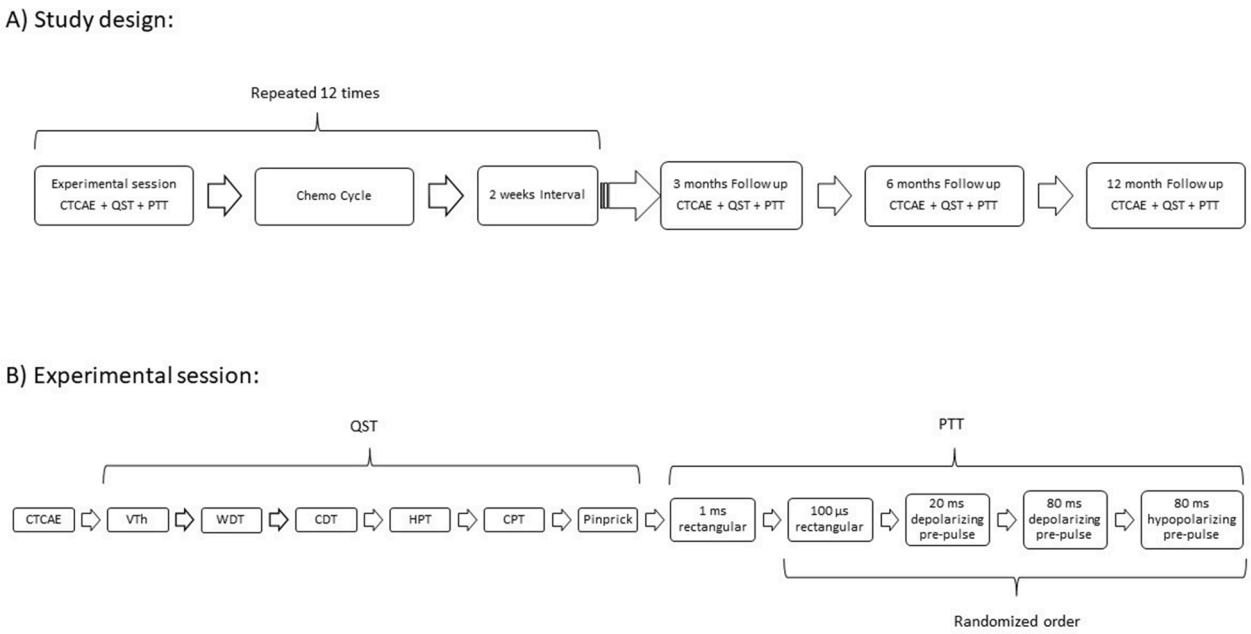

Fig. 1. (A) The Common Terminology Criteria for Adverse Events (CTCAE) score, quantitative sensory tests (QST), and perception threshold tracking (PTT) were performed before each of 12 chemotherapy cycles with two weeks intervals. The CTCAE, QST, and PTT were assessed at three follow-ups after 3, 6, and 12 months. (B) During each session, the CTCAE was first established. Then the QST was performed by assessing the vibration threshold (VTh), warmth detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), cold pain threshold (CPT), and perceived pain intensity to 12.8 g and 60 g pinprick (PP) stimulators. Then PTT was used to assess nerve fibre excitability by estimating the perception threshold to a 1 ms rectangular pulse, a 100 µs rectangular pulse, threshold electrotonus to a 20 ms depolarizing (TE20dep), an 80 ms depolarizing (TE80dep) and an 80 ms hyperpolarizing (TE80hyp) pre-pulse. The order of the last four pulses was randomized to minimize any systemic effect of habituation.

button. The heat and cold pain thresholds were estimated by increasing/decreasing the temperature by 1 °C/s from baseline until the patient indicated the stimulation as painful by pressing a button. The various tests were repeated three times and the average of the three values was used for data analysis.

The PTT tests consisted of estimating the Strength-Duration Time-Constant (SDTC), rheobase, and threshold electrotonus [19]. Nerve fibre excitability was assessed by PTT as described by [28] using a constant-current electrical stimulation (DS5, Digitimer, Ltd., Letchworth, Garden City, UK) through an Ag-AgCl 20 × 15 mm cathode (Neuroline 700, AMBU, Denmark) and a 40 mm x 64 mm anode (Pals, Axelgaard, USA). The cathode size was chosen to activate superficial cutaneous nerve endings of large sensory nerve fibres [33]. The cathode was placed on the dorsum of the right hand innervated by the superficial branch of the radial nerve and the anode was placed above the wrist. Perception thresholds were assessed via an adaptive staircase method; stimuli were administered at an interstimulus interval of 1 second and were increased by 15% until the patient indicated perception by pressing a handheld response button. Then, the intensity was decreased by 15% until the patient no longer perceived the stimulation. Subsequently, four similar sequences in which the intensity was increased and decreased by 7.5%, 3.5%, 3%, and 3% were performed. The perception threshold was calculated as the weighted average of all 10 measurements. The strength-duration properties were assessed by estimation of the perception thresholds according to rectangular constant-current pulses of 100 µs and 1 ms. The SDTC and rheobase were estimated using Weiss' law [45]. The threshold electrotonus was assessed as the reduction in the perception threshold with the application of depolarizing conditioning pulses at 20 ms (TE20msDep) and 80 ms (TE80msDep), respectively, and hyperpolarizing conditioning pulses at 80 ms (TE80msHyp) at an intensity of 20% of the perception threshold of a 1 ms pulse. The threshold electrotonus was expressed as the reduction in the perception threshold compared with that of the unconditioned 1 ms pulse. The threshold to the 1 ms rectangular pulse was assessed first as it was necessary to calculate the intensity of the threshold electrotonus pre-pulses. The remaining pulses were assessed in random order.

Data analysis

The times to dose reduction and the time to oxaliplatin discontinuation were illustrated by the Kaplan-Meier method and the median times were estimated. To analyse the temporal development of the OIPN symptoms, a Friedman's test was used to compare the CTCAE scores between treatment cycles and the three follow-up measures. This was followed by a post-hoc Bonferroni adjusted pairwise comparison using the Wilcoxon test.

Each of the QST and PTT measures were correlated to the treatment cycle number to evaluate the temporal development of each measure. A Friedman's test was performed to test if each measure was different between the timepoints. The 12th cycle and the three follow-up measurements were contrasted to the baseline measurement by a Wilcoxon test.

Three steps of the logistic regression models (LRMs) were performed to investigate the association of the QST and PTT measures to the clinical symptoms of OIPN as assessed by the CTCAE score. The CTCAE score was dichotomized as scores of 0 versus scores of 1 and above. All assessed measures were treated as continuous factors. First, a series of univariate LRMs were used to assess the relation between the individual measure and the CTCAE score. Second, a multivariate LRM was used to assess the relation between all measures in combination and the CTCAE score. Third, the likelihood-ratio test was used to remove factors from the multivariate LRM to establish an LRM with a minimal number of multivariate QST and PTT measures. The likelihood test uses the maximum partial likelihood estimates to remove measures until the likelihood-ratio statistic becomes significantly reduced.

Finally, all QST and PTT measures were correlated to each other to investigate their interrelation and redundancy.

Data were analysed in MATLAB, version R2020b (MathWorks, Natick, USA). Statistical tests were performed using SPSS, version 27 (IBM, New York, USA). $p<0.05$ was considered statistically significant.

Results

Peripheral sensory neuropathy caused oxaliplatin dose reduction and discontinuation

Eight females and nine males with a median age of 67 years (36–72) were eligible to be included in the final analyses.

Sixteen patients received all 12 scheduled chemotherapy cycles. However, during the treatment, all patients presented a CTCAE score of 2 or higher. Therefore, oxaliplatin was reduced or discontinued. The 5th cycle was the median cycle for oxaliplatin reduction (Fig. 2A). Thirteen patients had oxaliplatin discontinued due to OIPN. The 9th cycle was the median cycle for oxaliplatin discontinuation and ranged from the 6th to the 12th cycle (Fig. 2B). The last cycle of the treatment was omitted in one patient for personal reasons.

OIPN developed during the chemotherapy treatment and manifested as an increase in the CTCAE score. The mean CTCAE score increased rapidly during the first three cycles, after which the mean CTCAE score plateaued and decreased until cycle 9. This decrease was followed by a second increase in the CTCAE score (Fig. 2C). This bi-phasic development of the CTCAE score was statistically significant ($p < 0.001$). Further, the pairwise post-hoc comparison showed that the mean CTCAE score at cycle 1 was significantly lower than at cycles 4, 5, 6, 7, 11, and 12 ($p < 0.05$), but not different from 2, 3, 8, 9, and 10. Seven patients (41%) presented CTCAE scores of 2 or 3 at the end of the chemotherapy even though their oxaliplatin had been discontinued. The median oxaliplatin dose received by these seven patients was 36.3 mg/m^2/week and the median relative dose intensity was 85%.

The CTCAE score remained elevated during the 12-month follow up period (Fig. 2D) indicative of persistent OIPN. Five of 17 patients, corresponding to 29%, had CTCAE scores ≥2 after 12 months' follow up.

QST and PTT measures during chemotherapy

The temporal developments of the QST and PTT measures were estimated by the correlation coefficient between treatment cycle and the individual measures (Table 1). The correlation coefficients showed that the vibration threshold, the cold pain threshold, the rheobase, and the threshold to a triangular electrical stimulus pulse increased, whereas the cold detection threshold decreased (Fig. 3).

QST and PTT during twelve-month follow-up

The vibration threshold reduced towards the baseline after chemotherapy (Fig. 4A) and therefore does not reflect the OIPN reported by the patients in the CTCAE score (Fig. 2D). On the other hand, the heat pain threshold and the cold detection threshold were significantly decreased from baseline at the 12th cycle and at the 12-month follow-up (Fig. 4B and C). Similarly, the cold pain threshold remained elevated throughout the whole follow-up period (Fig. 4D). Out of five PTT measures, the rheobase correlated well with the treatment cycles (Table 1 and Fig. 3) and was elevated at the 12th cycle and at the 12-month follow-up (Fig. 4E). The other QST and PTT measures were not different between baseline and follow-up values.

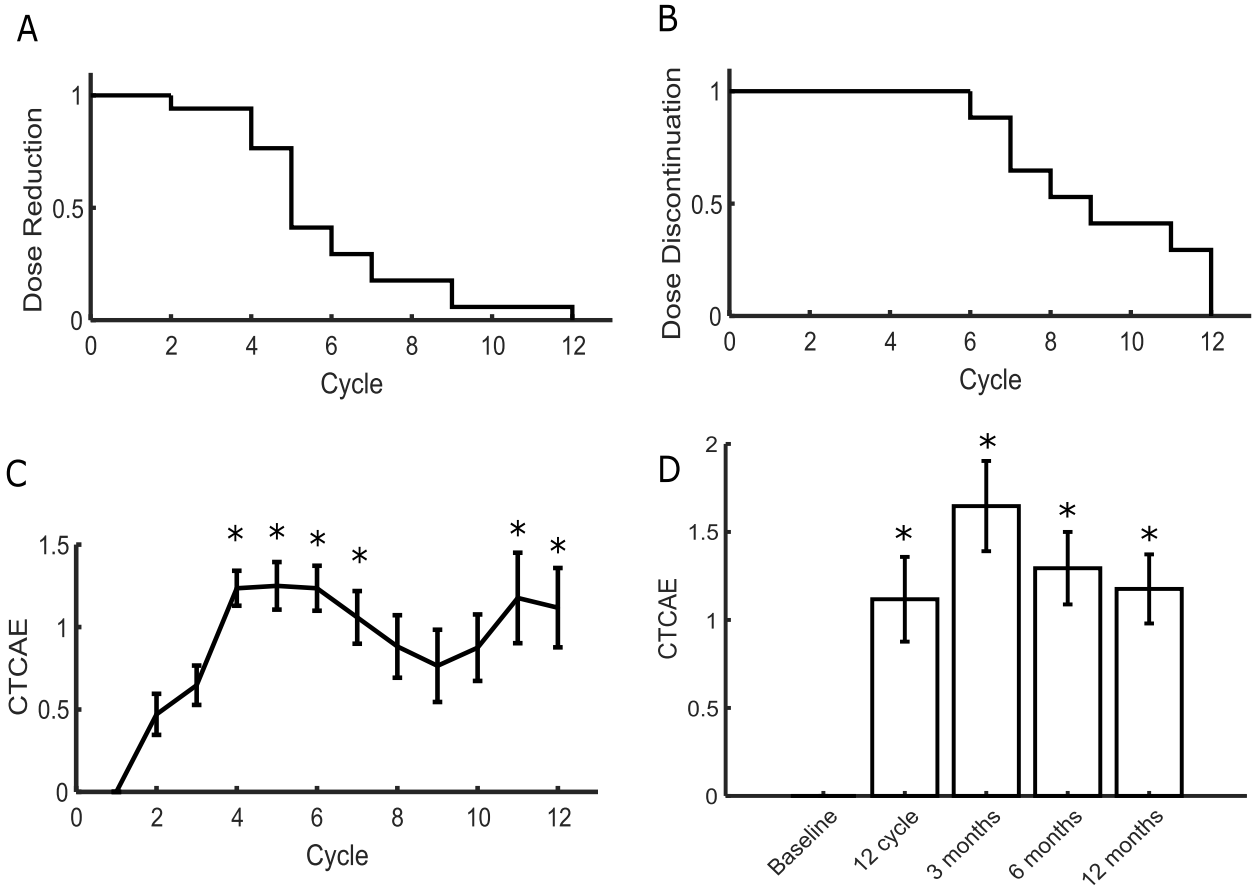

Fig. 2. (A) Kaplan–Meier curve of time to oxaliplatin dose reduction. All patients had their oxaliplatin dose reduced to 75% during treatment due to neuropathy symptoms. The median dose reduction time was equal to the 5th treatment cycle. (B) Kaplan-Meier curve of the time to oxaliplatin discontinuation. Thirteen patients had oxaliplatin treatment discontinuation during the treatment; median time was equal to the 9th cycle. (C) Development of the neuropathy during oxaliplatin treatment assessed by the CTCAE grading scale. (D) CTCAE scores during the 12-month follow up period in comparison to the baseline. Error bars indicate the standard error and the asterisk (*) indicates statistical difference from baseline ($p<0.05$).

Table 1
The correlation coefficients (R) to the temporal progression of OIPN were established. The correlation coefficient (R) was calculated between the cycle number and each quantitative sensory test: vibration threshold (VTh), warmth detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), cold pain threshold (CPT), perceived pain intensity to 12.8 g and 60 g pinprick (PP) stimulator, as well as the nerve fibre excitability measures: the strength-duration time-constant (SDTC) and rheobase (Rheo), the threshold electrotonus to a 20 ms depolarizing (TE20dep), an 80 ms depolarizing (TE80dep) and an 80 ms hyperpolarizing (TE80hyp) pre-pulse. Significant findings are indicated in bold.

	Correlation coefficient (R)	p-value
VTh	**0.25**	**<0.001**
WDT	-0.03	0.66
CDT	**-0.16**	**0.02**
HPT	-0.11	0.12
CPT	**0.17**	**0.02**
12.8 g PP	0.01	0.91
60 g PP	0.13	0.07
SDTC	-0.01	0.87
Rheo	**0.29**	**<0.001**
TE20Dep	-0.03	0.67
TE80Dep	0.02	0.78
TE80Hyp	-0.13	0.06

Relation between QST and PTT measures and the CTCAE score

The cold pain threshold, the rheobase, and the TE20Dep showed statistically significant relations to the CTCAE score as individual measurements (univariate LRM, $p < 0.05$, Table 2). Combining the QST and PTT measures in a single multivariate model revealed the rheobase as the most predictive sensory measure (multivariate LRM, $p<0.001$). Factor reduction of the multivariate LRM revealed the warmth detection threshold, the cold pain threshold, SDTC, rheobase, and TE20Dep as independently related to the CTCAE score (Table 2).

Correlation between QST and PTT measures

The QST and PTT measures showed a complex intercorrelation pattern as all measures assessed aspects of peripheral nerve functionality (Table 3). The heat pain and cold pain thresholds were negatively correlated indicating a common increased pain sensitivity of these two thermal modalities. Likewise, the cold pain and cold detection thresholds were negatively correlated indicating a narrower range in which cold temperatures were perceived as being non-painful (see also Fig. 3). The perceptions to pinprick stimulation with 12.8 g and 60 g were positively correlated indicating a relation between mechanical allodynia and hyperalgesia. The rheobase was negatively correlated to the SDTC indicating a relation between these excitability measures derived from the strength duration relation. The threshold electrotonus measures were intercorrelated indicating common variations in slow membrane properties. Except for the rheobase, the PTT measures were only sporadically correlated to the QST measures indicating non-redundant information from QST and PTT measures.

Discussion

The rheobase was significantly associated with the CTCAE score throughout the trial period. The QST and PTT measures were intercorrelated but still carried non-redundant information about OIPN symptoms. The most sensitive measure for OIPN seems to be rheobase and the cold pain threshold. As graded according to the CTCAE scale, the temporal development of OIPN during the 12 cycles of chemotherapy displayed a pronounced tri-phasic appearance. At least partly, this was due to oxaliplatin dose reductions and discontinuation. The CTCAE scores remained high during the 12-month follow-up period.

Acute and persistent symptoms of OIPN as assessed by the CTCAE score

Acute OIPN symptoms seemed to be more pronounced than chronic OIPN symptoms during the first eight cycles [29], consequently making this part of chemotherapy particularly sensitive to dose reductions and discontinuation. However, during the last part of chemotherapy, and particularly at the one-year follow up, the CTCAE score was elevated and reflected persistent OIPN. Therefore, the CTCAE score was not able to differentiate between acute and persistent OIPN during the first part of the treatment period during which dose reduction may still be viable. But in this study, persistent OIPN developed even after oxaliplatin treatment was reduced and even discontinued [5, 29]; a phenomenon often referred to as coasting [11].

QST measures

The current study is the first using PTT to examine the excitability of peripheral sensory nerves in patients going through oxaliplatin-containing chemotherapy. Of the six QST and five PTT tests investigated, the vibration threshold, the cold detection threshold, the cold pain threshold, and the rheobase displayed linear relationships to increasing numbers of chemotherapy cycles.

The vibration threshold increased significantly towards the end of the treatment, i.e., later than the initial increase in the CTCAE scores. Unlike the CTCAE scores, the vibration threshold returned towards baseline during the follow-up period and therefore seemed as a poor indicator of persistent OIPN.

The cold pain threshold increased and the cold detection threshold decreased during treatment resulting in a narrower temperature range in which cold temperatures could be perceived as non-painful. Therefore, cold temperatures that are normally being perceived as cold bot not painful were perceived as being painful (the phenomenon known as cold-induced allodynia) or not perceived at all. Cold-induced allodynia has previously been associated with acute OIPN [8, 14, 43], and the paradoxical phenomenon of decreased perception in combination with increased pain sensation has also been described by Patients with chronic OIPN [9, 32]. Previously, acute OIPN was hypothesised to resolve between infusions [25, 30], but the present study agrees with [29] in indicating that acute OIPN does not always resolve between infusions. Previous studies have found similar alterations in cold sensitivity [8, 12, 18, 35]. An increased CPT may indicate sensitized C fibres, whereas the decrease in the CDT may indicate a less cold-sensitive Aδ fibre activation [37]. Unlike the cold pain threshold, the cold detection threshold returned to baseline during the follow-up period indicating that this possible cold-induced allodynia was most pronounced during treatment.

PTT measures

The rheobase increased during treatment and remained elevated 12 months after treatment and was positively correlated to the CTCAE score. The current perception threshold to 2000 Hz electrical stimulation may be assumed to resample activation of large sensory nerve fibres and has shown similar association in a group of patients undergoing treatment for various cancer types [15]. The rheobase and current perception thresholds consonantly show promising results for assessment of nerve fibre integrity.

The strength-duration relation of large nerve fibres assessed by PTT showed a decreased SDTC during the 12-month follow-up period and an increased rheobase already during treatment. Excitability changes during oxaliplatin treatment have been observed using traditional threshold tracking [30]. The increase in rheobase indicated that more current was needed to activate the large cutaneous nerve fibres. This may be related to a decrease of the excitability of the nerves due to OIPN.

The SDTC showed a slight increase at the 12-month follow-up and a weak relation to the CTCAE score in general. Changes in SDTC may be

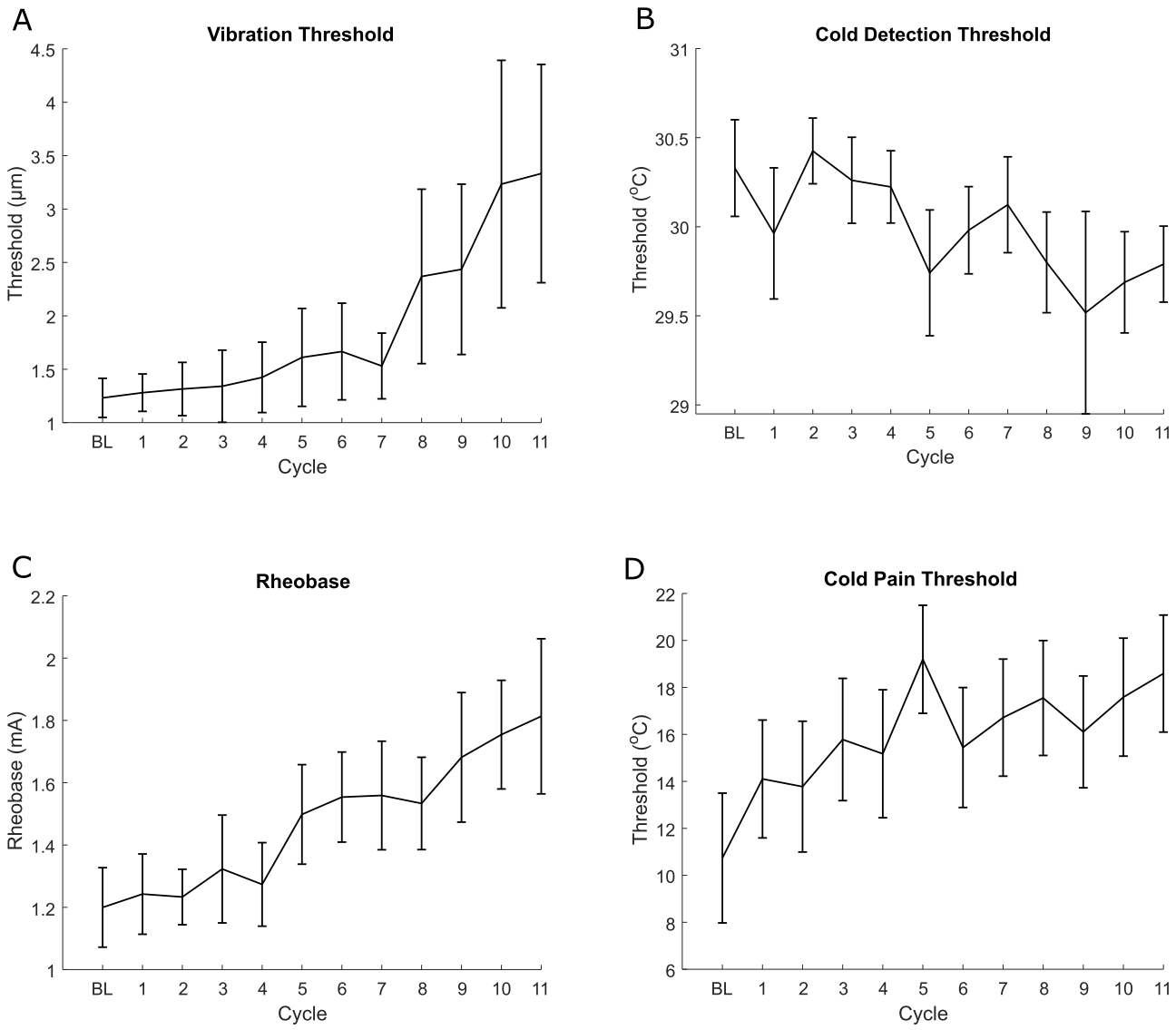

Fig. 3. The temporal development of quantitative sensory tests and nerve fibre excitability showed a statistically significant increase in the vibration threshold and the rheobase indicating decreased large fibre sensitivity. The cold pain threshold significantly increased whereas the cold detection threshold decreased indicating a narrower temperature range in which cold stimulation was perceived as being nonpainful. The mean values are plotted, and the error bars indicate the standard error of the mean.

caused by changes in the balance between rapidly activated Nav channels and persistent Nav channels ([10]; A. V [23, 40].). Previous studies in both humans and rodents have indicated that OIPN is closely related to alterations of the Nav channels [31, 39, 44]. The study by Park et al. [31] showed that the refractoriness, which is related to Nav inactivation, was decreased during acute OIPN, and although the SDTC was not significantly affected, the SDTC was correlated to the refractoriness. A more recent study observed a decreased SDTC of the motor nerve at recovery from oxaliplatin treatment compared with baseline [18]. This alteration of the nerve fibre excitability may be caused by increased resurgent and persistent sodium currents of the Nav1.6 [39]. Polymorphisms in the Nav channel alpha subunit 4 (SCN4A) and SCN10A genes coding for Nav1.4 and Nav1.8, respectively, have also been related to painful OIPN [4], which further suggests the importance of sodium current imbalances in the development and maintenance of OIPN. Furthermore, mitochondrial dysfunction has been shown in rodents with oxaliplatin-evoked peripheral neuropathy [48]. The consequently decreased ATP production may cause dysregulation of the Na/K pump and destabilize the nerve membrane. Therefore, assessment of the SDTC to quantify the excitability changes caused by oxaliplatin may serve as a mechanistic indicator of OIPN.

The polarizing pre-pulses and the possible involvement of potassium currents

The nerve fibre excitability assessments performed via PTT showed slight changes in the 80 ms depolarizing and the 80 ms hyperpolarizing threshold electrotonus that were not related to the clinical grading of OIPN by the CTCAE scale. The depolarizing or hyperpolarizing pre-pulse applied in the threshold electrotonus stimulation paradigms activates membrane currents that stabilize the membrane potential, most likely both potassium currents and sodium currents [21, 40]. Therefore, changes in thresholds caused by subthreshold pre-pulses are often interpreted as changes in potassium currents [10]. Like the present study, changes in the 90–100 ms hyperpolarizing, but not the depolarizing threshold electrotonus, during oxaliplatin treatment have been observed via traditional threshold tracking by Park et al., [30] but not in the study by Heide et al. [18]. Bennedsgaard et al., [8] only observed the decreased threshold reduction following 90–100 ms hyperpolarizing in the acute phase of OIPN when cooling the nerve. As discussed above,

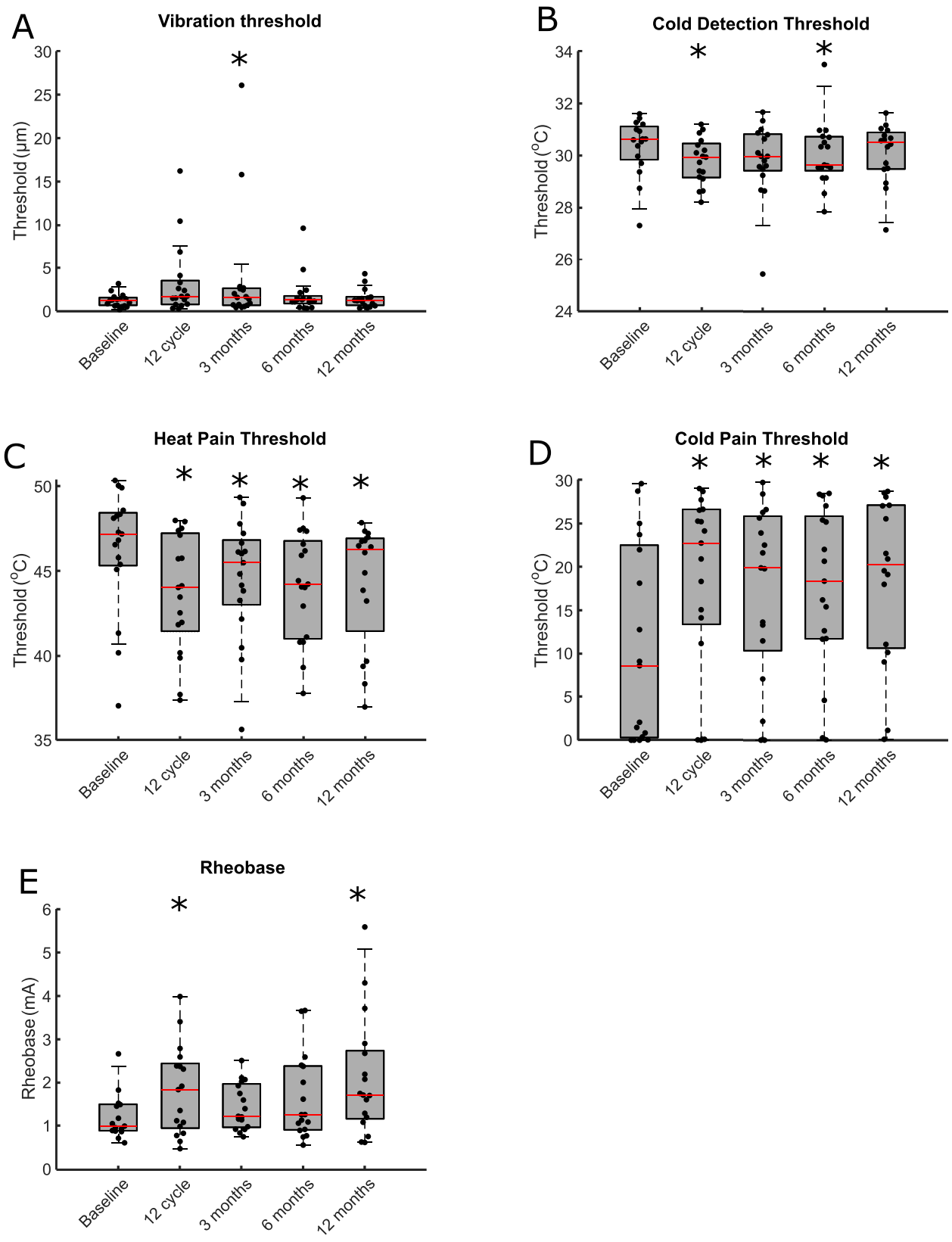

Fig. 4. The follow-up results 3, 6, and 12 months after chemotherapy showed that (A) the vibration threshold, (B) the cold detection threshold, (C) the heat pain threshold, (D) the cold pain threshold, and (E) the rheobase were different from baseline. The increased cold pain sensitivity which was observed during the treatment remained during the 12-month follow-up and was accompanied by heat pain sensitivity. The decreased large fibre sensitivity, which was observed during treatment, could only be assessed by the rheobase during the 12-month follow-up period. The median and the quartiles are indicated. * ($p < 0.05$) indicates statistically significant difference compared to baseline.

Table 2
Logistic regression models (LRMs) of the sensory neuropathy grading in relation to the quantitative sensory test (QST) and perception threshold tracking (PTT) measures. The neuropathy grading by the Common Terminology Criteria for Adverse Events scale was dichotomized as grades of 0 versus grades of 1 and above and treated as the dependant factor. The independent factors were the QST measures: vibration threshold (VTh), warmth detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), cold pain threshold (CPT), perceived pain intensity to static mechanical stimulation with a 12.8 g (12.8 g PP) and 60 g (60 g PP) pinprick stimulator, as well as the PTT measures: the strength-duration time-constant (SDTC) and rheobase (Rheo), the threshold electrotonus to a 20 ms depolarizing (TE20dep), an 80 ms depolarizing (TE80dep) and an 80 ms hyperpolarizing (TE80hyp) pre-pulse. The p-value, odds ratio, and the 95% confidence intervals (CI) of each of the independent values are given for univariate LRMs, the multivariate LRM including all independent variables, and a multivariate LRM in which independent factors were reduced based on the likelihood ratio.

	Univariate		Multivariate		Multivariate with factor reduction	
	p-value	Odds ratio	p-value	Odds ratio	p-value	Odds ratio
VTh	0.42	0.97	0.07	0.91		
WDT	0.37	0.95	**0.04**	0.86	**0.03**	0.87
CDT	0.22	0.86	0.17	0.80		
HPT	0.20	0.95	0.56	1.04		
CPT	**0.04**	1.03	0.08	1.04	0.06	1.03
12.8 g PP	0.47	1.23	0.48	1.32		
60 g PP	0.55	0.95	0.18	0.84		
SDTC	0.69	1.00	0.07	1.003	0.09	1.002
Rheo	**0.001**	2.14	**0.001**	3.39	**0.001**	3.12
TE20Dep	**0.011**	0.97	**0.04**	0.97	**0.02**	0.97
TE80Dep	0.55	1.00	0.90	1.00		
TE80Hyp	0.43	1.00	0.85	1.00		

there is ample evidence that Nav currents are related to OIPN, but it is still being debated to which extent slow voltage-gated potassium channels are involved in the generation of OIPN or affected by oxaliplatin. As an example, Basso et al., [6] found a relation between acute hyperexcitability and the number of CAG repeats in the potassium channel coding KCNN3 gene. However, a recent study did not observe a relation between the number of CAG repeats in the potassium channel coding KCNN3 gene and the severity of perceived OIPN [3].

Correlation between PTT and QST measures

The QST and PTT measures showed a complex intercorrelation pattern as all measures assess aspects of peripheral nerve functionality. The negative correlations between the heat pain and cold pain thresholds indicated that as the cold pain threshold increased, the heat pain threshold decreased. As a result, the temperature range in which thermal stimuli were perceived as unpainful decreased. Furthermore, the cold detection and cold pain threshold were negatively correlated, resulting in a decreased range of cold stimuli perceived as unpainful. This may relate to the pronounced cold-induced allodynia during the acute phase of OIPN [42, 43].

The ratings to the pinprick stimulations with different weights were positively correlated to each other. The rheobase and SDTC were negatively correlated. An increase in the rheobase means that the nerve fibres need a higher current to be activated, while a decreased SDTC means that the excitability of the nerve fibres has increased. This apparent paradox could be explained by a denervation or a withdrawal of the cutaneous nerve fibre endings while the excitability of the fibre increases. This could result in paraesthesia as reported by patients experiencing persistent OIPN [9, 32]. Denervation of the intra-epidermal nerve fibre endings has been reported in patients treated with oxaliplatin or docetaxel [24]. However, the electrodes used in the present study do not activate intra epidermal nerve fibres at perception threshold [33] but rather tactile nerve fibres terminating in the dermis. Denervation of these nerve fibres has not been investigated. The threshold electrotonus measures were intercorrelated indicating common variations in slow membrane properties [10].

Limitations

The study has some limitations. The estimation of nerve fibre activity is based on perception of electrical stimuli and QST. Perception is subjective; however, a rigid perception threshold estimation method applied in the PTT methods enabled an accurate estimation of the perception thresholds.

Symptoms of OIPN emerge in the hands during the treatment [29]. Thus, the QST and PTT assessments were performed at the dorsum of the hand. It seems that after the treatment has been completed or terminated, symptoms start to emerge in the feet and even begin to dominate. Therefore, it would be interesting to assess the changes in the peripheral nerves at the feet.

In the present study, the excitability of large sensory nerve fibres was assessed. However, it may be interesting to assess possible excitability changes in the small sensory nerve fibres. Especially during the acute phase, it seems that small sensory nerve fibres may be affected by oxaliplatin. This may be studied by PTT and selective activation of small sensory nerve fibres by specialized electrodes as, for example, the newly developed single use electrode [34].

The sample size was low in the present study. Sufficient statistical power was obtained because the measurements were repeated 15 times over the course of the study. However, the generalizability may be limited as the study was only completed in 17 subjects.

Table 3
Pearson's correlation coefficient table between the quantitative sensory testing measures: vibration threshold (VTh), perception to static mechanical stimulation with 12.8 and 60 g pinprick (12. g PP and 60 g PP), warmth detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), cold pain threshold (CPT) and perception threshold tracking measures: strength-duration time-constant (SDTC), rheobase (Rheo), threshold electrotonus to a 20 ms depolarizing (TE20dep) pre-pulse, threshold electrotonus to an 80 ms depolarizing (TE80dep) pre-pulse, and threshold electrotonus to an 80 ms hyperpolarizing (TE80hyp) pre-pulse. Statistical significance is indicated by bold and *: $p < 0.05$ and **: $p < 0.01$.

	VTh	WDT	CDT	HPT	CPT	12.8 g PP	60 g PP	SDTC	Rheo	TE20dep	TE80dep	TE80hyp
VTh		**0.17****	-0.10	**0.17****	0.02	0.05	-0.05	-0.07	**0.21****	0.07	-0.03	-0.10
WDT	**0.17****		**-0.39****	**0.17****	0.09	0.06	**0.16***	-0.10	**0.28****	0.04	0.07	0.07
CDT	-0.10	**-0.39****		0.08	**-0.16****	-0.10	**-0.18****	0.07	**-0.17****	0.07	0.09	0.03
HPT	0.17**	**0.17****	0.08		**-0.64****	**-0.31****	**-0.25****	-0.04	0.00	0.08	0.02	0.00
CPT	0.02	0.09	**-0.16****	**-0.64****		**0.20****	**0.13***	-0.09	**0.13***	-0.09	0.04	0.01
12.8 g PP	0.05	0.06	-0.10	**-0.31****	**0.20****		**0.51****	**0.17****	-0.04	-0.11	**0.14***	**0.13***
60 g PP	-0.05	**0.16***	**-0.18****	**-0.25****	**0.13***	**0.51****		**0.20****	-0.12	**-0.18****	-0.10	0.02
SDTC	-0.07	-0.10	0.07	-0.04	-0.09	**0.17****	**0.20****		**-0.54****	**-0.17****	**-0.20****	-0.10
Rheo	**0.21****	**0.28****	**-0.17****	0.00	**0.13***	-0.04	-0.12	**-0.54****		-0.01	**0.12***	-0.03
TE20dep	0.07	0.04	0.07	0.08	-0.09	-0.11	**-0.18****	**-0.17****	-0.01		**0.47****	**0.31****
TE80dep	-0.03	0.07	0.09	0.02	0.04	**0.14***	-0.10	**-0.20****	**0.12***	**0.47****		**0.50****
TE80dep	-0.10	0.07	0.03	0.00	0.01	**0.13***	0.02	-0.10	-0.03	**0.31****	**0.50****	

Conclusion

These preliminary findings suggest that the cold pain threshold and the rheobase tests are suitable for quantitative bedside assessment and prediction of persistent OIPN. Furthermore, the better temporal linearity of the cold pain threshold and the rheobase in comparison to the rougher CTCAE scoring method suggest a more accurate assessment of cumulative persistent OIPN during the early phase of chemotherapy. This may enable individual risk assessment of persistent OIPN at an early stage of oxaliplatin treatment and consequently facilitate a more finely tuned dose-adjustment schedule than that based on the CTCAE score alone. Furthermore, the objective character of the PTT test could be of a particular importance when investigating the efficacy of presumptive intervening treatments. The most sensitive parameters to follow and predict OIPN are the cold pain threshold and the rheobase of the perception threshold tracking. Further investigation on acute small fibre excitability changes is warranted to elucidate the underlying mechanisms leading to neuropathy and the relation between acute small and large fibre neuropathy. This could lead to a better risk stratification of persistent OIPN.

CRediT authorship contribution statement

Joanna E. Szpejewska: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Mette Yilmaz:** Conceptualization, Writing – review & editing. **Ursula G. Falkmer:** Conceptualization, Methodology, Resources, Writing – review & editing. **Lars Arendt-Nielsen:** Methodology, Resources, Writing – review & editing. **Carsten D. Mørch:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

Lars Arendt-Nielsen and Carsten Dahl Mørch co-authored a patent on the perception threshold method (WO/2016/146,758).

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