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Research article

Simple surface EMG recording as a noninvasive screening method for the detection of acute oxaliplatin-induced neurotoxicity: a feasibility pilot study

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ABSTRACT

Objectives: Oxaliplatin-induced neurotoxicity can be a dose-limiting side effect to effective chemotherapy. Acute hyperexcitability causes cold-evoked sensory and motor symptoms, which resemble neuromyotonia. An accessible and non-invasive technique for early detection could help select patients for potential treatments. We assessed the use of a simple surface electromyography (sEMG) in patients directly after oxaliplatin infusion.

Methods:In patients with colorectal cancer, acute neurotoxicity was evaluated by means of a physical examination, a questionnaire, and sEMG directly after the second and fourth cycle of oxaliplatin. Questionnaires were also assessed 1 day after infusion.

Results: 14 patients were measured after the second cycle and 8 patients were also measured after the fourth cycle of oxaliplatin. All patients reported to a variable degree oxaliplatin induced neurotoxicity symptoms: sensitivity to touching cold or swallowing cold items were reported as most severe. Clinical signs of hyperexcitability were observed in 55% of the measurements. Spontaneous activity compatible with neuromyotonia was observed in 82% of the sEMG recordings.

Conclusions: Patient reported symptoms, physical examination and simple sEMG are complementary measurements to detect acute oxaliplatin induced neurotoxicity. After further validation, sEMG recording can be used as a simple objective screenings tool to detect nerve hyperexcitability directly after oxaliplatin administration.

1. Introduction

Oxaliplatin is a third generation platinum based antineoplastic agent used for treating gastrointestinal cancer [1–3]. Up to 68.1% of the patients treated with oxaliplatin progressively suffer from neuropathy [4]. This neuropathy presents with an acute form, which is characterized by peripheral nerve hyperexcitability immediately after administration of oxaliplatin, and a chronic form that manifests as a sensory neuronopathy involving the dorsal root ganglia [5,6]. Both these forms can induce symptoms that are severe enough necessitating dose reduction and even premature discontinuation of treatment [7–10].

The acute neuropathy occurs in about 90% of the patients immediately after infusion of the drug. It will often diminish over the next days, only to reappear during the next infusion of oxaliplatin [11,12]. Symptoms include cold-induced paresthesia or dysesthesia of the extremities and the perioral or laryngeal region, accompanied by fasciculations, and muscular cramps [12–15]. The mechanism for the acute neurotoxicity is a sodium channelopathy [16–19]. This acute neurotoxicity shows substantial similarities with the clinical and electrophysiological presentation of neuromyotonia [15,20] a disease also caused by hyperexcitability of the peripheral axon due to channelopathy. This hyperexcitability is usually confirmed with needle electromyography (nEMG) examination of muscles, when repetitive myokymic discharges and neuromyotonic runs can be observed [20]. It can also be demonstrated by a newer technique called threshold tracking, but this is currently limited to research settings only [21].

Previous studies used nerve conduction studies (NCS) [20,22,23], nEMG [15,20], high-density surface electromyography (HD-sEMG) [24], and threshold tracking [21] for measuring oxaliplatin-induced neuropathy, but these methods are either not very sensitive for detecting acute hyperexcitability or focus on chronic neuropathy that occurs over time with oxaliplatin use (NCS), or invasive (nEMG), or too

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labor intensive for clinical use (HD-sEMG, threshold tracking). Very little is known yet about the ability of simple 2-channel surface electromyography (sEMG) to detect nerve hyper excitability [25–27]. Bipolar surface recording of muscle activity is a noninvasive, low-cost, and fast technique for collecting information on muscle activation. In oxaliplatin-induced neurotoxicity (OIN), sEMG may easily help to select patients for potential treatments that can reduce the acute symptoms [28,29].

In this prospective feasibility pilot study, we enrolled patients with colorectal adenocarcinoma, all receiving intravenous oxaliplatin treatment every 3 weeks. Acute neurotoxicity was assessed clinically directly after oxaliplatin infusion in cycle 2 and 4 by a standard neurological examination and questionnaire. A simple 2-channel sEMG signal was recorded from a single hand muscle. As a proof of principle test, our aim was to determine whether a short, simple and non-invasive sEMG measurement would be able to detect nerve hyper excitability in patients with acute OIN. Additionally, we evaluated if clinical symptoms correlated with sEMG findings.

2. Materials and methods

2.1. Participants

Participants were recruited prospectively from December 2015 until April 2017. Eligible participants were aged ≥18 years, and received an oxaliplatin containing chemotherapy regimen for the (curative of palliative) treatment of colorectal adenocarcinoma. Exclusion criteria involved pre-existing neuropathy of any cause, previous systemic chemotherapy, a history of chronic pain syndrome, use of opioid analgesics ≥6 months, diabetes mellitus, alcoholism or inability to comply with testing procedures or to give informed consent. The study population was recruited from the Medical Oncology outpatient department setting at the Radboud university medical center, Nijmegen, the Netherlands. The study protocol was approved by the institutional review board of Medical Ethical Committee of Arnhem/Nijmegen and participants provided informed consent to use their data. The chemotherapy regimen consisted of intravenous oxaliplatin (130 mg/m^2) with or without bevacizumab (7.5 mg/kg) in cycles of 3 weeks, which was followed by capecitabine (1000 mg/m^2) orally twice daily for 14 consecutive day. Dose reductions were applied (25% reduction) when participants reported grade ≥3 toxicities according to National Cancer Institute-Common Toxicity Criteria.

2.2. Measurements to detect acute neurotoxicity

Measurements to detect acute neurotoxicity were carried out during cycle 2 and 4 of the oxaliplatin treatment, since from cycle 2 on most patients tend to experience acute OIN symptoms [12]. Day 0 is directly after oxaliplatin infusion, and day 1 is 24 h after oxaliplatin infusion. On day 0 after cycle 2 and 4 sEMG recordings, a questionnaire and a standardized physical examination were performed. The questionnaire was repeated during a telephone interview on day 1.

2.2.1. Surface EMG recording

Participants remained fully dressed for this part of the study and were placed supine on the examination table upon a heated undersurface set at 37 °C placed below the bed sheet in order to keep the skin temperature > 30 °C during sEMG measurements. The sEMG signal was recorded from the left first dorsal interosseus muscle, in a tendon-belly montage with the active electrode over the motor point, using reusable stainless steel disc surface electrodes (Kendall TM H59 P Cloth Electrodes, 1 cm diameter). The screen time base was set at 100 ms/division and the amplitude was set at 20 μV/division. Participants were instructed to relax their arm and hand, using direct feedback from the running EMG signal played over 2 loudspeakers, and additional support of a small pillow for the hand if needed. EMG signals were captured from the muscle for a period of 2 min, using a Synergy EDX EMG machine (Natus Neurology Incorporated, Middleton, Wisconsin USA), and stored as "liveplay" files for offline analysis. As a quality control measure, 2 participants in whom spontaneous activity was detected during the measurement were asked and agreed to also undergo a single 30 gauge concentric nEMG exam of the left first dorsal interosseus muscle, measuring another 2 min of spontaneous activity at rest. Signals were exported for visual and auditive readback using the videocapture mode of the EMG machine during replay of the recorded signal. Videos were captured as. avi files, in addition captured signals were exported as. wav files for further quantitative analysis.

2.2.2. Questionnaire

Patient reported outcomes (PRO) of OIN were assessed: the degree of sensitivity when touching cold objects or swallowing cold food/drinks, throat complaints, the pain score in hands and feet [12]. These items were scored using a numeric rating scale (NRS) from 0 (= no problem) to 10 (=major problem) [30].

2.2.3. Physical examination

The presence of calf fasciculations, action myotonia in the hands and eyelids was examined. The participant sat on a chair and the right calf was inspected for 1 min, followed by active plantar flexion of the right foot for 30 s and again a visual inspection of the right calf for 1 min. If voluntary muscle twitching was seen at rest or after muscle contraction, fasciculations were noted to be present [31]. Eyelid closure action myotonia was tested by instructing the participant to close the eyes as forcefully as possible for 10 s and then rapidly to open their eyes on command, which was repeated 5 times. The time from the command to open the eyes was timed, and action myotonia was present if relaxation time was > 1 s during any of the trials [32]. Hand-grip action myotonia was tested by instructing the participant to forcefully close the fingers of the right hand in a fist for 10 s, and then rapidly open the fist on command, which was repeated 5 times. The time from the command to open the right fist until relaxation of the handgrip muscles was timed and action myotonia was present if relaxation time was > 1 s during any of the trials [32].

2.3. Data analysis

The clinical data collection was stored in a Castor database (Castor EDC 2017.6.1, Ciwit B.V.) and transferred to a SPSS Statistics file (version 22.0, IBM Corporation, Armonk, NY, USA) for analysis. Categorical data were presented as counts and percentages of cases, continuous variables were presented as mean ± SD, and skewed data were presented as median with interquartile range. As all analyses relate to comparisons within participants, paired *t*-test were used for analysis. The correlation between PRO and AUC of sEMG was analyzed using the Spearman's rank correlation coefficient. A P value < 0.05 was considered to be statistically significant. Figures were created using GraphPad Prism, Version 5.03 (GraphPad Software Inc., La Jolla, CA, USA).

Qualitative analysis of the sEMG data was performed twice, by offline playback of the captured EMG signals from the Synergy live play files and by revision from signal from the videocaptured.avi files. Signals were screened by the traditional method of visual and auditive inspection by an experienced clinical neurophysiologist (NvA). The presence or absence of any spontaneous muscle activity and any voluntary contraction activity was scored in a yes/no fashion and the type of activity (e.g. fasciculation potentials, myotonic runs, myokymic discharges, neuromyotonic discharges) was noted according to standard clinical practice as described by for example Preston and Shapiro [33]. Endplate noise (i.e. low-amplitude monophasic negative potentials with an irregular firing rate between 20–40 Hz) was ignored. Quantitative AUC analysis of sEMG data was performed using a dedicated software script created by one of the authors (JD), using MATLAB version

Table 1
Clinical characteristics of patients. M = Male, F = female, BMI = Body Mass Index, CAPOX = Capecitabine-Oxaliplatin, BEVA = Bevacizumab.

Patient no.	Sex / Age(yr)	BMI	Treatment/ Cancer stage	Intent	Cumulative dose oxaliplatin (mg/m^2) Cycle 2	Cycle 4	Measurement performed Cycle 2	Cycle 4
1	M/53	27.8	CAPOX T3N2M0	Curative	260	520	+	+
2	M/72	24.6	CAPOX-BEVA T3N0M1	Palliative	260	455	+	+
3	M/63	25.5	CAPOX T3N2M0	Curative	260	520	+	−, technical error
4	F/68	29.8	CAPOX-BEVA T4N1M1	Palliative	260	–	+	−, died after cycle 2
5	M/65	25.8	CAPOX-BEVA T3/N1M1	Palliative	260	–	+	−, stop after cycle 3, general weakness
6	F/48	30.0	CAPOX T4N1M0	Curative	260	487.5	+	+
7	F/65	19.5	CAPOX-BEVA T3N1M1	Palliative	260	520	+	+
8	M/63	21.3	CAPOX T4N1M0	Curative	227.5	422.5	+	+
9	M/67	22.6	CAPOX-BEVA T4N2M1	Palliative	260	–	+	−, stop after cycle 3, general weakness
10	M/53	28.8	CAPOX-BEVA T3N1M1	Palliative	260	455	+	−, general weakness
11	M/71	23.6	CAPOX-BEVA T2N1M1	Palliative	227.5	422.5	+	+
12	M/33	24.9	CAPOX T4N2M0	Curative	260	520	+	+
13	F/74	25.1	CAPOX T4N1M0	Curative	260	520	+	−, severe neuropathy
14	F/47	37.9	CAPOX-BEVA TxN1M1	Palliative	260	487.5	+	+

R2014b (The Mathworks Inc., version R2014B, Natick, Massachusetts U.S.A.). Analysis settings were a horizontal time axis of 1000 ms (100 ms/division) and a vertical EMG signal amplitude axis of −1 mV to + 1 mV (0.2 mV/division). The sEMG signals were rectified, and divided in 1 s epochs (10 divisions) per screen. Each epoch was manually scored for the presence of spontaneous activity by another author (NvA). Subsequently, the area under the curve (AUC) of the rectified signal was calculated above a noise threshold of 0.05 mV.

3. Results

Fourteen participants were included in the study (Table 1). All were measured for the first time after their second oxaliplatin infusion, and 8 participants were also measured a second time after the fourth infusion.

3.1. Surface EMG recording

Spontaneous activity was found in 18 of the total of 22 (82%) sEMG recordings. It was found 12 times during the first measurement and 6 times during the second measurement. The spontaneous activity observed consisted of myokymic discharges and/or neuromyotonic runs of varying amplitudes and durations; no other phenomena were observed. Examples of electrical discharges are shown in Fig. 1. This spontaneous activity was present in all participants measured only once. In 6 out of 8 participants who could be assessed twice the results were congruent, showing the presence (5/8) or absence (1/8) of spontaneous activity during both measurements. In 1 participant the activity was absent during the first measurement and present during the second. In the final participant measured twice, the second measurement could not be assessed for spontaneous activity because of continuous motor unit activation which could not be voluntary stopped by the participant. Needle

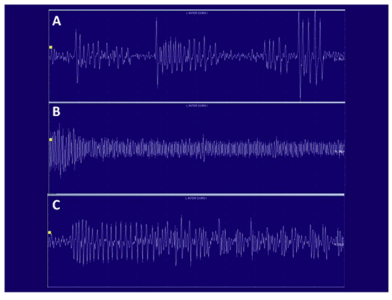

Fig. 1. A panel showing the different forms of spontaneous activity (A = several multiplets, B = a neuromyotonic run, C = a combination of repetitive multiplets and a neuromyotonic run). Time scale horizontal axis: 1 s, vertical amplitude scale 20 μV/division.

Table 2
Results of quantitative analysis of spontaneous activity (AUC in mV/s of the rectified surface EMG signal).

Patient no.	Cycle 2 Spontaneous activity (mV/s)	Cycle 4 Spontaneous activity (mV/s)
1	23.2	2.1
2	1.6	0.0
3	11.1	
4	0.7	
5	8.1	
6	1.0	0.4 (75% oxaliplatin)
7	2.1	0.1
8	0.0	0.0 (75% oxaliplatin)
9	25.9	
10	1.3	
11	0.7	0.3 (75% oxaliplatin)
12	0.0	3.2
13	3.3	
14	1.0	0.2 (75% oxaliplatin)

EMG examination in 2 participants with myokymic discharges and/or neuromyotonia corroborated the surface data findings. Quantitative analysis showed that the AUC of the spontaneous activity varied widely between measurements (Median 1.6 mV/s, IQR 0.7–5.7) (Table 2).

3.2. Patient reported outcomes

All participants (100%) experienced at least 1 acute neuropathy symptom during treatment with oxaliplatin. Only 1 participant reported no symptoms directly after the second cycle of oxaliplatin, though this participant did experience acute symptoms on the following day. Most symptoms, besides throat discomfort during cycle 4, increased in severity the day after oxaliplatin administration. There was a wide interindividual variability in grading of each symptom. For all 4 measurements sensitivity to touching and swallowing cold were rated significantly higher than the remaining components of the PRO ($P = 0.033$ for cycle 4, day 0; $P < 0.001$ for all other moments; mean differences ranged between 3 and 5) (Fig. 2).

3.3. Physical examination

Clinical signs of hyperexcitability were found in 12 of the 22 examinations (55%). During the physical exam after the second treatment cycle, 8 of the 14 participants showed signs of increased nerve hyperexcitability, with fasciculations in 7 participants, eyelid closure action myotonia in 1 participant, and hand-grip action myotonia in 1 participant. After the fourth cycle, 4 of the 8 participants showed clinical

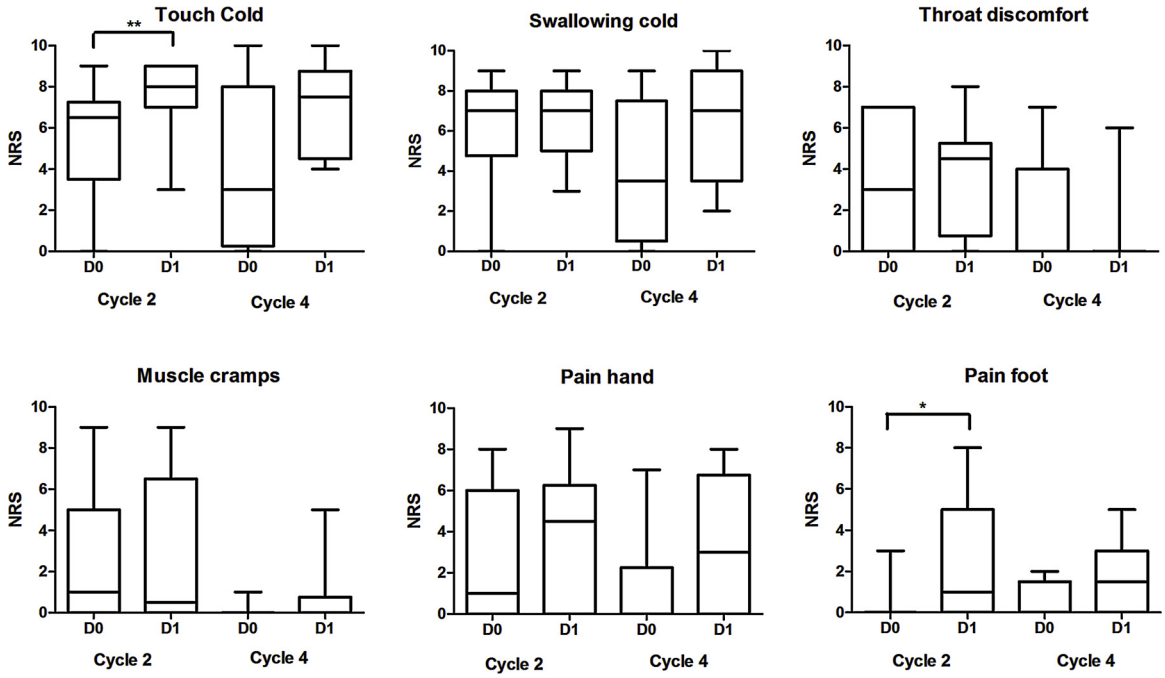

Fig. 2. Boxplots are shown of patient reported outcomes on acute neurotoxicity symptoms induced by oxaliplatin directly after (D0) and one day (D1) after oxaliplatin cycle 2 (n = 14) and cycle 4 (n = 8). A numeric rating scale (NRS; 0: no problem, 10: major problem) was used to assess 'sensitivity touching cold items', 'discomfort swallowing cold items', 'throat discomfort', 'muscle cramps', 'pain hand' and 'pain feet'.

increased nerve hyperexcitability, with fasciculations in 3 participants and hand-grip action myotonia in 1 participant.

3.4. Surface EMG recording and clinical measurements

All but 1 participant who had spontaneous activity on sEMG reported neuropathy symptoms directly after oxaliplatin treatment. No correlation with the AUC of the sEMG signal and any of the neuropathy symptom on D0 or D1 was found (Rho = 0.312, $P = 0.098$ for throat discomfort on Day 0; the P value of the Pearson correlation for all other neuropathy symptoms with AUC had higher P values). In 10 out of 18 measurements in which spontaneous activity on sEMG was found, clinical signs of hyperexcitability were observed. Thus, during 8 measurements where spontaneous activity was found on sEMG, no clinical signs of increased hyperexcitability were noticed. In 2 participants who had no spontaneous activity on sEMG, fasciculations were observed during the physical examination.

4. Discussion

This study demonstrates that a simple 2-channel sEMG study of the first dorsal interosseus muscle is a feasible and non-invasive method to screen for objective signs of nerve hyperexcitability directly after oxaliplatin administration. All participants reported to a variable degree symptoms of acute OIN; and signs of nerve hyperexcitability could be detected with physical examination in 55%, which was less sensitive than the sEMG (82% detection). Surface EMG recordings may have missed spontaneous discharges from motor units lying deep in the muscle, which hampers a 100% detection rate.

Other studies have established the presence of neuromyotonic discharge patterns within 1–4 days after the first oxaliplatin administration by performing nEMG of different leg muscles [15,20,34]. In 100% of the participants spontaneous high frequency discharges were found in 1 or more muscles when 3 muscles were sampled [15]. We explored a simplified method and found spontaneous activity in 82% of the sEMG measurements of the first dorsal interosseus muscle within 1–2 h after the second or fourth oxaliplatin infusion. Although nEMG corroborated our sEMG results in 2 participants, further study is needed to determine the optimal muscle sample size to detect hyperexcitability. In line with previous observations, participants reported cold evoked symptoms as most severe [7,12,16,22]. Contrary to other reports [10,12], there was a slight decrease in severity of symptoms during the fourth cycle, probably caused by dose reduction in some participants and by other participants dropping out the study. The severity of the acute symptoms has been shown to be one of the risk factors for developing high grade chronic OIN [35], so monitoring and preferably treating these of symptoms is of paramount importance to ensure chemotherapy compliance. A recent study demonstrated that motor nerve hyperexcitability was correlated with acute cold induced symptoms in 12 patients within 3 days after oxaliplatin infusion [19], though we did not find this. Our study has some limits. We excluded patients with a preexistent neuropathy, and we did not perform a baseline physical neurologic examination. The major aim of our study methodology was focused on detecting signs of hyperexcitability and normally no hyperexcitability is present in patients, although theoretically this could have biased our results. Also, during the second measurement 6/14 patients dropped out of the study due to a worsening clinical status, which may have influenced characteristics of the PRO, the physical examination and sEMG results. Finally, we did not perform serial measurements on consecutive days after oxaliplatin administration, so it is unknown if repeated measurements could improve the detection rate further and how the hyperexcitability evolves over time. In conclusion, 2-channel sEMG is a simple, non-invasive and feasible screening tool to complement the subjective reported symptoms for monitoring nerve hyperexcitability after oxaliplatin infusion. Surface EMG improves the objective detection of hyperexcitability compared with the physical examination. Further validation of the technique and studying a possible correlation with chronic OIN and sEMG findings can help guide in future intervention studies.

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