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ORIGINAL ARTICLE

Electrophysiologic evaluation of facial nerve functions after oxaliplatin treatment

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Abstract

Purpose This study analyzes the effect of oxaliplatin treatment on the facial nerve. The facial nerve is the most commonly paralyzed cranial motor nerve because it advances through a long, curved bone canal. Electroneurography and blink reflex are the electrophysiological measurements used for evaluating facial nerve function. Oxaliplatin is a cytotoxic agent used in adjuvant or palliative systemic therapy for colorectal cancer treatment.

Methods This study was performed on 20 individuals who were at least 18 years old at Hacettepe University Ear Nose Throat Department, Audiology and Speech Disorders Unit, and Neurology Division EMG Laboratory as they received oxaliplatin treatment from Hacettepe University Oncology Hospital. Electroneurography and blink-reflex values were recorded and examined. The parameters taken during the second and fourth months were compared for this purpose.

Results This study shows that the prolongation of distal latencies of compound muscle action potential is statistically significant, the amplitudes showed no difference. The ENoG results were analyzed, the prolongation of latency measurements between pre-treatment and the fourth month after treatment were statistically significant. The blink-reflex results showed that comparison with the baseline values, the prolongation of latencies in R1 measurements between pre-treatment, the second month, and the fourth month were significant.

Conclusions The facial nerve is affected asymptomatically by oxaliplatin treatment. During oxaliplatin treatment, the evaluation of facial nerve function could be beneficial for patients by improving their quality of life. Electroneurography and blink-reflex tests can be used in the early evaluations of different medicines to determine their neurotoxicity.

Keywords Polyneuropathy · Oxaliplatin · Electroneurography · Blink reflex

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Introduction

The chemotherapeutic agents used in cancer treatments can be applied alone or with other medications. However, during and/or after using those agents, side effects may occur depending on their specific features, such as their metabolites. Among the side effects targeting several organs and systems, neurotoxin exposure is a very damaging one for patients [1].

Neurotoxin-induced effects can be seen during or shortly after the implementation of a drug. Neurotoxicity may affect important bodily functions or disrupt quality of life. Sensory or sensory-motor neuropathies are frequently reported to be dominant symptoms of neurotoxicity [1].

Oxaliplatin is a cytotoxic agent usually used in colorectal cancer treatment with 5-fluorouracil (5-FU) and folinic acid (FA) (known as the FOLFOX combination) to perform adjuvant or palliative system therapy [2]. If metastasis is present, protocols involving irinotecan (FOLFIRI) are also an option. In metastatic patients, oxaliplatin or irinotecan protocols are applied alternatively [3, 4]. The cytotoxicity of these platinum compounds is derived from the inhibition of DNA synthesis in cancer cells. Oxaliplatin functions with DNA by making cross-linked connections with fibers inside and outside, which causes cell death by suppressing, copying, and regenerating DNA [5]. Thus, this has become the standard approach when using oxaliplatin to treat patients with advanced colorectal cancer [3, 4].

Since it precedes a long, bony canal (Fallopian canal) with many folds, the facial nerve experiences paralysis more often than any other motor nerve in the body. Motor fibers have an essential role in impacting the face's mimic muscles, and the facial nerve comprises of both motor and sensory fibers. When facial nerve diseases such as facial paralysis occur, they may negatively affect a patient's daily life and psychological well-being [6, 7].

Diagnostic tests were developed to apply appropriate early interventions and report further developments in facial nerve pathologies. Because of these advancements, topographical and electrical tests can be used to determine the localization of a lesion and predict the possible prognosis [8–10].

Electroneurography (ENoG), is an objective electrophysiological test that provides information on the integrity of the peripheral motor nerve by recording (CMAP). Basically, a low electrical current that does not disturb the patient is applied from one side of the nerve and then recorded at the side of the innervated muscle. The test results depend on any transmission problem in the nerve. In follow-up tests, the nerve's condition can be observed and the necessity of surgical operation can be decided. In the early period, ENoG is the best diagnostic criteria to determine nerve degeneration rate [11, 12].

The blink-reflex test allows for an objective digitized response from the orbicularis oculi muscle using controlled electrical stimulations to provide topographical information about diagnosis and lesion localization to assist in treating various neurological problems [13].

The aim of this study was to determine if oxaliplatin treatment affects the facial nerve's function using ENoG and blink-reflex tests on patients undergoing treatment.

Materials and methods

This study protocol was approved by the Non-interventional Clinical Research Ethics Board of the University. All procedures performed in the study followed relevant ethical guidelines and all the participants signed the informed consent form.

Participants

A pilot study was performed with five individuals who would not be included in the study, and it was decided that the number of individuals to be included in the study was 17. Then it was decided to include 24 persons in the study since the rate of participant loss was high in the colorectal cancer patients. Twenty-four individuals who were at least 18 years old and undergoing oxaliplatin treatment (FOLFOX4, FOLFOX6) participated in this study (Table 1). However, as four experienced malignancies, the study was completed with 20 individuals. None of the individuals who participated in this study had diabetes or a history of facial paralysis.

Audiological evaluation

The hearing evaluations were done between 125 and 16,000 Hz for each ear. These evaluations were conducted in the Industrial Acoustics Company's (IAC) soundproof rooms with stereo audiometers (Interacoustics AC40, GrasonStadler GSI 60, and Telephonics TDH-39P and R-80 Koss headphones).

Evaluation of facial nerve function

To examine the facial nerve's electrophysiological function, ENoG (Medelec Synergy-version 1.10-serial no: 8177/0901/Q262B) and blink-reflex tests (Neuropack M1 MEB-9200, Nihon Kohden, and Medtronic Keypoint EMG) were administered. Patients were informed about these procedures prior to their application by the clinician, and every patient's approval was obtained. Silver–silver chloride electrodes were used during recording. Before each test was conducted, these electrodes were placed over cleaned skin areas and impedance values were measured, with 8000 O or lower impedance values considered to be within normal range. Male patients were asked to shave before testing.

Table 1 Demographic features of participants

	Number (*n*)	Age range (year)	Average age (year)
Female	14	43–78	62, 36
Male	6	32–66	50, 83
Total	20	32–78	58, 90

While electrophysiological measurements were taken, the room's temperature was kept constant using a digital thermometer.

Electroneurography

Before initiating the test, active electrode was placed on the recorded side of the lip, reference electrode was placed on the recorded side of the nose, and ground electrode was placed on the forehead. Electrical stimulus was then given to the facial nerve's body using stylomastoid foramen (Fig. 1a, illustrating the electrodes located for ENoG). During recording, each patient was in the upright sitting position. Stimulation intensity was increased until a constant response was obtained.

In this study, ENoG was recorded with a single channel and responses from orbicularis oris muscles were analyzed with a side-to-side amplitude comparison. The normal ENoG response was a biphasic wave form, with the earliest response seen 5–7 ms after stimulation. The acquired wave structure is composed of two negative peaks (N1 and N2) and one positive peak (P1). The distance between P1–N2 is accepted as wave amplitude, and it has been determined by comparing the amplitudes from both sides.

Blink reflex

Before recording, bilateral active electrodes were placed on the lateral canthus, over the orbicularis oculi muscle, and the bilateral reference electrode was placed next to the same side of the nose. Recordings were taken while the individual was lying in supine position and her or his eyes were open. From both sides, the supraorbital nerves, a terminal branch of the trigeminal nerve, were, respectively, electronically simulated from the groove of the medial 1/3 part in the eye pit (Fig. 1b, illustrating the electrodes located for blink reflex). Stimulation intensity was increased until a constant response was obtained. To prevent habituation, electrical stimulation was applied within the intervals of 10–15 s.

Information from both orbicularis oculi muscles was recorded simultaneously. R1 and R2 replies from stimulation and the latency of R2's reply from the same and contralateral sides were measured from obtained records. Obtained ipsi-contralateral R2 responses were rectified, and the area under the rectified responses was calculated. Blink-reflex study parameters (latency of ipsilateral R1, ipsi- and contralateral R2, and ipsi- and contralateral R2 areas) were measured during pre-treatment and the second and fourth months of post-treatment.

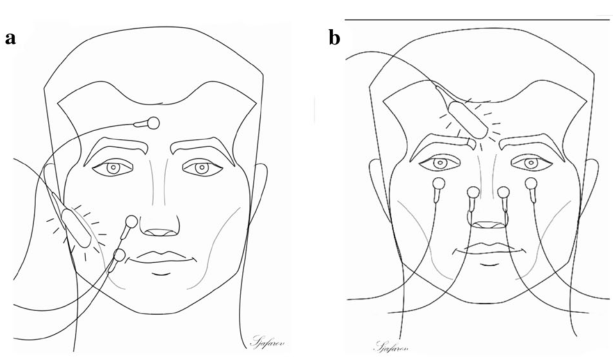

Fig. 1 **a** Illustrating the electrodes located for ENoG. Active electrode was placed on the recorded side of the lip, reference electrode was placed on the recorded side of the nose, and ground electrode was placed on the forehead. **b** Illustrating the electrodes located for blink reflex. Bilateral active electrodes were placed on the lateral canthus, over the orbicularis oculi muscle, and the bilateral reference electrode was placed next to the same side of the nose

Data analysis

Statistical analyses were done by SPSS for Windows Version 15.0. Numeric variables were summarized with average, standard deviation and median [min–max]; categorical variables were summarized with numbers and percentage. Data were checked for normal distribution, and nonparametric tests were used since the data showed a non-normal distribution. Time variables were (0, second and fourth month) searched with Friedman test. Paired comparisons were done with Wilcoxon test. Significance level is calculated as $p < 0.05$. Bonferroni reforming is done on p measure about paired comparisons. Blink-reflex parameters (latency and area values) difference in time were evaluated using Friedman test. Two-way comparisons were calculated with Wilcoxon test. For two-way comparisons, p value was accepted as 0.017 using Bonferroni correction.

Results

Electroneurography and eye-blink-reflex measurements were used to determine facial nerve functionality. The parameters taken during the second and fourth months were compared for this purpose.

Electroneurography

During the ENoG tests, the measurements of wave latencies and amplitudes were taken from both sides of every patient (Fig. 2, indicating wave latencies and amplitudes of ENoG). Tests were conducted during pre-treatment and in the second and fourth months of post-treatment. Each test was applied one day before treatment. Finally, the results were compared (Table 2).

The measurements of wave latencies and amplitudes at these different times were statistically analyzed using the

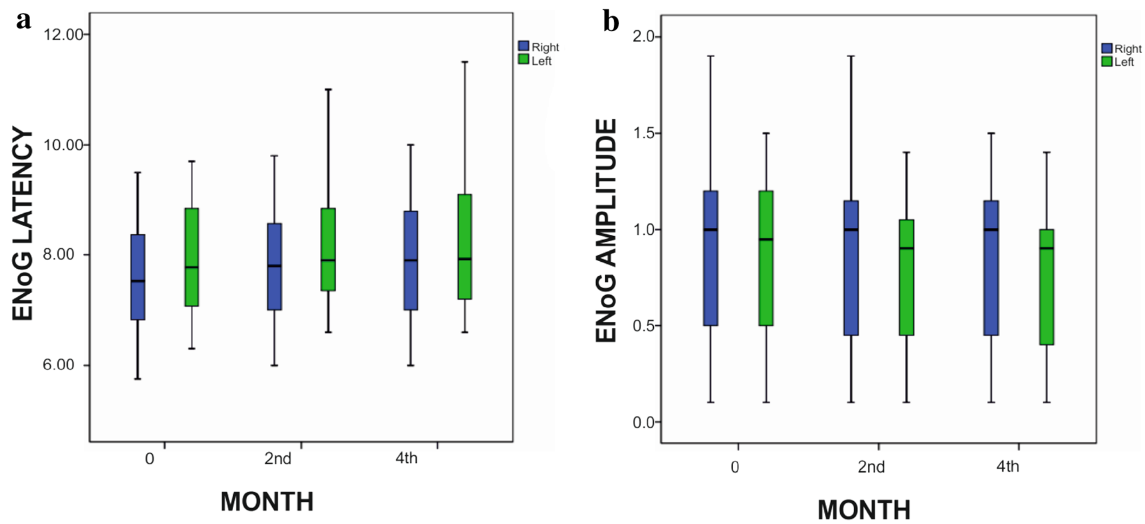

Fig. 2 Comparison of pre- and post-treatment ENoG measurements. **a** Prolongation of latency measurements between pre-treatment and the fourth month after treatment were statistically significant ($p < 0.017$). **b** The amplitude differences were not statistically significant ($p > 0.05$)

Table 2 Comparison of pre- and post-treatment ENoG measurements

	Right				Left			
	Latency		Amplitude		Latency		Amplitude	
	Median [min–max]	Mean ± SS	Median [min–max]	Mean ± SS	Median [min–max]	Mean ± SS	Median [min–max]	Mean ± SS
0 months	7.5 [5.8–9.5]	7.6 ± 1.0	1.0 [0.1–1.9]	0.9 ± 0.5	7.8 [6.3–9.7]	7.9 ± 1.0	1.0 [0.1–1.5]	0.9 ± 0.4
2nd month	7.8 [6.0–9.8]	7.7 ± 1.0	1.0 [0.1–1.9]	0.9 ± 0.5	7.9 [6.6–11.0]	8.1 ± 1.1	0.9 [0.1–1.4]	0.8 ± 0.4
4th month	7.9[6.0–10.0]	7.9 ± 1.1	1.0 [0.1–1.5]	0.8 ± 0.4	7.9 [6.3–11.5]	8.2 ± 1.2	0.9 [0.1–1.5]	0.8 ± 0.4
0–2 months	$p = 0.104$		$p = 0.196$		$p = 0.010$		$p = 0.087$	
0–4 months	$p = 0.007$*		$p = 0.046$		$p = 0.001$*		$p = 0.053$	
2–4 months	$p = 0.091$		$p = 0.102$		$p = 0.059$		$p = 0.257$	

*$p < 0.017$

Friedman test. Although the latency differences in time were statistically significant ($p < 0.05$), the amplitude differences in time were not statistically significant ($p > 0.05$).

The Wilcoxon test was used to analyze the differences in time for both sides. Prolongation of latency measurements between pre-treatment and the fourth month after treatment were statistically significant ($p < 0.017$). On the other hand, when compared to those of the pre-treatment and post-treatment in the second month, measurements of the second and forth months of post-treatment were not statistically significant ($p > 0.017$) (Table 2).

Blink reflex

For both sides, R1 latencies were prolonged during treatment (Fig. 3a, indicating R1 values of blink reflex). When compared with the baseline values, the prolongation of latencies in R1 measurements between pre-treatment, the second month, and the fourth month were significant ($p < 0.017$). However, the time between the second and fourth months was not significant ($p > 0.017$). Left-side R1 latency measurements were prolonged, those between pre-treatment and the second month and between pre-treatment and the fourth month being statistically significant ($p < 0.017$), and those between the second and fourth months not significant ($p > 0.017$) (Table 3).

Ipsilateral R2 latency measurement prolongation between pre-treatment and the fourth month and between the second and fourth month measurements were statistically significant ($p < 0.017$). Contralateral R2 latency differences in time were not statistically significant ($p > 0.05$). Left-side R2 latency differences in time were not statistically significant ($p > 0.05$). Ipsilateral R2 latency prolongation between pre-treatment and the fourth month and between the second and fourth month measurements were statistically significant ($p < 0.017$). Contralateral R2 latency differences in time

Table 3 Comparison of pre- and post-treatment blink-reflex measurements for right and left sides

	0 month Median [min–max] Mean ± SS		2nd month Median [min–max] Mean ± SS		4th month Median [min–max] Mean ± SS		0–2 months, *p*	0–4 months, *p*	2–4 months, *p*
Right									
R1	11.3 [10.5–13.0]	11.4 ± 0.7	11.90 [11–14]	11.8 ± 0.7	12 [11–14]	12.2 ± 0.8	0.001*	0.001*	0.04
R2	33.8 [28–37]	33.3 ± 2.4	34 [28–37]	34 ± 2.4	34.2 [28–38]	34 ± 2.5	0.1	0.005*	0.005*
CR2	34.9 [28–38]	34 ± 2.8	35 [28.3–39.3]	34.4 ± 2.9	35.3 [28–39]	34.4 ± 2.9	0.16	0.15	0.67
I Area	3393 [2097–5648]	3741 ± 1149	2968 [1670–5500]	3124 ± 1036	2925 [1700–5500]	3123 ± 1096	0.000*	0.001*	0.10
C Area	4345 [2050–6955]	4194 ± 1299	3023 [2000–5800]	3286 ± 1190	3155 [2004–5800]	3362 ± 1247	0.000*	0.000*	0.68
Left									
R1	11.6 [10.3–12.8]	11.4 ± 0.7	11.9 [11–13]	11.8 ± 0.7	12 [11–13]	11.9 ± 0.7	0.001*	0.001*	0.06
R2	34 [30–38]	33.8 ± 2.3	35.1 [28–38]	34.1 ± 2.8	36 [28–39]	34.6 ± 2.9	0.1	0.001*	0.005*
CR2	34.5 [30–38]	34 ± 2.4	35 [29–38]	34.4 ± 2.6	35 [28–40]	34.8 ± 3	0.16	0.15	0.67
I Area	4167 [3384–4167]	3741 ± 1149	3378 [1842–6900]	3505 ± 1222	3190 [1842–5800]	3262 ± 1105	0.001*	0.001*	0.19
C Area	3651 [2112–6263]	3925 ± 1071	2975 [2042–6063]	3292 ± 1112	2824 [1842–6004]	3109 ± 1100	0.000*	0.000*	0.8

CR2 contralateral R2, *I* ipsilateral, *C* contralateral

*$p < 0.017$

were not statistically significant ($p > 0.05$) (Fig. 3b, c, indicating ipsilateral and contralateral R2 values of blink reflex).

For both sides, there was a reduction in ipsilateral and contralateral area measurements. Ipsilateral and contralateral comparisons showed that decreases in values between pre-treatment and the second month and between pre-treatment and the fourth month were significant ($p < 0.017$) (Table 3). However, decreases between the second and fourth months in area values were not significant statistically ($p > 0.05$) (Fig. 3d, e, indicating ipsilateral and contralateral area values of blink reflex).

Discussion

Data obtained from the Council of Turkey Cancer Institute state that the mortality of colorectal cancer ranks second in women and third in men [14]. To increase a patient's survival rate, chemotherapy is applied. However, the treatment has many side effects, and the most common neurological complication in patients is peripheral neuropathy, which deteriorates with recurrent chemotherapy. Chronic neuropathy is cumulative, and its effects depend on the dose and duration of chemotherapy [15]. Patients often report that their symptoms improved when certain agents were no longer administered to them. Early diagnosis and treatment of neuropathy are critical for the life quality of patients who will receive chemotherapy [16].

Neuropathy associated with platinum anti-neoplastic compounds, namely, cisplatin, carboplatin and oxaliplatin, has been well-described for decades. Though not a life-threatening complication, neuropathy can mandate dose reductions, interruptions, and discontinuations, all of which can lead to suboptimal treatment and potentially, shorter survival of the patients. Neuropathy typically worsens the patients' quality of life and may be difficult to cope with. Efforts to prevent neuropathy have not been particularly successful, therefore, the mainstay of management remains timely recognition and drug dose modification or discontinuations, and if available, switching to a different agent with no or less neurotoxicity [17].

The development and presentation of neuropathy are highly variable, and symptoms and signs may not always match. Patients with minor symptoms may have prominent signs or vice versa [17]. The underlying reasons remain unclear. Pronounced acute neuropathic symptoms, decreased hemoglobin, hypoalbuminemia, high chlorine, hypomagnesemia, high body surface area, existing peripheral neuropathy have all been proposed as factors predisposing to chronic polyneuropathy, though not always consistently among studies. Cumulative oxaliplatin dose is invariably associated with development of neuropathy. Interindividual variability in the metabolism of oxaliplatin is certainly a plausible explanation

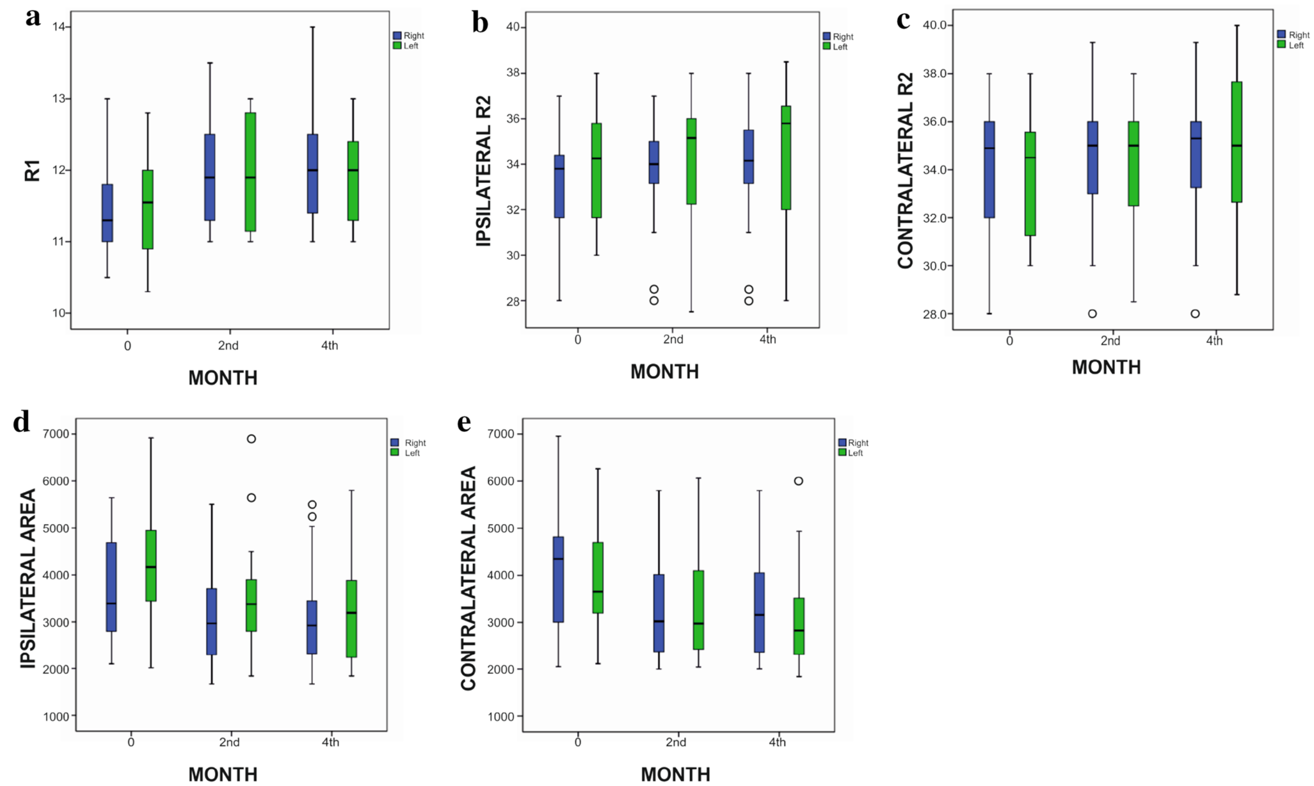

Fig. 3 Comparison of pre- and post-treatment blink-reflex measurements. **a** The prolongation of latencies in R1 measurements between pre-treatment, the second month, and the fourth month were ($p < 0.017$). **b** Ipsilateral R2 latency measurement prolongation between pre-treatment and the fourth month measurements were statistically significant ($p < 0.017$). **c** Contralateral R2 latency differences in time were not statistically significant ($p < 0.05$). **d**, **e** Ipsilateral and contralateral comparisons showed that decreases in values between pre-treatment and the second month and between pre-treatment and the fourth month were significant ($p < 0.017$)

for variations in the development of neuropathy, yet, it is hard to define. No studies have indicated an association with development of neuropathy and treatment outcomes, which may be considered an indirect measure of oxaliplatin exposure [18].

In this study, the participants who had received oxaliplatin treatment underwent another set of ENoG and blink-reflex tests in their fourth month post-treatment. This was to determine any decreases in nerve conduction speed. These findings were statistically significant when compared to the obtained pre-treatment data. In the related literature there were studies on peripheral nerves but no studies on cranial nerves.

Studies of blink reflex, evaluated as "late responses," are electrophysiological responses of physiological and involuntary blink in both sides of mammals due to various stimuli. Electrophysiological studies of the blink reflex allow for objective, digital responses from the orbicularis oculi muscle to be obtained using controlled electrical stimulations. Routine studies provide topographical information about diagnosis and lesion localization regarding various neurological diseases to evaluate both sides and record the response parameter outcomes of latency, amplitude, duration of ipsilateral R1 and R2 stimulates from same side, and contralateral R2 muscle responses [13, 19]. The supraorbital branch of the trigeminal nerve is an afferent part of the reflex arch, while the facial nerve is an efferent part of it. In addition to providing information about the functionality of these nerves, blink-reflex studies can also determine the integrity of brainstem functions, as affected nerves have complicated and long central connections to the Pons and lateral medulla level [13].

Abnormal R1 responses were obtained from poly-neuropathies, such as Guillain–Barre and diabetic neuropathy. The disappearances of R1 and delay in R2 in patients with acoustic neurinoma were also diagnosed [20]. In their study, Adelsberger et al. stated that oxaliplatin has little to no effect on acute sensory symptoms and axonal degeneration. They concluded that the acute effect of oxaliplatin was related to the sensory neuron and/or motor neuron or muscle cells. They showed that oxaliplatin caused hyperexcitability by affecting voltage gates.

Among the reasons for the slowing down of neuron conduction in neuropathy were considerable losses in fibers with myelin, second distal axonal atrophy, and the slowing down of conduction through distal regenerated fibers [21, 22].

In their studies on biopsy, Logician et al. stated that slowed conduction velocity and decrease in amplitude are more prominent in the distal of the neuron than the one in proximal. They found that amplitude was almost proportional to the decrease in conduction velocity. There are studies supporting that the slowing down of conduction in axonal neuropathy and ALS have a similar mechanism [23].

In the studies done by Feinberg et al., the neuro-motor conduction data of patients with ALS and axonal neuropathy were compared. According to their hypothesis, axonal neuropathy's prolongation of latency conduction speed is much longer. The effect that causes slowing down in axonal neuropathy is thought to be an additional secondary distal demyelization, not the loss of a fast conductor axon as in ALS [23].

Lehky et al. conducted a nerve conduction study with needle EMG in patients of metastatic colorectal. Twenty-four patients were evaluated in 48 h during the application of oxaliplatin, and fourteen patients were evaluated between the repetitions of the treatment's cures 3–9. They emphasized that this acute effect passed off in 3 weeks by itself. However, during the period after 8–9 treatments, a decrease in CMAP amplitude was observed, and they mentioned the change in conduction velocity in their findings. They pointed out that peripheral neuro hyperexcitability caused acute neurological symptoms and that the chronic effect of the treatment caused axonal neuropathy [24].

In our study, latency and amplitude values in electroneurography evaluation are compared. In treatment, process prolongation was determined, and when comparing pre-treatment and the fourth month, a considerable difference was obtained. Usually, ENoG is used to estimate a prognosis for patients with facial nerve dysfunction. Percentages were obtained from the test, and individuals' treatments and prognoses were followed. The prolongation and decrease in amplitude values obtained support the conclusion that the conduction velocity of facial nerve was affected.

In their blink-reflex studies on patients with diabetes, Kazem et al. obtained prolongation in R1, ipsilateral, and contralateral R2 values. Through this study, which aimed to compare healthy reflexes with unhealthy ones, they emphasized that blink-reflex reflex is a simple, fast, and non-invasive method for evaluating cranial nerves. In addition, they stated that the blink reflex could be observed as abnormally bilateral in patients with diabetes and that this was beneficial for early diagnose of sub-clinic contraction [25].

Of the 20 participants in our study, clinic neuropathy symptoms were observed in only two of them. This suggests that electrophysiological findings appear before clinical symptoms. Preforming ENoG and blink-reflex tests on individuals using oxaliplatin gave a reliable finding in respect to neurotoxicity.

Casale et al. [26] obtained normal R1 responses from individuals with asymptomatic systemic sclerosis and stated that having this normal response dispenses with peripheric neuropathy.

In our blink-reflex findings, prolongation was observed in the change of R1 values over time. This finding was statistically significant. Our findings were consistent with the literature. Prolongation in ipsilateral R2 values was statistically significant.

Cruccu et al. [27] stated that ipsilateral orbicularis of facial nerve lesions causes abnormality in both R1 and R2 responses. However, prolongation in contralateral R2 values was not systematically reasonable. Kimura, for the first time, explained R1 in diabetic neuropathy and elongation in ipsilateral and contralateral R2 values. In some other publications, it was stated that contralateral values also lengthen beside ipsilateral values [28].

In our study, it is thought that the reason why the contralateral R2 values are obtained as normal is that the contra R2 arch is longer and the brainstem is also included in this arch. Our study observed a statistically reasonable decrease in ipsilateral and contralateral area values. These areas indicate a number of axons and the depolarization status of muscle fibers. Contrary to our expectations, the decreases in field values and amplitude values noted in the ENoG tests were not proportional, and it is thought that it is because of technical reasons. The neurotoxicity we have observed is thought to affect the trigeminal nerve, but the decline in the area values also supports the neurotoxic interaction with the facial nerve.

Neurotoxicity may cover many physiopathological times, from the synthesis of myelin to the physiological integrity of axon to the conductivity of stimulation. Considered in this respect, we can say that the abnormal values of the ENoG and blink-reflex tests resulted from the neurotoxic effects of oxaliplatin treatment on the facial nerve.

Our findings showed that oxaliplatin treatment slows down the facial nerve's transmission speed. This study observes the early effects of neurotoxicity on the facial nerve. These evaluations were done using ENoG and blink-reflex tests. It was revealed that oxaliplatin causes the prolongation of ENoG latency, blink-reflex R1, and ipsilateral R2. However, there was no significant correlation between the amplitude of ENoG and both blink-reflex contralateral R2 and oxaliplatin treatment.

Oxaliplatin treatment decreased the value of the ipsilateral and contralateral blink-reflex response areas. ENoG and blink-reflex tests could be used in the early detection of neurotoxicity caused by different medications. As cancer mortality increases year by year, so does the need for chemotherapy. For an individual needing treatment, the use of electrophysiological measurements to analyze the facial nerve is crucial for his or her early diagnosis. With this diagnosis, a patient's quality of life could be protected or increased.

Co-medications were not recorded for this study. Drugs may indeed predispose and/or worsen neuropathy, yet, drugs resulting in severe neuropathy are generally avoided in patients who receive oxaliplatin. Similarly, vitamin levels were not documented. These could be recorded as limitations of our study.

Funding This study was not funded by any entity.

Compliance with ethical standards

Conflict of Interest Authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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