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Professional Paper

EVAULATION OF BLINK REFLEX BETWEEN PATIENTS WITH IDIOPATHIC TRIGEMINAL NEURALGIA AND HEALTHY VOLUNTEERS

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SUMMARY – The purpose of the study was to find differences in the parameters of the response to the blink reflex (BR) between patients with idiopathic trigeminal neuralgia (TN) and health volunteers. A prospective cohort study was conducted over 2 years. The TN-subgroup included 15 patients (mean age / SD 62.3 ± 10.7 years). Pain-free and healthy volunteers as a HV-subgroup (mean age / SD: 30.8 ± 8.1 years) were recruited from asymptomatic students of dental medicine. Diagnostic parameters were determined by measuring latency to the onset of the BR components from electric stimulation. The following branches of the trigeminal nerve were affected: maxillary branch only (26.7%), mandibular branch only (20%), combined: ophthalmic branch with maxillary branch (6.7 %), and ophthalmic branch with mandibular branch (6.7%) respectively, combined maxillary and mandibular branch (26.7%) and affected all three branches (13.4%). The latencies of the BR, left and right side together, between subgroups were significantly higher for values R1 (homolateral early response), R2 (homolateral late response), R2c latency (contralaterally expressed response) in the TN-subgroup ($p < 0.05$). On the basis of the presence of R1c and R3 latencies and upon considering the abnormal findings of the BR, no statistically significant differences were found between the examined subgroups ($p > 0.05$). Blink-reflex parameters (R1, R2 and R2c) were significantly abnormal comparing TN-patients with healthy volunteers. The R3 component of the BR was related to noxious stimuli, likewise by innocuous stimuli.

Key words: *orofacial pain, trigeminal neuralgia, blink reflex*

Introduction

Neuropathic pain attributed to the disease of the Vth (fifth) cranial nerve is one of the most unpleasant types of pain in the human body. It is located in the orofacial region and is chronic in duration. In 1756, the Frenchman Nicolas Andre introduced the name "tic doloreux", which meant "painful spasms" of the face since patients often contracted their facial muscles during an attack of neuralgia of the trigeminal nerve. In 1820, Charles Bell established the separation of trigeminal and facial nerve function, thus beginning the evolution of the term "trigeminal neuralgia" (TN)[1,2]

In the International Classification of Orofacial Pain (according to International Headache Society) TN is defined as a disorder characterized by recurrent uni-

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lateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve. The subforms of TN can be as follows: classical trigeminal neuralgia, secondary trigeminal neuralgia and idiopathic trigeminal neuralgia. Recurrent paroxysms of unilateral facial pain fulfilling criteria for this concomitant continuous or near-continuous pain could result from peripheral or central sensitization[3, 4].

In classical (primary) TN, where the cause is a pathomorophological relationship of the trigeminal nerve against potentially suspected causes of irritation (especially in cerebellopontine angle) and secondary type of TN (caused by intracranial tumor, multiple sclerosis etc.) we can talk about a specific etiology for this type of neuropathic orofacial pain [5-7].

For TN, the importance of the electroneurophysiological blink reflex (BR) procedure lies in the presentation of neurogenic abnormalities that manifest as dysfunction of the trigeminal sensory system (such as headaches, multiple sclerosis). Besides, the nociceptive BR procedure is particularly important as a diagnostic instrument for TN-related pain disease [7-19].

The nociceptive BR procedure is a non-invasive and painless method with the purpose of objectifying neuropathic pain in different groups of patients and healthy volunteers. Based on the interconnectedness of the nuclei of facial and trigeminal nerves in the *pons* and *medulla*, BR as by electricity evocated corneal reflex, is a type of polysynaptic reflex in which reflex (efferent) stimulation of the ophthalmic branch causes the reflex (efferent) activation of motor fibers of the facial nerve[20].

The purpose of the study was to find differences in parameters of the response to the BR between patients with idiopathic TN and asymptomatic and healthy volunteers.

Material and methods

A prospective cohort study was conducted over 2 years. It included 20 patients (mean age / standard deviation (SD) 58.9±13.5 years; 12 (60%) female patients), who were examined for clinical symptoms and signs of orofacial pain of non-dental origin. The study included only the patients with a confirmed diagnosis of idiopathic TN and it was carried out in cooperation between the neurological outpatient clinic (Department of Neurology, Clinical Hospital Centre "Sestre milosrdnice", Zagreb) and a subspecialist dental practice for orofacial pain at the Department of Removable Prosthodontics (School of Dental Medicine, University of Zagreb, Zagreb). A magnetic resonance imaging (MRI) was performed at the Department of Diagnostic and Interventional Radiology (Clinical Hospital Centre "Sestre milosrdnice", Zagreb) on a 1.5T device using thin layers for cerebellopontine angle and trigeminal root. BR was performed in the Center for Neurology, Polyclinic "St. Catherine" in Zagreb.

On the basis of their medical history and a clinical examination, patients with a history of stroke, cranial nerve lesions, polyneuropathy, drug-induced neuropathy, multiple sclerosis, epilepsy, intracranial neoplasm or intracranial infection were initially excluded. However, TMJ diagnosis with or without comorbidity with TN was also excluded.

Out of a total of 20 patients, 16 patients underwent BR testing (mean age / SD 62.1 ± 10.3 years; 10 (75%) female patients). However, the finding of BR could not be taken into account due to the constant contraction of muscles of the left side of the face in one male patient. Therefore, the final subgroup-TN consisted of 15 patients who suffered from TN (mean age / SD 62.3 ± 10.7 years; 10 (66.7%) female patients). The pain intensity related to TN (Subgroup-NT only) was measured rated on a visual-analogue scale (VAS with the range 0-10).

Pain-free and healthy volunteers, as a Subgroup-HV (mean age / SD: 30. 8±8.1 years; 12 (75%) female patients) were recruited from collected asymptomatic dental students who participated in a previous study, wherein the status of the disc in the joint but without symptoms was determined by MRI. Healthy volunteers did not have any painful conditions, neurodegenerative diseases, congenital facial abnormalities, diabetes, hypertension, or medications that could affect the BR outcome.

Upon the request of the Ethics Committee, School of Dental Medicine, University of Zagreb, all subjects (both patients and asymptomatic volunteer subgroups) signed an Informed Consent confirming their voluntary participation in this research[21]. The purpose of the research and the manner of conducting the BR testing were explained to them.

The BR testing was performed in a sitting position at the room temperature room without direct exposure to the sun's rays or their reflection in the office. Subjects were instructed to maximally relax their facial muscles,

to look in a relaxed way slightly downwards (without eye rotation) and without masticatory system activity (biting teeth, swallowing).

The active electrode was placed below the lower eyelid in the middle with respect to the position of the eye, while the references were placed from below, that is, from the lateral side of the eye corner. The ground electrode was placed in the middle of the chin.

A BR was induced by the stimulation of the supraorbital nerve on the skin at the forehead around the supraorbital foramen, first from one side and then from the other with a single square electric stimulation frequency of 1 Hz, duration 0.5 ms, stimulation intensity 5 to 10 mA (current up to 50 mA) and in the stimulation interval of 5-10 s. Other BR conduction parameters were: sweep speed 10 ms / division; sensitivity 100-200 V / division, bandpass of 10 kHz. For each side 4-6 electrical pulses were done. To avoid reflex habituation, 4-6 stimuli followed for each side with an interval of 5-7 s between them.

Diagnostic parameters were determined by measuring latency (in ms) to the onset of the reflex components from electrical stimulation. The shortest obtained value of latencies was taken into account. The latencies were composed of a homolateral early response R1 and bilateral late response R2 (homolateral response), and R2c (contralaterlly expressed response), and the occurrence of ipsilateral / contralateral R3 / R3c component (Figure 1).

As an abnormal BR finding, latency values > 12 ms for R1, > 42.4 ms for R2 and > 44.4 ms for R2c, the occurrence of contralateral component R1c, latency difference between left and right > 1.2 ms for R1, > 5 ms for R2i and > 7 ms for R2c and the occurrence of the R3 component (> 84 ms) in bilateral stimulation were taken into account[22].

Between TN and HV subgroups, numerical data values of variables R1, R2 and R2c latencies were compared first for the left side and then for the right side. For the same variables, categories were compared according to the cut-off values between subgroups. Side-to-side differences between the values of the same latencies were measured, as well as categorical data with respect to these limit values. In addition, numerical data value of the variables R1, R2 and R2c latencies were measured so that the values together (left and right) between TN and HV subgroups were compared.

For the TN subgroup, the difference between right and left side for each patient for R1, R2, and R2c latencies was also tested. The difference between the separately isolated affected side of each patient and their contralateral healthy side of the body was also analyzed. Only categorical data analysis was performed, due to low frequency of occurrence, for the variables of the presence of other abnormalities: detection of R1c latency, and both ipsilateral R3 and contralateral R3c.

Data processing, using the Kolmogorov-Smirnov Test, determined that there was a normality of data distribution. An independent samples t-test (comparison between subgroups of respondents) was used for continuous data, while paired-samples t-test was used to compare sides of the body of the same respondents. The Fischer's exact test was used for the categorical data. The statistical data analysis was performed by the STATISTICA (StatSoft Inc., Tulsa, Oklahoma, USA) program. P vales less than 0.05 were considered to be statistically significant.

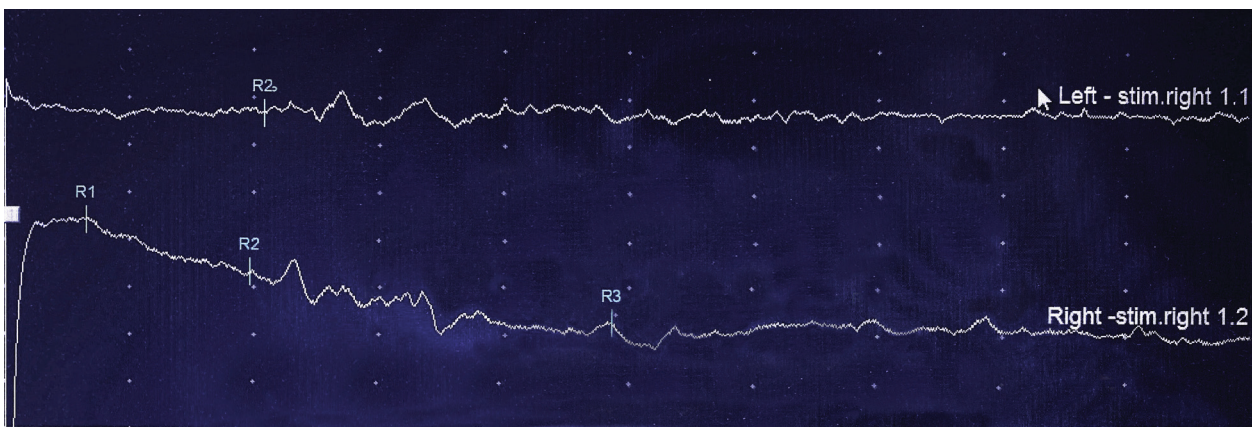

Figure 1 Blink reflex-related waves of the right side of stimulation composed of a homolateral: early response R, late response R2 (homolateral response), and occurrence of ipsilateral R3 component. R2c is a contralaterally expressed response.

Results

There was no difference in sex distribution between TN and HV subgroups (Fischer's exact test p = 0.4815). Patients included in the TN subgroup suffered severe pain (VAS mean / SD 8.79 ± 1.49). Maxillary and mandibular branches were most frequently affected in various combinations with or without the ophthalmic branch (Figure 2).

Between TN and HV subgroups, the numerical data values of variables R1, R2 and R2c latencies for left and right side were compared separately for each side. There are summarized latencies in a separate comparison of values for left and right side (Table 1).

The fact that in some cases the values of individual blink-reflex latencies were higher than the limit normal values was taken into account. Only the values of R2 > 42.4 ms showed a statistical significance in the TN subgroup for latency of the right side (Fischer's exact test p = 0.083) and left (Fischer's exact test p = 0.037) side.

The difference between the compared right and left R1, R2 and R2c latencies between subgroups was analyzed, which proved to be completely statistically significant (Table 2). There were statistically significant side-to-side differences between the limit values for R1, R2 and R2c latencies (Table 3).

There were no statistically significant differences between the symmetry of the BR latencies for the TN subgroup between the right and left side (Table 4). The differences between the healthy and diseased side are analyzed, and the latencies of the TN-group are summarized in Table 5. There was no statistically significant difference in latency values since patients were unilaterally affected with TN.

Other BR parameters were analyzed such as the presence of R1c, R3, and R3c latencies. Although all of these variables were abnormal findings of the BR, no statistically significant differences were found between the subgroups examined (Table 6).

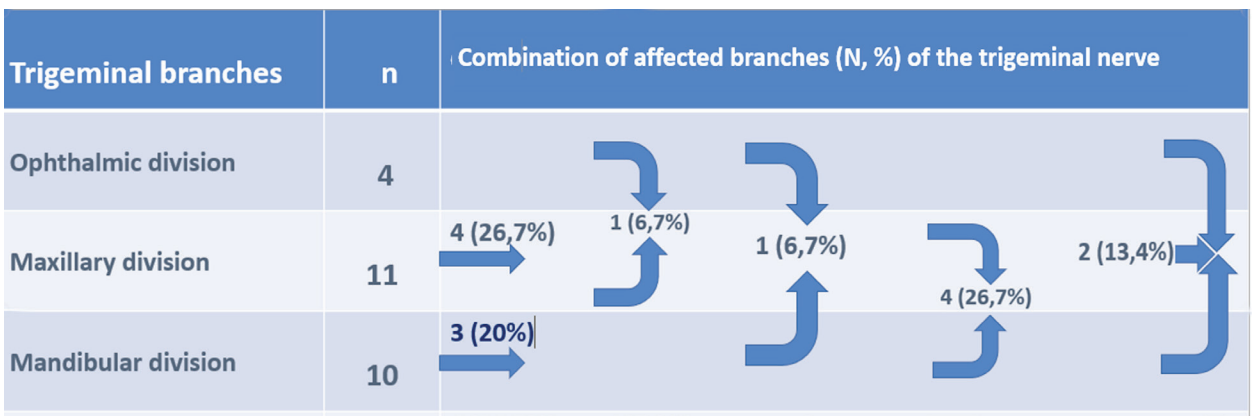

Figure 2 Distribution of frequencies with trigeminal neuralgia affected branches of the trigeminal nerve.

Table 1 Blink reflex latencies of stimulation right / left side between subgroups

Variable, side of stimulation (ms)	TN-subgroup (mean ±SD)	HV-subgroup (mean ±SD)	t-test	p
R1 right	15.66±5.19	13.40±1.53	-1,66	0.054
R1 left	14.78±2.25	13.35±1.85	-1.97	0.029*
R2 right	40.18±15.51	37.31±4.98	-0.70	0.243
R2 left	41.17±9.40	37.25±9.73	-1.41	0.084
R2c right	39.41±14.65	36.29±6.09	-0.79	0.219
R2c left	40.81±11.16	35.90±9.37	-1.35	0.093

TN -subgroup of trigeminal neuralgia; HV -subgroup of health volunteers; SD -standard deviation; * -with statistical significance

Table 2 Blink reflex latencies of stimulation values left and right side together between subgroups

Variable, stimulation (ms)	TN-subgroup (mean ±SD)	HV-subgroup (mean ±SD)	t-test	p
R1 right +left side	15.13±3.86	13.57±1.43	2.13	0.019*
R2 right +left side	42.99±10.88	37.28±5.27	2.66	0.005*
R2c right +left side	44.42±12.49	37.05±5.76	3.01	0.002*

TN -subgroup of trigeminal neuralgia; HV -subgroup of health volunteers; SD -standard deviation; * -with statistical significance

Table 3 Comparison of blink reflex latencies in groups of participants for side-to side differences

Variable, side-to-side difference (ms)	TN-subgroup (mean ±SD)	HV-subgroup (mean ±SD)	t-test	p
R1 >1.2	2.01±4.23	0.88±0.74	-1.06	0.150
R2 >5.0	7.35±8.05	1.78±1.69	-2.89	0.004*
R2c >7.0	8.33±7.62	2.44±1.94	-2.99	0.003*

TN -subgroup of trigeminal neuralgia; HV -subgroup of health volunteers; SD -standard deviation; * -with statistical significance

Table 4 Comparison of latency values between right and left sides for patients (TN-subgroup)

Variable, side of stimulation (ms)	TN-subgroup (mean±SD)	Paired t-test	p
R1 right	15.65 ± 5.19	-0,74	0.472
R1 left	14.74 ± 2.33		
R2 right	42.80±11.88	-0.56	0.582
R2 left	41.17±9.40		
R2c right	41.68±12.02	-0.29	0.772
R2c left	40.81±11.16		

TN -subgroup of trigeminal neuralgia; SD -standard deviation

Table 5 Blink reflex results of latencies for patient group (TN) according to the unilateral affected side with trigeminal neuralgia

Variable, side of stimulation (ms)	TN-subgroup (mean ±SD)	t-test	p
R1 Affected side	14.50±2.62	-0,28	0.787
R1 Normal side	14.41±2.08		
R2 Affected side	43.65±10.40	-1.66	0.123
R2 Normal side	38.36±7.56		
R2c Affected side	46.52±12.94	-2.05	0.063
R2c Normal side	37.90±7.95		

TN -subgroup of trigeminal neuralgia; SD -standard deviation

Table 6 Comparison of other parameters describing the consideration of the blink reflex abnormality

Variables	TN-subgroup (n)	HV-subgroup (n)	Fischer's exact test
Presence of R1c	3	1	p=0.333
Presence of R3	7	2	p=0.054
Presence of R3c	2	2	p=1.000

TN -subgroup of trigeminal neuralgia; HV -subgroup of health volunteers; n -number of subjects

Discussion

Diversity of origin orofacial pain includes the involvement of a number of specialists in the field of neurology and dental medicine[23, 24]. Pretrigeminal neuralgia also requires differential diagnostics in order to avoid misdiagnosing the patients with TN. However, the differential diagnosis of orofacial pain is dominated by musculoskeletal pain related to the temporomandibular disorders (TMDs). Musculoskeletal pain is related to TMDs, while TN represents neuropathic pain, which most commonly affects the area of the teeth and jaws (affecting maxillary and / or mandibular branch) [25, 26]. Likewise, it was shown in our research that the rarest neuralgic pain occurred in the ophthalmic branch.

Obermann et al.[10] used a novel concentric electrode (produces only a polysynaptic R2 response) for conducting the unconventional BR procedure in order to stimulate different divisions of trigeminal nerve, (VAS pain mean 7.2; 41% of involvement of the ophthalmic branch, which is the most frequent maxillary branch in 79% of patients) between the patient sample suffering from typical and atypical TN. Stimulating all three branches of the trigeminal nerve, regardless of pain location related to affected branch of the nerve, these authors[10] found no differences in abnormalities of the blink reflex related to affected branches and delayed latencies on symptomatic side. They concluded that trigeminal nerve damage (demyelination and/or axonal dysfunction) should be situated near the root entry zone in the brainstem.

According to Cesarik et al.[12] there was a probability of BR abnormality in 85% of patients with migraine, and in 15% of asymptomatic controls. Cruccu et al.[13] compared different symptomatic and idiopathic trigeminal pain neuralgias: neurophysiological abnormalities were less prominent in patient group with idiopathic TN and the most sensitive reflex was the BR with absent R1 or delayed R1 and R2 responses. On the other hand, nociceptive afferents were involved in the reflex arc of the ultra-late latency R3 as a component of the BR evoked by noxious stimulation. However, R3 component is strongly dependent on the participant's attention, which means that it can be part of innocuous-related activation[14].

The BR is a way of monitoring the sensory part of trigeminal nerve related to microvascular decompression surgery of patients who suffer from primary TN. In 6.8% of patients, the blink reflex showed the absence of R1 on the ipsilateral side. However, the R1 remained in 83.5% of patients [15].

Mikula et al.[16] used the BR method and concluded that it can be useful in differential diagnostics: the BR may prove a significant aid in distinguishing the idiopathic TN (normal latencies R2 and R2c) and symptomatic (prolonged latencies R2 and R2c) disease types. The incidence of R3 component was higher (84%) in patients with idiopathic TN than in patients who suffered from symptomatic TN (20%), and also in subjects included in the normal control sample (40%). The prolonged latencies of late reflex components after stimulation of the afflicted side were typical of symptomatic TN. Nociceptive information is transmitted by distinct sensory afferents from those that detect innocuous stimuli. Mikula et al.[16] concluded that the functional status of the trigeminal reflex pathways is reflected trough the BR. However, various attentive, cognitive and startle effects could have affected testing results even in the controlled and standardized procedure, which was used in the current study.

One of the contributions to the determination of BR parameters (R1, R2 and R2c latencies) in normal subjects were the studies of Brooks et al.[17] and Pandey et al.[18]. In our study with younger asymptomatic sample, some higher values of the same time parameters were obtained; however these values were still statistically significantly lower than those in patients.

Mikula et al.[19] did not find a significant difference between the values of R1, R2 and R2c latencies between patients with idiopathic TN and healthy controls. However, there was a difference in the number of subjects depending on whether they had the following: a prolonged R2 duration, the occurrence of R3 latency, and the R1c occurrence (contralaterally R1) which was significantly higher in the patient group. In our recent research, there were some limitations with our smaller sample of participants, because parameter abnormalities were found to be insignificant in the HV subgroup compared to the patient TN subgroup.

Over the past decade, it has been shown that the original definition of TN does not match clinical criteria for an accurate diagnosis of orofacial pain. Highly variable clinical pictures in patients point to the fact that paroxysmal attacks can last longer than 2 minutes. Furthermore, sensory changes are strongly present in patients without any expansive processes related to cerebellopontine angle or multiple sclerosis. Addition-

ally, a positive neurovascular conflict finding is also lacking [1,7,27].

In conclusion, there is no gold standard for assessing neuropathic pain caused by idiopathic TN. In addition, the BR method can be a useful diagnostic tool to distinguish asymptomatic patients from symptomatic patients with TN. However, the limitation of this research is a relatively small sample. Maxillary and mandibular branches were most frequently affected in various combinations with, or without, the ophthalmic branch. BR latencies were significantly abnormal not only upon comparing TN-patients with healthy volunteers. The R3 component of the reflex occurred in both, the patients and healthy volunteers, and this may be explained by the fact that this component of the BR was related to noxious stimuli, likewise to innocuous stimuli.

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This article is written *in memoriam* of Professor Ivan Mikula, PhD from the Center for Neurology, Polyclinic St. Catherine, Zagreb, Croatia

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Sažetak

EVAULACIJA BLINK REFLEKSA IZMEĐU PACIJENATA S IDIOPTASKOM NEURALGIJOM TRIGEMINUSA I ZDRAVIH DOBROVOLJACA

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Svrha istraživanja bila je pronaći razlike u parametrima latencija blink refleksa (BR) između pacijenata s idiopatskom neuralgijom trigeminusa (NT) i zdravih dobrovoljaca. Prospektivna kohortna studija provedena je tijekom 2 godine. Podskupina NT uključivala je 15 pacijenata (srednja dob / SD 62, 3±10, 7 godina). Bezbolni i zdravi dobrovoljci kao podskupina HV (srednja dob / SD: 30, 8±8, 1 godina) regrutirani su od asimptomatskih studenata stomatologije. Dijagnostički parametri određeni su mjerenjem latencije do početka refleksnih komponenti od električne stimulacije. Zahvaćene su sljedeće grane trigeminalnog živca: samo maksilarna grana (26,7%), samo mandibularna grana (20%), kombinirano: oftalmička grana s maksilarnom granom (6,7%), odnosno oftalmička grana s mandibularnom granom (6,7%), kombinirana maksilarna i mandibularna grana (26,7%) i zahvaćene sve tri grane živca (13,4%). Latencije BR-a zajedno lijeve i desne strane između podskupina bile su značajno veće za vrijednosti R1 (homolateralni rani odgovor), R2 (homolateralni kasni odgovor), R2c latencije (kontralateralno izražen odgovor) u NT-podskupini ($p<0,05$). S obzirom na prisutnost R1c i R3 latencije, što se smatra abnormalnim nalazom BR-a, nije pronađena statistički značajna razlika između ispitivanih podskupina ($p>0,05$). Parametri BR-a (R1, R2 i R2c) bili su značajno abnormalni pri usporedbi NT-pacijenata sa zdravim dobrovoljcima. R3 komponenta refleksa bila je povezana sa noksičnim podražajima, a isto tako s bezazlenim podražajima.

Ključne riječi: *orofacijalna bol, trigeminalna neuralgija, blink refleks*