

The diagnostic value of pain evoked potential by electrical stimulation combined with nociceptive blink reflex in trigeminal neuralgia

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DOI: [10.31083/j.jin2002044](https://doi.org/10.31083/j.jin2002044)

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Submitted: 22 February 2021 Revised: 9 March 2021 Accepted: 12 April 2021 Published: 30 June 2021

Microvascular decompression is the first choice for treating the primary trigeminal neuralgia to provide the most extended duration of pain freedom. However, in microvascular decompression, we found that this kind of operation is only suitable for some patients. It is of great value to objectively judge the function and abnormality of the trigeminal pain conduction pathway in guiding the operation process. This brief report investigates the value of pain evoked potential by electrical stimulation and nociceptive blink reflex in trigeminal neuralgia. We detected the pain evoked potential in 34 patients with trigeminal neuralgia and 48 healthy controls treated by electrical stimulation and blink reflex. We demonstrated no significant differences in the latencies of V_1 , V_2 , V_3 , and R_2 of the affected side and the contralateral side in patients with trigeminal neuralgia. The latencies of those four indicators of the affected side in patients with trigeminal neuralgia were notably decreased compared to those on the same side in healthy controls. The receiver operating characteristic curve analysis showed that the area under curve, sensitivity and specificity of the combined diagnosis of latency and amplitude were significantly higher than the single diagnosis. The latency and amplitude of V_1 were highly sensitive, while those of V_2 was highly specific. Trigeminal neuralgia can be effectively diagnosed by combining pain evoked potential by electrical stimulation and nociceptive blink reflex. The pathogenesis of trigeminal neuralgia should be combined with peripheral pathogenicity and the theory of central pathogenicity.

Keywords

Trigeminal neuralgia; Electrical stimulation; Pain evoked potential; Nociceptive blink reflex

1. Introduction

Trigeminal neuralgia (TN), including primary TN and secondary TN, is the most common neuralgia in brain diseases or neuropathic pain [1]. It is characterized by recurrent electric shock, transient and severe pain in the area of facial trigeminal nerve distribution [2]. Globally, 15 out of 100,000 people suffer from trigeminal neuralgia [3]. In addition, it was reported that the prevalence rate of females was higher than that of males, the incidence rate of the right side was higher than that of the left side, and it was more common

in middle-aged and older people [4]. Trigeminal neuralgia seriously affects people's daily work and life and will have a specific impact on mental health [5].

Up to now, the main treatments for trigeminal neuralgia are drug therapy, including carbamazepine (CBZ) and oxcarbazepine (OXC) [6], gamma knife radiosurgery (GKRS) [7], percutaneous balloon compression (PBC) [8], glycerol rhizotomy (GR) [9], radiofrequency thermocoagulation (RFTC) [10], microvascular decompression (MVD) [11] and so on. Based on the vascular compression theory [12]. MVD is the first choice for the treatment of primary TN to provide the most prolonged duration of pain freedom [13]. However, in MVD, we found that this operation is only suitable for some patients but not for other patients [14]. Therefore, the microscopic endoscopic-assisted (MEA) technique was used when the conflict was not identified under microscopic view or was not certainly resolved. In patients with ineffective MVD, trigeminal nerve combing and partial sensory root section (PSRS) are used for treatment [15, 16]. Therefore, it is of great value to objectively judge the function and abnormality of the trigeminal pain conduction pathway in guiding the operation process. The purpose of this study was to investigate the clinical diagnostic value of pain evoked potential by electrical stimulation and nociceptive blink reflex (NBR) in TN.

2. Patients and methods

2.1 Patients

The Ethics committee approved this work based on 34 patients with TN diagnosed in our Hospital between March 2015, and May 2017 were included as the observation group. There were 14 men and 20 women aged 17 to 78 years with an average age of (54.09 ± 14.32) years. At the same time, 48 cases were randomly selected from the healthy persons who performed physical examinations in our hospital as the control group. Among them, 17 men and 31 women aged from 22 to 46 years with an average age of (30.83 ± 6.11) years. Inclusion criteria: (1) the patients met the diagnostic criteria of trigeminal neuralgia [17]; (2) the patients had no history

of craniocerebral trauma, hypertension, diabetes and other neurological diseases; (3) the patients did not receive vascular decompression treatment; (4) the subjects voluntarily participated in the study and signed the informed consent. Exclusion criteria: (1) secondary trigeminal neuralgia caused by space-occupying lesions, multiple sclerosis, etc.; (2) Patients cannot cooperate with the electrophysiological examination.

2.2 Examination of electrical stimulation of pain evoked potential and NBR

Electromyography/evoked potential instrument (Oxford Medelec Synergy Plinth) and concentric pain stimulation electrode (inomed) were used for electrophysiological measurement. The temperature of the operation room is controlled at 22–26 °C.

Before the examination, the subjects lay on their back, closed their eyes slightly and avoided eye rotation, teeth biting and swallowing. The subjects were instructed to memorize the stimulation times to concentrate on preventing interference in the experiment.

First of all, the pain stimulation thresholds of patients were determined. From 0 to 2 mA, each stimulation was increased by 0.2 mA. One round in ascending and one round in descending was performed to determine the threshold of pain stimulation. The sharp sensory threshold was 0.2–0.6 mA, and the pain sensation threshold was 0.3–1.3 mA. More than 2 mA was easy to excite deep A-b fibers. Secondly, the time course of square wave stimulation was 0.5 ms when the electrodes were placed 1 cm above the supraorbital foramen, 1 cm below the infraorbital foramen, or 1 cm outside the mental foramen. Several consecutive string stimulations (2–5) were separated by 5 ms, each series of stimulation period was 12–18 s, and the number of times of bridging was 15. Besides, the number of times of bridging can be set according to the result. Next, record the results. Pain-related evoked potentials (PREP) were located in the central zone (CZ), and the reference electrode was located on the same side of the ear. NBR was located in the bilateral infraorbital margin. Bandwidth ranged from 1 Hz to 1 kHz, sampling frequency was 2.5 kHz and scanning time was 300 ms. The data included pain evoked potential and pain induced NBR.

2.3 Assessment standard

The normal values of latency and amplitude of pain evoked potential and NBR was determined according to the standard of a healthy person in the control group.

2.4 Statistical analysis

Statistics for all data were performed using the software package Systat 10.2 (Systat Software Inc., San Jose, CA). The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm SD$). Differences of data inside the group were compared with paired *t*-test. Two independent sample *t*-test was used to compare the data with normal distribution between the two groups. In addition, the Wilcoxon rank-sum test was used to compare the data without normal distribution between the two groups. The receiver operating charac-

teristic (ROC) curve analyzed the diagnostic value of electrophysiology in trigeminal neuralgia by the receiver operating characteristic (ROC) curve. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1 Electrophysiological comparison between the affected side and the contralateral side in the observation group

The latencies of V_1 , V_2 , V_3 , and R_2 (NBR) of the affected side in the observation group were 113.04 ± 45.49 , 109.87 ± 45.27 , 111.95 ± 45.02 , 44.59 ± 33.01 , respectively. The latencies of V_1 , V_2 , V_3 , and R_2 of the contralateral side in the observation group were 105.15 ± 56.71 , 117.90 ± 17.97 , 111.38 ± 44.62 , 46.55 ± 36.59 , respectively. There were no statistically significant differences in the latencies of V_1 , V_2 , V_3 , and R_2 between the affected and contralateral sides in the observation group ($P > 0.05$). The amplitudes of V_1 , V_2 , V_3 , and R_2 of the affected side in the observation group were 24.02 ± 14.50 , 23.15 ± 17.97 , 26.73 ± 16.74 , 322.82 ± 388.86 , respectively. The amplitudes of V_1 , V_2 , V_3 , and R_2 of the contralateral side in the observation group were 22.33 ± 15.87 , 23.09 ± 11.75 , 21.93 ± 11.91 , 268.35 ± 222.82 , respectively. There were no statistically significant differences in the amplitudes of V_1 , V_2 , V_3 , and R_2 between the affected and contralateral sides in the observation group ($P > 0.05$). The results were shown in Table 1.

3.2 Electrophysiological comparison between the affected side in the observation group and the same side in the control group

The latencies of V_1 , V_2 , V_3 , and R_2 of the affected side in the observation group were 113.04 ± 45.49 , 109.87 ± 45.27 , 111.95 ± 45.02 , 44.59 ± 33.01 , respectively. The latencies of V_1 , V_2 , V_3 , and R_2 of the same side in the control group were 119.48 ± 12.94 , 118.75 ± 19.03 , 122.95 ± 24.52 , 42.55 ± 8.11 , respectively. There were no statistically significant differences in the latencies of V_1 , V_2 , V_3 , and R_2 of the same side between the control and observation groups ($P > 0.05$). The amplitudes of V_1 , V_2 , V_3 and R_2 of the affected side in the observation group were 24.02 ± 14.50 , 23.15 ± 17.97 , 26.73 ± 16.74 , 322.82 ± 388.86 , respectively. The amplitudes of V_1 , V_2 , V_3 , and R_2 of the same side in the control group were 46.65 ± 44.41 , 46.53 ± 39.09 , 38.60 ± 21.14 , 422.87 ± 272.93 , respectively. There were remarkable differences in the amplitudes of V_1 , V_2 , V_3 , and R_2 of the same side between the observation and control groups ($P < 0.01$). The results were shown in Table 2.

3.3 The value of electrophysiological indexes in the diagnosis of TN

The ROC curve analysis showed that the area under the curve (AUC), sensitivity and specificity of the combined diagnosis of latency and amplitude of V_1 , V_2 , V_3 , and R_2 were significantly higher than the single diagnosis (Table 3, Fig. 1). Furthermore, the results showed that the latency and amplitude of V_1 were highly sensitive in the diagnosis of TN, while the amplitude and latency of V_2 and R_2 were highly specific (Table 3).

Table 1. Electrophysiological comparison between the affected side and the contralateral side in the observation group.

Groups		Affected side	Contralateral side	<i>t</i> values	<i>P</i> values
Cases		34	34	-	-
Latencies (ms)	V ₁	113.04 ± 45.49	105.15 ± 56.00	0.531	0.143
	V ₂	109.87 ± 45.27	117.90 ± 17.97	0.386	0.645
	V ₃	111.95 ± 45.02	111.38 ± 44.62	0.657	0.331
	R ₂	44.59 ± 33.01	46.55 ± 36.59	0.015	0.076
Amplitudes (mV)	V ₁	24.02 ± 14.50	22.33 ± 15.87	0.043	0.981
	V ₂	23.15 ± 17.97	23.09 ± 11.75	1.143	0.067
	V ₃	26.73 ± 16.74	21.93 ± 11.91	0.194	0.952
	R ₂	322.82 ± 388.86	268.35 ± 222.82	0.595	0.148

Table 2. Electrophysiological comparison between the affected side in the observation group and the same side in the control group.

Groups		Affected side in the observation group	Same side in the control group	<i>t</i> values	<i>P</i> values
Cases		34	34	-	-
Latencies (ms)	V ₁	113.04 ± 45.49	119.48 ± 12.94	0.931	0.354
	V ₂	109.87 ± 45.27	118.75 ± 19.03	1.198	0.234
	V ₃	111.95 ± 45.02	122.95 ± 24.52	1.423	0.158
	R ₂	44.59 ± 33.01	42.55 ± 8.11	0.412	0.681
Amplitudes (mV)	V ₁	24.02 ± 14.50	46.65 ± 44.41	-	0.0001*
	V ₂	23.15 ± 17.97	46.53 ± 39.09	-	0.0001*
	V ₃	26.73 ± 16.74	38.60 ± 21.14	-	0.0001*
	R ₂	322.82 ± 388.86	422.87 ± 272.93	-	0.0001*

**P* < 0.0001, the observed group's affected side vs. the same side in the control group.

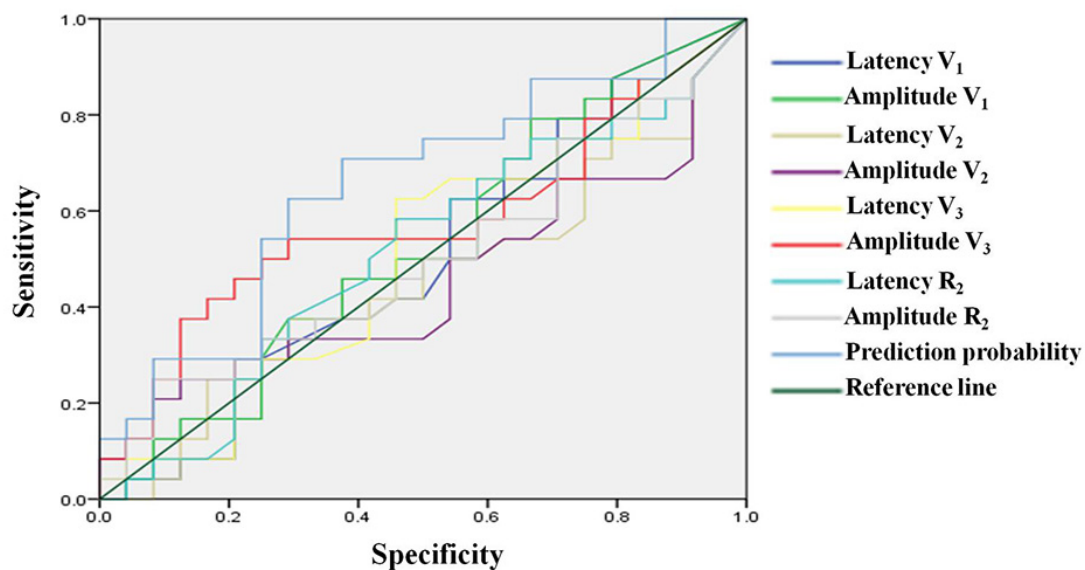


Fig. 1. ROC curve of electrophysiological indicators for diagnosis of trigeminal neuralgia.

4. Discussion

TN is a kind of recurrent neuropathic pain characterized by the sudden appearance, short duration, and acupuncture-like pain on one side of the face. It often involves one or more trigeminal nerves [18]. A previous epidemiological survey showed that the onset age of TN was mainly 37–67 years old, the ratio of male to female was about 1 : 3 [19]. At present, the pathogenesis of TN has not been clear, mainly including

“peripheral pathogenic theory” and “central pathogenic theory”. The most popular peripheral pathogenic theory is vascular compression theory, which holds that demyelination of trigeminal nerve is the key to TN [20, 21]. According to the theory of central pathogenesis, the key to TN is the impairment of the nerve fiber network and functional connection in the spinal trigeminal nucleus, brain stem, thalamus and cerebral cortex [22–24].

Table 3. The value of electrophysiological indexes in the diagnosis of TN analyzed by ROC curve.

Groups	Sensitivity	Specificity	Youden index	Standard error	AUC (95% CI)
Latency V ₁	0.79	0.29	0.08	0.085	0.500 (0.334–0.666)
Amplitude V ₁	0.79	0.33	0.13	0.084	0.526 (0.360–0.692)
Latency V ₂	0.38	0.71	0.08	0.085	0.455 (0.289–0.621)
Amplitude V ₂	0.25	0.87	0.13	0.086	0.453 (0.285–0.621)
Latency V ₃	0.63	0.54	0.17	0.085	0.505 (0.339–0.672)
Amplitude V ₃	0.54	0.71	0.25	0.085	0.576 (0.410–0.743)
Latency R ₂	0.08	0.83	0.17	0.085	0.516 (0.349–0.682)
Amplitude R ₂	0.25	0.92	0.17	0.085	0.503 (0.337–0.670)
Combined diagnosis	0.63	0.71	0.33	0.080	0.658 (0.502–0.814)

Physiological examination of pain evoked potential by electrical stimulation is a new, fast and convenient examination to judge the nerve function of patients with pain. It can stimulate the skin of the trigeminal nerve distribution area through a specially designed concentric electrode, which can excite the pain nerve fibers of the corresponding area alone to objectively judge the function and abnormality of the trigeminal pain conduction pathway [25]. Blink reflex (BR) is a critical electrophysiological method to detect trigeminal and facial nerve injury [26]. In addition, BR, including early response R₁ on the stimulation side and late response R₂ and R₂ on both sides, is a critical electrophysiological index reflecting brainstem function, which is widely used in the clinical evaluation of brainstem function [27].

We found that the latency and amplitude of V₁, V₂, V₃ and R₂ of the affected side in the observation group were not statistically significant compared to the opposite side. In addition, the latency of V₁, V₂, V₃ and R₂ of the affected side in the observation group was not statistically significant compared to that of the same side in the control group. Still, the amplitude was statistically significant compared to that of the same side in the control group. Our results suggested that the amplitudes of pain evoked potential and blink reflex were more clinically significant than the latencies. This is consistent with the previous research of some scholars. Papagianni *et al.* [28] found that the amplitude of pain evoked potential can reflect the function of pain nerve fibers. Hansen *et al.* [29] have also confirmed this point. It has been found that the R₂ amplitude of BR is significantly reduced when the brainstem level lesions cause hypoesthesia [30]. In addition, previous studies have shown that the R₂ response of blink reflex is mostly central neuropathy [31, 32]. This study also showed that the R₂ amplitude of patients with TN had significant changes in blink reflex examination. Whether a pain evoked potential or blink reflex, the latency represents demyelinating lesion, while the amplitude represents axonal lesion. Therefore, we speculated that the pathogenesis of TN could not be fully explained by the theory of vascular compression, which needed to integrate “peripheral pathogenic theory” and “central pathogenic theory”.

ROC curve analysis showed that the AUC, sensitivity and specificity of the ROC curve of the joint diagnosis of the la-

tency and amplitude of V₁, V₂, V₃ and R₂ were significantly higher than those of the single diagnosis. Therefore, combined diagnosis is more clinically useful for the diagnosis of TN. At the same time, we also found that the latency and amplitude of V₁ were highly sensitive in the diagnosis of TN, while the amplitude and latency of V₂ and R₂ were highly specific. We considered that the difference was related to the pathway of the trigeminal nerve and the site of injury. This needs to be further studied with a large number of samples in the future.

In conclusion, our results suggested that TN can be effectively diagnosed by combining pain evoked potential by electrical stimulation and BR. The pathogenesis of trigeminal neuralgia should be combined with peripheral pathogenicity and the theory of central pathogenicity.

Abbreviations

TN, Trigeminal neuralgia; OXC, oxcarbazepine; GKRS, gamma knife radiosurgery; PBC, percutaneous balloon compression; RFTC, radiofrequency thermocoagulation; MVD, microvascular decompression; PSRS, partial sensory root section; BR, blink reflex; AUC, area under curve; NBR, nociceptive blink reflex.

Author contributions

JR and GL conceived and designed the experiments; YH, YL, XZ performed the experiments; JR, YH, YL and XZ carried out clinical studies; JR analyzed the data; JR contributed definition of intellectual content and literature research; YL, XZ contributed data acquisition; JR and YH wrote the paper. GL reviewed the paper.

Ethics approval and consent to participate

The ethics committee approved this work of the Sanbo Brain Hospital, Capital Medical University. In addition, written informed consent was obtained from all individual participants included in the research.

Acknowledgment

Not applicable.

Funding

This work was supported by the Beijing Municipal Science & Technology Commission's grants/Award Number: Z141107002514152.

Conflict of interest

The authors declare no conflict of interest.

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