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Comparison of the Blink Reflex and R2 Recovery Cycle Parameters Between Blepharospasm and Healthy Subjects

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ABSTRACT

Background & Objective: The blink reflex recovery cycle indicates the excitability of interneurons in the brainstem. In this study, we aimed to investigate the blink reflex and R2 recovery cycle in patients with benign essential blepharospasm (BEB).

Materials & Methods: This prospective case-control study compared the blink reflex and R2 recovery in 18 BEB patients with 18 age- and gender-matched healthy individuals. The blink reflex was measured in a stimulation duration of 0.2 ms, and R1, R2, and R2' were recorded for all subjects. The R2 recovery cycle was measured by stimulation of the supraorbital nerve at four interstimulus intervals (ISI) of 200, 300, 500, and 1000 ms, with the same intensity as the previous test. The R2 recovery index was calculated and compared with the control group via independent sample t-test. Two-tailed P-value less than 0.05 was considered statistically significant.

Results: The blink reflex (R1, R2, and R2' responses) distal latencies and amplitudes in the BEB group were not significantly different from the control group (P>0.05). The R2 recovery index in all intervals was significantly higher in the BEB group than the control group (P=0.00). The most significant difference between the BEB and control groups regarding the R2 recovery indices was observed at ISIs of 300 and 200 ms (80.36 vs. 16.99 and 75.70 vs. 12.57, respectively). There was a negative correlation between the patient's age at the onset of disease and the R2 recovery index; however, it was not statistically significant (P>0.05).

Conclusion: Our findings showed that the R2 recovery reflex was higher in BEB patients than the normal population. Therefore, it can be a helpful index for differentiating BEB cases from psychogenic or malingering ones.

Keywords: Blepharospasm, Blink reflex, Recovery cycle

Introduction

Benign essential blepharospasm (BEB) is a focal dystonia, characterized by an increased blink rate and sustained involuntary eyelid closure that can be often long-lasting due to the bilateral hyperactivity of the orbicularis oculi muscles (1). The periocular injection of botulinum neurotoxin type A (BTX) has been approved as the first choice of treatment (2, 3). The diagnosis of BEB is based on clinical findings. However, it is sometimes difficult to differentiate it from its mimics, such as eye closure tics and psychogenic blepharospasm (4). There is a primary suspect of secondary blepharospasm in patients with atypical features, such as early and acute onset, constant spasms, or unusual response to BTX injections (5). Therefore, using a test for differentiating idiopathic blepharospasm from other causes of eyelid closure (e.g., psychogenic or malingering) can be helpful.

Some studies have shown an increase in the blink reflex recovery cycle due to enhanced excitability of brainstem interneurons in BEB, which is not influenced by BTX injections (6-8). The blink reflex, elicited by stimulation of the supraorbital nerve, is an electrophysiological analogue of the corneal reflex, which indicates the excitability of brainstem interneurons and comprises two components: R1, an early ipsilateral response mediated by the oligosynaptic pathway through the pons that is ipsilateral to the stimulation site; and R2, a late bilateral response mediated through the polysynaptic medullary pathway

(9, 10). The R1 and R2 components of the recovery cycle can be evaluated by applying two stimuli to the supraorbital nerve at varying interstimulus intervals (ISI) to determine the excitability of brainstem interneurons (10).

In the present study, we aimed to evaluate and compare the R1 and R2 responses of blink reflex and R2 recovery cycle in patients with BEB and the healthy controls.

Materials and Methods

Study Design

In this prospective case-control study, patients with a diagnosis of blepharospasm (n=18), according to the diagnostic criteria (i.e., the presence of stereotyped, bilateral, and synchronous orbicularis oculi spasms inducing narrowing/closure of the eyelids and the presence of effective sensory tricks or increased blinking) (4), were recruited from were recruited from the Movement Disorder Clinic of Rasoul-Akram Hospital in Tehran, Iran. Meanwhile, 18 individuals with no history of neurologic conditions, who were matched in terms of age and gender with the case group, were enrolled in the control group. This study was performed during 2017-2018 in Rasoul-Akram Hospital, Tehran, Iran.

The current study was approved by the Research Committee of Iran University of Medical Sciences (ethical code: IR.IUMS.SMD.REC.1396.9411158003). All participants were informed about the study objectives and methods and signed the informed consent forms before participating in the study.

Blink Reflex and R2 Recovery Cycle

For patients who had received BTX, the blink reflex test was performed three months after injections. The electromyography (EMG) recordings were documented and calculated by Natus UltraPro S100 EMG system. To evaluate the blink reflex, the subjects were requested to relax on a bed in a room with moderate temperature, while slowly closing their eyes. Data were recorded by bipolar stimulation with a double channel recorder. The surface nerve conduction study (NCS) electrodes were placed bilaterally on the orbicularis oculi muscle. The device sensitivity was 200 mV, and the duration of each stimulus was 0.2 ms. The R1, R2, and R2' responses were obtained by stimulating the supraorbital nerve on each side, and the amplitude and latency of each wave were calculated and recorded.

We evaluated the R2 recovery cycle for each subject. The R2 recovery cycle was measured by applying bilateral stimulation to the supraorbital nerves. Stimulation was applied at ISIs of 200, 300, 500, and 1000 ms. To minimize habituation, we considered 50-60 seconds of rest between the stimuli. The intensity of all stimuli was recorded at the lowest intensity, reaching the response threshold. The R2 recovery index was calculated for each bilateral stimulation at each ISI, according to the data recorded by the device. This index measures the ratio of R2 amplitude in the first stimulation (condition) to the R2 amplitude in the second stimulation (test).

Statistical Analysis

Qualitative and descriptive analysis for demographic characteristics were reported as mean±standard deviation (SD) (11, 12). To compare variables between case and control groups, independent sample t-test was used (13, 14). The Kolmogorov–Smirnov test was used to assess the normal distribution of variables (14). Pearson's correlation test was performed to show correlation of variables and outcomes (15, 16). The two-tailed P-value<0.05 was considered as statistically significant. All statistical analysis was performed using Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, Ill., USA).

Results

In this study, 36 participants (18 females and 18 males) with an average age of 57.61 years (range: 39-72 years) were recruited. The mean age of the BEB group (9 females and 9 males) was 57.67±9.60 years, and the mean age of the control group (9 females and 9 males) was 57.67±10.01 years. There was no significant difference in terms of age or gender between the two groups. Also, the mean duration of disease was 3.67±3.21 years in BEB group. Family history of the disease was negative in all participants. Only one patient had a positive drug history of neuroleptics (5%). Overall, 77% of patients had been previously treated with BTX (n=14).

Table 1. Blink reflex responses

Values		BFS (n=18)	Control (n=18)	P-value
Distal latency	RT R1(ms)	12.09±1.37	11.82±0.95	0.50
	RT R2(ms)	36.56±5.23	34.44±3.35	0.16
	RT R2'(ms)	37.63±5.69	37.03±4.13	0.72
	LT R1(ms)	11.97±1.28	13.57±7.20	0.36
	LT R2(ms)	37.45±5.31	35.25±2.79	0.13

Values		BFS (n=18)	Control (n=18)	P-value
	LT R2'(ms)	38.06±5.42	37.76±3.22	0.84
Amplitude	R1	0.27±0.54	0.28±0.50	0.70
	R2	0.16±0.32	0.18±0.33	0.87
R2 recovery index	1000 ms	90.17±13.19	68.88±11.05	0.00**
	500 ms	86.17±12.44	41.22±8.65	0.00**
	300 ms	80.36±13.01	16.99±11.56	0.00**
	200 ms	75.70±12.20	12.57±10.27	0.00**
Stimulus Intensity (mA)		12.96±1.54	13.20±1.89	0.68

** P-value <0.05

The results of blink reflex analysis and comparisons between the two groups have been summarized in Table 1. There were no significant differences in R1, R2, and R2' distal latencies between the groups (*P*>0.05) (Table 1). There was no significant difference in the amplitude of R1 or R2 response (*P*>0.05) (Table 1). The stimulus intensities were 13.20±1.89 mA and 12.96±1.54 mA in the control and BEB groups, respectively, indicating no significant difference (*P*>0.05). please change number 2 to 1 (Table 1) The R2 recovery index was improved in all patients at all four ISIs (1000, 500, 300, and 200 ms) (Table 1). The most remarkable improvement was observed at 200 and 300 ms intervals (75.70 vs. 12.57 and 80.36 vs. 16.99, respectively) (Figure 1).

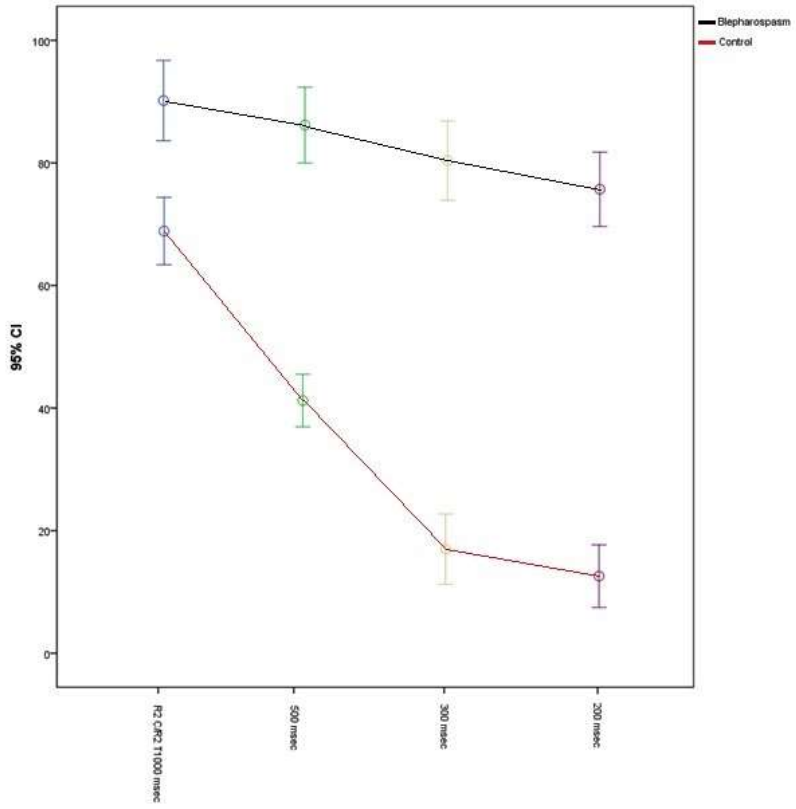

Figure 1. R2 Recovery Index

R2 recovery index in controls and patients with blepharospasm. Means are shown for the R2 amplitude at the first stimulus (condition) to the R2 amplitude at the second stimulation (test). Data is shown as Mean ± Standard deviation (SD). X-axis: interstimulus intervals (ISI) in milliseconds. Y-axis: ratio of the conditioned to the tested amplitude of R2 response in percent

Discussion

In the current study, we evaluated the blink reflex at least three months after the injection of BTX for a more consistent investigation. However, the literature suggests that BTX injection has no significant effect on the excitability of brainstem interneurons, which mediate the R2 response of the blink reflex circuit **(2, 6, 7)**. In the present study, the stimulus intensity to elicit blink reflex responses was 12.96 mA in the BEB group and 13.2 mA in the control group, which is not significantly different. This intermediate stimulus intensity (12 mA) was also reported by Sommer *et al.* as the most appropriate intensity to indicate differences in responses between the control and BEB groups **(17, 18)**.

The R1 and R2 components of blink reflex have been appraised in previous studies, and no significant difference has been reported between the BEB and control groups. Also, the peak amplitude of the cycles showed no significant difference between the BEB and control groups **(10)**. In the present study, the R1 and R2 amplitudes were not significantly different between the BEB and control groups. Also, there was no significant difference between the BEB and control groups in the distal latencies of R1, R2, and R2′ circuits, which is in line with previous studies **(5, 18)**.

The significant increase in R2 recovery has been reported in parkinsonism, hemifacial spasm, cervical dystonia, and focal dystonia **(10, 19)**, including BEB at all stimulation intervals **(10, 18, 19)**. In this regard, Schwingenschuh *et al.* demonstrated the significant enhancement of the R2 recovery component in BEB patients, compared to the controls and patients with atypical presentations of BEB, suggesting psychogenic blepharospasm **(5)**. Our findings revealed that the R2 recovery reflex was enhanced in BEB patients. Previous studies have attributed the increased blink reflex excitability in blepharospasm to the abnormal function of brainstem interneurons. This finding suggests that a pathology in the basal ganglia dopamine system mediates the blink reflex excitability by inhibiting the superior colliculus **(7, 20, 21)**.

However, recent studies have shown that BEB is more likely to be associated with abnormal neural pathways **(22, 23)**, and owing to its different manifestations, different pathologies have been suggested for the disease **(22)**. The different abnormalities in the excitability of various R2 recovery cycles suggest two hypotheses. First, BEB has different subtypes with different severities and pathophysiological mechanisms; and second, different groups of BEB with different severities have a common pathophysiology **(1)**. In this regard, Ferrazzano *et al.* suggested a common pathophysiological mechanism. However, the recovery cycle of the blink reflex deteriorated with the disease progression **(24)**.

Previous studies on patients with blepharospasm have indicated an abnormal R2 recovery index, as well as hemi-facial spasm, post-facial syndrome, segmental cranio-cervical dystonia, and torticollis **(9, 10, 19)**. In this regard, Yaman *et al.* found the most significant difference in the R2 recovery index at an interval of 200 ms and the smallest difference at an interval of 800 ms **(19)**. Similarly, our comparison of the blink reflex recovery cycle between the BEB and healthy groups at ISIs of 200, 300, 500, and 1000 ms indicated the significant improvement of the R2 recovery index in the BEB group, which was the most significant at intervals of 200 and 300 ms. Some previous studies have reported similar results, indicating an abnormal R2 recovery index in the majority of blepharospasm patients **(5, 9, 10, 18, 24)**. The upper limit of normal for the index was defined as the mean value plus 2 or 2.5 SDs of the values obtained from healthy subjects in some studies. In a study by Schwingenschuh *et al.*, 90% of patients with blepharospasm showed an abnormal R2 recovery index. They argued that the R2 recovery index is a helpful diagnostic tool to distinguish BEB from psychogenic blepharospasm, with 90% specificity and 100% sensitivity **(5)**.

The mean duration of BEB was 3.67±3.21 years in the patients, which was not significantly correlated with the R2 recovery index. However, further investigations with a longer follow-up period are needed to compare the R2 recovery index over time. Also, we found no significant correlation between the age of disease onset and the R2 recovery index. This finding was supported by earlier reports, which indicated no significant correlation between the R2 index and the duration of disease, severity of disease, or age **(10)**.

Conclusion

The findings of this study revealed that the R2 recovery reflex was higher in BEB patients than the controls. Therefore, it can be a suitable tool for diagnosing and differentiating BEB from its mimics.

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Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

Authors declared no conflict of interest.

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