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Blepharospasm Patients after Botulinum Toxin – Sleep Approach

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Abstract

Background Blepharospasm is a focal dystonia that affects the orbicularis oculi muscles. The interest in nonmotor symptoms is due to their impact on quality of life.
Objective We evaluated the frequency of sleep disorders and circadian rhythm in a sample of Brazilian blepharospasm patients.
Methods A total of 51 patients, who met the clinical criteria for blepharospasm, evaluated by 2 specialists in movement disorders, were recruited from the outpatient clinic for movement disorders of two reference centers in the city of São Paulo: Universidade Federal de São Paulo and Hospital do Servidor Público do Estado de São Paulo. The selected 13 patients were evaluated from 13 days before to 13 days after using botulinum toxin. They were interviewed, underwent physical examination and actigraphy, and completed sleep diaries.
Results After using botulinum toxin, the group that reported sleep improvement exhibited a 50% decrease in sleep latency. There was no change in restless leg syndrome or circadian rhythm. Patients who reported no sleep improvement after using botulinum toxin presented poorer synchronization of the light-dark cycle.
Conclusion Blepharospasm patients have poor sleep quality. About 50% of the patients had sleep improvement after using botulinum toxin. The synchronization of the light-dark cycle should be influenced by this finding.

Keywords
- blepharospasm
- sleep
- dystonia
- circadian rhythm
- actigraphy

Introduction

Blepharospasm is a form of focal dystonia characterized by hyperactivity of the orbicularis oculi muscle and the muscles around the eyes, resulting in bilateral, synchronous, and symmetrical, sustained muscle spasms, and partial or total closure of the eyelids. The prevalence ranges from 20 to 133 cases per 1 million inhabitants, depending on the geographic region, predominantly occurring in females.[1] Age appears to be the leading risk factor. Other risk factors include a high level of urbanization, occupation in executive and labor-intensive industries, sleep disorders, psychiatric disorders, dry eye diseases, systemic disorders (systemic arterial hypertension and dyslipidemia), Parkinson's disease, and

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rosacea.[2] Recently, computer vision syndrome has also been identified as a risk factor.

Botulinum neurotoxin is considered the first line drug in the treatment of blepharospasm. It works by causing flaccid paralysis of the orbicularis oculi muscle temporarily. After local infiltration of botulinum neurotoxin into the synaptic space, the light chain is internalized and cleaves the SNARE proteins required for exocytosis of acetylcholine, resulting in a nonfunctional complex and attenuation of extracellular neurotransmitter release. Diminished acetylcholine release decreases the probability of firing an action potential required for muscle fiber contraction and results in localized flaccid paralysis.[3]

Data in the literature about sleep quality after treatment of primary dystonias are restricted, with clinical and methodological heterogeneity.[4,5] To evaluate sleep disorders in patients with blepharospasm, the patients were recruited at an outpatient clinic for movement disorders in the city of São Paulo, state of São Paulo, Brazil. The evaluation was subjective, using questionnaires and sleep diaries, and objective, using actigraphy.

Material and Methods

Participants and Procedures

A cross-sectional study was conducted in the outpatient clinic for movement disorders. This outpatient clinic was in operation under the Department of Neurology of the Universidade Federal de São Paulo (UNIFESP-EPM, in the Portuguese acronym) from April 2016 to May 2018 and the Hospital do Servidor Público Estadual (HSPE-SP, in the Portuguese acronym) from May 2018 to May 2019.

A total of 51 blepharospasm patients were recruited, but only 13 were selected for the study. Patients who met the selection criteria were >18 years old, met the clinical criteria for blepharospasm, and were evaluated by 2 specialists in movement disorders. The exclusion criteria were illiteracy, previous history of exposure to neuroleptics, presence of other neurological abnormalities, blepharospasm secondary to central nervous system (CNS) injury, and concomitance with other dystonia. All patients received botulinum toxin A 500 U. The total dose injected for both eyes together ranges from 160 to 200 U. Four injections in the *orbicularis oculi* muscle and one injection in corrugator.

All patients had temporary improvement of blepharospasm with botulinum toxin in previous treatments and signed the Helsinki informed consent form. The data collected included questionnaires, physical examination, sleep diaries, and actigraphy results during the outpatient follow-up. The Ethics Committee of UNIFESP – Hospital São Paulo approved the present study.

Measures

Physical Examination and Epidemiological Questionnaires

The patients were evaluated 6 months after the last use of botulinum toxin and 13 days before the subsequent treatment. They were interviewed to document demographic information, comorbidities, use of medications, smoking habits, alcohol consumption, caffeine use, and sleep environment.

Evaluation Instruments

Thirteen days before and 13 days after using botulinum toxin, patients gauged the intensity of the blepharospasm based on the Jankovic Rating Scale. To identify sleep disorders, patients completed the Epworth sleepiness scale, the Pittsburgh sleep quality index (PSQI), the WHOQOL-BREF method (quality of life), the insomnia severity index, the BERLIN questionnaire (assesses the risk of sleep-disordered breathing), the hospital depression and anxiety scale, the Beck depression inventory (BDI), and the Horne and Ostberg morningness-eveningness questionnaire (determines chronotype).

Actigraphy and Sleep Diary

After an interview and evaluation, the patients received the actigraph unit and the first sleep diary, in which they documented, for 13 days, the time they slept, woke up, and napped throughout the day. They received the second sleep diary on the day botulinum toxin treatment was administered. In the second diary, patients were to document when the medication began to take effect on blepharospasms and any changes in sleep. After 13 days, they returned both the actigraph unit and the sleep diaries.

Statistical Analysis

The results of the patients' questionnaires, notes from the sleep diaries, and data obtained from the actigraph were tabulated in a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet and exported to IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). The results were analyzed with descriptive statistics, yielding percentages, means, and frequencies.

The comparison of scores between the tests before and after treatment with botulinum toxin was statistically analyzed with the Fisher exact chi-squared test, the Mann-Whitney and Wilcoxon nonparametric U tests, and the Spearman correlation. A $p < 0.05$ was considered significant in discovering the relationship strength between the variables associated with sleep and the circadian cycle.

Results

Sample and Sociodemographic Characteristics

Of the 13 patients evaluated, 10 were female (76.9%) with a mean age of 68.62 ± 5.93 years old. The patients had been diagnosed with blepharospasm for a mean of 12.77 ± 5.23 years. Seven (53.8%) were professionally active. Eleven were of Caucasian descent (84.6%). The average body mass index (BMI) was 27.1 (standard deviation [SD] = 5.6). The most prevalent comorbidities were systemic arterial hypertension (53.8%) and diabetes mellitus (30.8%).

Of these, 69.2% of the patients consumed less than three cups per day. Mobile phones, tablets, or television sets were

Table 1 Results of the scales used with patients before and after the treatment with botulinum toxin.

Tests used (categorical variables)		Initial evaluation	Evaluation after treatment	*p-value*
INSOMNIA	Without Mild Moderate	9 (69.2%) 2 (15.4%) 2 (15.4%)	9 (69.2%) 2 (15.4%) 2 (15.4%)	0.005
BERLIN	No risk	6 (46.2%)	5 (38.5%)	0.005
BECK	Minimum Mild Moderate	8 (61.5%) 2 (15.4%) 3 (23.1%)	9 (69.2%) 1 (7.1%) 3 (23.1%)	0.004
HORNE/OSTBERG	Moderate eveningness Intermediate Moderate morningness Morningness	1 (7.7%) 2 (15.3%) 5 (38.5%) 5 (38.5%)	1 (7.7%) 3 (23.1%) 3 (23.1%) 6 (46.1%)	0.001
Spasm intensity	Absent Increased blinking at external stimuli Mild spasm. not incapacitating Moderate spasm with mild incapacitation Severely incapacitating spasm	——— ——— 1 (7.7%) 8 (61.5%) 4 (30.8%)	3 (23.1%) 6 (46.2%) 3 (23.1%) 1 (7.7%) ———	0.005

Tests used: Chi-squared and Fisher's exact ($n \leq 5$)

present in 84.6% of the cases in the sleep environment. Most patients did not use psychotropics (69.2%) or alcoholic beverages (92.3%).

Scales Used to Evaluate Sleep, Psychiatric Disorders, and Chronotype

►**Table 1** lists the scales and indices that produced statistically significant results ($p < 0.05$).

Four patients (30.8%) reported mild to moderate insomnia, but no improvement was noted after using the toxin. The majority of the patients had a morning chronotype. The Berlin questionnaire identified 7 patients (53.8%) at an increased risk for developing obstructive sleep apnea (OSA).

The Beck depression scale showed that 8 patients (61.5%) had a minimum score for depression. After the treatment with botulinum toxin, one patient with mild depression improved; however, the other seven patients reported no improvement.

Before using the botulinum toxin, 8 patients (61.5%) had moderate spasms with mild incapacitation, and 4 (30.8%) had severe debilitating cramps. After treatment, 6 patients (46.2%) presented with only increased blinking at external stimuli, and 3 (23.1%) presented with no spasms.

The quality of sleep was poor in 61.5%, and 38.5% met the criteria to be diagnosed with restless leg syndrome. There was no significant improvement after using botulinum toxin ($p = 0.055$).

The patients scored > 60% in all domains of quality of life assessed by the World Health Organization Quality of Life Instruments (WHOQOL-BREF) method. There was a statistically significant difference ($p < 0.05$) in domains 3 (social relations) and 4 (environment) after the use of botulinum toxin.

The variables were correlated before and after using botulinum toxin to evaluate the interaction between psychological disorders (anxiety and depression), insomnia, chronotype, and intensity of spasm on the quality of sleep. Depression and the PSQI showed a moderate positive correlation.

Sleep Diary and Actigraphy

The comparison of sleep variables between the sleep diary and actigraphy showed a significant statistical difference ($p > 0.05$) in almost all parameters (►**Table 2**).

After the treatment with botulinum toxin, 7 patients (53.8%) reported improved sleep when they were asked about this on the sleep diary.

After using the botulinum toxin, the group that reported sleep improvement had a 50% reduction in sleep latency. The patients' self-perception of sleep was analyzed through the efficiency of sleep by actigraphy. Approximately 50% had an adequate perception of their sleep.

Circadian Rhythm

The analysis of the circadian rhythm in terms of rest-wake rhythm used nonparametric variables: intraday variability (IV), interdaily stability (IS), the least active five-hour period (L5), the most active ten-hour period (M10), and rhythm amplitude (RA).[6] No statistically significant differences ($p < 0.05$) were seen before and after using botulinum toxin in these variables. Only the analysis of improvement in sleep perception using data from the sleep diaries showed a significant difference ($p < 0.05$) in IS, before the use of botulinum toxin, and in RA, after the use of botulinum toxin (►**Table 3**).

Discussion

Of the 13 patients evaluated, most were female (76.9%), and the mean age was 68.62 years old (SD = 5.93). The patients

Table 2 Comparison of sleep diary and actigraphy results before and after the use of botulinum toxin.

		Sleep diary	Actigraphy	P-value
Initial total sleeping time (hours)	Mean ± SD Median	7.6 ± 1.4 8	6.7 ± 0.9 6.5	0.016
Initial latency (minutes)	Mean ± SD Median	47.3 ± 56.3 15	15.8 ± 13.8 15	O.050
Efficiency	Mean ± SD	90.4 ± 11.1	82.8 ± 7.3	0.016
Total sleeping time after treatment (hours)	Mean ± SD Median	7.6 ± 2.0 7	6.7 ± 0.7 6.4	0.084
Latency after treatment (minutes)	Mean ± SD Median	34.6 ± 45.9 20	13.7 ± 7.8 11	0.043
Efficiency (%) after treatment	Mean ± SD Median	92.4 ± 8.3 94.5	82.9 ± 5.9 82.0	0.003

Abbreviation: SD, standard deviation.
Wilcoxon Nonparametric Test

Table 3 Evaluation of circadian rhythm before and after the use of botulinum toxin with perception of sleep improvement (sleep diary).

	With perception of improvement ($n = 7$)	Without perception of improvement ($n = 6$)	*p-value*
IS (before)	0.72(0.73 ± 0.10)	0.52(0.51 ± 0.20)	**0.046**
IS (after)	0.67(0.66 ± 0.13)	0.59(0.60 ± 0.19)	0.391
IV (before)	0.48(0.56 ± 0.13)	0.72(0.73 ± 0.24)	0.153
IV (after)	0.63(0.58 ± 0.12)	0.66(0.66 ± 0.19)	0.391
M10 (before)	250528.17 (237645.57 ± 105601.03	200991.41 (188861.89 ± 60856.10)	0.317
M10 (after)	218496.67 (224768.64 ± 95576.28)	177922.50 (180406.31 ± 32489.68)	0.391
L5 (before)	2869.67 (3445.21 ± 2225.62)	5752.67 (5525.02 ± 2091.47)	0.086
L5 (after)	3791.33 (3742.19 ± 1561.38)	5271.25 (5456.42 ± 2153.12)	0.153
RA (before)	0.97(0.97 ± 0.15)	0.95(0.93 ± 0.05)	0.086
RA (after)	0.97(0.96 ± 0.02)	0.94(0.94 ± 0.03)	**0.046**

Abbreviations: IS: interdaily stability; IV: intradaily variability; L5: least active 5-hour period; M10: most active 10-hour period; RA: rhythm amplitude.
Mann-Whitney Nonparametric Test
Median (Mean ± SD)

were diagnosed with blepharospasm on average 12.77 years ago. These demographics are similar to those of previous studies reported in the literature.[2,7–9] In our sample, 61.5% of the patients were nonsmokers, and 69.2% reported daily consumption of fewer than three cups of coffee. Systemic arterial hypertension (53.8%) and diabetes mellitus were the most common comorbidities. There are few reports in the literature on cardiovascular risk factors associated with blepharospasm. These results corroborate the retrospective study by Lee et al.[10] Another retrospective epidemiological study with 1,325 blepharospasm patients in Taiwan showed systemic arterial hypertension followed by dyslipidemia as the most common systemic disease associated with blepharospasm in highly urbanized areas. In such regions, executive workers and stressful lifestyles are predominant; having computer vision syndrome is another risk factor for blepharospasm.[2] The presence of a cell phone, TV, or tablet in the sleep environment was identified in 84.6% of the patients in our sample. However, it is challenging to associate computer vision syndrome as a risk factor for the disease since, on average, the patients were diagnosed 12.77 years ago, when electronic devices were not as popular.

Nine patients (69.2%) described poor sleep quality (score > 5) measured by the PSQI before and after the use of botulinum toxin. It is unclear whether the poor quality of sleep is secondary to depression. A total of 23.1% of the patients scored for moderate depression in the present study and 15.4% for mild depression. The low rate of depression found in the present study was also reported by Yang et al.[11] A review by Defazio et al. defined depression as a psychiatric

disorder inherent to blepharospasm, but the relationship between blepharospasm and anxiety requires future studies.[1] Avanzino et al.[4] reported no correlation between BDI and PSQI scores in a case-control study. There are no reports in the literature on the use of the Berlin Questionnaire, a screening method for OSA, for patients with blepharospasm or other types of dystonia. Of the 13 patients, 7 (53.8%) were at risk for OSA. Since intermittent oxygen desaturation leads to sleep fragmentation, diagnosing OSA in these patients is essential.

The Horne & Ostberg questionnaire showed that 77% were morning patients. Sunlight is the primary excitatory stimulus for the suprachiasmatic nucleus, synchronizing light-dark cycles. Since orbicularis oculi muscle spasms compromise proper eye-opening, there may be reduced entry of light into the retina of these patients. To evaluate the circadian rhythm, the patients used the actiwatch unit for >7 days before and after using botulinum toxin.

A systematic review of sleep disorders in primary dystonia revealed several studies on cranial focal dystonia that used self-evaluation scales and 3 studies that used polysomnography for up to 3 days. The results are conflicting about sleep architecture and sleep continuity disorders.[3] There are no reports of actigraphy studies in the literature for such patients. Actigraphy can evaluate sleep efficiency, total sleep time, sleep latency, wake after sleep onset (WASO), and sleep-wake patterns. Although the patients with blepharospasm had made an estimative with higher values though the sleep diary and the PSQI, mainly for sleep latency and efficiency, the actigraphy showed a reduction in total sleep time, a slightly reduction of the sleep efficiency and a normal latency to non-REM sleep. This difference can be attributed to misperception that occurs in the advanced age group of these patients. The actigraphy verified that the patients who reported sleep improvement after toxin administration (on their sleep diary) had a 50% reduction in sleep latency. However, the PSQI assesses sleep only for the previous month, and a more accurate record of the effect of the botulinum toxin may be lost.

Analysis of circadian rhythm variables showed no statistically significant differences before and after using botulinum toxin. The only difference in the two variables was intermediary stability (IS) and rhythm amplitude (RA). Patients who reported no sleep improvement after using botulinum toxin presented with worse light-dark cycle synchronization. Intermediary stability increased in this group after using botulinum toxin, but it was not significant. Likewise, the RA was higher in the patients who reported improved sleep.

Botulinum toxin injection has been used to treat patients with bruxism and sleep complaints. The local action, which weakens muscle contraction by interrupting acetylcholine neurotransmission to the muscles, is the most known mechanism.[12] However, a few authors describe an action through supraspinal mechanisms with inputs on the sensorimotor cortex and consequent reorganization of the cerebral cortex in patients after stroke. It is possible that this central action can influence sleep characteristics and quality of life in these patients.[13,14]

Although there are no studies in the literature on actigraphy or circadian rhythm related to dystonia, the main limitations of the present study were the small sample size and a lack of polysomnography. A few more studies must be done to explain the impact of botulinum toxin in the sleep of patients with this kind of dystonia.

Conclusion

The present study suggests that blepharospasm patients suffer from poor sleep quality. There was a low prevalence of anxiety and depression and minimal use of psychotropics among patients, suggesting that poor sleep quality cannot be secondary to these factors. About 50% of the patients had an increased risk for OSA. Actigraphy showed a reduction in total sleep time, while the sleep diaries decreased sleep efficiency with improvement after botulinum toxin treatment. There was no change in the activity-rest rhythm after using botulinum toxin.

Conflict of Interests

The authors have no conflict of interests to declare.

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References

1 Defazio G, Hallett M, Jinnah HA, Conte A, Berardelli A. Blepharospasm 40 years later. Mov Disord 2017;32(04): 498–509.
2 Sun Y, Tsai PJ, Chu CL, Huang WC, Bee YS. Epidemiology of benign essential blepharospasm: A nationwide population-based retrospective study in Taiwan. PLoS One 2018;13(12):e0209558.
3 Hwang CJ, Eftekhari K. Benign Essential Blepharospasm: What We Know and What We Don't. Int Ophthalmol Clin 2018;58(01): 11–24.
4 Avanzino L, Martino D, Marchese R, et al. Quality of sleep in primary focal dystonia: a case-control study. Eur J Neurol 2010;17 (04):576–581.
5 Hertenstein E, Tang NK, Bernstein CJ, Nissen C, Underwood MR, Sandhu HK. Sleep in patients with primary dystonia: A systematic review on the state of research and perspectives. Sleep Med Rev 2016;26:95–107.
6 Gonçalves BS, Adamowicz T, Louzada FM, Moreno CR, Araujo JF. A fresh look at the use of nonparametric analysis in actimetry. Sleep Med Rev 2015;20:84–91.
7 Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28(07):863–873.
8 Hallett M, Evinger C, Jankovic J, Stacy MBEBRF International Workshop. Update on blepharospasm: report from the BEBRF International Workshop. Neurology 2008;71(16):1275–1282.
9 Peckham EL, Lopez G, Shamim EA, et al. Clinical features of patients with blepharospasm: a report of 240 patients. Eur J Neurol 2011;18(03):382–386.
10 Lee JM, Baek JS, Choi HS, Kim SJ, Jang JW. Clinical Features of Benign Essential Blepharospasm in Korean Patients. Korean J Ophthalmol 2018;32(05):339–343.

11 Yang J, Song W, Wei Q, et al. Screening for Cognitive Impairments in Primary Blepharospasm. PLoS One 2016;11(08):e0160867.
12 Ali SM, Alqutaibi AY, Aboalrejal A, Elawady DM. Botulinum toxin and occlusal splints for the management of sleep bruxism in individuals with implant overdentures: A randomized controlled trial. Saudi Dent J 2021;33(08):1004–1011.
13 Veverka T, Hluštík P, Otruba P, et al. Cortical somatosensory processing after botulinum toxin therapy in post-stroke spasticity. Medicine (Baltimore) 2021;100(25):e26356.
14 Weiss D, Hieber L, Sturm J, et al. Health-related quality of life outcomes from botulinumtoxin treatment in blepharospasm. Clin Neurol Neurosurg 2018;172:130–133.

