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Original Scientific Paper

THE EFFECT OF BOTULINUM TOXIN TYPE A IN PATIENTS WITH ESSENTIAL BLEPHAROSPASM

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SUMMARY – The aim of this study was to determine the effect of botulinum toxin type A and satisfaction in patients with essential blepharospasm. The study included 12 subjects suffering from essential blepharospasm who received therapy with botulinum toxin type A injections. Respondents were given a *Blepharospasm Disability Index* (BSDI) survey before and three weeks after the procedure with questions related to quality of life. They were also given a *Jankovic Rating Scale* with questions related to the severity and frequency of symptoms. The overall level of difficulties was reduced, meaning the quality of life increased after the application of botulinum toxin, and the study found that the increase was statistically significant (p = 0.003). The severity of symptoms after the application of botulinum toxin was reduced, which meant that there was a decrease in the severity of the difficulties, and the study found a statistically significant difference (p=0.003). The frequency of symptoms was reduced after botulinum toxin administration, and the study revealed a statistically significant difference (p = 0.012). From the results of this study, we can determine that the use of botulinum toxin type A increases the quality of life and that the severity and frequency of symptoms are statistically significantly reduced.

Key words: *notulinum toxin type A; essential blepharospasm; dystonia; Blepharospasm Disability Index; Jankovic Rating Scale*

Introduction

Benign essential blepharospasm is a focal dystonia characterized by involuntary eyelid closure. It is relatively rare disease which occurs between the fifth and seventh decade of life, and the risk of developing the disease increases with age. The etiology of primary blepharospasm is thought to be multifactorial and involves a complex interaction of genetic predisposition and environmental factors. Initially, it may be unilateral, but it usually affects both of the orbicularis oculi muscles, causing significant disability[1-4]. Symptoms of blepharospasm often begin as excessive eye twitching and blinking usually followed by a feeling of dryness or eye irritation[5].

Patients with blepharospasm may have other motor manifestations, including apraxia of eyelid opening characterized by a temporary failure to voluntarily reopen the eyes without obvious spasm of the orbicularis oculi muscle and despite continuous contraction of the frontal muscle[6]. Blepharospasm is also characterized by nonmotor symptomatology that includes sensory symptoms, psychiatric disorders, sleep disorders, and cognitive impairment[3]. Although blepharospasm is not usually task-specific, like other dystonias it may

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have task-specific exacerbations that may occur after exposure to bright light, reading, watching television, or using a computer[1].

The diagnosis of blepharospasm is based on medical history and clinical characteristics. The lack of validated diagnostic criteria sometimes makes it difficult to distinguish blepharospasm from other conditions of involuntary eyelid closure. It can be diagnosed several years after the first symptoms appear, delaying the start of treatment[7]. There are several treatment options for blepharospasm, including oral pharmacotherapy, botulinum toxin injections, and surgical treatment[8]. Standard therapy in the treatment of blepharospasm is the administration of botulinum neurotoxin type A injections which are best for short-term relief of symptoms[9]. Botulinum toxin is used in the treatment of disorders characterized by excessive muscle contraction, hypersecretory disorders of the autonomic nervous system, and pain disorders, and is also used for cosmetic purposes[10,11].

This study aimed to determine the effect of botulinum toxin type A and satisfaction in patients with essential blepharospasm. We hypothesized that injection of botulinum toxin type A significantly reduces symptoms and improves quality of life in patients with essential blepharospasm.

Patients and methods

We examined 12 patients aged 49 to 86 diagnosed with essential blepharospasm. Prior to the start of the study, all patients signed informed consent and the study was approved by the local Ethics Committee. All procedures were performed according to the 1964 Declaration of Helsinki. The research was conducted at the Department of Ophthalmology of University Hospital Center Split between December 2019 and June 2021. All patients underwent neurological examination and were diagnosed with essential blepharospasm. We excluded patients under the age of 18, patients without prior neurological examination, and those who were allergic to the drug.

Patients were given a *Blepharospasm Disability Index* (BSDI) survey before and three weeks after injections of botulinum neurotoxin type A. The survey contains questions related to quality of life covering difficulties in reading, driving a vehicle, watching television, doing everyday activities, walking, and shopping in the store. Patients rated the difficulty level on a scale of 0 to 5, with 0 being no impairment and 5 being no longer possible due to illness or rated as non-applicable. They were also given the *Jankovic Rating Scale* (Jankovic and Orman, 1987), consisting of two subscales relating to the severity and frequency of symptoms. The subscales consist of 5 points ranging from 0 to 4, where 0 means no symptoms and 4 indicates the most severe or most common symptoms[12].

Botulinum toxin type A (Botox), Allergan USA, packaged in a bottle of 100 IU, was used. The drug was diluted with 4 mL of saline so that there were 25 units of the drug in an insulin syringe with an integrated one-milliliter needle. All patients received 25 units per side (50 units per patient), at five points (5 units per point) subcutaneously in two places on the upper eyelid, then in the central region of the *m. orbicularis oculi* on the lower eyelid and at two points in the lateral part of the muscle. Prior to injection, the skin was cleansed with 70% alcohol. After application, the patients were given a cold compress on the eyelids. A follow-up examination and survey were conducted three weeks after application when the greatest effect of the drug was expected.

Statistical analysis

Statistical data processing was performed using the Statistica 12 program (StatSoft Inc., Tulsa, OK, USA). Numerical values are presented using the methods of descriptive statistics, namely the median as the mean, and the interquartile range as an indicator of the scatter around the mean. The difference test was performed by the Wilcoxon test for repeated measurements, which examines whether there is a statistically significant change in the values in the repeated measurements compared with the initial measurement. The significance level $p < 0.05$ was used as a statistically significant difference.

Results

Of the 12 respondents included in this experimental prospective study, 11 were women (92%) and 1 was a man (8%).

Most of the respondents were in the age group 61-70 and 71-80 years, which represented 8 respondents (4x2), while there was only one respondent in the age groups 41-50 and 51-60 years.

In the first survey, the Blepharospasm Disability Index, which examines quality of life and includes difficulties in reading, driving a vehicle, watching televi-

sion, doing everyday activities, shopping and walking, patients rated the difficulty level on a scale of 0 to 5.

The mean value of reading difficulties was reduced, and the study found a statistically significant difference (3.0 (2.5-3.5) vs. 1.5 (1.0-2.0); p = 0.003). Of the 12 patients observed before botulinum toxin therapy, two subjects (2/12) confirmed that they were unable to drive due to illness, and one continued to drive without difficulty after treatment, while the other stopped driving. Difficulties in watching television decreased after the application of botulinum toxin, and the study found a significant difference (3.0 (2.5-3.5) vs. 1.0 (0.5-2.0); p = 0.003). The level of difficulty in doing everyday activities was reduced after the application of botulinum toxin, but the difference was not statistically significant (2.0 (2.0-3.0) vs. 1.0 (0.0-2.0); p = 0.097). Difficulties in shopping in the store were reduced after the application of botulinum toxin, and the

Table 1. Blepharospasm Disability Index survey results

	Measurement	N	Median	IQR	p value*
Reading	before	12	3.00	(2.50-3.50)	0.003
	after	12	1.50	(1.00-2.00)	
Driving a vehicle†	before	2	n/a	n/a	n/a
	after	1	n/a	n/a	
Watching television	before	12	3.00	(2.50-3.00)	0.003
	after	12	1.00	(0.50-2.00)	
Doing everyday activities	before	12	2.00	(2.00-3.00)	0.097
	after	12	1.00	(0.00-2.00)	
Shopping	before	12	3.00	(2.00-3.50)	0.022
	after	12	1.00	(0.00-2.00)	
Walking	before	12	3.00	(2.00-3.00)	0.009
	after	12	1.00	(1.00-2.00)	

*Wilcoxon test
† Insufficient amount of valid data

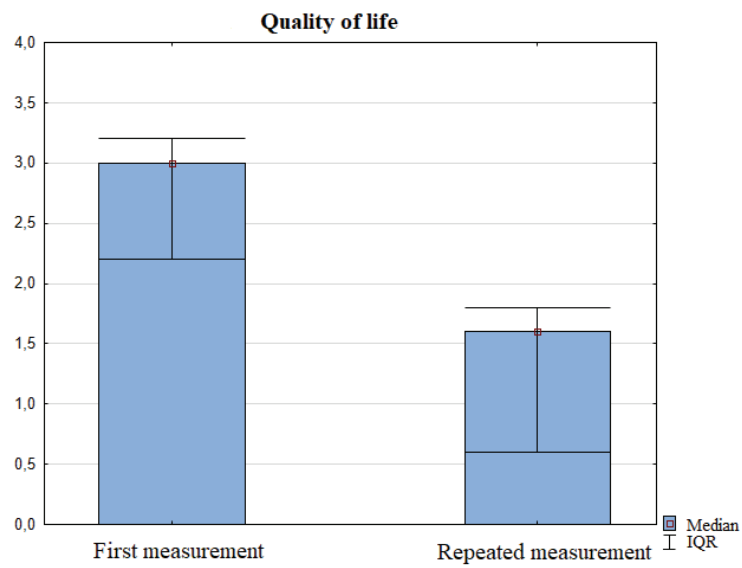

Fig. 1. Level of difficulties before and after botulinum toxin administration
** Wilcoxon test*

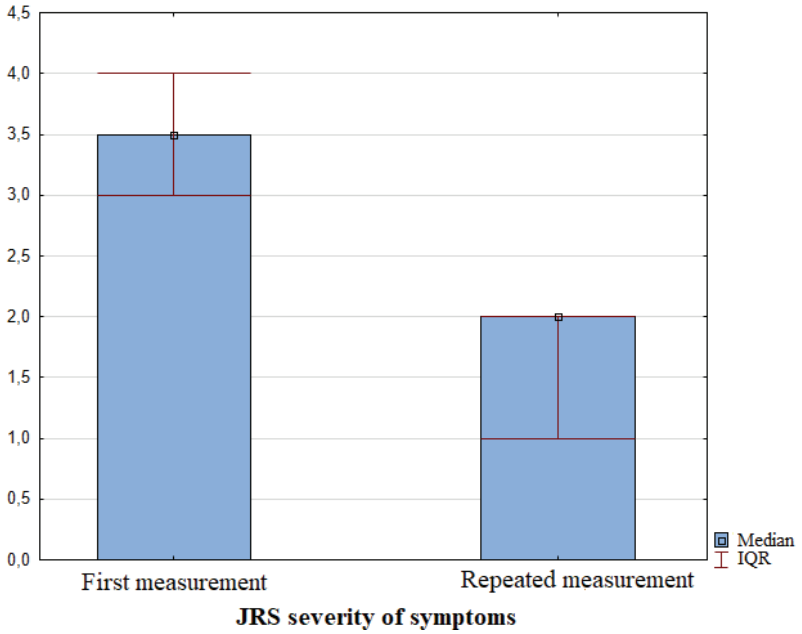

Fig. 2. Severity of symptoms before and after botulinum toxin administration
** Wilcoxon test*

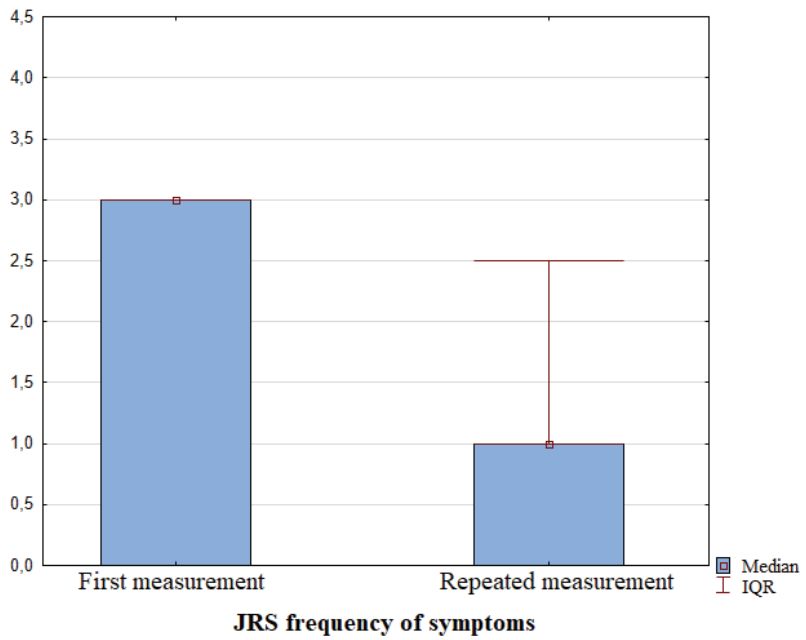

Fig. 3. Frequency of symptoms before and after botulinum toxin administration
** Wilcoxon test*

difference as statistically significant (3.0 (2.0-3.5) vs. 1.0 (1.0-2.0); p = 0.022). The level walking difficulties after botulinum toxin administration was reduced, and the study found a statistically significant difference (3.0 (2.0-3.0) vs. 1.0 (1.0-2.0); p = 0.009). The results are shown in Table 1.

Fig. 1 shows level of difficulties before and after botulinum toxin administration. The overall level of difficulties was reduced (3.0 (2.2-3.2) vs. 1.6 (0.6-1.8)), i.e. the quality of life increased after the application of

botulinum toxin, and the study found that increase was statistically significant (p = 0.003).

In the second part of the questionnaire, we used the *Jankovic Rating Scale* (JRS), where out of 5 offered answers (0-4) a 0 indicates the absence of symptoms of essential blepharospasm and 4 indicates the most serious or most common symptoms. Fig. 2 shows severity of symptoms before and after botulinum toxin administration. The severity of symptoms after botulinum toxin administration was reduced, which means that there was a reduction in the severity of the problem, and the study found a statistically significant difference (3.5 (3.0-4.0) vs. 2.0 (1.0- 2.0); p = 0.003). Fig. 3. shows the frequency of symptoms before and after botulinum toxin administration. The frequency of symptoms was reduced after administration of botulinum toxin (3.0 (3.0-3.0) vs. 1.0 (1.0-2.5)), and the study found a statistically significant difference (p = 0.012).

Discussion

The use of botulinum neurotoxin type A injections is the standard therapy in the treatment of essential blepharospasm and is considered the best choice for short-term relief of blepharospasm symptoms[9]. This study demonstrated an improvement in quality of life in patients with essential blepharospasm after administration of botulinum toxin type A, as well as a reduction in the severity and frequency of blepharospasm symptoms, and, to our knowledge, it is the first such study in our population.

Essential blepharospasm is more common in women, most often begins between the fifth and seventh decades of life, and the prevalence increases with age[3]. Therefore, as expected, women were represented in a larger number in our study (92%) and most patients were in the seventh and eighth decades of life.

Genetic, environmental, functional, and structural factors are known to play a role in the development of essential blepharospasm, but the exact pathophysiology of essential blepharospasm is still unknown[13]. For that reason, it is possible to act only on the consequences and not on the cause of the disease.

Blepharospasm tends to spread to other muscle groups, most commonly the oromandibular area, which manifests in involuntary spasms of the tongue, jaw, throat, and face muscles[14]. Furthermore, as the disease progresses, there are sensory symptoms such as grittiness in the eye, dry eyes, and photophobia that are resistant to local therapy[15]. Since these manifestations significantly affect the quality of life, and the use of botulinum toxin injections only affects excessive contractions of the subcutaneous eyelid muscles, this study should take into account the possible dissatisfaction of patients with advanced disease.

There are possible adverse reactions after botulinum toxin injection involving dry eye, blurred vision, tearing, ecchymosis, entropy, lower eyelid sagging, and ptosis[1]. The occurrence of adverse reactions, which we did not have in this study, may affect the outcome of the study.

In this study, the *Jankovic Rating Scale* was used to assess the symptoms of blepharospasm, which focuses primarily on objective signs of blepharospasm but also includes some subjective symptoms, such as increased blinking and spasms, as estimated by the observer. One of the disadvantages of the scale is that it does not take into account how blepharospasm affects the patient's daily activities, which is why we also used the *Blepharospasm Disability Index*[12].

Jankovic et al. have also used JRS and BSDI to assess the effectiveness of botulinum toxin injections in patients with blepharospasm[16]. In their randomized, placebo-controlled, double-blind trial of efficacy and safety, a single injection of incobotulinumtoxin A proved to be significantly more effective than placebo in treating blepharospasm. Six weeks after the injection, there was a clinically significant reduction in the severity of JRS symptoms, as well as a significant improvement in daily activities and quality of life.

In their study, Troung et al. administered injections of incobotulinumtoxin A in 5 cycles with flexible dosing intervals of a minimum of 6 weeks[17]. There were significant improvements in the severity and frequency of blepharospasm symptoms and significant reductions in functional impairment assessed by BSDI. During the study, the mean baseline JRS scores gradually decreased, and significant improvements were observed from the first to the fifth injection, suggesting cumulative and sustained improvements in subjects treated with incobotulinum toxin A in this long-term study. Additionally, flexible dosing intervals allowed patients to receive a new injection before the treatment effect of previous injections had completely subsided. This study showed that repeated injections of incobotulinumtoxin A at flexible intervals provide lasting efficacy in the long-term treatment of blepharospasm.

Fang et al., in their retrospective study, collected data on patients diagnosed with blepharospasm over

the past 16 years to elucidate the effect of long-term botulinum toxin treatment[18]. Clinical evaluation results (JRS, BSDI) were significantly reduced by botulinum toxin treatment, suggesting that in addition to physical symptoms it may also improve anxiety and depression. Analyzing the data for each interval, they found that the delay in response to therapy was significantly prolonged 10 years after the first injection, and the dosage of therapy was significantly increased after 5 years. However, the duration of the response was not significantly reduced, indicating that a higher dose of botulinum toxin is required to maintain reliable long-term efficacy.

Patients with benign essential blepharospasm may have mental and social disorders, such as depression and anxiety, that may affect their daily lives and interpersonal communication. Dong et al. have shown that botulinum toxin type A, by treating the motor symptoms of essential blepharospasm, reduces anxiety and depression in these patients, and early and timely treatment reduces the incidence of social and occupational dysfunction[19].

The main limiting factor of this study was the small number of subjects and the use of the same dose of the drug. In patients with prolonged blepharospasm, especially in those with other facial muscles affected, the effect on spasms outside the eye area is insufficient, which may explain incomplete satisfaction in some patients. We applied the drug only in the area of the orbicularis muscles, and not to other facial muscles, which is not recommended. Therefore, additional research is needed on a larger number of subjects and different doses depending on the severity and duration of the disease.

Conclusion

After conducting the study, it was found that the use of botulinum toxin type A in patients with essential blepharospasm led to an increase in quality of life and that the severity and frequency of symptoms of essential blepharospasm were statistically significantly reduced.

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Sažetak

UČINAK BOTULINUM TOKSINA TIP A U BOLESNIKA S ESENCIJALNIM BLEFAROSPAZMOM

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Cilj je bio utvrditi učinak botulinum toksina tip A i zadovoljstvo u bolesnika s esencijalnim blefarospazmom. U istraživanje je uključeno 12 ispitanika u dobi od 49 do 86 godina s esencijalnim blefarospazmom kojima je primijenjena terapija injekcijama botulinum toksina tip A. Ispitanicima je prije te tri tjedna nakon postupka dana anketa *Blepharospasm Disability Index* (BSDI) u kojoj su bila pitanja vezana za kvalitetu života. Dana im je i ljestvica *Jankovic Rating Scale* s pitanjima koja se odnose na težinu i učestalost simptoma. Ukupna razina poteškoća je smanjena, što znači da se kvaliteta života povećala nakon primjene botulinum toksina, a studija je pokazala da je povećanje statistički značajno (p = 0,003). Ozbiljnost simptoma nakon primjene botulinum toksina smanjena je, što znači da je došlo do smanjenja težine poteškoća, a istraživanje je utvrdilo statistički značajnu razliku (p=0,003). Učestalost simptoma smanjena je nakon primjene botulinum toksina, a studija je pokazala statistički značajnu razliku (p = 0,012). Iz rezultata ovog istraživanja možemo utvrditi da primjenom botulinum toksina tipa A dolazi do povećanja kvalitete života, te da se ozbiljnost i učestalost simptoma statistički značajno smanjuju.

Ključne riječi: *Botulinum toksin tip A, Esencijalni blefarospazam, Distonija, Indeks invaliditeta blefarospazma, Jankovićeva skala ocjenjivanja*