



## Efficacy of botulinum toxin type A in treatment of different forms of focal dystonias in the Serbian population: experience of the Botulinum Toxin Outpatients Department

Efikasnost terapije botulinskim toksinom tipa A u lečenju različitih formi fokalnih distonija u srpskoj populaciji: iskustvo Centra za botulinski toksin

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### Abstract

**Background/Aim.** Botulinum toxin (BTX) irreversibly inhibits presynaptic acetylcholine release with subsequent relaxation of abnormally contracting muscles. It is an effective and well tolerated treatment with long-term benefit in a variety of movement disorders and other neurological and non-neurological disturbances. The aim of our study was to present our experience with BTX type A in treatment of different forms of focal dystonias. **Methods.** A hundred of patients with different focal dystonias (spastic torticollis, blepharospasm and graphospasm) from the Botulinum Toxin Outpatients Department, Clinic for Neurology, Clinical Center of Serbia, were included in the study. All the patients were examined and rated at baseline visit prior to BTX application and on the following visit, after 3–4 months, using self-assessment improvement questionnaire and standardized rating scales. **Results.** The improvement of  $\geq 50\%$  was presented in 68.2% of all (199) the analyzed applications. Independent predic-

tors of good response to the therapy (improvement  $\geq 50\%$ ) were male sex ( $p = 0.011$ ), the presence of sensory trick ( $p = 0.013$ ) and the total number of BTX applications ( $p = 0.002$ ). The patients with spastic torticollis and blepharospasm showed a statistically significantly better BTX effect (improvement  $57.3 \pm 27.5\%$  and  $54.1 \pm 28.3\%$ ), respectively than the graphospasm group ( $26.7 \pm 25.6\%$ ). Most of the patients did not have therapy complications (81.4% and 72% in two applications). Side effects in the remaining patients (muscle weakness, dysphagia, ptosis, double vision, neck weakness and lacrimal dysfunction) lasted for  $28.3 \pm 18.6$  days after the first treatment and  $32.5 \pm 36.2$  days after the second one. **Conclusion.** BTX is safe and highly effective in long-term treatment of patients with different forms of focal dystonia, with only mild and well-tolerated side-effects.

**Key words:** dystonia; botulinum toxins; serbia; questionnaires; quality of life.

### Apstrakt

**Uvod/Cilj.** Botulinski toksin (BT) ireverzibilno inhibira presinaptičko oslobađanje acetilholina sa posledičnom relaksacijom prekomerno kontrahovanih mišića. To je efikasna i bezbedna terapija sa dugotrajnim povoljnim dejstvom kod brojnih bolesti nevoljnih pokreta, kao i kod drugih neuroloških i neneuroloških oboljenja. Cilj ovog istraživanja bio je predstavljanje našeg iskustva sa BT tipa A u lečenju različitih formi fokalnih distonija. **Metode.** U studiju je bilo uključeno 100 bolesnika sa različitim formama fokalnih distonija (spastični tortikolis, blefarospazam, grafospazam) lečenih u Centru za botulinski toksin Klinike za neurologiju, Kliničkog centra Srbije. Svi bolesnici su pregledani i ocenjeni pre primene BT, a zatim pri sledećoj poseti, nakon 3–4 meseca. Korišćeni su upitnik za samoprocenu poboljšanja i standardne skale za procenu težine bolesti. **Rezultati.** Poboljšanje  $\geq 50\%$  utvrđeno je kod 68,2% od ukupnog broja analiziranih primena BT (199). Nezavisni prediktori dobrog

odgovora na terapiju (poboljšanje  $\geq 50\%$ ) bili su muški pol ( $p = 0,011$ ), prisustvo senzornog trika ( $p = 0,013$ ) i ukupan broj aplikacija BT ( $p = 0,002$ ). Efekat BT bio je statistički značajno bolji kod bolesnika sa tortikolisom i blefarospazmom (poboljšanje  $57,3 \pm 27,5\%$ , odnosno  $54,1 \pm 28,3\%$ ), nego kod bolesnika sa grafospazmom ( $26,7 \pm 25,6\%$ ). Većina bolesnika nije imala komplikacije terapije (81,4% i 72% u dve primene). Neželjeni efekti kod preostalih bolesnika (slabost mišića, disfagija, ptoza, diplopije, slabost vrata i poremećaj lakrimacije) trajali su  $28,3 \pm 18,6$  dana posle prve primene i  $32,5 \pm 36,2$  dana posle druge. **Zaključak.** Botulinski toksin je bezbedan i veoma efikasan u dugotrajnoj terapiji kod bolesnika sa različitim formama fokalnih distonija. Neželjeni efekti su blagi i dobro se podnose.

**Ključne reči:** distonija; botulin toksini; srbija; upitnici; kvalitet života.

## Introduction

Botulinum toxin (BTX) irreversibly inhibits presynaptic acetylcholine release with subsequent relaxation of abnormally contracting muscles<sup>1</sup>. Although there are 7 different BTX serotypes named A, B, C, D, E, F and G, only BTX type A (BTX-A) has been widely studied for therapeutic purposes, and more recently, BTX type B<sup>2</sup>. BTX-A is an effective and well tolerated treatment with long-term benefit in a variety of movement disorders and other neurological and non-neurological disturbances which appear as a consequence of abnormal muscle contractions<sup>1</sup>.

In a meta-analyses BTX-A therapy of spasmodic torticollis (TS) generated statistically significant clinical improvements on objective and subjective rating scales, as well as on subjective scales for pain relief in over 85% of cases<sup>3,4</sup>. In blepharospasm (BS), BTX-A was found to be superior to placebo with the benefit reported by 90% of patients<sup>5</sup>. Good efficacy of BTX-A treatment in patients with focal task-specific dystonia (musician's dystonia, occupational dystonia and writer's cramp) was proven in 67–93% of patients, but many of them discontinued therapy because it failed to meet their expectations or needs<sup>6,7</sup>, with mostly mild and transient weakness of the hand as an important side effect<sup>8</sup>. Follow-up studies showed a substantial 5-year benefit in most patients (90% in BS, 63% in TS, 56% in writer's cramp) with improvement maintained for up to 10 years<sup>9</sup>.

The aim of our study was to present our experience with BTX-A in treatment of different forms of focal dystonias, treated at the Botulinum Toxin Outpatients Department of Clinic for Neurology, Clinical Center of Serbia.

## Method

A hundred of patients with different focal dystonias from the Botulinum Toxin Outpatients Department, Clinic for Neurology, Clinical Center of Serbia, Belgrade were included in the study. The diagnosis of primary focal dystonia was made by the experienced movement disorders specialists, based on standardized criteria<sup>10</sup>. The study included patients with cervical

dystonia, i.e. spasmodic torticollis (TS), blepharospasm (BS) and writer's cramp (i.e. graphospasm – WC).

The study was approved by the Ethic Committee of Clinical Center of Serbia, Belgrade. Upon signing informed consent, the patients were interviewed in order to obtain demographic and clinical data on the disease course, therapy, previous BTX applications, complications of therapy, etc.

BTX type A (Dysport, 500 U) was used in this survey. All the patients were examined and rated at baseline visit prior to BTX application. They were asked to rate efficacy of previous application using self-assessment improvement questionnaire. Afterwards, the severity of symptoms was evaluated by specific rating scales: Toronto Western Spasmodic Rating Scale (TWSTRS)<sup>11</sup>, Blepharospasm Disability Index (BSDI)<sup>12</sup>, Jankovic Rating Scale (JRS) for Blepharospasm<sup>13</sup> and Writer's Cramp Rating Scale (WCRS)<sup>14</sup>. Muscle injection spots and BTX dosage for previous and actual application were noted. The next rating was performed on the following visit, 3–4 months after the baseline visit, when self-assessment improvement questionnaire was applied. Sustained benefit was defined as continued improvement of  $\geq 50\%$  from baseline.

Our patients were injected by observation and palpation of specific muscles activity, without electromyography (EMG) guidance, as well as without ultrasound control. None of our patients were given "booster" injections because of the risk of antibody development. Data were analyzed using methods of descriptive statistic,  $\chi^2$  test, analysis of variance (ANOVA) and multivariate regression analysis.

## Results

The study comprised 100 patients (48 with TS, 38 with BS and 14 with WC) whose demographic and clinical characteristics are summarized in Table 1. The patients with BS were statistically significantly older than the patients in other two groups ( $p < 0.001$ ). The mean disease duration was similar in all the groups (8.3–11.0 years), sensory tricks were statistically significantly more frequent in the patients with TS (68.8%,  $p = 0.001$ ), as well as it was dystonic tremor (45.8%,  $p < 0.001$ ).

Table 1

Demographic and clinical characteristics of patients with focal dystonias				
Variables	Spasmodic torticollis	Blepharospasm	Writer's cramp	<i>p</i>
Number	48	38	14	
Sex (m/f), n	17/31	12/26	3/11	0.613
Age*	51.1 ± 10.4 (24–72)	65.9 ± 8.2 (49–84)	50.2 ± 11.2 (31–67)	< 0.001
Age at onset*	40.5 ± 10.4 (15–63)	57.6 ± 9.8 (33–73)	40.2 ± 12.8 (17–62)	< 0.001
Disease duration*	11.0 ± 7.3 (2–32)	8.3 ± 6.2 (2–27)	10.0 ± 7.2 (2–30)	0.228
Number of applications of BTX <sup>‡</sup>	20.2 ± 15.2 (1–60)	21.0 ± 15.4 (2–80)	3.7 ± 4.2 (0–14)	0.001
Associated movement disorders <sup>†</sup>				
without	45 (95.8)	37 (97.4)	14 (100)	0.431
Dystonic tremor <sup>†</sup>	22 (45.8)	0 (0)	2 (14.3)	< 0.001
Sensory trick <sup>†</sup>	33 (68.8)	19 (50)	2 (14.3)	0.001
Pain <sup>†</sup>	32 (66.7)	2 (5.3)	3 (8.1)	< 0.001
Positive family history <sup>†</sup>	14 (29.2)	1 (2.6)	1 (7.1)	0.002

\*The values presenting the average duration and standard deviation in years with the range in brackets; †values presenting the number of patients with percentage in brackets; ‡values presenting the number of injections and standard deviation with the range in brackets; m – male; f – female; BTX – batulinum toxin.

The patients with WC had statistically significantly longer latency to response ( $12.6 \pm 9.4$  days,  $p < 0.001$ ) comparing to TS ( $7.2 \pm 4.7$ ) and BS ( $6.1 \pm 4.9$ ), as well as duration of therapeutic effect lasted significantly shorter in WC ( $1.9 \pm 2.0$  months,  $p = 0.002$ ) than in TS ( $2.9 \pm 1.1$  months). Furthermore, the patients with TS and BS showed a statistically significantly better BTX effect (improvement  $57.3 \pm 27.5\%$  and  $54.1 \pm 28.3\%$ , respectively) than WC group ( $26.7 \pm 25.6\%$ ) (Table 2).

Although most of the patients did not have therapy complications (81.4% and 72% in two applications), side effects in remaining patients lasted for  $28.3 \pm 18.6$  days after the first treatment and  $32.5 \pm 36.2$  days after the second treatment. Complications of the therapy appeared with the latency of 2–50 days after the first application and 1–30 days after the second one. Rare complications included: muscle weakness (7.2% and 14%, respectively), dysphagia (4.1%

and 7%, respectively), ptosis (4.1% and 2%, respectively), double vision (3.1% and 2%, respectively), neck weakness (1%), lacrimal dysfunction (1%), and others (1%).

The improvement of  $\geq 50\%$  was presented in 68.2% of all (199) the analyzed applications (Figure 1). Impairment was reported in 1.5%, while 8% of applications had no effect, and improvement  $< 50\%$  was noticed in 22% of all the applications.

Multivariate linear regression analysis showed that independent predictors of good response to the therapy (improvement  $\geq 50\%$ ) were male sex ( $p = 0.011$ ), the presence of sensory trick ( $p = 0.013$ ) and the total number of BTX applications ( $p = 0.002$ ) (Table 3).

Objective rating of clinical severity and subjective assessment of improvement showed a correlation in 2 TWSTRS domains: disability subscore ( $r = -0.294$ ,  $p = 0.05$ ) and total score ( $r = -0.286$ ,  $p = 0.05$ ).

Table 2

Botulinum toxin therapy characteristics in different forms of focal dystonia				
Variable	Spasmodic torticollis	Blepharospasm	Writer's cramp	<i>p</i>
Number of applications	96	76	27	
Latency to response*	$7.2 \pm 4.7$ (1–21)	$6.1 \pm 4.9$ (1–30)	$12.6 \pm 9.4$ (5–30)	$< 0.001$
Duration of response <sup>†</sup>	$2.9 \pm 1.1$ (0–6)	$2.7 \pm 1.1$ (0–5)	$1.9 \pm 2.0$ (0–7)	0.002
Self assess. improvement <sup>‡</sup>	$57.3 \pm 27.5$ (50–100)	$54.1 \pm 28.3$ (50–100)	$26.7 \pm 25.6$ (0–75)	$< 0.001$

\*The values presenting the average number and standard deviation in days with the range in bracket; <sup>†</sup> the values presenting the average number and standard deviation in months with the range in brackets; <sup>‡</sup> the values presenting the percentage of improvement and standard deviation with the range in brackets.

Table 3

Multivariate linear regression analysis			
Variable	Standardized $\beta$ coefficient	95% Confidence Interval	<i>p</i>
Male gender	0.238	0.50–0.373	0.011
Sensory trick	0.231	0.41–0.344	0.013
Number of BTX application prior to testing	-0.290	-0.013– -0.003	0.002

Dependent variable: self-assessment questionnaire improvement  $\geq 50\%$  ; BTX – botulinum toxin.

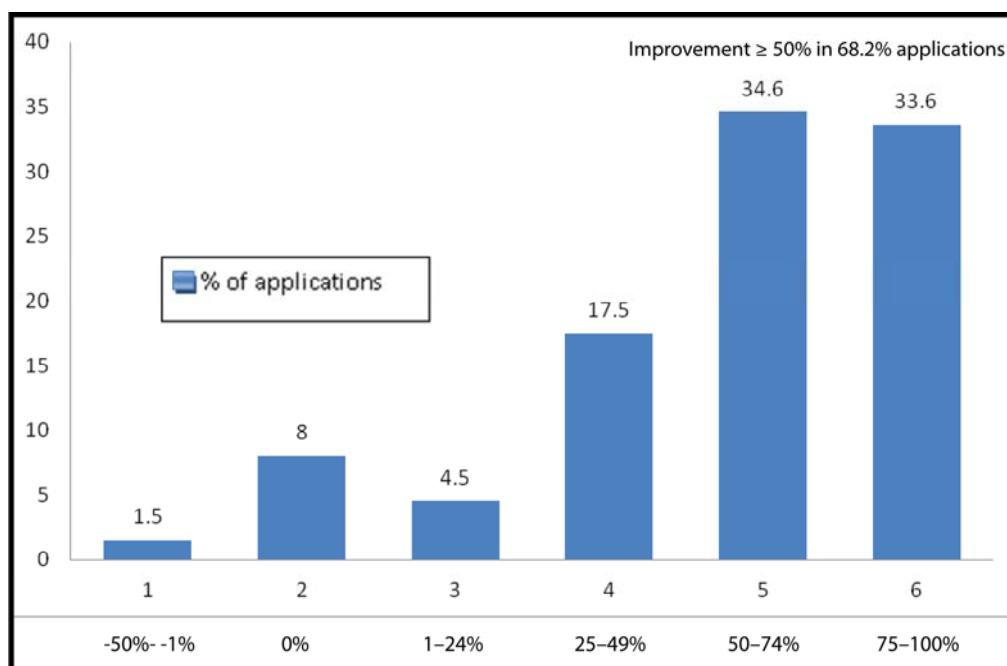


Fig. 1 – Self-assessment of improvement in percentage in 199 applications of botulinum toxin (BTX).

## Discussion

We examined 100 patients with focal dystonia who were injected twice (overall 199 applications of BTX). The improvement of  $\geq 50\%$  in all analyzed treatment sections was present in about 70% of patients. Both applications achieved marked and similar functional and clinical improvement.

Our patients with TS estimated their mean improvement at about 57%. At the time of analyzed injection sections they had disease duration of about 11 years (2–32) with more than 20 previous injections of BTX A. Some of these TS patients were included in our previous study on BTX-A efficacy, which showed that 86% of patients improved<sup>15</sup>. Among 155 patients with TS treated with BTX-A injections over a period of 6 years, 78% continued the therapy, two thirds of which reported injections as “always helpful”<sup>16</sup>. Other studies on patients with TS treated for median of 5.5 years showed a high degree of patients’ satisfaction evaluated by them and their neurologists (i.e. 67% of patients had good therapeutic effect)<sup>17</sup>.

Our patients with BS found their mean improvement of about 54%. At the time of analyzed injection sections their disease duration was about 8 (2–27) years, with approximately 21 previous injections. According to the results of previous studies, BTX-A showed the best efficacy in patients with BS comparing to other forms of focal dystonia<sup>9, 18, 19</sup>. Bentivoglio et al.<sup>19</sup> demonstrated in a 15-year period follow-up study with 128 BS patients that in a six-point scale the mean efficacy of BTX-A was  $3.9 \pm 1.2$ . In another study with 73 BS patients, 96% of them, reported a significant relief of their symptoms.

A total of 20 patients with focal hand dystonia followed for up to 16 years had mild benefit in 50% of cases<sup>20</sup>, while more than one third of musicians reported a long-term benefit and improvement in their performance ability<sup>6</sup>. In a study with 39 participants with WC, BTX-A injections had a significantly greater improvement compared to placebo, and about 50% of them were still treated after one year<sup>8</sup>. Moreover, reorganizational changes in the primary motor cortex have been shown in patients with WC receiving BTX-A injections<sup>21</sup>. In our WC group improvement was significantly less than in other 2 groups (26.7%), which is in accordance with other studies that showed worse BTX-A efficacy in patients with task specific dystonia comparing to other forms of focal dystonia<sup>9</sup>.

Although our study was not longitudinal, it is important to stress that all our patients were regularly treated for a long period (1–80 injections *per* patients). There are only few studies with long-term follow-up<sup>1</sup>. Retrospective analysis of the long term efficacy of BTX-A over a 10-year period in 355 subjects with focal dystonia found that at 2 years the highest response rate of sustained benefit (defined as continued improvement of  $\geq 50\%$  from baseline) was in patients

with BS (92%), TS (68%), and WC (57%), and that was similar at 5 years. Patients’ satisfaction increased after 5 years of treatment with average reported benefit of 75.8%<sup>9</sup>. A slightly lower number of patients with sustained benefit in our study can be explained with the fact that the results are done for the whole group and that the patients with WC generally have worse treatment response.

We use a subjective, self-assessed improvement rating for detection of the level of improvement. Interestingly, these rating scales showed a correlation with the TWSTRS objective scale (total and severity subscores)<sup>11</sup>. The mean total duration of clinical improvement in our patients was  $2.7 \pm 1.3$  months (range, 0–6). Latency to response was statistically significantly longer (12.5 days) and improvement and therapy duration inferior in the patients with WC than in the groups with TS and BS.

The frequency of complications in our group was low. Adverse events can be local (pain, edema, erythema, ecchymosis, headache and short-term hyperaesthesia) and reactions following migration of the toxin into the adjacent muscles, as well as systemic reactions (nausea, fatigue, malaise, flu-like symptoms and rush). A total of 81% of our patients had no complications after the first treatment, and 72% after the second one, which is in accordance with the results of a meta-analysis on the safety of BTX-A in different indications, showing the overall rate of adverse events of approximately 25% in BTX-A treated subjects, compared with 15% in the control group<sup>22</sup>. The most frequent adverse events were muscle weakness, dysphagia, ptosis and double vision. Rare adverse events were neck weakness and lacrimal dysfunction. Complications in our patients were rare, mild and transient. Our results demonstrate that a total number of BTX-A applications, accompanied with male sex and the presence of sensory trick are the most significant predictors of improvement. Mejia et al.<sup>23</sup> followed 45 patients during 12 years and showed that both global efficacy score and the peak effect score, likewise duration of maximal response, improved comparing the first and last treatments, thus pointing out increasing long-term efficacy of BTX-A.

## Conclusion

The results obtained in this study confirm that botulinum toxin is safe and highly effective in long-term treatment of patients with different forms of focal dystonia, with only mild and well-tolerated side-effects.

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