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 botulinskih 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 ≥ 50% was presented in 68.2% of all (199) the analyzed applications. Independent predictors of good response to the therapy (improvement ≥ 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 ± 27.5% and 54.1 ± 28.3%, respectively) than the graphospasm group (26.7 ± 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 ± 18.6 days after the first treatment and 32.5 ± 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 presinaptni acetylcholinjev skup sa posledičnom relaksacijom preko kontrakcije mišića. To je efikasna i bezbedna terapija sa oduzimanjem troška. Cilj ovog istraživanja bio je predstavljanje našeg iskustva sa BTX tipa A u lečenju različitih formi fokalnih distonija.

Metode. U studiju je bilo uključeno 100 bolesnika sa različitim formama fokalnih distonija (spastich tortikolis, blefarospazam i grafospazam) iz Centra za botulinski toksin Klinike za neurologiju, Kliničkog centra Srbije. Svi bolesnici su pregledani i ocenjeni pre primene BTX, a zatim pri sledećoj poseti, nakon 3–4 meseci. Korišćeni su upitnik za samopostavljenu lećenju poboljšanju i standardizovane skalice za procezu težine bolesti.

Rezultati. Poboljšanje ≥ 50% utvrđeno je kod 68,2% od ukupnog broja analiziranih primena BTX (199). Nezavisni prediktori dobrog odgovora na terapiju (poboljšanje ≥ 50%) bili su muški pol (p = 0,011), prisustvo senzornog trka (p = 0,013) i ukupan broj aplikacija BTX (p = 0,002). Efekt BT bio je statistički značajno bolj kod bolesnika sa tortikolisom i blefarospažom (poboljšanje 57,3 ± 27,5% i odnosno 54,1 ± 28,3%), nego kod bolesnika sa grafospazom (26,7 ± 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 lakrmatike) trajali su 28,3 ± 18,6 dana posle prve primene i 32,5 ± 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. 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. 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.

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. In blepharospasm (BS), BTX-A was found to be superior to placebo with the benefit reported by 90% of patients. 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, with mostly mild and transient weakness of the hand as an important side effect. 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.

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. 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), Blepharospasm Disability Index (BSDI), Jan-kovic Rating Scale (JRS) for Blepharospasm and Writer’s Cramp Rating Scale (WCRS). 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 ≥50% from baseline.

Our patients were injected by observation and palpation of specific muscles activity, without electromyography 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, χ² test, analysis of variance (ANOVA) and multivarant 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).

| Variables | Spasmodic torticollis | Blepharospasm | Writer’s cramp | p   |
|-----------|-----------------------|---------------|---------------|-----|
| 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* | 20.2 ± 15.2 (1–60) | 21.0 ± 15.4 (2–80) | 3.7 ± 4.2 (0–14) | 0.001 |
| Associated movement disorders † | 45 (95.8) | 37 (97.4) | 14 (100) | 0.431 |
| Dystonic tremor † | 22 (45.8) | 0 (0) | 2 (14.3) | < 0.001 |
| Sensory trick † | 33 (68.8) | 19 (50) | 2 (14.3) | 0.001 |
| Pain † | 32 (66.7) | 2 (5.3) | 3 (8.1) | < 0.001 |
| Positive family history † | 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 – botulinum toxin.
The patients with WC had statistically significantly longer latency to response (12.6 ± 9.4 days, \( p < 0.001 \)) comparing to TS (7.2 ± 4.7) and BS (6.1 ± 4.9), as well as duration of therapeutic effect lasted significantly shorter in WC (1.9 ± 2.0 months, \( p = 0.002 \)) than in TS (2.9 ± 1.1 months). Furthermore, the patients with TS and BS showed a statistically significantly better BTX effect (improvement 57.3 ± 27.5% and 54.1 ± 28.3%, respectively) than WC group (26.7 ± 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 ± 18.6 days after the first treatment and 32.5 ± 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 ≥ 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 ≥ 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

| Variable                                  | Spasmodic torticollis | Blepharospasm | Writer’s cramp |
|-------------------------------------------|-----------------------|---------------|---------------|
| Number of applications                    | 96                    | 76            | 27            |
| Latency to response*                      | 7.2 ± 4.7 (1–21)      | 6.1 ± 4.9(1–30)| 12.6 ± 9.4 (5–30)| \( < 0.001 \) |
| Duration of response†                     | 2.9 ± 1.1 (0–6)       | 2.7 ± 1.1 (0–5)| 1.9 ± 2.0 (0–7)| \( 0.002 \) |
| Self assess. improvement‡                 | 57.3 ± 27.5 (50–100)  | 54.1 ± 28.3 (50–100)| 26.7 ± 25.6 (0–75)| \( < 0.001 \) |

*The values presenting the average number and standard deviation in days with the range in brackets; † the values presenting the average number and standard deviation in months with the range in brackets; ‡ the values presenting the percentage of improvement and standard deviation with the range in brackets.

### Table 3

| Variable                                  | Standardized \( \beta \) coefficient | 95% Confidence Interval | \( p \) |
|-------------------------------------------|--------------------------------------|-------------------------|-------|
| 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 ≥ 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 ≥ 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. 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”. 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).

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. Bentivoglio et al. 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 ± 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, while more than one third of musicians reported a long-term benefit and improvement in their performance ability. 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. Moreover, reorganization changes in the primary motor cortex have been shown in patients with WC receiving BTX-A injections. 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.

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. 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 ≥ 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%. 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). The mean total duration of clinical improvement in our patients was 2.7 ± 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 hyperesthesia) and reactions following migration of the toxin into the adjacent muscles, as well as systemic reactions (nausea, fatigue, malaise, flu-like symptoms and rash). 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. 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. followed 45 patients during 12 years and showed that both global efficacy score and the peak effect score, likewise duration of maximal response, improved compared to 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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REFERENCES

1. Ramírez-Castanedo J, Jankovic J. Long-term efficacy and safety of botulinum toxin injections in dystonia. Toxins 2013; 5(2): 249–57.

2. Dreissler D, Adit SF. Botulinum Toxin: Mechanisms of Action. Eur Neurol 2005; 53(1): 3–9.

3. Costa J, Estévez-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, et al. Botulinum toxin type B for cervical dystonia. Cochrane Database Syst Rev 2005; 25(1): CD004315.

4. Jankovic J. Treatment of cervical dystonia with botulinum toxin. Mov Disord 2004; 19 (Suppl 8): S109–15.

5. Costa J, Estévez-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev 2005; 25(1): CD004900.

6. Schade S, Jablonski H, Leibman RJ, Alter K, Hallett M. Botulinum toxin injections in the treatment of musician's dystonia. Neurology 2005; 64(2): 341–3.

7. Karp BI. The role of botulinum toxin type A in the management of occupational dystonia and writer's cramp. In: Brin MF, Jankovic J, Hallet M, editors. Scientific and therapeutic aspects of botulinum toxin. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 251–8.

8. Kründijk JJ, Koulman JH, Ongerboer de Visser BW, de Haan RJ, Spelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatr 2007; 78(3): 264–70.

9. Hsiung GY, Das SK, Ranawaya R, Lafontaine AL, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord 2002; 17(6): 1288–93.

10. Albanese A, Asmus F, Bhutia KP, Elia AE, Elöök B, Filippini G, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol 2011; 18(1): 5–18.

11. Coskey ES, Lang AE. Clinical assessments in patients with cervical dystonia. In: Jankovic J, Hallet M, editors. Therapy with botulinum toxin. New York, NY: Marcel Dekker; 1994. p. 211–37.

12. Gurtelmeijer R, Brinkmann S, Couess G, Dolker A. The Blepharospasm Disability Index (BSDI) for the assessment of functional health in focal dystonia. Clin Neurophysiol 2002; 113(1): S77–8.

13. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study. Neurology 1987; 37(4): 616–23.

14. Wieland J, Kabou C, Wenzel R, Klepisch S, Schwarz U, Nebe A, et al. Botulinum toxin in writer's cramp: objective response evaluation in 31 patients. J Neurol Neurosurg Psychiatry 1996; 61(2): 172–5.

15. Kastić V, Cwikla-Sterni N, Filipović S. Local treatment of spasmodic torticollis with botulinum toxin. Neurologija 1990;39(1):29–33.

16. Brashear A, Bergan K, Wojciechszk J, Siemens ER, Ambrosius W. Patients' perception of stopping or continuing treatment of cervical dystonia with botulinum toxin type A. Mov Disord 2000; 15(1): 150–3.

17. Skogseid IM, Kertę E. The course of cervical dystonia and patient satisfaction with long-term botulinum toxin A treatment. Eur J Neurosurg 2005; 12(3): 163–70.

18. Cillino S, Raimondi G, Guépratte N, Damiani S, Cillino M, Di Pace F, et al. Long-term efficacy of botulinum toxin A for treatment of blepharospasm, hemifacial spasm, and spastic entropion: a multicentre study using two drug-dose escalation index. Eye (Lond) 2010; 24(4): 600–7.

19. Bentivoglio AR, Fasano A, Lalongo T, Soliti F, La FS, Albanese A. Fifteen-year experience in treating blepharospasm with Botox or Dysport: same toxin, two drugs. Neurotox Res 2009; 15(3): 224–31.

20. Lang G, Karp BI, Alter K, Zuljord R, Hallett M. Long-term follow-up of botulinum toxin therapy for focal hand dystonia: outcome at 10 years or more. Mov Disord 2011; 26(4): 750–3.

21. Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stel R, et al. The corticomotor representation of upper limb muscles in writer’s cramp and changes following botulinum toxin injection. Brain 1998; 121(Pt 5): 977–88.

22. Naumann M, Albanese A, Heinen Y, Molemau G, Rejha M. Safety and efficacy of botulinum toxin type A following long-term use. Eur J Neurol 2006; 13(Suppl 4): 35–40.

23. Mejia NF, Vuong KD, Jankovic J. Long-term botulinum toxin efficacy, safety, and immunogenicity. Mov Disord 2005; 20(5): 592–7.