Original Article / Çalışma - Araştırma

Botulinum Toxin Type A Application for the Treatment of Cervical Dystonia

Servikal Distoni Tedavisinde Botulinum Toksin Tip A Uygulaması

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Objectives: In this study we aimed to identify clinical and demographic characteristics of patients with cervical dystonia (CD) and evaluate their response to treatment with botulinum toxin type A (BoNT/A). We also compared the outcomes of the patients with a disease duration of <5 years and ≥5 years and the patients receiving BoNT/A treatment for <5 years and ≥5 years.

Patients and Methods: Between March 2001 and December 2011, the data obtained from 17 patients with CD (11 females, 6 males; mean age 48.2±12.0 years) who visited Bezmialem Vakif University, School of Medicine, Department of Neurology, Botulinum Toxin Outpatient Clinic were retrospectively analyzed. Detailed clinical and demographic information were obtained for each patient.

Results: The mean age at onset of CD was 39.1±11.6 years. The mean disease duration was 9.1±4.1 years. Nine patients had right-sided CD. The mean time from the onset of the symptoms to BoNT/A treatment was 4.5±3.6 years. The mean duration of BoNT/A treatment was 4.6±2.9 years. Two different brands of BoNT/A (Botox® and Dysport®) were used with a mean dose ratio of 4 between toxins. A total of 181 BoNT/A treatments with multiple sites injections were administered during this period. The mean response rate was assessed based on a five-point scale at each visit. After the last injection, the mean response rate was 3.1±0.5 and the mean total duration of response was 3.0±1.9 months. After dosage adjustment, a significant increase was found between the mean dose injected (531.2±230.2 versus 788.5±259 units; p=0.01) of BoNT/A and the number of muscle (2.7±0.7 versus 3.8±0.8) in the first and last injections (p=0.005).

Conclusion: Our results showed that a statistically significant increase was found between the mean dose of BoNT/A and the number of muscles over time.

Key Words: Botulinum toxin; cervical dystonia; dystonia.

Amaç: Bu çalışmada servikal distonili (SD) hastaların klinik ve demografik özelliklerinin tanımlanması ve botulinum toksin tip A (BoNT/A) tedavisine verilen yanıtların değerlendirilmesi amaçlandı ayrıca hastalık süresi beş yıldan az ve beş yıldan çok olan hastalar ile beş yıldan kısa süre ve beş yıldan uzun süre BoNT/A alan hastaların sonuçları karşılaştırıldı.

Hastalar ve Yöntemler: Bezmialem Vakıf Üniversitesi Tıp Fakültesi Nöroloji Kliniği Botulinum Toksin polikliniğinde, Mart 2001 - Aralık 2011 tarihleri arasında görülen 17 SD'li hastanın (11 kadın, 6 erkek; ort. yaş 48.2±12 yıl) verileri retrospektif olarak değerlendirildi. Her hasta için ayrıntılı klinik ve demografik veriler alındı.

Bulgular: Ortalama SD başlama yaşı 39.1±11.6 yıl idi. Ortalama hastalık süresi 9.1±4.1 yıl idi. Dokuz hastada sağa dönüşlü SD vardı. Semptomların başlamasından BoNT/A tedavisine kadar geçen ortalama süre 4.5±3.6 yıl idi. Ortalama BoNT/A tedavi süresi 4.6±2.9 yıl idi. İki farklı BoNT/A (Botox® and Dysport®) markası aralarında 4 oranıyla kullanıldı. Bu süre içinde toplam 181 BoNT/A tedavisi çoklu noktalara yapıldı. Her vizitte ortalama yanıt oranı beş puanlık skala üzerinden değerlendirildi. Son enjeksiyondan sonra ortalama yanıt oranı 3.1±0.5, yanıtın ortalama toplam süresi ise 3.0±1.9 ay idi. Doz ayarlaması sonrasında, her bir hasta için ilk ve son enjeksiyonlarda ortalama BoNT/A dozu (788.5±259 üniteye kıyasla, 531.2±230.2; p=0.01) ve kas sayısı (3.8±0.8'e kıyasla 2.7±0.7; p=0.005) arasında anlamlı artış bulundu.

Sonuç: Çalışmamızın sonuçlarına göre BoNT/A ortalama dozu ve kas sayısında zamanla istatistiksel olarak anlamlı bir artış olduğu görülmüştür.

Anahtar Sözcükler: Botulinum toksin; servikal distoni; distoni.

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Received / *Geliş tarihi:* February 22, 2012 Accepted: / *Kabul tarihi:* April 5, 2012

Cervical dystonia (CD) is a focal dystonia, characterized by sustained twisting and turning of the neck musculature, resulting in involuntary movements of the neck as well as various undesired head positions.[1] Cervical dystonia is the most frequent form of focal dystonia of which the etiology and the precise prevalence are unknown.[2,3]

Cervical dystonia causes head rotation (torticollis), head tilt (laterocollis), neck flexion (anterocollis) or neck extension (retrocollis), sometimes combined with elevation or anterior shifting of the shoulders.[1,4]

Botulinum toxin type A (BoNT/A) has been shown in numerous controlled studies to be safe and effective for, and is recommended as the first line treatment of, CD.[5,6]

The objectives of this study were to identify the clinical and demographic characteristics of CD patients in our outpatient clinic, to document the effects of prolonged use of BoNT/A in the treatment of these patients and to compare the patients with disease duration longer than five years with those less than five years and the patients receiving BoNT/A treatment for more than five years with those less than five years.

PATIENTS AND METHODS

Subjects and data collection

A total of 17 patients with primary CD (11 females, 6 males; mean age 48.2±12 years) who had attended the BoNT/A outpatient clinic in the Neurology department of Bezmialem Vakıf University between March 2001 and December 2011 were selected for clinical assessment. A retrospective analysis was conducted using the medical records of these patients.

The diagnosis of CD was based on published criteria.[7] We classified the patients according to the clinical presentation of the CD such as torticollis, laterocollis, retrocollis, anterocollis or combined forms and excluded patients with pure anterocollis or retrocollis. All patients had a complete neurological examination on admission and known causes of secondary dystonias such as post-anoxia, previous use of neuroleptic drugs, stroke, metabolic disorders, central (brain and spinal cord) or peripheral trauma, neuropathy, tumor, postencephalitic and other neurodegenerative diseases had been excluded on the basis of history, neurological examination and magnetic resonance imaging (MRI) of the brain and cervical portion of the spinal cord. Patients who had incomplete medical records and irregular follow-up were excluded.

Patients with CD treated with BoNT/A were retrospectively evaluated for the following clinical and demographic parameters: gender, current age, age at CD onset, disease duration, pattern of head deviation, right or left deviation, the interval between symptom onset and first BoNT/A treatment, the duration of BoNT/A treatment, onset form of the disease (acute, chronic), medical history, the family history of dystonia or other movement disorders, consanguinity of the parents, presence of pain and/or tremor, response rating after the last injection and peak-time and duration of improvement of functional capacity of the patient and total number of session. Two different preparations of BoNT/A were injected: Dysport (Ipsen, Ltd., Slough, Berkshire, UK); Botox (Allergan Inc., Irvine, CA, USA) and a mean dose ratio between toxins of 4 was used. The response to the previous BoNT/A injection was evaluated at each follow-up visit. However, since all patients had had multiple BoNT/A applications, we took the last response to BoNT/A injection for assessment. We compared the doses and the number of muscles at first and last injection, the severity of abnormal head and neck movements was measured with the severity section of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS-Severity) at each visit before BoNT/A injection.[8] In terms of cervical pain, all patients were assessed using visual analog pain scale-VAS (0= absence of pain, 1-3= mild pain, 4-6= moderate pain, 7-9= strong pain, 10= disabling pain) at each visit. The side effects of BoNT/A injections were recorded at each follow-up visit. We classified the patients into subgroups depending on disease duration (less or more than 5 years) and the period of time receiving BoNT/A treatments (less or more than 5 years) and compared the differences between

patients with disease duration longer than five years with those less than five years and the patients receiving BoNT/A treatment for more than five years with those less than five years. The choice of muscles was determined based on clinical evaluation with electromyography.

Statistical analyses

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 for Windows XP. Some results are given as mean ± standard deviation (SD). The differences were considered significant when $p<0.05$.

RESULTS

The age of onset of symptoms varied from 13 to 58 years (mean=39.1±11.6 years). The mean duration of dystonia was 9.1±4.1 (range 1 to 15) years. The mean time between onset of dystonia and the start of BoNT/A treatment was 4.5±3.6 (range 0.5 to 14) years. Head tremor ('no-no' type) was present in six patients (35.2%) and significantly more common in women (83.3%). Of the 17 patients with CD, 94.1% (n=16) had pure rotational torticollis, and only one patient had laterocollis in addition to rotational torticollis. Slightly more than half (52.9%) of patients presented with right-sided CD. One patient had both family history of dystonia and consanguinity. The mean TWSTRS-Severity score was 2.8±0.9 for last application. The acute onset of dystonia was reported in two patients. Pain in the cervical area was noted in 10 patients and the mean rate was 2.5±2.9 based on visual analog pain scale. The adverse effect was noted in four patients. The clinical characteristics of the patients are shown in Table 1.

A total of 181 treatment-sessions with multiple sites injections of BoNT/A were administered during this period. The mean number of applications was 10.64 (range 2 to 25). In most patients (n=15), Dysport® was injected. The interval between BoNT injections was at least three months. The mean duration of BoNT/A treatment was 4.6±2.9 years (range 0.5-10 years). Their mean response rate based on a global assessment efficacy rated on a five-point scale at each visit (4= very good; 3= good; 2= moderate; 1= insufficient; 0= no effect) obtained after the last injection was 3.1±0.5, and the mean total duration of response was 3.0±1.9 months. After dosage adjustment, a significant increase was found between the doses (in unit) of BoNT/A in the first and last injections (531.2±230.2 versus 788.5±259) (p=0.01) and the number of muscles in the first and last injections (2.7±0.7 versus 3.8±0.8) (p=0.005). None of the patients

Table 1. Demographic and clinical variables of patients with cervical dystonia

	n	%	Mean±SD	Range
Number of patients	17			
Age			48.2±12.0	26-69
Age onset			39.0±11.6	13-58
Education				
Illiterate	2	11.8		
Primary education	9	53		
High school	5	29.4		
University	1	5.9		
Women	11	64.7		
Disease duration			9.1±4.3	1-15
Cervical dystonia duration 5 years	15	88.2		
Family history of dystonia	1	5.8		
Duration of the CD before the first BoNT/A			4.5±3.6	0.5-14
Number of patients with head tremor	6	35.2		
Number of patients with pain	10	58.8		
Torticollis	16	94.1		
Right/left deviation	9R/8L			
Acute onset form	2	11.7		

SD: Standard deviation; CD: Cervical dystonia; BoNT/A: Botulinum toxin type A.

Table 2. Summary of BoNT/A treatment in patients with cervical dystonia

	n	%	Mean±SD	Range
Total BoNT/A applications	181			
Mean number of applications			10.6±7.4	2-25
Duration of BoNT/A treatment			4.6±2.9	0.5-10
Patients with adverse effects	4	23.52		

SD: Standard deviation; BoNT/A: Botulinum toxin type A.

developed primary or secondary resistance to the toxin. The treatment characteristics of the patients are shown in Table 2 and 3.

DISCUSSION

The response to long-term BoNT/A treatment is satisfactory in most CD patients.[5,9,10] Since CD is a chronic neurological disorder, long-term BoNT/A treatment is needed in most CD patients. However, although BoNT/A has been used for a long time in the majority of patients with CD,[9,11,12] the long-term BoNT/A treatment evolution is largely unknown.

The question frequently asked by patients -how long this satisfactory well-being obtained with BoNT/A would last- was also the most important purpose of our study. Most patients with CD deteriorate during the first five years and then tend to show slight improvement. [13] Therefore, we divided the 17 idiopathic CD patients into subgroups depending on the disease duration and the period of disease with BoNT/A treatment.

Although the number of our patients may appear as insufficient for evaluation and comparisons, parameters such as mean age at evaluation,[14,15] mean age at onset,[16,17] mean duration of dystonic symptoms,[17] the most frequent type of dystonia[5,14,18-20] and gender distribution are consistent with those reported in previous studies.[21,22]

Table 3. Summary of BoNT/A treatment for last application

	Mean±SD	Range
TWSTRS-S	2.8±0.9	0-4
Onset of response	8.1±7.5	1-30
Mean duration of response	3.0±1.9	0.3-7.5
Mean response rating	3.1±0.5	0-4
Mean dose (units)	788.5±259	
Mean number of muscles	3.8±0.8	
Pain VAS score	2.5±2.9	

SD: Standard deviation; TWSTRS-S: Toronto Western Spasmodic Torticollis Rating Scale; BoNT/A: Botulinum toxin type A; VAS: visual analog pain scale.

As previously reported in the literature,[4,23,24] there was no statistically significant preponderance of right or left deviation in CD. In our series, slightly more than half of the patients had right-sided CD. However, in terms of demographic and clinical features and response to BoNT/A treatment, we did not find a statistically significant difference between right or left deviation groups. Patients with CD typically report a gradual onset of dystonia. However, it is known that there is a history of head or neck trauma in 5% to 21% of patients with CD and the onset of CD may occur following this traumatic event.[23,25,26] Although the acute onset of dystonia was reported in 11.7% of our patients, none of them reported any trauma. Furthermore there was no statistically significant difference between acute and chronic onset with regard to demographic and clinical features and response to BoNT/A treatment.

Some of our data contrast with previous studies that evaluated patients with primary CD. One of our findings that differed from the literature was the small percentage of patients with family history of a movement disorder, which is as high as 44% as reported by Jankovic et al.[1,24] The reported interval between symptom onset and first BoNT/A injection was longer than that reported by Jankovic et al.[27] Since CD is an insidious disease, our patients had presumably delayed medical consultation. Another reason may be related to under- or misdiagnosis. A high incidence of pain was reported in most patients with CD.[17,28,29] However, unlike the previous studies, we find a lower percentage of patients with different degrees of pain in the cervical region in our series.

Whether head tremor in CD patients is a part of the dystonia is a controversial issue and the mechanism underlying them is unknown.[22] Our finding of head tremor in 35% of the patients was much lower than the 80% found by Felicio et al.[16] or the 68.4% found by Pal et al.[22]

None of our patients reported spontaneous remission and none of the patients had primary or secondary resistance.

Adverse effects such as neck weakness and mild transient dysphagia which were reversible, developed in 23.5% of our patients at any application. There was no serious or life-threatening adverse effect and none of the patients discontinued therapy due to adverse effects.

One of the important observations from this study is that the doses of BoNT/A and the number of muscles was statistically more significant at the last application than the first. Another observation from this study is that CD patients with longer duration of disease and period of BoNT/A treatment had similar clinical patterns and BoNT/A responses than those with less.

Consequently, this study has shown that long-term BoNT/A is a safe and most effective therapy for CD and that the duration of disease and duration of BoNT/A treatment do not affect response to BoNT/A treatment. We think that our findings need to be confirmed in a larger series of CD patients.

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