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Original Article / Özgün Araştırma

Retrospective Evaluation of 118 Cervical Dystonic Cases Treated with Botulinum Toxin

Botulinum Toksini Tedavisi Almış 118 Servikal Distonili Olgunun Retrospektif Değerlendirmesi

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Summary

Objective: In this article the aim is to investigate the efficacy and adverse effects of Botulinum toxin. Botox and Dysport were compared when appropriate.
Material and Method: This is a retrospective study. Between July 1996 and July 2006, 470 sessions of botulinum toxin injection were applied to 118 patients with cervical dystonia. The initial time of improvement, duration and degree of improvement, frequency and duration of adverse effects, and when appropriate, differences between Botox and Dysport were analysed.
Results: An average value of 153.4 units (Botox equivalent dose) was used. The patients felt the first improvement after 8.7 days and they returned to their baseline conditions before injection after 2.9 months. Patients expressed 57.5% improvement on average on a visual analog scale. While no side effects were observed in 72.3% of injections, dysphagia was seen in 8.3%, neck pain in 7.7%, weakness in the neck and neck drop in 5.1%, , a change in the type of dystonia in %3.2 , and dry mouth in 2.2%. Aphonia, prickling in the neck, vertigo, itching, ptosis, fatigue, stuffiness, atrophy in neck muscles, syncope during injection was observed in 1.2% of patients. When commercial preperations were compared, average improvement was 58.7% with Botox and 44.1% with Dysport, duration of improvement was 2.9 months with Botox versus 2.3 months with Dysport, and frequency of adverse effects was 25.3% with Botox compared with %62.5 with Dysport.
Discussion: Although results of the previously reported controlled studies are highly variable, our results are within the reported limits. Botox and Dyport were frequently reported to be equivalent when correct dilution ratios were used. In our opinion, the reason Botox is more effective with less frequent adverse effects, in this study, is our having less experience with Dysport and using the incorrect dilution ratio of 1/5 at the time when the study was conducted. *(Turkish Journal of Neurology 2012; 18:104-7)*
Key Words: Cervical dystonia, botulinum toxin, brands of botulinum toxin

Özet

Amaç: Bu makalede amaç botulinum toksininin etkinliği ve yan etkilerini araştırmak ve Botox (onabotilinumtoksinA) ve Dysport (abobotilinumtoksinA) ticari preparatlarının karşılaştırılmasıdır.
Gereç ve Yöntem: Retrospektif bir çalışmadır. Servikal distonili (SD) 118 hastaya Temmuz 1996 ile Temmuz 2006 tarihleri arasında uygulanan 470 seans botulinum toksini enjeksiyonunun dökümü ve analizidir.
Bulgular: En az iki seans enjeksiyon yapılan 78 hasta çalışmaya alınmıştır.
Toplam 430 seans uygulamada hastalara ortalama 153,4 ünite toksin (Botox eşdeğer dozu) uygulanmıştır. Hastalar ilk iyiliği ortalama 8,7 gün sonra hissetmiş ve ortalama 2,9 ay sonra enjeksiyon öncesi durumlarına dönmüşlerdir. Hastalar vizüel analog skalada ortalama %57,5 düzelme oranı bildirmiştir. Enjeksiyonların %72,3'ünde yan etki saptanmamış olup, %8,3'ünde yutma güçlüğü, %7,7'sinde boyun ağrısı, %5,1'inde boyunda güçsüzlük ve öne düşme, %3,2'sinde distoninin şekil değiştirmesi, %2,2'sinde ağız kuruluğu saptanmıştır. Ses kısıklığı, boyunda uyuşma hissi, dengesizlik, kaşıntı, ptoz, halsizlik, burun tıkanması, boyun kaslarında erime, enjeksiyon sırasında senkopa %1,2 oranında rastlanmıştır. Botox uygulanan hastalarda ortalama iyileşme %58,7, etkinlik süresi 2,9 ay, yan etki görülme oranı %25,3, buna karşılık Dysport uygulanan hastalarda ortalama iyileşme %44,1, etkinlik süresi 2,3 ay, yan etki görülme oranı ise %62,5 olarak saptanmıştır.
Sonuç: Yayınlanan kontrollü çalışma sonuçları çok değişken olup bu çalışmada hesaplanan klinik parametreler daha önce bildirilen sınırlar içerisindedir. Daha önce yapılan Botox ve Dysport ticari preparatlarının karşılaştırma çalışmalarında sonuçlar değişkenlik göstermektedir. Uygun sulandırma oranları kullanıldığında birbirinden farklı olmayan ticari preperatların bu dökümde farklı çıkmalarının nedeni, bizce, çalışmanın yapıldığı dönemde Dysport deneyimimizin yetersiz oluşu ve uygun olmayan bir eşdeğer doz kullanmış olmamız olabilir. *(Türk Nöroloji Dergisi 2012; 18:104-7)*
Anahtar Kelimeler: Servikal distoni, botilinum toksini, botulinum toksini ticari formlar

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Introduction

Cervical dystonia (CD) (spasmodic torticollis) is a mobility disorder resulting from contorting, turning, involuntary and lengthy muscle contractions and characterized with abnormal head and neck posture. It is the most common form of focal craniocervical dystonias (1), and mostly idiopathic. The incidence of CD was found to be 0.39%, 0.009% and 0.006% in various studies (2,3,4). Onset is usually between ages 30 and 50, and it affects women more frequently than men (5,6). The most common type of CD is rotational torticollis (twisting of the neck); it may also present as laterocollis (sideways tilting of the neck), retrocollis (extension of the neck), anterocollis (flexion of the neck) and a combined form of these four clinical forms (7). Most of the patients complain of disabling neck pain as well as contractions (8). Muscle hypertrophy and tremor of the head can also be seen (9). It is possible to correct the abnormal head ane neck posture for varying periods by touching the chin, cheek, neck or the forehead; this is known as a sensory trick (geste antagonistique) (10). CD causes dysfunction in many patients, difficulties in driving, daily activities including self-care, as well as shyness (social anxiety) and anxiety (11). Medical treatment options in CD include tryhexyphenidyl, baclofen, benzodiazepines, clozapine, tetrabenazine and dopamine receptor antagonists (12,13). Botulinum toxin was shown to be a safe and effective treatment method in patients with CD (14,15). Selective peripheral denervation, globus pallidus deep brain stimulation may be the preferred surgical treatment options for patients not benefiting from medical treatment (13). We investigated the time to first improvement, efficacy of treatment, time to return to pre-injection status, side effects following administration in CD patients after botulinum toxin was administered, as well as the comparison of Botox (Btx hereafter) and Dysport (Dys hereafter) for effectiveness, duration of efficacy and side effects.

Materials and Methods

One hundred and eighteen (118) patients (68 female, 50 male) diagnosed with CD between July 1996 and July 2006 were evaluated retrospectively. Patients included in the study had at least two coursed of botulinum toxin treatment. Information on the patients' ages, total number of botulinum injection courses, quantity of toxin administered (as units per muscle), when patients felt the first improvement after the injection (as days), corresponding percentage of this improvement on the visual analog scale (VAS), the duration of improvement, side effects, duration of side effects, and the commercial product used (Btx vs Dys) was entered in a database and evaluated.

Results

The average age of the patients was 39.0 years. The total number of courses was 470, with an mean number of courses of 5.5 (range: 1-24). Seventy-eight (78) patients among the 118 had at least two injections administered and these patients were included in the study. A total of 430 injections were administered to these 78 patients in a mean 5.5 (range 2-24) courses. Patients received an average or 153.4 units of toxin (Btx equivalent dose) (range 40-310), and they felt the first improvement after 8.7 (mean, range 1-30) days, reported an improvement rate of 57.5% (range 0-100) on VAS, and this improvement lasted for 2.9 months (range 0-36 months).

No side effects were observed in 72.3% of the injections, whereas patients experienced dysphagia in 72.3%, neck pain in 7.7%, weakness and falling forward in 5.1%, change in the type of dystonia in 3.2%, and dry mouth in 2.2%. Hoarseness, numbness in the neck, loss of balance, itching, ptosis, weakness, nasal congestion, atrophy in neck muscles and syncope during injection are side effects seen at a rate of 1.2% (Table 1).

The Btx patient group returned to pre-injection status in 2.9 months (range 0-36), whereas the mean duration of effect in the Dys patient group was found to be 2.3 months. In a cohort of 78 patients who had received at least two courses of injections, the mean improvement on VAS was 58.07% (range 0-100) for Btx patients, and 44.1% for Dys patients (Table 2).

The mean rate of side effects was 25.3% in Btx patients, and 62.5% in Dys patients. When the effectiveness of Btx and Dys preparations was compared, Btx was found to be statistically significantly more effective, whereas duration of effect was similar in both preparations ($p=0.622$) (Table 2). Comparing side effects in the two patient groups, it was seen that side effects occurred statistically significantly more frequently in the Dys patient group ($p<0.001$) (Table 2).

Discussion

Botulinum toxin is the initial and most effective treatment option in CD (16,17). Here we compare our findings with those from other studies. The mean duration of improvement in our study was 2.9 months, whereas it was reported in literature as 3.8 months by Bhaumik et al. (18) and 3.9 months by Brashear et al. (19). In our study, it took the patients an average of 8.7 days to feel any improvement; Bhaumik et al. reported the time to improvement as 9.7 in another study (18). In the study by Benecke et al. where only Btx was administered, the first improvement was reported after 7.2 days (20). In our study, mean rate of improvement in CD following botulinum toxin injection was

shown to be 57.5%, whereas Skogseid et al. and Haussermann et al. reported mean rates of improvement of 67% and 86%, respectively (21,22). The most common side effect after botulinum toxin injection in our study was dysphagia, with a rate of 8.3%; this finding is consistent with previous studies. Dysphagia was reported to occur by Benecke et al. as 8.2% (20), by Skogseid et al. as 28% (21), and by Haussermann et al as 15% in a group administered exclusively Dys (22). Marchetti et al. compared the dose – effect of Dys and Btx, and reported that dysphagia was the most common side effect with both preparations (23). In this study, 12 of the 130 patients (9.2%) administered Btx injections had dysphagia, whereas 19 of 63 patients (30.1%) administered Dys had the same side effect. No side effects were seen in 72.3% of the patients administered botulinum toxin injections in our clinic. The percentage of patients not experiencing any side effects in literature vary between 89.6% in a study by Bhaumik et al. (18), 88.3% reported by Brashear et al. (19) and 42% by Skogseid et al. (21).

Botulinum toxin is available in two commercial products, Dysport and Botox, which contain 500 units of Clostridium botulinum type A toxin-hemaglutinine complex, and 100 units with 0.9 mg sodium chloride and 0.5 mg albumin, respectively (7). In addition, Dys and Btx contain 12.5 ng and 5 ng protein, respectively (23). In our study, the rate of improvement was 58.7% in Btx patients, and 44.1% in Dys patients. Truong et al. reported an improvement rate of 38% in another study for the effectiveness of Dys (7). In our study, the duration of effect was 2.9 months and 2.3 months with Btx and Dys, respectively. Benecke et al. report that the duration of effect for Btx was 3.1 months (20), whereas Naumann et al. report 3.4 months of improvement with Btx (24). In other studies with Dys, duration of effect was found to be 4.5 months by Haussermann et al. (22) and 4.6 months by Truong et al. (7). In our clinic, side effects occurred at a rate of 25.3% with Btx and 62.5% with Dys injections. The rate of side effects in the Btx study of Benecke et al. was 24.1% (20), whereas this rate was 31-34% in the Btx study of Naumann et al. (24). On the other hand, side effects were reported at a rate of 34% by Hausserman et al. (24), 43% by Wissel et al. (27), and 92% by Truong et al (7) following Dys injections. In our study, consistent with previous studies, we found that botulinum toxin is effective in the treatment of CD. The percentage of patients with no side effects (72.3%) in our study confirms the safety and low side effect rate of botulinum toxin treatment in CD, in addition to its effectiveness. The difference between our findings and previously published findings may be due to the retrospective nature of our study.

Table 1. Rate of occurrence of side effects in patients administered Botulinum toxin

Side Effects	Rate of Side Effects
Non	72.3%
Dysphagia	8%
Neck pain	7.7%
Weakness in the neck, difficulty holding head erect	5.1%
Change in the type of dystonia	3.2%
Dry mouth	2.2%
Other (hoarseness, numbness in the neck, loss of balance, itching, ptosis, weakness, nasal congestion, atrophy in neck muscles and syncope during injection)	1.2%

Table 2. Comparison of Botox – Dysport

	Botox (245 courses)	Dysport (22 courses)	p
Duration of effect (months)	2.9	2.3	0.622 (T test)
Rate of improvement	58.1%	44.1%	0.025 (T test)
Rate of side effects	25.3%	62.5%	<0.001 (Chi square test)

Studies comparing the commercial products, Btx and Dys in CD, are found in literature. Odergen et al., in their 1998 study with 73 CD patients (equivalent dose ratio Btx/Dys:1/3) did not find a significant difference between Btx and Dys patients for effectiveness and side effects (26). Ranoux et al., in their 2002 study of 54 CD patients, divided the patients into 3 groups: those administered only Btx, injected with an equivalent dose ratio of Btx/Dys:1/3 and 1/4. The randomized and double-blind groups were evaluated for efficacy and side effects. Side effects were seen in 17% of the only-Btx group, compared to 33% in the equivalent dose ratiot 1/3 group and 36% in the 1/4 group. Similar to our study, the most common side effect was dysphagia, its frequency was high in both Dys groups. Duration of effect was 93 days in the Btx group, compared to 97 days and 117 days in the equivalent dose ratio 1/3 and 1/4 groups, respectively (27).

In conclusion, the reason for the difference in these findings between two commercial products that are similar when appropriate dilution ratios are used, may be our lack of experience with Dys at the time of this study, and using an inadequate equivalent dose (Btx/Dys=1/5). Currently, it is recommended to use a patient-specific dilution rate for each commercial product (23).

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