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Comparison of two Different Formulations of Botulinum Toxin a for the Treatment of Blepharospasm and Hemifacial Spasm

Blefarospazm ve Hemifasiyal Spazmda Botulinismus Toksininin İki Farklı Formülünün Karşılaştırılması

Chuan-jie WU, Ji-hong SHEN, Yuan CHEN, Ya-jun LIAN

The First Affiliated Hospital of Zhengzhou University, Department of Neurology, Zhengzhou, China

Correspondence address: Lian YA-JUN / E-mail: lianyajun369@gmail.com

ABSTRACT

AIM: Aim: To confirm and compare the therapeutic efficacies and adverse effects of Chinese botulinum toxin type A (CBTX-A, Lanzhou Biological Products Institute, China) and current Botox (Allergan Inc., CA, USA) in the treatment of blepharospasm (BS) and hemifacial spasm (HFS).

MATERIAL and METHODS: We performed an open, prospective, comparative trial comparing CBTX-A and Botox for the treatment of BS and HFS in 273 patients since 2006. 107 patients were treated with current Botox and166 with CBTX-A, with the age, disease durations and severity of spasm matched. The patients enrolled were followed up for 6 months.

RESULTS: There were no significant differences in the clinical effects of the two preparations, including the onset of response, peaked effect time and duration of effects ($p>0.05$). The Cohen scores showed a significant reduction after BTX-A injections. Considerable improvement of symptoms for the BS and HFS patients was observed 7days, 4weeks, 12weeks, and 24 weeks after the injection with either current Botox or CBTX-A ($p<0.05$). There was no significant difference in the effectiveness rate for both HFS patients and BS patients between CBTX-A group and Botox group ($p>0.05$). No statistical differences were noted in adverse reactions between them ($p>0.05$).

CONCLUSION: The two preparations were both simple and effective for the patients with blepharospasm and hemifacial spasm.

KEYWORDS: Botulinum toxin type A, Blepharospasm, Hemifacial spasm, Comparison

ÖZ

AMAÇ: (CBTX-A, Lanzhou Biological Products Institute, China) Blefarospzm ve hemifasial spazmda Çin üretimi (CBTX-A, Lanzhou Biological Products Institute, China) Botulinismus toksininin (Tip A) etkinliği ile Amerikan üretimi Botulinismus toksininin (Allergan Inc., CA, USA) etkinliği karşılaştırılmıştır.

YÖNTEM ve GEREÇLER: Prospektif karşılaştırmalı çalışmada Çin üretimi (CBTX-A, Lanzhou Biological Products Institute, China) Botulinismus toksininin (Tip A) etkinliği ile Amerikan üretimi Botulinismus toksininin (Allergan Inc., CA, USA) etkinliği bleforaspazmı veya hemifasial spazmı olan 273 hasta üzerinde 2006 yılından başlanarak incelenmiştir. Hastalardan 107'sine Amerikan üretimi Botulinismus toksini (Allergan Inc., CA, USA) verilirken 166 hastaya Çin üretimi Botulinismus toksini (CBTX-A, Lanzhou Biological Products Institute, China) blefarospazm ve hemifasial spazmda tedavi için kullanılmıştır. Hastaların yaşı, hastalığın süresi ve spazmların şiddetleri tedavi sonrası 6 ay boyunca takip edilmiştir.

BULGULAR: Etkinin başlama süresi, etkinin en üst düzeye ulaştığı dönem ve etkinliğin süresi göz önüne alındığında iki farklı madde arasında anlamlı bir fark saptanmadı ($P>0.05$). Çin malı toksinin injeksiyonundan sonra Kohen ölçütlemesine göre belirgin düşüş gözlendi. Her iki farklı üretim toksininin injeksyonundan sonra 7. gün, 4. hafta, 12. hafta ve 24. haftada bleforaspazm ve hemifasial spazmda belirgin düzelmeler görüldü ($p<0.05$). Her iki farklı toksinin etkinliği ve yan etki sıklığı arasında anlamlı bir fark bulumamıştır ($p>0.05$).

SONUÇ: Bleforospazm ve hemifasial spazmda basit bir uygulama ile kullanılan iki farklı Botulinismus toksini arasında etkinlik açısından fark saptanmamıştır.

ANAHTAR SÖZCÜKLER: Tip A botulinismus toksini, Blefarospazm, Hemifasiyal spazm, Karşılaştırma

INTRODUCTION

Blepharospasm (BS) and hemifacial spasm (HFS) are two chronic distressing and embarrassing movement disorders in the neurology department. BS is a form of focal dystonia characterised by involuntary spasmodic closure of eyelid on one or both sides. In contrast, HFS is a disorder characterised by episodic and intermittent twitching, tonic spasm and synkinesis of the muscles of one side of the face innervated by the facial nerve. These two neurological disorders are fundamentally different in nature, but can be treated in the same fashion. Botulinum toxin type A has been reported to provide excellent symptomatic relief for patients with BS and HFS.

Botulinum toxin type A is used with remarkable success to treat various muscle hyperactivity syndromes by inhibiting the release of acetylcholine from vesicles at the presynaptic nerve terminal at the neuromuscular junction.The FDA approved the use of Botox (Allergan, Inc, Irvine, CA, USA) for the treatment of strabismus, blepharospasm, and focal spasms including hemifacial spasm in 1989. Subsequently, the use of these toxins is skyrocketing and different formulations are available worldwide. To reduce the risk of antibodies (ABF), a new formulation of Botox with increased specific biological potency was introduced in 1997 and this was the current Botox (Allergan, Inc, Irvine, CA, USA). Chinese botulinum toxin type A (CBTX-A, Lanzhou Biological Products Institute) has been approved for clinical use by the Ministry of Health in China since October 1993. There are few articles comparing the two different formulations. Tang X (8) conducted a clinical study retrospectively to compare the therapeutic efficacies and remote effects of CBTX-A and the precious Botox (before 1997). Rieder (6) treated 8 Blepharospasm and 18 Hemifacial Spasm patients. Quagliato (5) treated 21 Blepharospasm and 36 Hemifacial Spasm patients. Both studies were conducted in Brazil and the authors concluded that current Botox and CBTX-A had similar efficacy and safety. As there is little information about CBTX-A and current Botox, we have been collecting relevant data ever since 2006 in China.

METHODS and PATIENTS

Patients

All included patients, between the ages of 21 and 82, had a confirmed diagnosis of essential blepharospasm or hemifacial spasm. The patients were recruited from the outpatients who attended the neurology department of the First Affiliated Hospital of Zhengzhou University since 2006. All patients gave their written informed consent for participating in the study, which was approved by the ethical committee of our institution. After a complete neurological evaluation, 273 patients were divided into CBTX-A group and current Botox group, according to their wishes. As is shown in Table I, there was no difference in the distribution of age, sex, disease duration and severity of spasm between the two groups in both the BS and HFS patients ($p>0.05$).

Inclusion and Exclusion Criteria

Inclusion criteria

The following requirements had all to be met for entry into the study:

1. Patient has a confirmed diagnosis of primary blepharospasm or hemifacial spasm
2. Patient was never treated with BTA or had not underwent the procedure for the previous 24 weeks
3. Patient was older than 18 years

Exclusion criteria

The following were grounds for exclusion from participating in the study:

1. Patient had a neuromuscular junction transmission disorder or was taking any medications (e.g., pyridostigmine, neostigmine, dantrolene, tubocurarine, streptomycin, aminoglycosides) that could affect neuromuscular junction transmission
2. Patient was involved in another investigational drug study or participating in a clinical trial during the relevant chart review period
3. Patient had an unstable medical condition (e.g., diabetes, hypertension, heart surgery)
4. Patient was hypersensitivity to BTA or to the components in the formula
5. Patient had active infection or inflammation on face
6. Patient was in pregnancy or puerperium
7. Patient was postsurgical or after Bell palsy hemifacial spasm or with known contraindications to BTX-A

Treatment, Follow-up, Spasticity-grading

Patients were randomized to CBTX-A or Botox at the usually effective dose, at a ratio of 1:1 (1 CBTX-A unit=1 Botox unit). The potency of each preparation was expressed in units, 1 unit representing the estimated LD50 for mice. Each 100-U BTX-A vial was reconstituted with 2 mL of 0.9% sterile saline solution (5 U/0.1 mL) and injected within 4 hours to ensure its efficacy. The dose of BTXA per injection site was 2.5 to 5 U. Patients were evaluated every week after injections. Efficacy variables assessed were as follows: onset of response, duration of effect, changes of spasm degree, and adverse events. The severity of spasm for both BS and HFS was graded clinically from grade 0 to grade 4 according to Cohen's scale (2): 0-no spasm; 1- mild spasm at stimulation only; 2- visible spasm without impairment of daily life; 3- visible spasm with impairment of daily life; 4- severe spasm with impairment of daily life.

Statistical Analysis

Data were analyzed with the SPSS V13.0 software package. The quantitative data were assessed using the Median or Mean ± SD ($\chi \pm s$). The u-test and t-test were performed to show the age, duration of disease, onset time, peak effect time and duration of the effect between CBTX-A and current Botox. The χ^2 test was performed to show the differences of their gender, efficiency, effective rate and adverse events; the Ridit analysis was used to show the changes of the grade level before and after treatment. A P value of 0.05 was set for statistical significance.

RESULTS

1. The onset of response, peaked effect time and duration of effect between CBTX-A and current Botox

There were no differences between the two formulations for all efficacies including the onset of response, peaked effect time and duration of effect ($p>0.05$), as shown in Table II.

2. The changes in severity of spasm.

The Cohen scores showed a significant reduction after BTX-A

Table I: Demographic Characteristics of the Patients (n=273)

	CBTX-A (n=131)	Botox (n=95)	P
HFS Age	45.83±9.25	45.30±11.80	>0.05
F:M	53:78	31:64	>0.05
Durations	49.36±34.31	45.12±31.97	>0.05
SS pre-injection 1 2 3 4	 2 20 72 37	 2 12 44 37	>0.05
BS Age	54.19±10.40	57.12± 11.78	>0.05
F:M	14:21	3:9	>0.05
Durations	47.33±36.52	36.06±30.31	>0.05
SS pre-injection 1 2 3 4	 2 6 14 13	 2 3 4 3	>0.05

*Data are shown as mean±SD, * t-test (age), *Mann-Whitney U test (other data); χ2 test were used for statistically analysis. **F**=female; **M**=male; **n**=number; **SS**=severity of spasm.*

Table II: Comparison of Effects between CBTX-A and Botox (t-test)

HFS	CBTX-A	Botox	P
Onset of response (days)	4.40±1.64	4.16±2.43	>0.05
Peaked effect time (days)	11.81±1.42	8.25±4.55	>0.05
Duration of effect (weeks)	16.21±19.54	16.50±5.92	>0.05
BS	CBTX-A	Botox	P
Onset of response (days)	3.21±1.88	5.25±2.01	>0.05
Peaked effect time (days)	7.50±5.40	7.75±4.69	>0.05
Duration of effect (weeks)	11.55±2.11	17.58±5.34	>0.05

injections and considerable improvement of symptoms for the BS and HFS patients was observed 7days – 4weeks - 12weeks - 24weeks after the injection with either current Botox or CBTX-A. By definition, the expected value of R for the reference data set is always 0.5. As is shown in Table III and Table IV, the severity of spasm changed greatly after the injection, and the R values were all greater than 0.5 at 7d - 4 wk - 12 wk - 24 wk after the treatment, indicating that the differences of SS were significant between CBTX-A and Botox for both HFS and BS patients ($p<0.05$).The R value decreased and was close to 0.05 12wk and 24 wk after the injection, indicating that some patients relapsed.

3. Effective rate

As is shown in Table V, 4 weeks after the injection, there was no difference in the effective rate between CBTX-A (97%) and Botox (99%) for HFS patients ($p>0.05$). At the same time, there was no difference in the effective rate between CBTX-A (100%) and Botox (100%) for BS patients ($p>0.05$).

4. Adverse events

There was no difference in the occurrence of each type of adverse events between the two formulations, as shown in Table VI ($p>0.05$). Tightness in face and droopy mouth, the two most common adverse effects reported, were similar in both groups. There were no serious adverse events.

DISCUSSION

Botulinum toxin A injections are a well-established treatment for blepharospasm and hemifacial spasm. Botulinum toxin A is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulphide bond to a 50-kDa light chain. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular

junction, preventing vesicles from anchoring to the membrane to release acetylcholine. By inhibiting acetylcholine release, the toxin interferes with nerve impulses and causes flaccid paralysis of muscles in botulism, as opposed to the spastic paralysis seen in tetanus.

BOTOX for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A, and intended for intramuscular and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying. Each

Table III: Comparison of SS between CBTX and Botox in HFS (Ridit analysis)

	CBTX-A 4 3 2 1 0 R ± S	Botox 4 3 2 1 0 R ± S
0d	37 72 20 2 0 0.50	37 44 12 2 0 0.50
7d	0 8 5 44 34 0.94±0.26	1 21 28 24 21 0.91±0.27
4w	0 4 8 45 74 0.98±0.26	0 2 13 23 57 0.98±0.27
12w	0 8 12 46 65 0.96±0.26	0 7 12 24 27 0.96±0.27
24w	12 45 40 30 4 0.74±0.26	7 17 20 27 24 0.85±0.27

Table IV: Comparison of SS between CBTX and Botox in BS (Ridit analysis)

	CBTX-A 4 3 2 1 0 R ± S	Botox 4 3 2 1 0 R ± S
0d	13 14 6 2 0 0.50	3 4 3 2 0 0.50
7d	0 9 10 12 4 0.84±0.32	0 3 3 5 1 0.75±0.35
4w	0 0 8 6 21 0.96±0.32	0 0 3 4 5 0.90±0.35
12w	0 1 7 6 21 0.90±0.32	0 1 2 4 5 0.88±0.35
24w	0 7 7 13 8 0.82±0.32	0 3 2 5 2 0.77±0.35

Table V: Comparison of Effects Between CBTX-A and Botox (4weeks after the treatment) (χ^2 test)

	HFS		BS	
	CBTX-A (n=131)	Botox (n=95)	CBTX-A (n=35)	Botox (n=12)
Complete remission	74 (56%)	57 (60%)	21 (60%)	5 (42%)
Obvious remission	37 (28%)	32 (34%)	9 (26%)	4 (33%)
Partial remission	16 (12%)	5 (5%)	5 (14%)	3 (25%)
Invalidation	4 (3%)	1 (1%)	0 (0%)	0 (0%)
Effective rate	127 (97%)	94 (99%)	3 (100%)	12 (100%)
P value	>0.05		>0.05	

Table VI: Number of Patients with Clinical Adverse Effects (n = 273)

Adverse Events	CBTX-A(n=166)	Botox (n=107)	χ^2	P
Tightness in face	35 (21.1%)	17 (15.9%)	1.139	0.286
Droopy mouth	19 (11.4%)	12 (11.2%)	0.003	0.953
ptosis	8 (4.8%)	4 (3.7%)	0.015	0.902
Entropion/Ectropion	13 (7.8%)	3 (2.8%)	2.981	0.084
Ecchymosis	7 (4.1%)	1 (0.9%)	1.445	0.229
Flu-like symptoms	3 (1.8%)	2 (1.9%)	0.000	1.000
Eyelid edema	2 (1.2%)	1 (0.9%)	0.000	1.000
Epiphora	1 (0.6%)	1 (0.9%)	0.000	1.000
Blurred vision	4 (2.4%)	1 (0.9%)	0.191	0.671
Lower eyelid back	2 (1.2%)	1 (0.9%)	0.000	1.000

vial of BOTOX contains 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride, vacuum-dried form without a preservative. Current Botox with increased specific biological potency was introduced to reduce the risk of ABF; with current Botox, the specific biological potency could be increased from 4 MU/ng neurotoxin-non-toxic protein complex of previous Botox to 20 MU/ng neurotoxin-non-toxic protein complex (4).As a consequence, the risk of ABF in patients with cervical dystonia could be reduced from about 5% to, 1%.3 However, there was a case reported indicating that current Botox does not eliminate the risk of ABF entirely (3).

CBTXA has not been widely investigated. Each vial of CBTXA contains 100 Units of Clostridium botulinum type A neurotoxin complex, 5mg of gelatin, 25mg of dextran, and 25mg of saccharose, which is different from BOTOX. In a small crossover study with 8 BS and 18 HFS patients, CBTX-A appeared to provide equivalent global improvement, onset time to response, and duration of efficacy with a similar side effect profile to BOTOX (6). Long-term data from 305 patients with hemifacial spasm, blepharospasm and cervical dystonia have conformed that the injection of CBTXA significantly improves the quality of life of most patients and it is a safe, effective and comparatively economical treatment (9).

The availability of the most common botulinum toxins to treat dystonias and hemifacial spasm has led to a debate concerning the comparative effectiveness and safety and the dose equivalency ratio that should be used in clinical practice (7). This study compared the therapeutic efficacies and adverse effects between CBTX-A and current Botox for the treatment of BS and HFS. The conclusion was in accordance with a previous Brazilian crossover study (6), which demonstrated that there were no differences in short-term efficacy or safety between these two toxins for BS and HFS treatments. Tang XF (8)compared CBTX-A and the precious Botox, and indicated that both preparations are safe and effective for patients with focal dystonia and muscle spasm. In our study, patients were treated with the same dosage, dilution of CBTX-A or current Botox in the same way. The results showed that there were no significant differences in the latency of response, maximal benefit, duration of improvement, the effective rate and the adverse reactions. We concluded that the two formations are equally safe and effective in the treatment of BS and HFS, which is in accordance with the literature (5, 6). Both studies of Rieder et al. and Quagliato et al. were conducted in Brazil. All the patients in our study were Chinese but we reached the same conclusion. This shows that current Botox and CBTX-A are comparable in the treatment of blepharospasm and hemifacial spasm in different ethnic groups.

The two products also have some differences. Botox contains a certain proportion of human serum albumin, an ingredient of blood, so it has the potential dangers of antigenicity. Gelatin, contained in the CBTX-A, is a potent skin sensitizer. CBTX-A can cause skin allergies after any exposure, so it has greater hypersusceptibility than Botox. Erythra was reported a few days after the injection with CBTX-A, which may due to the composition and purity of the preparation, because this has not yet been reported in the application of Botox. The current Botox contains lower toxin protein, so the possibility of antibody production is smaller than CBTX-A. Brin reported that no immune resistance was found in patients with continuous treatment for cervical dystonia with current Botox (1). In this study we did not compare the doses of the two drugs statistically, but the patients treated with Botox were more prone to adverse reactions such as ptosis, mouth drooling and facial hair tight than CBTX-A, even if they were similar in age, body type, spasm grade, or they were injected at the same site with the same dosage. We concluded that unit dose Botox may have stronger efficacy than CBTX-A, and maybe this was also associated with stability of the agent or measurement of detecting the biological activity. In addition, the price of Botox is 2-3 times higher than CBTX-A, which limits the clinical application of Botox. As seen in our study, 131 patients chose CBTX-A because of economic reasons, Compared 95 with Botox, the patients treated with Botox are less than those with CBTX-A for both HFS and BS patients.

In conclusion, local injection of BOTOX or CBTX-A is a safe, effective and feasible treatment, and our results suggest that current Botox and CBTX-A are comparable in the treatment of blepharospasm and hemifacial spasm. As botulinum toxin treatment is considered as a high-cost neurological treatment, our findings increased the clinical data about CBTX-A and could be of interest from a pharmacoeconomic point of view, especially in developing countries.

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