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Double-Blind, Randomized, Comparative Study of Meditoxin® Versus Botox® in the Treatment of Essential Blepharospasm

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Purpose: To compare the efficacies and safeties of Meditoxin® (Medy-Tox, Korea) and Botox® in the treatment of essential blepharospasm.
Methods: We performed a double-blind, randomized, comparative trial comparing Meditoxin® and Botox® for treatment of blepharospasm in 60 patients from the intention-to-treat (ITT) population and 52 patients from the per-protocol (PP) population. We analyzed the improvements in severity of spasm (SS) at four weeks post-injection as a primary efficacy outcome. Changes in eyelid closing force (CF) and functional visual status (FVS) after injection were analyzed for secondary efficacy outcomes, and adverse effects were demonstrated for the safety evaluation.
Results: Improvement in SS was noted in 90.3% of the Meditoxin® group and 86.2% of the Botox® group. There were no significant differences between treatment groups in the changes of CF and FVS post-injection (p>0.05). Since the lower limit of the 95% confidence interval (-1.76% for ITT, -1.64% for PP) was over the -15% threshold, we determined that Meditoxin® was not inferior to Botox® in either the ITT or PP populations. Adverse effects developed in 16.1% of the Meditoxin® group and 27.6% of the Botox® group, but no serious adverse events were found in either group.
Conclusions: Meditoxin® and Botox® were comparable in efficacy and safety in the treatment of essential blepharospasm.

Key Words: Botox®, Essential blepharospasm, Meditoxin®

Botulinum toxin type A (BTX-A) is currently the first treatment of choice for benign essential blepharospasm due to its safety and efficacy. Scott and coworkers first used isolated BTX-A to treat blepharospasm over 20 years ago.[1] Since then, a number of BTX-A preparations have been approved in different countries. Currently, there are four different BTX-A preparations available on the market in one or more countries, all of which contain Botox® (Allergan Inc., Irvine, CA, USA),[2-5] Dysport (Ipsen Ltd, Slough, UK),[6-8] Xeomin (Merz Pharmaceuticals, Frankfurt am Main, Germany)[9] and Prosigne (Lanzhou Biological Products, China).[10] Several studies have compared the different formulations of BTX-A for the treatment of blepharospasm with regard to duration of the effect or adverse events.[2-11] Recently, equivalent efficacies were reported for Xeomin and Prosigne with Botox®.[9, 10]

Meditoxin® (Medy-Tox, Seoul, Korea another name: Neuronox®) was introduced for the treatment of BTX-A and is currently available in Korea. In a murine model, a dose-response curve and time course of recovery for Meditoxin® (Neuronox® in this study) were established.[12] Botox® and Meditoxin® produced a nearly equivalent decrease in muscle force (30-90%) at four days after toxin injection, and the muscle force had recovered from the effects of both toxin preparations at 28 days post-injection.[12] As there was little information about the clinical efficacy and safety of Meditoxin®, we set out to perform a double-blind, randomized, controlled clinical study designed to compare Meditoxin® and Botox® in the treatment of essential blepharospasm. This is the first report to compare the treatment efficacies and safeties of Meditoxin® and Botox®. In addition, we qualitatively evaluated the presence and absence of BTX-A antibodies in patients after the disappearance of the therapeutic effects in both Botox® and Meditoxin® groups.

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Materials and Methods

Study design

Table 1. Scoring definition for severity of spasm, eyelid closing force and the functional visual status

Severity of spasm	
Grade	Definition
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
Eyelid closing force	
Grade	Definition
1	Flaccid
2	Overcome with minimum resistance
3	Overcome with moderate resistance
4	Normal strength
Functional visual status	
Grade	Definition
1	Functional blindness
2	Dependent; unable to go out alone
3	Poor function; unable to watch TV, read or drive
4	Moderate function; unable to read but able to work
5	Inconvenience; intermittent discomfort but able to drive, work
6	Normal

This double-blind randomized, prospective, multi-center, phase III, comparative clinical trial was conducted ethically and scientifically in accordance with KGCP (Korean Good Clinical Practice) guidelines and the principles of the Declaration of Helsinki. The study protocol, protocol amendments, patient information and informed consent forms were reviewed and approved by the KFDA (Korean food drug administration) and the institutional review board at each institution site prior to study initiation. All participants in the study signed a consent form approved by the institutional review board.

Study population

All included patients, between the ages of 18 and 75, had confirmed diagnoses of bilateral essential blepharospasm. The patients were recruited from two botulinum toxin clinics (Yonsei University and Chung-Ang University, Seoul, Korea) between June 7, 2005 and September 27, 2005. Patients were not included in the study if they had undergone either myectomy or neurectomy, had received anti-spastic, muscle relaxant medication within one month of study entry, had been injected previously with BTX-A within three months of study entry, or had any muscle disorder. Women with a positive urine pregnancy test, or who were pregnant or lactating, were also excluded from the study. In addition, patients who had previously shown hypersensitivity to BTX-A were not eligible for inclusion in the study.

Randomization and assessor blinding

At each center, eligible patients were randomly assigned to either the Meditoxin® or Botox® group according to a computer-generated randomization schedule, and all of the randomized patients were part of the intention-to-treat (ITT) population. A pack containing one vial of study medication was allocated to each patient. Investigators were blinded throughout the study to the treatment dose and type of treatment. A double-blind method was maintained until the results were analyzed. The per-protocol (PP) population excluded patients who violated the protocol and did not complete the study.

Study medications and injections

Each vial of Botox® (Allergan Inc., Irvine, CA, USA) and Meditoxin® (Medy-Tox, Seoul, Korea) contained 100 U of BTX-A, 0.5 mg of serum albumin, and 0.9 mg of sodium chloride in a sterile vacuum-derived form without preservatives. The Meditoxin® vials were identical to the Botox® vials, and all vials were reconstituted with 2.0 mL of 0.9% sterile, non-preserved saline solution for a final dilution of 5 U/0.1 mL. Two independent investigators blindly prepared and administered the BTX-A. The dose of BTX-A per injection site ranged from 2.5 U to 5 U, and the location, number of injection sites, and total dose of each treatment were maintained throughout the study. When the patient was treated with BTX-A for the first time, the dose per injection was 1.25 to 2.5 U. The total dose was limited to 60 U per person. Using a 30-gauge needle, injections were angled away from the center of the lid to reduce the risk of spread into the levator muscle. Injection sites included the upper medial and lateral eyelid margins, lower lateral lid margins and above the eyebrow.

Outcome Measures

The severity of spasm (SS) was graded clinically from grade 0 to 4 (Table 1).[13,14] The primary efficacy outcome was assessed as the number (%) of patients with an improvement in SS of more than one grade at four weeks post-injection. Secondary efficacy outcome measures included the change in SS scores from baseline, closing force of eyelids (CF)[13] and functional visual status (FVS)[14] at four weeks post-injection (Table 1). The duration of action (days), which was the time interval

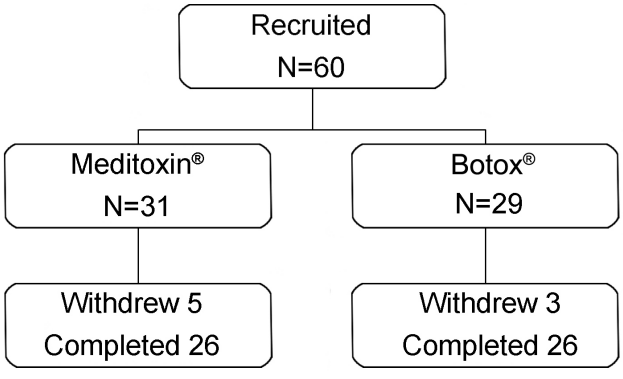

Fig. 1. Flow of patients throughout the trial. N, number of patients with data.

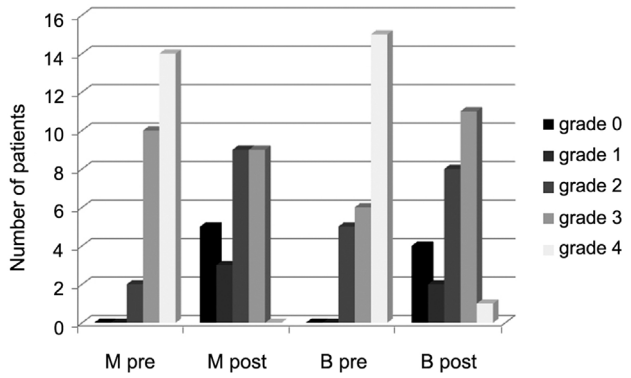

Fig. 2. Distribution of severity of spasm scores (grade 0-4) before injection and at four weeks after injection in both Meditoxin® and Botox® treatment groups.
M pre, Meditoxin® group before injection; M post, Meditoxin® group at four weeks post-injection; B pre, Botox® group before injection; B post, Botox® group at four weeks post-injection.

between injection and the moment that the patient felt the need for retreatment, was also subjectively assessed based on the patients' self-reports at the time of retreatment. Patients in the PP populations were assigned to a group according to the BTX-A application number; patients with five BTX-A injections or less were classified as the L group and those who had more than five injections were classified as the H group. In both the L and H groups, both primary and secondary efficacy outcomes were compared between the Meditoxin® and Botox® groups.

To evaluate safety, adverse effects were documented and classified as either not serious or serious. Serious side effects included debilitating symptoms such as an obscured visual axis lasting for more than three months.

BTX-A antibody testing was performed using a mouse diaphragm assay.[15] Serum samples were collected before injection and after the disappearance of the BTX-A effect. Blood samples were refrigerated at -20℃ prior to analysis for Botulinum toxin antibodies (ABS). Results of this qualitative bioassay were reported as either positive or negative.

Statistical Analysis

The efficacy and safety outcomes were analyzed in both ITT and PP populations. Change in SS scores, CF and FVS were evaluated and compared within and between groups using a *t*-test. Fisher's exact test or χ^2 tests were performed to compare categorical values between groups such as the number of patients with improvement in SS, and adverse effects. A p value of less than 0.05 was considered statistically significant.

To demonstrate that Meditoxin® is not inferior to Botox®, a non-inferiority trial based on primary efficacy outcomes was performed. After study completion, a two-sided 95% confidence interval on primary efficacy outcomes between the two agents was constructed. The non-inferiority margin was defined as 15% (Δ=0.15), and the test drug was considered non-inferior if the lower limit of the confidence interval for the difference between the two drugs was greater than -Δ.

Results

A total of 60 patients were enrolled in the study, with 31 patients randomly assigned to Meditoxin® treatment and 29 patients to Botox® treatment (Fig. 1). Of the 60 patients randomized to treatment (ITT population), five patients in the Meditoxin® group and three patients in the Botox® group were excluded from the study (Fisher's exact test, p=0.708). Therefore, there were 26 patients in both the Meditoxin® and Botox® PP groups. Six patients completed the study, but violated the protocol, and another two patients did not follow-up for unrelated causes. Three patients had a previous Botox® injection within three months of study entry, one was over 75 years of age, and two received muscle relaxants during the study period. Of these eight patients, none withdrew from treatment due to lack of efficacy.

Table 2. Comparison of demographics and clinical characteristics of the patients in the intention-to-treat (ITT) group

	Meditoxin® (n=31)	Botox® (n=29)	p
Age	61.2±9.1	62.2±7.0	0.665*
F : M	25 : 6	25 : 4	0.732†
No. of previous Botox® injection	9.9±9.9	8.3±6.8	0.492*
L : H group	13 : 13	15 : 11	
SS pre-injection	3.5±0.6	3.4±0.8	0.734*
No. patients with SS 4	17 (55%)	16 (55%)	0.377†
CF pre-injection	3.7±0.5	3.8±0.5	0.658*
No. patients with CF 4	23 (74%)	23 (79%)	0.872†
FVS pre-injection	4.6±0.9	5.0±0.9	0.074*
No. of patients with grade 3/4/5/6	5/ 9/ 12/ 5	4/ 1/ 15/ 9	0.041†
Total amount of BTX-A injection	41.5±7.4	41.9±6.4	0.818*

Data are shown as mean±SD, except for several categorical values (number of patients).
* *t*-test (age), * Mann-Whitney U test (other data); † χ^2 test were used for statistically analysis.
BTX-A=botulinum toxin A; CF=eyelid closing force; F=female; FVS, functional visual status; H group=patients with more than five BTX-A injections; L group=patients with five BTX-A injections or less; M=male; No=number; SS=severity of spasm.

Table 3. Comparison of primary and secondary efficacy outcomes between the Meditoxin® and Botox® treatment groups

	Meditoxin®	Botox®	*p*
Primary efficacy outcome in ITT			
n (%)	28/31 (90.3%)	25/29 (86.2%)	0.702*
95% CI	(79.9-100)	(73.6-98.7)	
Secondary efficacy outcome in PP			
SS at 4 weeks	1.9±1.0	2.0±1.2	0.635†
SS pre-post	1.6±1.0	1.3±0.9	0.215†
CF pre-post	2.7±0.5	2.8±0.5	0.792†
FVS pre-post	0.3±0.9	0.1±0.6	0.398†
SS 0 or 1 at 4 week	8/26 (30.8%)	6/26 (23.1%)	0.587†
≥2 scores of SS at 4 weeks	11/26 (42.3%)	8/26 (30.7%)	0.387†
Duration of action (days)	136.8±33.8	138.7±28.2	0.835†

Data are shown as mean±SD except several categorical values (number of patients).
* χ^2 test; † Mann-Whitney U test were used for statistical analysis.
BTX-A=botulinum toxin A; CF pre-post=difference in mean scores of eyelid closing force between pre-injection and at four weeks after injection; CI=confidence interval; FVS pre-post=difference in mean scores of functional visual status between pre-injection and at four weeks after injection; ITT=intention-to-treat; SS pre-post=difference in mean scores of severity of spasm between pre-injection and at four weeks after injection; SS 0 or 1 at 4 weeks=patients with SS score of 0 or 1 at four weeks post-injection; PP=per-protocol; ≥2 scores of SS=patients with improved 2 or more scores in SS at four weeks post-injection.

There were no significant differences in the mean age, sex, number of previous Botox® injections, baseline SS, CF and FVS scores, and total amount of BTX-A injected between the Meditoxin® and Botox® groups (Mann-Whitney U test, χ^2 test, $p>0.05$, Table 2).

Efficacy and safety outcomes were evaluated in both the ITT and PP populations. In the ITT group, the SS score (before injection; mean±SD, 3.5±0.6) significantly improved at four weeks post-Meditoxin® injection (mean±SD, 1.5±0.9) (Wilcoxon signed-rank test, $p<0.001$). In the Botox® group, the baseline SS score (before injection; mean±SD, 3.4±0.7) also improved significantly at four weeks post-injection (mean±SD, 1.3±1.1) (Wilcoxon signed-rank test, $p<0.001$). This significant improvement was also found in the PP population for both the Meditoxin® and Botox® groups (Wilcoxon signed-rank test, $p<0.001$) (Fig. 2).

The number (%) of patients with improvement in SS (primary efficacy outcome) and the change in scores from baseline at four weeks post-injection for the SS, CF and FVS scores were not different between the Meditoxin® and Botox® groups in the analysis of both the ITT and PP populations (Table 3). Also, the duration of action was similar following Meditoxin® and Botox® injections (Mann-Whitney U test, $p=0.835$). For the non-inferiority trial on primary efficacy outcome, Meditoxin® was not inferior to Botox® in either the ITT or PP populations, as the lower limit of the 95% confidence interval (-1.76% for ITT, -1.64% for PP) was over the -15% threshold.

In comparing the outcomes in each L and H group, there were no significant differences in the primary or secondary efficacy outcomes between the Meditoxin® and Botox® groups ($p>0.05$, data not shown). The number of patients with an SS score of 0 or 1 at four weeks post-injection was not different between the Meditoxin® and Botox® groups in either the L (5/13 versus 2/15, Fisher's exact test, $p=0.201$) or H (3/13 versus 4/11, $p=0.651$) groups. In addition, the number of patients with SS scores that improved by two points or greater was not different between the two groups in either L (6/13 versus 4/15, $p=0.433$) or H (5/13 versus 4/11, $p=1.000$) group.

Using a multiple regression model, none of the evaluated factors, including sex ($p=0.917$), age ($p=0.516$), L or H group ($p=0.565$), past illness history ($p=0.594$), baseline SS score ($p=0.159$), or total injection dose ($p=0.857$), influenced the primary efficacy outcome.

Adverse effects were evaluated in the ITT population (Table 4). The frequency of adverse effects was not different between the Meditoxin® and Botox® groups (χ^2 test, $p=0.282$). All of the adverse effects were mild and temporary, and no serious adverse effects occurred during the study period.

Botulinum toxin antibody testing was performed in all 60 patients during their initial visits, and in 58 of the patients at the last visit. None of the patients showed positive antibody test results.

Table 4. Adverse effects following Meditoxin® and Botox® injections

	Meditoxin®	Botox®	*p*
Ptosis	2	3	
Dry eye	0	1	
Ocular foreign body sensation	2	0	
Ocular irritation	1	0	
Headache	0	1	
Eyelid edema	0	2	
Pain	0	1	
Total	5 /31 (16.1%)	8/29 (27.6%)	0.282

Discussion

Botulinum toxin A has been successfully used to treat blepharospasm for more than 20 years and is considered the treatment of choice. Meditoxin® was recently approved by the KFDA and is widely used in Korea for the treatment of wrinkles, essential blepharospasm and hemifacial spasms. Since one Meditoxin® vial is equivalent to one Botox® vial in terms of units of BTX-A, equivalent units of Meditoxin® with Botox® can be used. In our study, we used a 1:1 ratio of Meditoxin® and Botox® and found equivalent clinical efficacy with a significant reduction infunctional impairment in patients with essential blepharospasm.

This is the first double-blind, randomized, phase III study comparing Meditoxin® and Botox® in the treatment of essential blepharospasm. In this study, we demonstrated that Meditoxin® was similar to Botox® for short-term primary and secondary efficacies. Khoo et al. reported similar results for the scores of mean spasm severity and eyelid closure force, which were 3.2±0.8 and 3.2±0.6 before injection and 0.9±0.5 and 1.1±0.6 after injection, respectively.[13] The mean duration of action was similar in the four months following injection in both groups. In addition, we found that Meditoxin® was not inferior to Botox® in our analysis of non-inferiority.

The adverse effects found in our study were similar to those previously reported in the literature.[16,17] No differences were noted in the frequency of adverse effect between the Meditoxin® (16.1%) and Botox® (27.6%) groups. There were no serious, long-standing adverse effects following Meditoxin® injections. The adverse effects that did manifest in the Meditoxin® group were ptosis, foreign body sensation and irritation, all of which were mild and short-lived. Ptosis may result from local effusion of a drug to the levator aponeurosis, and is not specific to this type of drug. No adverse effects were apparent when examining vital signs or the results of clinical laboratory tests.

There is concern that botulinum toxin therapy may become ineffective due to the formation of antibodies against BTX-A. Usually this phenomenon appears some years after using BTX-A in higher doses for treatment of cervical dystonia.[18] Botulinum toxin antibodies were not found in either the Meditoxin® or Botox® groups in our study, maybe because we did not use the toxin in high enough concentrations to induce antibody formation, or because the follow-up duration was not long enough.

This controlled study confirmed in a double-blind, randomized manner that Meditoxin® is a new drug that is both effective and safe for the treatment of essential blepharospasm. We found that Meditoxin®, when used at the same dose as Botox®, was sufficient to decrease the degree of muscle spasm and to relieve symptoms, and that the duration of effect was similar to that of Botox®. In conclusion, Meditoxin® can be safely used as an alternative to Botox® treatment at a 1:1 equivalence.

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