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12-year effectiveness and safety of botulinum toxin type A for the treatment of blepharospasm and hemifacial spasm

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Abstract

Objective: *The objective of this study was to perform a long-term evaluation of the efficacy and safety of treatment with botulinum toxin A (BoNT-A) in patients with blepharospasm (BS) and hemifacial spasm (HFS) from January 2007 to December 2019.* **Methods:** *In each application of BoNT-A, the date of treatment, number of units applied, and time elapsed since the previous application were recorded. Outcome data was: mean latency of the clinical effect, mean duration of the clinical effect, mean improvement on Jankovic rating scale, side effects were self-reported, and evaluated 2 weeks after injection, including non-responding patients to BoNT-A for two consecutive sessions. The comparison between the first and last dose of BoNT-A was analyzed by Student's t-test, for which a value of $p < 0.05$ was considered statistically significant.* **Results:** *A total of 136 patients were analyzed; 60 had BS, 76 had HFS, and 75% were female. The duration between onset and referral for BoNT-A treatment was 18 ± 3 months, and the mean age at the time of the first therapeutic injection was 50 ± 12 years. The mean dose per session was 16 ± 4 for BS and 36 ± 12 for HFS. The therapeutic interval for injections was 4.4 ± 1 month. The mean latency of the clinical effect was 8 ± 3 days, the mean duration of the clinical effect was 112 ± 9 days, and the mean improvement on the Jankovic scale was 2 ± 1 points. Side effects were observed in 9 patients (6.6%), that is, ptosis (7 patients) and hematoma (2 patients).* **Conclusions:** *BoNT-A is a safe and effective long-term treatment for BS and HFS.*

Keywords: *Facial dystonia. Blepharospasm. Hemifacial spasm. Botulinum toxin type A.*

Eficacia y seguridad durante 12 años de la toxina botulínica tipo A para el tratamiento del blefaroespasmo y el espasmo hemifacial

Resumen

Objetivo: *Realizar una evaluación de largo plazo de la eficacia y seguridad del tratamiento con Toxina Botulínica A (BoNT-A) en pacientes con Blefaroespasmo y Espasmo Hemifacial entre Enero 2007 y Diciembre 2019.* **Métodos:** *En cada aplicación de BoNT-A se registraron la fecha de tratamiento, número de unidades aplicadas, y el tiempo transcurrido desde la última aplicación. Los datos de desenlace fueron: el promedio de latencia del efecto clínico, el promedio de duración del efecto clínico, el promedio de mejoría en la Escala de Valoracion de Jankovic, los efectos secundarios fueron reportados por el paciente y evaluados 2 semanas después de la inyección, incluyendo pacientes no respondedores en 2 sesiones terapeúticas consecutivas. Las comparaciones de resultados entre la primera y la última dosis de BoNT-A fueron analizadas con la prueba t de Student, considerandose estadísticamente significativo un valor $p < 0.05$.*

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Resultados: *De un total de 136 pacientes analizados, 60 tenían blefaroespasmo, 76 tenían espasmo hemifacial, y 75% fueron femeninos, La duración entre el inicio y la referencia para tratamiento con BoNT-A fue de 18 ± 3 meses, la edad al momento de la primera inyección terapeútica fue de 50 ± 12 años de edad. El promedio de dosis por session fue 16 ± 4 en casos de blefaroespasmo, y 36 ± 12 en pacientes con espasmo hemifacial. El intervalo entre sesiones terapeúticas fue de 4.4 ± 1 meses. El promedio de latencia del efecto clínico fue de 8 ± 3 días, el promedio de duración del efecto clínico fue de 112 ± 9 días, y el promedio de mejoría en la Escala de Jankovic fue de 2 ± 1 puntos. Los efectos secundarios se observaron en 9 pacientes (6.6%) que presentaron ptosis (7 pacientes) y hematoma (2 pacientes).* **Conclusiones:** *BoNT-A es segura y efectiva en la terapeutica de largo plazo en pacientes con blefaroespasmo y espasmo hemifacial.*

Palabras clave: *Distonía facial. Blefaroespasmo. Espasmo hemifacial. Toxina botulínica tipo A.*

Introduction

Blepharospasm (BS) and hemifacial spasm (HFS) are two of the most frequent forms of focal cranial dystonia that chronically affect quality of life[1].

BS is a chronic focal dystonia with excessive involuntary contractions of the orbicularis oculi muscle[2]. The prevalence of BS is 4.24/100,000 inhabitants, affecting more women (4.78/100,000 inhabitants) than men (3.08/100,000 inhabitants)[3].

HFS is characterized by unilateral, intermittent, tonic, or clonic contractions of muscles innervated by the facial nerve[4]. In Rochester and Olmsted County, Minnesota, from 1960 to 1984, the prevalence rate in women was 14.5/100,000, and 7.4/100,000 in men. Most patients were between 40 and 79 years of age[5].

Different treatments have been used to treat BS and HFS, such as baclofen, gabapentin, orphenadrine, clonazepam, phenytoin carbamazepine, levetiracetam with insufficient results; microsurgery has an 80-90% rating success, but 25% of patients relapse in 2 years and has potential complications such as hearing loss, unilateral facial palsy, cerebral hemorrhage. The advent of botulinum toxin A (BoNT-A) has improve the treatment results on both conditions. BoNT-A injection is now a first-line treatment for HFS[1].

At present, it is not known whether the clinical efficacy of botulinum toxin decreases with time and repeated treatment sessions and if there is a possible loss of efficacy in clinical settings. Future studies comparing any form of BoNT-A should address the comparative proportion of participants who develop a nonresponse secondary to treatment[6].

Immune resistance tends to occur in the first 1-4 years of treatment, and the formation of antibodies seems less likely after that period[7]. Patients positive for antibodies against BoNT-A tend to have an earlier age of onset, higher mean dose per visit and higher cumulative dose than patients negative for antibodies[7].

The longest studies of treatment with BoNT-A refer to follow-ups of 15.8 years[7] and 16 years[8]. The present study was designed to retrospectively evaluate the efficacy and safety of BoNT-A in a cohort of the Mexican population treated for chronic BS and HFS.

Materials and methods

Design and participants

This study has a retrospective longitudinal design. Patients who attended the Botulinum Toxin Clinic at the ISSSTE Veracruz Hospital (Hospital ISSSTE Veracruz) from January 2007 to December 2019 were identified. Subjects were eligible if they were between 18 and 80 years of age, had a diagnosis of BS or HFS, had received treatment for 12 years, and had received at least one injection per year. The exclusion criteria were as follows: previous surgical treatment, incomplete data, or patients who did not attend follow-up for 12 months or more. Informed consent was obtained from all patients. This study complied with the ethical principles for research on human subjects in accordance with the Declaration of Helsinki.

Procedures

The injections were prepared as follows: dilution of BoNT-A (500 units or 100 units, regardless of brand) in 1 mL of 0.9% saline solution in a 1 mL syringe; a dilution of 100 units was obtained in a 1 mL syringe with 100 graduation marks. Patients were scheduled to return 2 weeks after the injection to observe the results. The BoNT-A brand names supplied over 12 years, 1 at a time, by Hospital Pharmacy were Botox® (Allergan) Onabotulinum toxin A, Xeomeen® (Merz) Incobotulinum toxin A, and Dysport® (Ipsen) Abobotulinum toxin A.

Measurement of results

From the records of the patients included in the study, data on sex, age at the time of the first treatment injection, duration between onset and referral for BoNT-A treatment, unilateral or bilateral symptoms, and focal or multisegmental manifestations were recorded.

For each application of BoNT-A, the date of treatment, number of units applied, and time elapsed since the previous application was recorded.

Follow-up schedule was: Evaluation 2 weeks after injection, and reinjection every 3 months at each follow-up visit, patients were asked about the results of the previous session.

For the evaluation of the effectiveness and long-term safety, dose per session, number, and location of injections, latency (defined as the time between the injection and the first sign of improvement), duration (defined as the interval between treatment and the recurrence of symptoms intense enough to lead the patient to receive another application), presence of side effects were evaluated by patient self-report and clinical evaluation at the 2-week follow-up visit, after every treatment session.

The data were analyzed and grouped by BS and HFS and are presented as the mean dose per session, interval between injections, mean latency of the clinical effect, mean initial latency, mean last latency, mean duration of the clinical effect, mean initial duration of the clinical effect, mean last duration of the clinical effect, mean improvement in the Jankovic scale[6], mean initial improvement in the Jankovic scale, mean last improvement in the Jankovic scale, and percentage of side effects. The Jankovic rating scale measures clinical features at basal and follow-up evaluation of severity and improvement, allowing to assess the efficacy of BS and HFS therapy.

Results

In the Botulinum Toxin Clinic of the ISSSTE Veracruz Hospital, the records of 141 patients were identified. Five patients lost to follow-up were excluded from the study. One hundred and thirty-six patients treated for 12 years between January 2007 and December 2019 who met the inclusion criteria (60 with BS and 76 with HFS) were analyzed. The mean duration from onset to referral for treatment with BoNT-A was 18 ± 3 months. Table 1 shows the demographic characteristics of the patients included in the study.

Table 1. Demographic characteristics of the long-term follow-up group consisting of 136 patients treated with BoNT-A for 12 years

Variable	Data (%)
Total patients (n)	136
Age at first injection	50 ± 12 years
Sex, n (%), female/male	102 (75) / 34 (25)
Blepharospasm	60 (44.1)
Hemifacial spasm	76 (55.9)
Unilateral symptoms	124 (91.1)
Bilateral symptoms	12 (8.8)
Focal symptoms	134 (98.5)
Multisegmental	2 (1.4)
BS, mean units per session	16 ± 4
HFS, mean units per session	36 ± 12
Treatment interval between injections	4.4 ± 1 months

BoNT-A: botulinum toxin A; BS: blepharospasm; HFS: hemifacial spasm. Data are presented as the mean ± standard deviation.

BS (n = 60)

Table 2 provides the mean and standard deviation of the measurements associated with the first and last applications of BoNT-A for the treatment of BS. In all the items analyzed, there was a statistically significant difference between the two measurements.

The mean dose per treatment session was 16 ± 4 U. Importantly, no primary resistance was detected, and no secondary resistance was reported with the first or last application of BoNT-A.

The comparison between the initial and final values allowed the identification of an increase in the dose of 2 units accompanied by a latency period shorter than 0.6 days, a 7-day increase in the duration of therapeutic effect, and an improvement in the Jankovic scale of 0.6. The interval between injections was slightly lower by 3 days at the final evaluation session.

HFS (n = 76)

Table 2 provides the mean and standard deviation of the measurements associated with the first and last application of BoNT-A for the treatment of HFS.

The mean dose of BoNT-A was 36 ± 12 U. In patients with HFS, there were no patients with primary resistance,

Table 2. Long-term follow-up of patients with BS and HFS treated with BoNT-A for 12 years. Analysis using student's t-test

Parameter	Initial	Final	p-value
Blepharospasm (n = 60)			
BoNT-A (units)	16 ± 2.7 (SD)	18 ± 2.1 (DE)	0.0001
Treatment interval (months)	4.4	4.3	0.0012
Latency (days)	9.2 ± 3.1	8.6 ± 4.5	0.020 (*)
Duration (days)	107 ± 6	114 ± 7	0.0001
Improvement in the Jankovic scale	2.7 ± 1.3	3.3 ± 0.3	0.0001
Primary resistance (%)	0	0	NS
Secondary resistance (%)	0	0	NS
Hemifacial spasm (n = 76)			
BoNT-A (units)	38 ± 7.1 (SD)	41 ± 6.3 (SD)	0.069 (*)
Treatment interval (months)	4.2	4.1	0.0001
Latency (days)	9.4 ± 3.1	9.2 ± 3.7	0.44 (*)
Duration (days)	109 ± 8	116 ± 5	0.0001
Improvement in the Jankovic scale	2.5 ± 1.5	3.1 ± 0.9	0.0001
Primary resistance (%)	0	0	NS
Secondary resistance (%)	0	0	NS

BoNT-A: botulinum toxin A; BS: blepharospasm; HFS: hemifacial spasm. Data are presented as the mean ± standard deviation (SD). (*) NS, not significant.

and no secondary resistance was reported with the first or last application of BoNT-A.

Comparing the units applied, there was a non-significant increase of 3 units and a non-significant decrease of 0.2 in days of latency; however, there was a significant difference in the decreased application interval of 0.1 months, in the duration of therapeutic effect, which increased by 7 days, and in the improvement in the Jankovic scale, which increased by 0.6 points.

Table 3. Side effects

Parameter	Initial	Final	p-value
Blepharospasm (n = 60)			
Ptosis	1	1	NS
Hematoma	1		NS
Hemifacial spasm (n = 76)			
Ptosis	3	2	NS
Hematoma		1	NS

Side effects

Side effects occurred with very low frequency in both groups. In the population with BS, 2 patients (3.3%) presented side effects after the initial injection, and 1 patient (1.6%) presented side effects after the last injection. In the population with HFS, 3 patients (3.9%) presented side effects from the first injection, and 3 patients (3.9%) presented side effects from the last injection. Table 3 lists the side effects recorded.

Discussion

Although botulinum toxin has been considered the first-line treatment for BS and HFS[1], few studies have considered the long-term follow-up of patients who receive BoNT-A. The analyzed cohort exclusively included Mexican patients from a hospital in the state of Veracruz.

This cohort had a predominance of women (3:1), similar to previous studies long-term studies that had a predominance of female patients[9]. Patients were referred to treatment on average 18 ± 3 months after the onset of symptoms.

In the present retrospective study, only one physician (HCO) treated the patients, and both investigators participated design and implementation of the research. In general, a study includes the results from the first session, reporting the changes observed during the follow-up, but Czyz[10] used the fourth visit as the "initial visit" to control for the confounding factor of the dosing adjustment phase, which usually starts with a dose of BoNT-A that is progressively modified over time, depending on changes in the spasm, the needs of the patient, the latency to improvement, the duration of improvement and the side effects.

The degree of improvement has been reported using several different methods: percentage of patients who

improved; number of injections needed for improvement; and percent improvement in spasms, as assessed using quantitative scales ranging from 0 to 7 or using a percentage from 0% to 100%. It has also been evaluated using a visual analog scale, as a subjective satisfaction scale to determine the degree of spasm remission[8].

In this study, the BS group the mean dose per treatment session was 16 ± 4 units, similar to previous long-term reports that indicate a dose range of 7.5U -140 U for onabotulinum toxin A and of 40U-400 U for abobotulinum toxin A[11].

HFS patients in this study were treated with 15 U or 25 U of onabotulinum toxin A[12], with a mean dose of 36 ± 12 units, results that are similar to previous long-term literature with no significant difference in response rate and duration of improvement.

With respect to the purpose of this study, there was an increase in the final dose at the 12th year, compared to the initial dose of BoNT-A, similar to the majority of long-term reports.

For the treatment of BS, in this study, the increase in the mean dose from 16 U to 18 U of BoNT-A was significant; the duration of the effect was significantly longer, improvements in the score for the Jankovic scale were significant, the latency time was shorter by 0.6 days, and the treatment interval decreased by 0.1 months, at the last evaluation of 12 years of follow-up.

With respect to the follow-up at 12th year for the treatment of HFS comparing with the first evaluation, the present study found a non-significant increase in the mean dose from 38 U to 41 U of BoNT-A, improvements in the score for the Jankovic scale with 0.6 points and an increase in the duration of therapeutic effect, by 7 days, similar to other long-term reports that indicate an increase in the dose of BoNT-A over-time with[11,13,14] or without[10] statistical significance.

The treatment interval in this study was 4.4 ± 1 months, 123 days/17.6 weeks, similar to the period between therapeutic sessions previously reported for long-term studies[10,15,16].

The mean latency to obtain therapeutic effect in this report was 8 ± 3 days, a finding similar to that reported in the literature, that is, 2-14 days[8,10,17,18].

In this study, the mean duration of the clinical effect was 112 ± 9 days, with an initial duration of 109 ± 6 days and a final duration of 137 ± 7, similar to long-term reports in the literature[8,10,17,18]. The longer final duration of therapeutic effect in this study, as mentioned previously, can be explained in part by a longer-lasting effect detected in patients with HFS, as reported in the literature[15].

The mean improvement in this report, evaluated with the Jankovic scale, was 3.1 ± 1.4 points, with an initial improvement of 3.0 ± 0.9 points and an improvement with the last injection of 3.3 ± 0.7 points, similar to previous long-term reports of 2.5 ± 1.5 points for the first injection and 3.4 ± 0.9 points for the last[7]. Despite the differences in the study designs using different scales and methods, other long-term studies report overall improvement with BoNT-A treatment in 73.7[8]-89% of patients[14], and improvement in 96% of patients with BS and 98% of those with HFS[13], findings that confirm that in long-term studies, apart from the method to evaluate improvement, treatment with BoNT-A offers an adequate lasting effect for patients with BS and HFS.

Treatment with BoNT-A is very safe. A meta-analysis that included 2,309 subjects reported mild to moderate adverse effects in 25% of the group treated with BoNT-A (353/1,425 patients), compared to 15% in the control group (133/884 patients)[7]. In this study, there were side effects in 9 patients (6.6%), that is, ptosis in 7 (77.7%) and hematoma in 2 (22.2%). The general profile of side effects in this study is consistent with that reported in the literature of long-term follow-up, that is, 5-30%[10]. The highest frequency of side effects in this report occurred with the initial treatment, 4.4%, and the lowest frequency of side effects was observed with the last treatment 2.2%.

Contrast of hypotheses, it is assumed that variables with $p > 0.05$ follow a normal distribution and that variables with $p < 0.05$ do not follow a normal distribution. The justification for the use of the Student's t-test was to contrast if a significant difference could be found in the variable mean result between the two measurements.

A major concern with BoNT-A, especially with prolonged treatment, is the possibility of developing antibodies against BoNT-A. In a study with 303 patients, 17 of the 169 (10.4%) who discontinued treatment had stopped responding, nine of them due to blocking antibodies, as analyzed by the mouse protection assay[7]. In the present study, the identification of antibodies against BoNT-A was not performed, which is a limitation of this study.

The results from this study support the conclusion that BoNT-A, as a first-line treatment for focal facial dystonia, is an effective and safe treatment in a long-term cohort of the Mexican population with BS and HFS treated for 12 years.

Limitations of this study include the retrospective nature of analysis without a control group and without blinding, and the lack of antibody detection for BoNT-A. This long-term follow-up study in a real-world scenario did not intend to compare results between BoNT-A

brands, because indeed, the BoNT-A brand names (Botox®, Xeomeen®, Dyspor®t) were supplied over 12 years, 1 at a time, by Hospital Pharmacy, according to the institutional annual material purchase plan.

The long-term follow-up in a real-world scenario might be seen as strength of this study. Future trials should study also the quality of life, injection techniques, and immunogenicity.

Discussion

HES patients in this study were treated with a mean dose of 36 + 12 units, results that are similar to previous long term literature with no significant difference in response rate and duration of improvement12.

Conclusion

BonT-A is a safe and effective long-term treatment for BS and HFS in this real-world scenario follow-up. Future long-term trials, should address quality of life, iniection techniques, and immunogenity.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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