Original Article

Efficacy and tolerability of a new botulinum toxin type A for cosmetic treatment of dynamic facial wrinkles: a prospective, phase III multicenter study

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ABSTRACT

Introduction: The botulinum toxin is a valuable option for the treatment of dynamic facial wrinkles. The Lanzhou botulinum toxin type A (LBTX-A) was introduced in China in the early 90's and was approved in Brazil in 2003. **Objective:** To evaluate the efficacy and tolerability of LBTX-A for the cosmetic treatment of dynamic wrinkles of the upper face. **Material and methods:** In a multicenter, prospective, open-label study, 110 subjects of both genders (aged from 25 to 65 years) were treated with a total of 53 U of LBTX-A each, distributed in fifteen sites in the frontal, corrugator, procerus, and orbicular muscles. The patients were evaluated 7 times within 180 days. Efficacy was assessed by electromyography, photographic analysis and the investigator's and patient's opinions. Tolerability was assessed by the incidence of adverse events. **Results:** Two weeks after injection, 94% of the patients considered the result good or excellent. The effects of the toxin were present after 90 days in most cases. After injection, most patients reported mild or no pain, and minimal and reversible side effects as facial edema (6 patients), rigidity (3 patients), and eyelid ptosis (2 patients). **Conclusions:** We conclude that LBTX-A is efficient and well tolerated for the treatment of dynamic facial lines.

Keywords: botulinum toxin type A, injectables, wrinkles, facial dynamic lines.

INTRODUCTION

Crystalline botulinum toxin type A was introduced in the medical practice in 1980 for the treatment of strabismus. Since then, several other indications were proposed including blepharospasm, facial spasms, spasticity, and cosmetic uses.[1-4]

In 1988, the Lanzhou Institute of Biological Products, a research group from China, introduced the Lanzhou Botulinum Toxin type A (LBTX-A) under the trade name BTX-A®, claiming high purity and stability and low toxicity.

The National New Drug Evaluation Committee from the People's Republic of China approved its use in 1997 for hemifacial spasm, blepharospasm, and strabismus after reviewing both preclinical and clinical data.[5-10] The Brazilian Health Authority (ANVISA) approved LBXT-A for clinical use in 2003, and for cosmetic use in 2005 under the trade name PROSIGNE®. The product is also marketed in Korea, Hong Kong, India, Ukraine, Kuwait, Peru, Indonesia, and Philippines.

OBJECTIVE

The purpose was to assess the efficacy and tolerability of the product for the cosmetic treatment of dynamic facial wrinkles in the upper third of the face. The study was sponsored by Cristália Produtos Químicos e Farmacêuticos LTDA., a Brazilian pharmaceutical company.

MATERIAL AND METHODS

This is a multicenter, prospective, open-label study using LBTX-A, conducted in three Dermatology centers and two Plastic Surgery centers. The study was conducted under the

ethical guidelines of the Helsinki Declaration of 1975, the Good Clinical Practices and all applicable Brazilian regulatory requirements. The protocol and the informed consent form were approved by the institutional review boards of all institutions involved and also by the Brazilian health authorities. Signed informed consent was obtained from all subjects.

One hundred and ten subjects of both genders, aged from 25 to 65 years and presenting facial wrinkles were randomized (25 to 45 years old corresponding to 38.5% of the patients; 46 to 55 years old corresponding to 49.5%; 56 to 65 years old corresponding to 12%). There were 3 male and 107 female patients; 103 were Caucasian and 7 were Hispanic. Four centers had 20 patients, and one center had 30 patients

The exclusion criteria were: any cosmetic procedure, as dermal fillers or botulinum toxin treatment, six months before this clinical trial; known hypersensitivity to botulinum toxin or other formula ingredients; presence or suspicion of active infection or inflammation; participation in any clinical trial within the last two months; pregnancy or puerperium; ethanol consumption greater than 10 g/day; current therapy with aminoglycosides or other drugs interfering with the neuromuscular transmission; any condition that could render the patient ineligible for the study or that may increase the patient's risk according to the Investigator's evaluation.

The vials of lyophilized LBTX-A, serial number L200 20504, were stored frozen at –20°C to –5°C, and used shortly after the reconstitution with 1 ml of saline (drug concentration of 100 U/ml).

For 6 months, each patient attended 9 visits including the screening visit (V0), the injection visit (V1), and 7 follow-up visits (V2-V8), in which the product efficacy and tolerability were assessed.

In visit 1, the patients had their facial skin cleaned and disinfected with 70% ethanol, and received a total of 53 U of BTX-A distributed on 15 crucial sites in the frontal, corrugator, procerus, and orbicular muscles (Figure 1). Repeated product injection was allowed for all patients at visit 3 as deemed necessary by the investigators in order to repair possible imperfections leading to a better final result. Efficacy was evaluated as per the investigator's and the patient's opinion on every post-injection visit. Investigator's rating was standardized as marked improvement, moderate improvement, mild improvement, unchanged, and worsening comparing to the last visit. Patient's opinion was standardized as: excellent, very good, good, fair, or bad comparing to the last evaluation. During visits 6 and 8, both patients and investigators were asked to do an overall evaluation of the treatment.

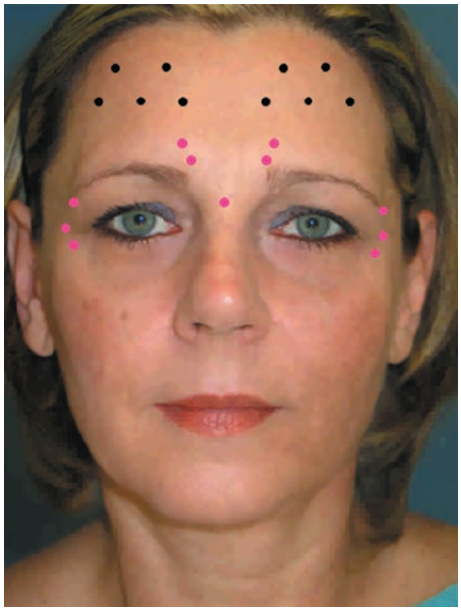


Figure 1: Graphic representation of the injection sites.

Photographic documentation was performed before the injection (V1) and after 14 days (V3), 90 days (V5), and 120 days (V6). The photos were taken by a professional photographer following standardized specifications. All photos were also analyzed by the investigators at V6 and V8, in order to reach final observations (Figure 2 and 3).

Eight randomly selected patients underwent electromyography exams before the injection (V1), and after 14 days (V3) and 120 days (V6). All of them signed an additional informed consent allowing the exam. A TECA® LBM 3 device with monopolar MF 37 needle electrodes was employed. The electrode was inserted nearby the injection sites into the procerus muscle, right and left aspects of frontal muscle and right and left eye's orbicular and corrugator muscles. The muscle electrical activity was recorded at rest and during light and maximal voluntary contraction, showing motor units' recruitment rate, triggering frequency and morphologic characteristics.

Tolerability was assessed based on the occurrence of drug-related or suspect-drug-related adverse events reported by the patients in all post-injection visits. The adverse event was rated as no related to the treatment, possibly related, probably related, or definitively related. Suspect drug-related adverse events were those regarded by the investigators as possibly or probably related. Adverse events were also rated for severity (mild, moderate, severe, or serious). A serious adverse event was defined as one that resulted in hospitalization or significant disability or death, was life threatening, or was the cause of a

congenital anomaly. Pain and burning were assessed by asking specific questions during and immediately after the injection (V1) and 3 days post-injection (V2), and classified as: much, moderate, little, or no pain.

Data were recorded on clinical research forms and manually transferred to Microsoft Access®. Descriptive data analysis and graphic representations were carried out using Microsoft Excel®.

RESULTS

The overall evaluation of the treatment was considered from patients' and investigators' impressions at visits 6 and 8. At visit 6, excellent, very good and good results were reported by 87.4% of the patients. Investigators confirmed these results in 98.2% of the patients treated at visit 6. At visit 8, the overall evaluation decreased to 42.0% and 47.1% in the patients' and investigators' opinions respectively. Figure 4 summarizes the doctor´s and the patient´s opinions about LBTX-A efficacy and tolerability.

TOUCH UP

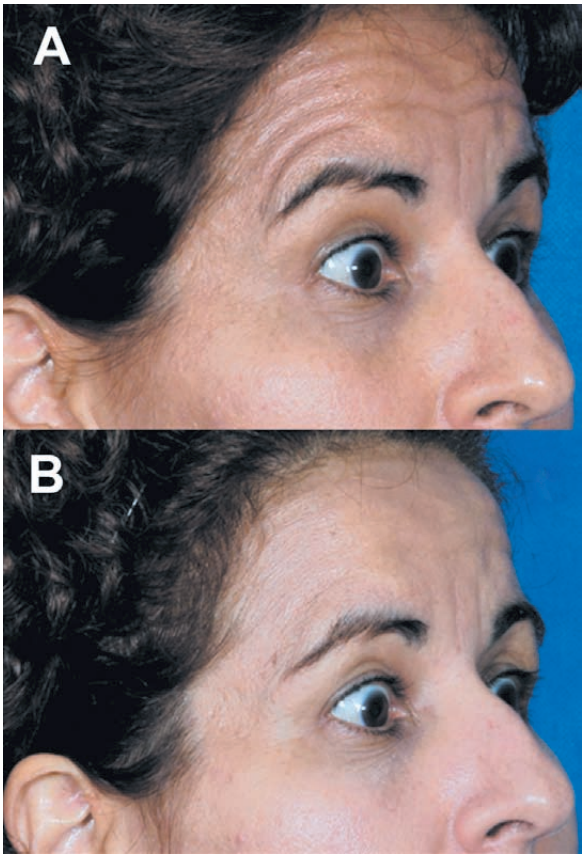
Repeated product injection was required by 16 patients at V3 (17% of the 108 who attended the visit).

PHOTOGRAPHIC DOCUMENTATION

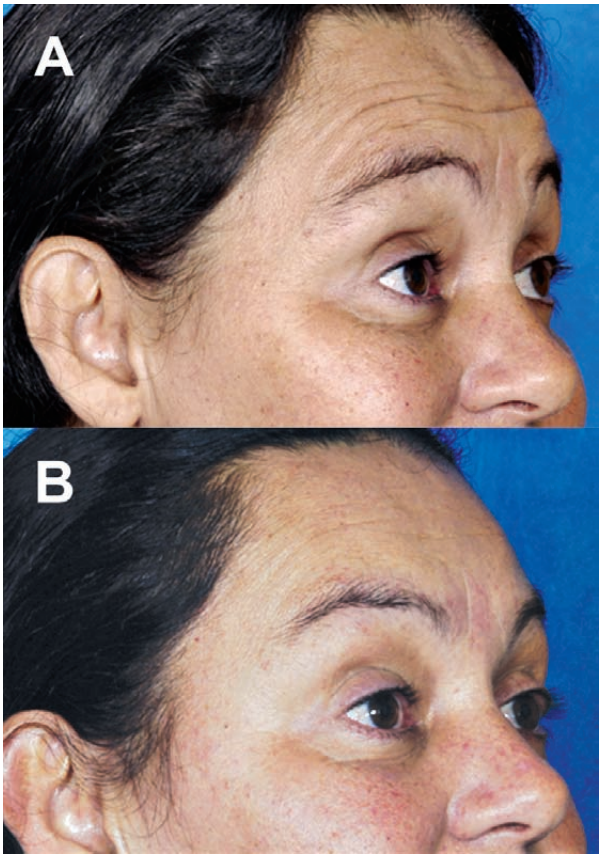
Photos were taken from 96% of the patients who attended visits 1, 3, and 6. The improvement was maintained 3 months after the injection (Figures 2 e 3).

ELECTROMYOGRAPHY

All selected patients studied had normal electromyographic records before the injection. Two weeks after the injection (V3), all records showed a marked decrease in the number of functioning motor units. Four to five months post-injection (V6), the number of functional motor units was widely reestablished for all patients. Neither triggering frequency nor neuropathic or myopathic pattern was detected on any record.



Figures 2A, 2B: Patient from Sérgio Talarico, M.D. Study Site.
2A: Prior to the treatment (06/03/2004).
2B: 6 months after injection (03/09/2004).



Figures 3A, 3B: Patient from Lydia Masako, M.D. Study Site.
3A: Prior to the treatment (03/17/2004).
3B: 3 months after injection (06/15/2004).

TOLERABILITY

After the injections (V1), of the 110 patients 1% referred much pain, 26% moderate pain, 50% little pain, and 23% no pain during injection. The post-injection pain was considered moderate by 11%, mild by 38%, and absent by 51% of the patients. Regarding burning upon the injection, the same pattern was observed, that is, 87% of the patients reported mild (41%) or no burning (46%).

Other than pain, there was a total of 38 adverse events considered related or possibly related to the product and 12 whose relationship was considered doubtful. Most of them were mild (31 events), and 6 were moderated.

The most commonly reported adverse events related or possibly related to the drug were: headache (6 patients – 5.45%), facial edema (6 patients – 5.45%), facial rigidity (3 patients – 2.27%), eyelid ptosis (2 patients – 1.81%), eyebrow ptosis (2 patients – 1.81%), local pain (2 patients – 1.81%), local bruise (2 patients – 1.81%), minor pruritus and nausea (1 patient each – 0.90%). Those events were considered as mild (21) or moderate (4), and one case of sensation of rigidity was considered severe by investigators. Besides, there were 2 other severe adverse events considered by the investigators as not related to the drug: one case of appendicitis, and one case of prostate surgery. Neither any serious adverse effects were reported, nor cutaneous infections, rash or other allergic reactions were observed.

DISCUSSION

This study followed 110 patients using botulinum toxin for the treatment of expressional wrinkles of the upper third of the face. The selected patients composed a representative sample of people who are interested in the use of botulinum toxin for cosmetic purposes.

While the study was conducted, investigators stored the LBTXA vial frozen from –20°C to –5°C before reconstitution, although, since 2005, the vials could be stored before and after reconstitution refrigerated at 2°C to 8°C, according to the manufacturer's information.

Efficacy was assessed as per the patient's' and investigators' subjective rating. Although subjective, this approach was considered reliable by other authors,[11,12] among other reasons, since this was an aesthetic intervention. In such case, the patients' satisfaction is probably the main target. However, patient's rating may be affected by the placebo effect of any intervention or by unrealistic goals and expectations.[13] The investigators are less prone to be influenced by this factor, and the photographic documentation provides an additional objective parameter.[13]

After two weeks, the probable drug action peak, patients and investigators expressed favorable opinions in 90% and 99% of the cases, respectively. This rate decreased with time, what could be attributed to the product activity reduction.

Touch up was performed in 17% of the patients for correcting any imperfection or asymmetries considering the anatomical differences of each patient.

In the investigators' opinion, the product maintained its activity for 45 days in almost all patients, lasting 90 days for 66% of the cases, and decreasing to 38% after 4 months. In the patients' opinion, satisfactory results were observed by two third of the patients up to 5 months. Both patients' and investigators' overall opinions about the intervention were favorable at visit 6 and satisfactory at visit 8 (Graph 1).

Objective electromyography data showed reestablishment of the pre-injection patterns four to five months after injection in all patients. Photographic documentation provided additional objective means for analyzing the results and was also consistent with the doctors' opinion. This is comparable to the literature data about the use of botulinum toxin.[14-18]

After completing the study, authors agreed that longer-lasting muscle inhibition could have been obtained if the doses were individually adjusted considering the muscle size. In the study design, treatments were not settled for individual and gender differences. The distribution of the injection sites and doses should have been changed, and the results should have been analyzed separately from each group of muscles, as glabella (procerus and corrugator muscles), frontal region (frontalis muscle venter), and periocular region (orbicularis ocular muscles). Although the standardization of the application sites for all patients allowed comparisons, it failed in providing the best possible results for each subject, thus leading to a slight negative bias.

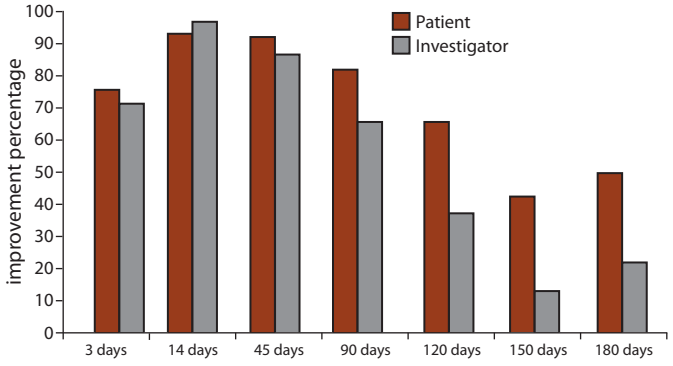
Comparisons between different presentations of botulinum toxin type A have been the source of much discussion.[19-22] The aim of most published papers is to provide adequate means to obtain similar clinical results, other than to prove a molecular equivalence, which is not possible with biological substances.

The Botox® suggested dose for facial wrinkles is approximately 25 U to 35 U for the glabella, 12 to 15 U for each side of the periocular region, and 1 or 2 U per injection site of the frontal region (total of 10-20 U). The effects were sustained from 3 to 6 months, according to the area.[23,24.]

The doses of LBTX-A used in this study were 25 U for the glabella, 6 U per side of the periocular wrinkles, and 16 U for the forehead lines. With those doses, it was not possible to obtain the same results described with Botox®, especially in the periocular and frontal regions[24] (Figure 1).

On the other hand, it may suggest that the doses required to produce similar clinical results may be very close between those two different 100-U formulation of

Efficacy evaluation – comparing evaluation of patient and investigator according to time



botulinum toxin type A. Considering this hypothesis, lower doses were used to treat the periocular region, as it was the study standardization.[25] For the frontal region, this study used 4 U per site, higher than the predicted amount for this area with Botox® studies.[23,24] However, it is also known that efficacy improves at higher dosing regimens.[26] This may have been the cause of palpebral ptosis and rigidity sensation at the forehead region reported by some patients. Eyelid ptosis was seen in 2 patients (1,8%), and it is believed to result from the diffusion of botulinum toxin to the upper eyelid elevator muscle and therefore it is expected to be technique-dependent. Rates reported for this event ranges from 2% to 20% (pooled incidence is 6.5%).[27,28]

Considering other tolerability aspects, only 1% of the patients reported much pain or burning upon the injection and no patient reported significant post-injection pain. The reported adverse events were mostly mild. The most common adverse event considered to be related to drug was headache, but its incidence was similar to that reported in patients receiving placebo in placebo controlled-studies of Botox.[26,29] Thus, the injection procedure might have been the cause of those events, other then the LBTX-A treatment.

Although in 2000 Tang and Wan showed slightly more cases related to the use of LBTX-A, comparing to Botox®, in our study, no cutaneous rash or other allergic or systemic reactions were observed[30] as we have found in clinical trials published using high doses of LBTX-A to treat neurological diseases.[31] This is better than the reports about Botox®.[32] Unlike the report in which the LBTX-A formulation contained approximately 25 ng of neurotoxin complex protein per 100 U,[30] the new preparation used in this study contained approximately 4.5-5.0 ng/100 U vial. Botulinum toxin preparations with lower protein load formulation is proven to be is less allergenic.[13,33,34] Therefore, the overall tolerability of the drug was very good.

CONCLUSION

As an overview of the collected results, it was possible to conclude that the use of the LBTX-A in the treatment of dynamic facial wrinkles is safe and well tolerated in the physicians' and patients' opinions. According to their opinions, the toxin effects were sustained for 90 days or more in most patients. As this is a biological substance, further studies should be designed in order to determine the optimal efficient dose to each muscular group that could produce longer-lasting results and higher satisfaction. S&CD

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