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EXPERIMENTAL STUDY

Use of the type A botulinum toxin in patients submitted to cheiloplasty to improve results in scarring in patients with nonsyndromic cleft lip and palate

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Abstract

Background Cleft lip, and its association with cleft palate, is the most common craniofacial malformation worldwide, having a high incidence in the Hispanic population, with 9.6 cases being reported per 10,000 newborns. The standard treatment is cheiloplasty with satisfying functional result. However, the presence of the hypertrophic scar constitutes the most frequent sequel, requiring, in some cases, a new surgery. Said scar often becomes a social stigma of this pathology.

Methods Aim: To determine if the application of type A botulinum toxin prior to the surgery, improves the aesthetical results of the surgery evaluated by the Vancouver scale.

A randomized triple-blind clinical trial was performed that included all patients from 4 to 24 months of age, with unilateral or bilateral cleft lip and palate, without any history of prior surgery, at the HRAEB in Mexico. The surgery was performed by the same senior surgeon in both groups. Patients were randomized into two groups: a study group of 11 patients who received a type A Botulinum toxin injection at least 7 days before the surgery and a control group of 11 patients who received placebo. Both groups were evaluated by a different investigator, 3 and 6 months postoperatively using the Vancouver scale.

Results There was statistical significance in the width of the scar in millimeters, in the study group, of 2 mm (0–3) and in the control group of 4 mm with p value of < 0.001. There was also a difference in Vancouver scale, obtaining in the study group a mean of 2 points (IC 0–3) and in the control group one of 4 points (IC 0–6) with a p value of < 0–001. No side effects of the toxin were documented during the study and there were less surgical complications.

Conclusion The use of type A botulinum toxin decreases the presence of a hypertrophic scar in patients with a cleft lip who undergo primary cheiloplasty; however, more studies with a larger number of patients are needed.

Level of evidence: level II, therapeutic study.

Keywords Cleft lip · Botulinum toxin · Cheiloplasty

Introduction

Bilateral or unilateral lip and cleft palate constitute the most common craniofacial malformation worldwide, estimating that 1/700 newborns has this condition (WHO 2003) with a prevalence of 3.4–22.9/10,000 in newborns [1]. The incidence in Mexico is unusually high in proportion to other Hispanic countries; Trigos and colls reported 9.6 new cases each day and a total of 10,573 new cases in 3 years (2003–2006) [2].

There are several techniques for cleft lip correction, among the most popular are the LeMesurier, Tennison, and Millard, with their variations for unilateral or bilateral. The result varies from surgeon to surgeon and depends on a myriad of variables [3, 4]. Several scales have been proposed for grading scar quality, one of the most used is the Vancouver scale [5–7].

The most frequent complication of the cheiloplasty is the presence of a hypertrophic scar, and, according to Soltani and colls, it can be as high as 32% in the Hispanic population. The hypertrophic scar together with the maxillary growth

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restriction [8] are the main indications of a revision surgery with increasingly poorer results [7, 9], often with the outcome of the whistle deformity and the consequently social stigma [10, 11].

Botulinum toxin type A has been used to decrease scarring [12, 13], showing improvement in experimental models. Li Hu and colls [14], in 2018, performed a prospective study demonstrating improvement in facial surgery scarring in microvascular structures. The effects of botulinum toxin in the muscular plate are well established; however, its ability to improve the scarring is hypothesized by the reduction of mechanical stress to the healing process, allowing alienation of collagen deposition and organization, improving the overall scar. Nonetheless, the evidence in the cleft lip is limited, only one clinical trial has been performed by Chang and colls [15] with promising clinical results but not achieving statically significance.

The aim of the study was to determine the use of type A botulinum toxin preoperatively in preventing a hypertrophic scar in patients with unilateral or bilateral cleft lip who underwent cheiloplasty applied preoperatively.

Material and methods

A prospective randomized triple-blind clinical trial was conducted. Each consecutive patient in the period between December 2015 and January 2017, diagnosed with unilateral or bilateral cleft lip regardless of the palate, who went to the Division of Plastic and Reconstructive Surgery (PRS) of the Regional High Specialty Hospital (HRAEB) in Leon, Mexico, was included.

The inclusion criteria for this study were the following: age less than 3 years and over 3 months, the absence of a prior history of surgical procedures, the absence of contraindications for surgery, and parents' signed consent to be a part of the study.

A sample size was estimated for a proportion, calculated with the following parameters: alpha = 0.05; beta, 0.2, proportion differences of 50% (reduction in the incidence of hypertrophic scar from 33% to 15%), with an approximation of 25 cheiloplasties per year and being a one-tailed analysis. Obtaining a size of 11 patients per group, calculating losses of 15%, a total of 22 patients were obtained per group and randomized using SPSS 21®.

Because this was a triple-blind clinical trial, the surgeon, the patient's parents, and the final evaluator did not know if the patient was assigned in the study or control group. All of the syringes were given to the surgeon by the investigator.

For the study group, the syringe contained 8 IU of botulinum toxin (if the dose does not exceed the 2 IU/kg maximum) at a dilution of 100 IU/1 ml [16]. And for the control group, the syringe contained the same amount of saline solution.

The solution was injected 7 to 10 days prior to surgery, bilaterally into the orbicularis oris muscle, placing 2 superficial infiltration points. Benzocaine topic cream was used to improve patient comfort 40 min prior to application. Surgery was performed by the senior surgeon under general anesthesia using Tennison Randall Technique for unilateral clefts, Fischer for bilateral cleft. In each patient, Nylon 6-0 was used for skin closure, no adjuvants were applied on the scar, and oral intake started 8 h after surgery with a 24-h average hospital stay. Follow-up included the following: in 1 week, removal of skin suture; at 3 and 6 months, consultation; Vancouver scale evaluation and width measurements performed by an independent evaluator. No adjuvants were prescribed Fig 1 and 2

Results

A total of 22 patient were included in the study. All data were analyzed using SPSS 21® for Mac; demographic data from both groups were analyzed, with T student test, searching for differences between groups, in which no statistical differences were found in age, sex, and width of the cleft (Table 1). Follow-up measurements of width (Caliper Hergom ®) and Vancouver scale (vascularity, pigmentation, pliability, and height) were performed by an independent research team (excluding the surgeon) at 3 months and 6 months in outpatient consult. No adverse outcome was recorded of the botulinum toxin application; no erythema or rash was documented, only 1 case of asymmetric oral commissure, which lasted 4 months, with no lasting sequel. In the control group, one patient presented total and another partial wound dehiscence.

Analyzing main goal, using the Mann-Whitney test, we found that there is a clinical and statistical difference between the experimental and control group, in the width of the scar (3 months) with a mean of 4 (± 1.65) mm in control group, and 1.70 (± 0.67) mm experimental group with p value = 0.003. The width of the scar (6 months) has a mean of 3.89 (± 1.69) mm in the control group, and 1.90 (± 0.56) mm experimental group with p value = 0.008. The Vancouver scale score (3 months) has a mean of 3.78 (± 1.20) mm in the control

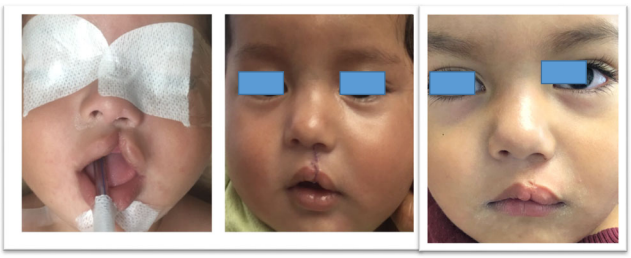

Fig. 1 Patient (study group) with unilateral cleft lip preop and 1 week postop result and 6 months after surgery

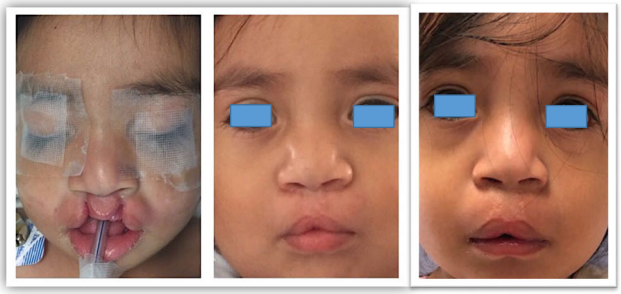

Fig. 2 Patient (Control group) with bilateral cleft lip, with preop and 3 & 6 months postop results

group, and 2.0 (± 1.05) mm experimental group with p value = 0.004. The Vancouver scale score (6 months) has a mean of 3.22 (± 1.20) mm in the control group, and 1.10 (± 1.05) mm experimental group with p value = 0.002.

Discussion

The presence of hypertrophic scar constitutes the most common sequel of cleft lip surgery (cheiloplasty), causing an important social stigma and discomfort for the patient and their family. Ethnical differences were reported by Chang and colls, with the highest incidence in Asian patients (36.3%), followed by Hispanics (32.2%) and Caucasians (11.8%) [15].

Mexico is a high prevalence country in which there is no standard of care in patients with cleft lip, and the already proven technics (silicone plate, special tapping to decrease tension) [17, 18] to diminish the rate of hypertrophic scar are not affordable to the majority of the Mexican population, because of its cost, lack of availability, or low educational level of the parents for their application.

There have been several efforts that aimed to prevent or minimize the hypertrophic scar in these patients.

Some authors have studied the benefits of botulin toxin use in scarring. For example, Holger et al. reported that type A toxin can minimize scars and prevent muscle contraction of the skin at the time of healing by altering the signaling pathway in fibroblast. Xiao et al. demonstrated that type A toxin inhibits muscle tension and affects the cell cycle of the distribution of fibroblasts derived from hypertrophic scars [19]. Also, Carrillo and colls proved that botulinum toxin improves the microenvironment in the wound with the devolvement of a richer vascular support increasing the synthesis of pro-angiogenic factors, while diminishing the muscular contraction, therefore, reducing the tension in the edges of the wound causing less ischemic environment. Also, the Botulinum toxin increases the expansion of messenger ARN of CD31 reducing the hypoxic state with sustainable increase in angiogenesis ensuring a better healing process [20]. This could translate clinically in better healing of the muscle, decreasing the whistle deformity, and allowing better alignment of the collagen and a more efficient remodeling phase by the increased amount of oxygen and nutrients secondary to a better vascularity.

However, there is too little evidence reported on the use of Botulin toxin for improving the results of cheiloplasty. Chang and colls. published a randomized clinical trial of the use of botulinum toxin in patients with cleft lip who underwent cheiloplasty [15], in which the Vancouver scale was applied with no statistical difference encounter. Nevertheless, this work has several biases that our study improves upon (the application of silicon plates in both groups by Chang and colls) [15].

We found statistic and clinical differences in the Vancouver grades and the width of the scar in milliammeters, and the result can be explained through the use of the toxin before the surgery, allowing the full effect to establish before the scar starts to form.

There are some limitations to this study: the small number of subjects included, the follow-up time, the lack of a more objective scale. Unfortunately, the study is too small to suggest that the Botulin toxin should be a standard of care in patients that have a cheiloplasty performed.

Also, the use of botulin toxin constitutes a cost-effective tool reducing the probability of future surgeries and constitutes a one-time intervention in a population that has limited access to specialized treatment, and it's more comfortable for the patient and parents than other treatments as silicon plates or tension bands.

Table 1 Demographic data

	Control (n = 11)	Cases (n = 11)	p
Gender	Female 6 (66%) Male 5 (34%)	3 (27.7%) 8 (72.3%)	0.19 **
Age (months)	4.82 * (1.47)	8.91* (5.39)	0.0097 *
Size of the cleft (mm)	Left (6) 10.83 (54.5%) Right (5) 9.40(45.5%)	(9) 8.67 (81.8%) (2) 3.0 (18.8%)*	0.703 **

*Patients with bilateral (two) clefts, the more width side was the one included in the analysis

Conclusion

The use of type A botulinum toxin decreases the presence of a hypertrophic scar in patients with a cleft lip who undergo primary cheiloplasty; however, more studies with a larger number of patients are needed.

The use of Botulin toxin before cheiloplasty has no adverse effects, improving the results of the surgery and achieving a more esthetical scar, with less risk of hypertrophic scar, therefore, offering more comfort for the patient and the family, and diminishing the stigma of cleft lip.

Compliance with ethical standards

Ethical statement The clinical trial was approved by the hospital committee of ethics and clinical research, with the number CEI 00420170731. Informed consent was explained and provided to patient parent before the intervention and attached to its clinical file.

Conflict of interest David Felipe Navarro-Barquín, Edgard Efren Lozada-Hernández, Myriam Tejeda-Hernández, Gerardo Adrian DeLeon-Jasso, Freya Estefania Morales-Rescalvo, Eduardo Flores-González, Felipe Piña-Aviles declare that there is no conflict of interest and have no ties with the pharmaceutical industry.

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Patient consent Patients provided written consent for the use of their images.

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