Prospective study for the treatment of rosacea flushing with botulinum toxin type A

Estudo prospectivo para tratamento do rubor da rosácea com toxina botulínica tipo A

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ABSTRACT

Introduction: Rosacea is a chronic facial condition characterized by erythema, edema, telangiectasias, papules and possibly pustules and nodules. There are four subtypes: erythematous-telangiectatic rosacea (I), papulopustular rosacea (II), phymatous rosacea (III) and ocular rosacea (IV). Its pathogenesis is multifactorial, and the treatments, diverse.

Objective: To demonstrate the effect of botulinum toxin in the improvement of flushing and erythema in patients with erythematous-telangiectatic rosacea.

Methods: Six patients with Subtype I rosacea were selected in the Dermatology Department's outpatient clinic of a university medical service. The patients received applications of botulinum toxin type A (dilution of 100 units to 5 ml of saline solution), with intradermal injections of 0.2 to 0.5 units per point in the affected region. Evaluations were carried out after one, two, three and six consecutive months.

Results: There was improvement of the facial erythema and flushing during the three months following the application, with symptoms returning around the sixth month after the treatment, in line with the estimated duration of toxin effectiveness.

Conclusions: There was improvement of the patients' symptoms and satisfaction, and it was deemed a treatment of easy application, associated with a low index of adverse effects and prolonged duration of outcomes.

Keywords: Botulinum Toxins, Type A; Erythema; Quality of Life; Rosacea

RESUMO

Introdução: *Rosácea é afecção crônica da face caracterizada por eritema, edema, telangiectasias, pápulas e eventualmente pústulas e nódulos. Existem quatro subtipos: rosácea eritêmato-telangiectásica (I), rosácea papulopustulosa (II), rosácea fimatosa (III) e rosácea ocular (IV). A patogênese é multifatorial, e os tratamentos são diversos.*

Objetivo: *Demonstrar o efeito da toxina botulínica na melhora do flushing e eritema, em pacientes com rosácea eritêmato-telangiectásica.*

Métodos: *Foram selecionadas seis pacientes com rosácea do subtipo I, no ambulatório do Departamento de Dermatologia de um serviço universitário. As pacientes receberam aplicações de toxina botulínica tipo A, em diluição de 100 unidades para 5ml de solução salina, com aplicação intradérmica de 0,2 a 0,5 unidades por ponto de aplicação na região acometida, tendo sido avaliadas após um, dois, três e seis meses consecutivos.*

Resultados: *Observou-se melhora do eritema facial e do flushing nos três meses consecutivos à aplicação, com retorno dos sintomas por volta do sexto mês após o tratamento, adequado ao tempo estimado de atuação da toxina.*

Conclusões: *Houve melhora dos sintomas e satisfação das pacientes, sendo um tratamento de fácil aplicação, com baixo índice de efeitos adversos e duração prolongada do resultado.*

Palavras-Chave: *Eritema; Qualidade de vida; Rosácea; Toxinas botulínicas tipo A*

Original Articles

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INTRODUCTION

Rosacea is a chronic condition of the face characterized by erythema, edema, telangiectasia and papules, which may be accompanied by pustules and nodules.[1] Despite the fact that it is a relatively common dermatosis, the clinical and histological parameters of the disease are still poorly defined.[2]

In 2002, the USA National Rosacea Society Expert Committee issued a consensus establishing a classification for rosacea aimed at standardizing subtypes and variants, having been since widely accepted and used.

Four subtypes were defined based on clinical characteristics: Subtype I, or erythematous-telangiectatic rosacea, includes individuals prone to flushing, associated with persistent facial erythema and sometimes telangiectasias; Subtype II, or papulopustulosa rosacea, characterized by central facial eruption of multiple small erythematous papules (<3mm), sometimes topped by a pustule, isolated or in groups; Subtype III, or phymatous rosacea, in which there is thickening of the skin with irregular contours covering ears (otophyma), eyelids (blepharophyma), mentum (gnatophyma), forehead (metophyma) and nose (rhinophyma), with the latter being the most common manifestation, predominantly occurring in males; Subtype IV, or ocular rosacea, which may occur without cutaneous manifestation or may still be seen in patients with any of the other Subtype of the disease; is characterized by nonspecific complaints, such as pruritus, tearing, dryness, as well as frequent blepharitis.[1-3]

Subtype I – or erythematous-telangiectatic rosacea – will be the focus of the present study. It can be clinically graded by frequency and intensity (0 = fair skin with no signs of erythema, 1 = slight erythema, 2 = slight erythema with defined redness, 3 = moderate erythema with marked redness, and 4 = persistent and pronounced erythema with intense redness) according to the Clinician's Erythema Assessment (CEA). [5-7] Redness episodes can occur without provocation or in response to emotional stress, alcohol, hot drinks, spicy foods, physical exercise, cold or hot weather, and hot baths [5,8]

The prevalence of rosacea in the last few years varied between 1 and 22%, depending on the methodology used and the population analyzed. The most recent rates, obtained from retrospective study databases, range from 1.3% to 2.1%. These low rates are due to the fact that only data from patients with more severe symptoms of the disease is recorded, overlooking a significant portion of patients with milder symptoms.[3,9,10]

It affects more women than men, and Subtype I is the most prevalent, followed by Subtype II. Phymatous rosacea is seen mainly in males of over 40 years of age.[11] Ocular rosacea arises with nonspecific symptoms, being therefore of difficult diagnosis, with incidence rates varying between 6% and 72%, affecting both genders equally.[12] Taking all these factors into account, rosacea is a more common dermatological entity than previously suspected.[3]

The exact pathogenesis of rosacea is still unknown, however some factors are deemed relevant for its occurrence, such as: dysfunction in the innate immune system; exposure to ultraviolet radiation, which causes increased angiogenesis and the production of reactive oxygen species; vascular changes, increasing the expression of vascular endothelial growth factor and lymphatic endothelial markers; epidermal barrier dysfunction; neurogenic inflammation (sensory nerves release neuromediators at the site of inflammation resulting in vasodilation); recruitment of inflammatory cells; extravasation of plasma proteins; and microbial action - *Demodex foliculorum* and *Demodex brevis*, and intense perifollicular inflammatory infiltrate. Such factors lead to a persistent inflammatory state that becomes chronic.[2,3]

The treatments proposed for this pathology are diverse, including topical and oral therapies, and associations with lasers and other technologies. Some casual outcomes of reduction of erythema and acne with the use of botulinum toxin for cosmetic purposes inspired a study by Dayan et al., conducted in 2012 with 13 rosacea patients. Patients received microinjections of botulinum toxin in the affected areas over two years, with results indicating a significant reduction of erythema and redness of the treated area between 2 and 4 weeks after the application. [13]

Since its initial approval for the treatment of strabismus, spasms and hemifacial blepharospasm, botulinum toxin has become one of the most broadly used products for rejuvenation worldwide.[14] After years of successful use and proven safety, treatment with botulinum toxin has expanded to many other indications.[13] The application of botulinum toxin in dermatology currently mainly consists of smoothing dynamic facial and cervical region wrinkles, and treating localized hyperhidrosis (axillary, palmoplantar and craniofacial).[14,15] Nevertheless, new studies have been proposed aimed at expanding indications: trigeminal and post-zoster neuralgia, dyshidrosis, Hailey-Hailey's disease, inverted psoriasis, congenital pachyonychia, cutaneous texture improvement and oiliness control, healing, keloids, notalgia paresthetica, Raynaud's phenomenon, and anal fissure among others.[16]

Botulinum toxin is produced by the culture of *Clostridium botulinum*, a gram-positive anaerobic bacterium. There are seven immunologically distinct neurotoxin serotypes (from A to G), with type A (BTX-A) being the strongest and most frequently used. Its mechanism of action corresponds to the blockade of the release of the neurotransmitter acetylcholine from the peripheral nerves. It has been proposed that acetylcholine plays a role in cutaneous vasodilation and consequently in rosacea reactive erythema.[5,13,17] Several botulinum toxin presentations are available in the market on five continents. There are five presentations of BTX-A available in the Brazilian marketplace: Botox (ONA - onabotulinum toxin A), Dysport (ABO - abobotulinum toxin A), Prosygne (BTA - botulinum toxin A), Xeomin (INCO - incobotulinum toxin A), and Botulift (BTA - botulinum toxin A), according to their introduction precedence in Brazil.[17,18]

The objective of the present study is to observe the efficacy of Botulinum toxin type A injections in the treatment of erythema-telangiectasic rosacea redness or erythema. This is a treatment of straightforward application and low side effects rates.

METHODS

A prospective, interventional study of a case series evaluated 6 female patients aged from 20 to 70 years, selected at the Outpatient Dermatology Clinic of the Universidade de Mogi das Cruzes, located in the city of São Paulo, in Southeast Brazil. The patients had Fitzpatrick's phototypes ranging from I to IV, and clinical diagnosis of erythematous-telangiectatic rosacea. The study was appropriately inserted in the Plataforma Brasil base and approved by the Ethics and Research Committee of the University de Mogi das Cruzes. One hundred units of botulinum toxin type A (BTA - Botulift®, Medy-Tox Inc., South Korea, represented in Brazil by Laboratório Bergamo) were diluted in 5ml 0.9% of saline solution (2 units / 0.1 ml), with 0.2 to 0.5 units being injected per application point. Intradermal injections were performed in the malar regions, with an interval of 0,5cm per application point, totaling a volume ranging from 6 to 15 units per affected malar region (a total of 12 to 30 units, equivalent to 0.6 to 1.5ml of the dilution). The following tools were used for evaluating patients: photographic records taken before, during and after the treatment; assessment of the clinical improvement through the Clinician's Erythema Assessment (CEA); satisfaction questionnaire (DLQI-Dermatology Quality of Life Index); and objective visual evaluation of the improvement of the redness using the CR-300® colorimeter (Konica Minolta Brazil, São Paulo, Brazil), which is a compact color analyzer for measuring reflective surface colors. This device consists of a measuring tip and a DP-301 data processor. The tip's measuring area is 8mm in diameter, and uses diffuse lighting and zero angle viewing (specular component included) for the accurate measurements of a wide variety of surfaces. A pulsed xenon arc lamp in a mixing chamber provides lighting on the sample's surface. Six high-sensitivity silicon photocells, filtered to match the observer's standardized response (Commission Internationale de l'Eclairage - CIE standard), are used by the meter's dual-beam feedback system to measure incident and reflected light. The meter thus detects any slight deviation in the extra light beamed by the pulsed xenon arc lamp and compensates it automatically. The absolute measurements can be shown as tristimulus values of Yxy, L*a*b*, L*C*Ho, Hunter Lab or XYZ. The data can be converted between color systems or between absolute and difference measurements by the data processor. The authors of the present study used the system L*a*b*, in which *L** is the luminosity, which varies from black (0) to white (100); *a** is the gradation from green to red; and *b** is the gradation from blue to yellow. The results were statistically analyzed using the Friedman, Wilcoxon and equality of two proportions tests, confidence interval for the mean value and p-value. The following statistical softwares were used: SPSSV20, Minitab 16 and Excel Office 2010.

RESULTS

The non-parametric Friedman and Wilcoxon tests were used to verify whether the treatments applied to the patients were effective or not. It was possible to conclude that there is a statistically significant difference between the times for the three parameters of the Colorimeter (Table 1).

For the analysis of the improvement in rosacea erythema, the parameter A was predominantly used. For instance, there were higher values of A in the sixth month (mean = 24.23), while they are lower in the second (19.76) and third (18, 08) months, as shown in Table 1. Thus, it was inferred that in months two and three of the study there were statistically significant improvements ($p < 0.001$) in the erythema (Figures 1, 2 and 3), which coincides with the longer duration of the botulinum toxin's action, meaning a better control of the rosacea's malar redness. The higher mean value in the sixth month is also compatible with the fact that the botulinum toxin's effect is already reduced in the site, entailing the worsening of the erythema. The second parameter evaluated was the clinical improvement regarding the reduction of redness, erythema and inflammation based on the Clinician's Erythema Assessment (CEA): 0 = fair skin with absence of signs of erythema, 1 = slight erythema, 2 = slight erythema with defined redness, 3 = moderate erythema with marked redness, and 4 = persistent and pronounced erythema with intense redness. For instance, the result for the distribution of the answer "Moderate erythema with marked redness", which corresponded to 67% in before the treatment, was decreased to zero in the first three months (Table 2, Figures 4 and 5), with statistical significance (Table 3). Six months after, the time lapse necessary for the drug to have effect on the erythema's mechanisms, the percentage increased to 33%. Finally, the progression of the results of the distribution for the ten questions (DLQI questionnaire) was analyzed using the test for equality of two proportions. It was possible to conclude that there are no statistically significant differences between the months of treatment regarding the baseline, meaning that the frequencies vary, but not significantly, since the findings are pulverized due to the small sample size.

Table 1: Development according to the colorimeter's parameters

Colorimeter		Mean	Median	Standard deviation	N	IC	*p-value*
	Before	21.70	21.38	2.67	12	1.51	
	Month 1	22.71	22.80	1.88	12	1.06	
A	Month 2	19.76	19.66	1.69	12	0,95	< 0.001
	Month 3	18.08	20.63	7.03	12	3.98	
	Month 6	24.23	24.43	2.03	12	1.15	
	Before	12.58	12.82	2.44	12	1.38	
	Month 1	12.19	12.69	2.27	12	1.28	
B	Month 2	13.83	14,82	2,03	12	1.15	0.002
	Month 3	10.25	12.03	4.15	12	2.35	
	Month 6	12.51	11.48	3.56	12	2.02	
	Before	61.55	55.06	16.32	12	9.23	
	Month 1	58.36	59.23	2.84	12	1.60	
L	Month 2	55.52	55.56	1.54	12	0.87	< 0.001
	Month 3	68	63.45	13.47	12	7.62	
	Month 6	59.75	58.98	3.72	12	2.10	

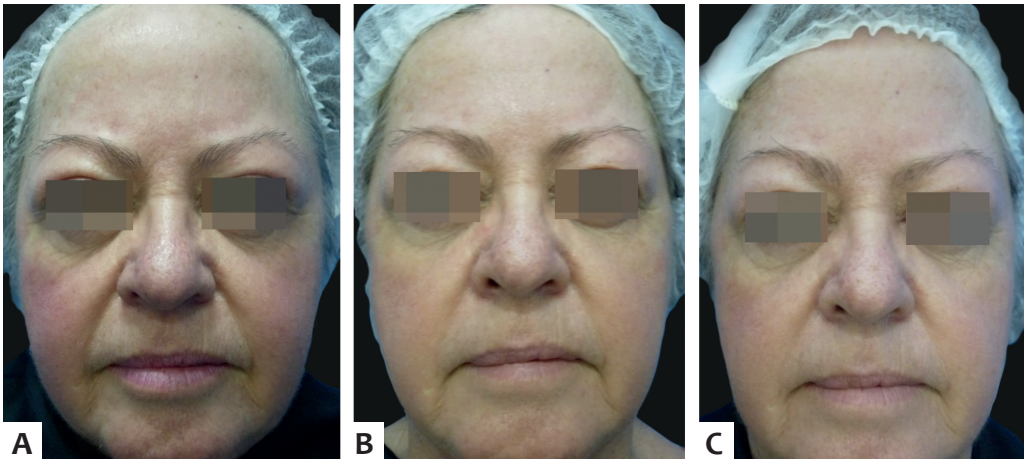

Figure 1: A - Pre-treatment; **B -** Two months after the application of the toxin; **C -** Three months after the application

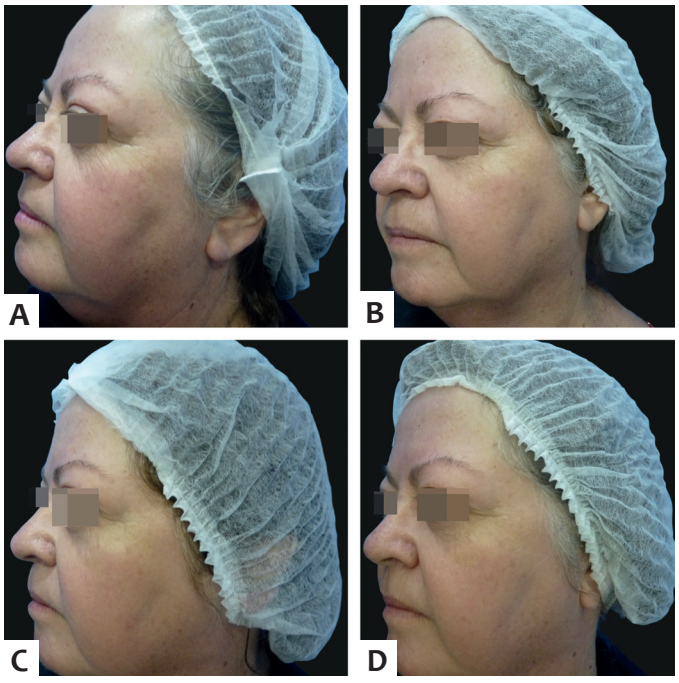

Figure 2: A- Pre-treatment; **B -** One month after the application; **C -** Two months after; **D -** Three months after the toxin application

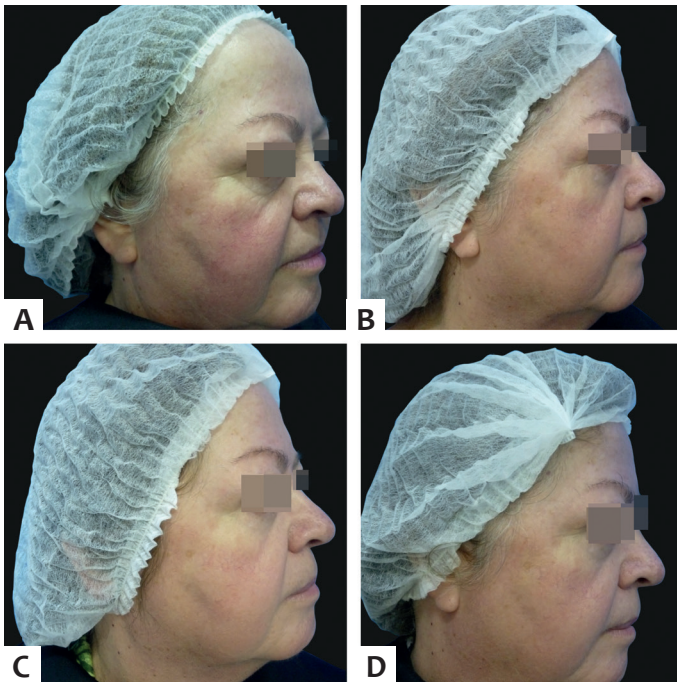

Figure 3: A - Pre-treatment; **B -** One month after the application; **C -** Two months after; **D -** Three months after the toxin application

DISCUSSION

Rosacea is an inflammatory cutaneous disease whose main manifestations include facial erythema, papules, pustules, telangiectasias and recurrent flushing, with heat and burning sensation, and local dryness. Facial erythema can cause discomfort, reduced self-esteem, anxiety and depressive symptoms, leading to a major impact on the patient's quality of life.[1,2,19] There are some treatments proposed for erythema / rosacea flushing, including topical brimonidine, oral beta-blockers, and laser and intense pulsed light based therapies.[19] Botulinum toxin has been recently studied as a therapeutic modality for these patients. Its mechanism of action is the transient blockade of presynaptic acetylcholine receptors at the neuromuscular junction. Since the 1980s, it has been used for dystonias, hemifacial spasms, strabismus correction, treatment for migraine and, more recently, has been applied in cases of sialorrhea, hyperhidrosis and aesthetic treatments.[14,15,20] Its application in cases of rosacea is recent, with few studies published.[2,3,13,20] A study carried out in 2012 by Dayan et al. analyzed 13 patients with erythematous-telangiectatic rosacea for over two years. Patients received botulinum toxin microinjections (7ml saline solution per 100 units of botulinum toxin) with 0.5cm spacing between the application points, in the affected areas, averaging eight to 12 units per area. Results indicated a significant reduction of erythema and flushing of the treated area between the second and fourth week after, with a sustained outcome for up to three months after the treatment.[13] Later on (in 2015), Bloom et al. demonstrated a similar

Table 2: Progression of the erythema's distribution

Erythema	Before		Month 1		Month 2		Month 3		Month 6	
	N	%	N	%	N	%	N	%	N	%
Fair skin with no signs of erythema	0	-	2	33	0	-	0	-	0	-
Slight erythema	0	-	2	33	4	67	1	17	1	17
Mild erythema with defined redness	1	17	2	33	2	33	5	83	3	50
Moderate erythema with marked redness	4	67	0	-	0	-	0	-	2	33
Erythema persistent and pronounced, with intense redness	1	17	0	-	0	-	0	-	0	-

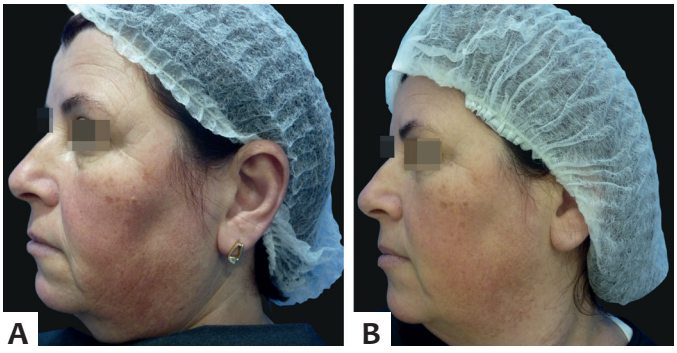

Figure 4: A - Pre-treatment**; B -** Three months after the application of botulinum toxin

Table 3: Table 2 p-values

Erythema	Month 1	Month 2	Month 3	Month 6
Fair skin with no signs of erythema	0.121	1	1	1
Slight erythema	0.121	0.014	0.296	0.296
Mild erythema with defined redness	0.505	0.505	0.021	0.221
Moderate erythema with marked redness	0.014	0.014	0.014	0.248
Erythema persistent and pronounced, with intense redness	0.296	0.296	0.296	0.296

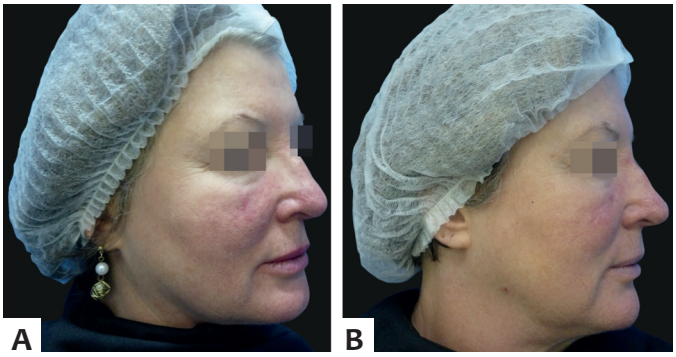

Figure 5: A - Pre-treatment; **B -** Two months after the application of botulinum toxin

treatment with a statistically significant outcome in the patients studied, showing improvement in erythema scores in the first three months after the treatment.[5] The present study employed botulinum toxin in a dilution of 100 units per 5ml saline solution, with intradermal application of 0.2 to 0.5 units per application point, which observed a spacing of 0.5cm between them, yielding results aligned with those of the reviewed literature, and statistical significant improvement of facial erythema in the first three months following the application, as well as reappearance of symptoms by the sixth month after the end of the treatment. As in other treatments for hyperhidrosis and hyperkinetic disorders, diverse amounts of the toxin were applied to each patient according to the area affected by erythema. A greater dilution and intradermal application of the drug in certain points allow better spreading of the product and less possibility of muscular involvement, which could lead to impairment in the facial mimicry's muscles.

CONCLUSION

It was possible to conclude that intradermal injections of botulinum toxin have been showing effectiveness and safety as an option for the treatment of rosacea-related facial erythema, offering straightforwardness in the application, a low rate of adverse effects and prolonged duration of outcomes. These results prevent the use of daily topical and oral therapies, making it easier for patients to adhere to the treatment, thus improving their quality of life. It has been proposed that acetylcholine, an important neuromediator linked to the mechanism of neurogenic inflammation through peripheral nerves, plays a role in cutaneous vasodilation – and consequently in rosacea-reactive erythema. The precise mechanism of action in the improvement of erythema has not yet been fully elucidated, however the action in the blocking of acetylcholine is one of the main evidences. Limitations of the present study include the reduced number of sample patients and the absence of a placebo group for controlling the outcomes. Further studies with larger groups of patients are necessary for determining the optimal dose and better estimating the duration of the treatment. ●

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