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Use of botulinum toxin for rosacea: a pilot study

Uso da toxina botulínica para rosácea: estudo-piloto

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ABSTRACT

Introduction: Rosacea is a chronic inflammatory skin disease. The intradermal application of botulinum toxin (BT) has been studied as a therapeutic option for patients who struggle to manage flushing and/or persistent facial erythema. There is no standard protocol for BT application in rosacea.

Objective: To evaluate the effectiveness of botulinum toxin application on erythematotelangiectatic rosacea.

Methods: Pilot study with case series. We applied intradermal BT in 10 patients with a diagnosis of rosacea and symptoms of persistent erythema and/or facial flushing. Patients received 10 to 15 injections per hemiface (1 unit of onabotulinum BT per injection) and 0 to 5 injections in the nasal region, totaling 25 to 35 units per patient.

Results: Seventy-five percent of the patients presented a reduction in flush and erythema intensity. The follow-up time was three months, and no serious adverse events were observed.

Conclusions: The therapeutic arsenal to control erythema and facial flushing of rosacea, especially refractory to the usual treatment, should consider the intradermal application of BT type A.

Keywords: Erythema; Rosacea; Flushing; Botulinum toxins

RESUMO

Introdução: rosácea é uma doença inflamatória crônica da pele, e a aplicação intradérmica de toxina botulínica (TB) tem sido estudada como uma opção terapêutica aos pacientes de difícil manejo do flushing *e/ou eritema facial persistente. Ainda não há protocolo-padrão para aplicação da TB na rosácea.*

Objetivo: *avaliar o efeito da aplicação de toxina botulínica na rosácea eritêmato-telangiectásica.*

Métodos: *estudo-piloto com série de casos. Foi realizada a aplicação intradérmica da TB em 10 pacientes com diagnóstico de rosácea e sintomas de eritema persistente e/ou flushing facial. Os pacientes foram submetidos a 10 a 15 injeções por hemiface (1 unidade de TB onabotulínica por injeção) e 0 a 5 injeções na região nasal, totalizando 25 a 35 unidades por paciente.*

Resultados: *apresentaram redução na intensidade do* flush *e do eritema 75% dos pacientes. O tempo de acompanhamento foi de três meses e nenhum evento adverso grave foi observado.*

Conclusões: *a aplicação intradérmica de TB tipo A deve ser considerada no arsenal terapêutico para controle do eritema e flushing facial da rosácea, especialmente em casos refratários ao tratamento habitual.*

Palavras-chave: *Eritema; Rosácea; Rubor; Toxinas botulínicas*

Original Article

Authors:
Jaqueline Barbeito de Vasconcellos[1]
Isabele Oliveira Santos[1]
Daniela Alves Pereira Antelo[1]

[1] Universidade do Estado do Rio de Janeiro, Dermatology Service, Rio de Janeiro (RJ), Brazil.

Correspondence:
Jaqueline Barbeito de Vasconcellos
Email: jaqueline_vasconcellos@hotmail.com

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INTRODUCTION

Rosacea is a chronic inflammatory skin condition that predominantly affects the midfacial region. It is characterized by recurrent episodes of flushing, transient or persistent erythema, papules, pustules, and telangiectasias.[1,2] Its prevalence ranges from 1% to 22%, according to different studies and populations.[3]

Although its pathophysiology has not yet been fully understood, the literature shows that innate immune deregulation and commensal skin microbiota imbalance occur. Triggering factors include mite *Demodex folliculorum* infection, ultraviolet radiation exposure, alcohol, heat, exercise, and spicy foods, which support the role of neurogenic inflammation in disease development.[4,5] It is assumed that activating the peripheral sensory neurons of transient receptor potential vanilloid type 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) receptors stimulates the release of vasoactive neuropeptides that cause the disease exacerbation.[5] In addition to vascular hyperreactivity, innate immune system deregulation through cathelicidin abnormal levels (antimicrobial peptides from human skin) also plays a central role in the pathogenesis of rosacea.[5]

Rosacea can be classified into four clinical presentations: erythematotelangiectatic, papulopustular, phymatous, and ocular. According to the 2017 ROSCO panel, this classification is shifting, and one or more characteristics may be present simultaneously in the same patient. The phymatous changes can be individually diagnostic for rosacea, and persistent centrofacial erythema, associated with periodic intensification by potential aggravating factors, is a feature of this condition. In their absence, the diagnosis can also be established by two or more main characteristics: papules and/or pustules, facial flushing, telangiectasia, and specific ocular manifestations.[1,4]

Management regimens aim to suppress inflammatory lesions, erythema, and, to a lesser degree, telangiectasia involved with rosacea.[2] Treatment is based on the phenotype of each patient, and they often overlap. Topical agents such as metronidazole, azelaic acid, ivermectin, brimonidine, and oral agents such as tetracyclines are widely used. Technologies like intense pulsed light and off-label oral medications, such as antihypertensive beta-blockers and adrenergic agonists, can be used to control flushing. However, oral medications often have adverse events and, even with optimized treatment, it can be challenging to treat persistent erythema and flushing in refractory rosacea cases. The intradermal application of botulinum toxin (BT) has been studied as a therapeutic option in patients in whom flushing and/or erythema compromise the quality of life.[6]

This study aims to evaluate the effect of botulinum toxin type A (Botox®) application on rosacea erythema in a series of patients.

METHODS

This is a pilot study with a series of cases. We selected ten patients from the Cosmiatry Clinic of the University Hospital Pedro Ernesto of the State University of Rio de Janeiro (UERJ). Patients of both genders diagnosed with erythematotelangiectatic rosacea (persistent facial erythema and episodes of facial flushing) were enrolled. All individuals agreed to participate in the research and signed the informed consent form (ICF).

We turned off the air conditioner and exposed the skin to the LED red light mask for five minutes to stimulate the erythema. Antisepsis of the face was performed with an alcoholic 2% chlorhexidine solution, followed by delimitation of the erythema region. Erythema was classified into: (1) absence of erythema; (2) erythema and/or mild flushing; (3) erythema and/or moderate flushing; (4) erythema and/or intense flushing; (5) very intense erythema and/or flushing.

We marked 10-15 application points per hemiface and 0-5 application points in the nasal region, with a distance of 1cm between them (Figure 1). Onabotulinum toxin (Botox®Allergan Inc., Irvine, CA, USA) was used, reconstituting the 100 U vial in 1 ml of 0.9% saline solution (1 U per 0.01 ml) and applying intradermally 1 U per marked point.

Clinical evaluation, photographic documentation, and quantification of erythema intensity were performed after 30 and 90 days.

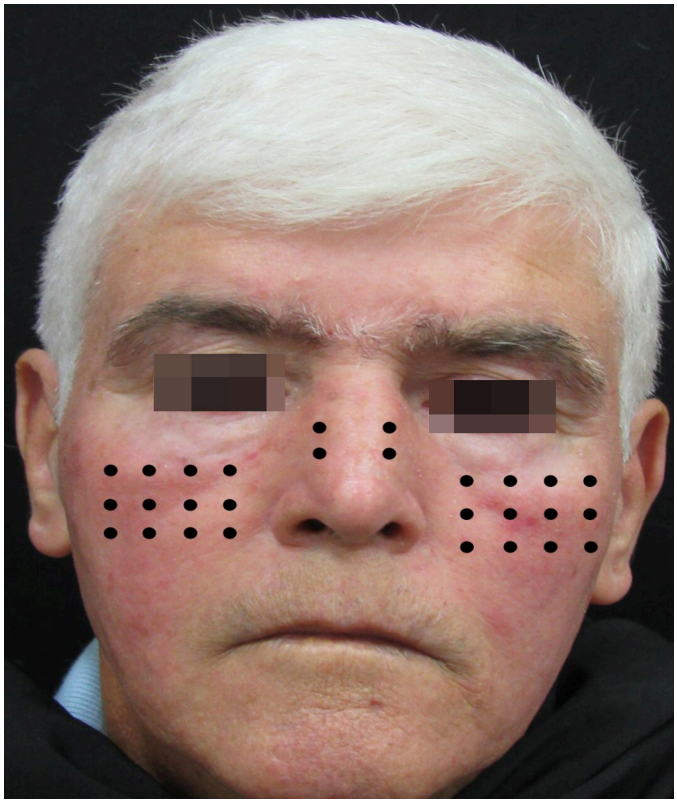


Figure 1: 10 to 15 points were performed in each hemiface and 0 to 5 points in the nasal region

RESULTS

We conducted the treatment in eight women and two men. Age ranged from 19 to 60 years, and skin phototypes, from I to III. Among the triggering factors for erythema and flushing, sun exposure was the most reported, followed by exposure to heat, emotional stress, and physical activity (Table 1).

Of the 10 treated patients (P1 to P10), eight returned for reassessment on the scheduled dates (P1, P2, P3, P4, P7, and P10 showed up in 30 days; P1, P2, P3, P4, P5, and P6 showed up in 90 days).

Of the eight reassessed patients, five reported improvement in erythema and flushing symptoms within 30 days, one reported improvement within 90 days, and two subjects reported no improvement in symptoms. All patients who described enhancement within 30 days maintained the same positive report within 90 days (Figures 2 and 3).

Regarding the analysis and clinical classification of facial erythema and flushing intensity after exposure to LED light, 63% of patients (n=5) decreased their intensity stage, 25% (n=2) remained in the same stage, and 12% (n=1) increased one intensity stage (Graph 1).

Statistical analyzes with non-parametric tests were performed, assessing the results at 30 and 90 days. For the D0-D90 test, the p-value was 0.035 (<0.05), rejecting the null hypothesis. Thus, we can say that there is a reduction in erythema after treatment, with statistical significance.

Adverse events were observed in only two patients: one presented ecchymosis at the BT application site with resolution within five days, and another presented mild asymmetrical smile (not perceived by the patient), corrected with the application of 1U of BT in the region of the contralateral zygomaticus major muscle.

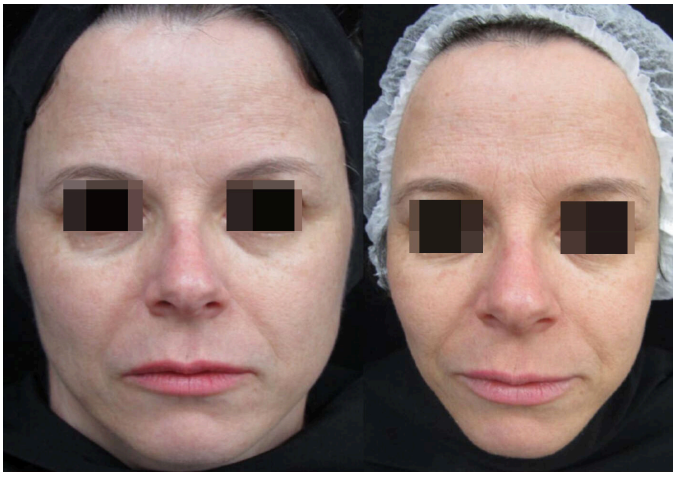


Figure 2: Before BT application and after 30 days

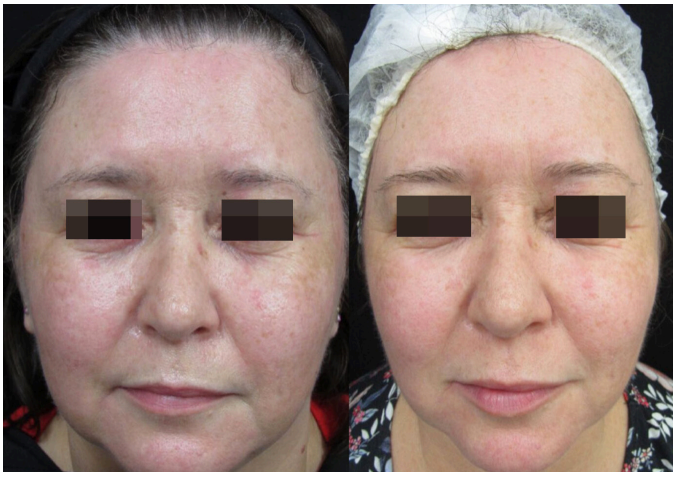
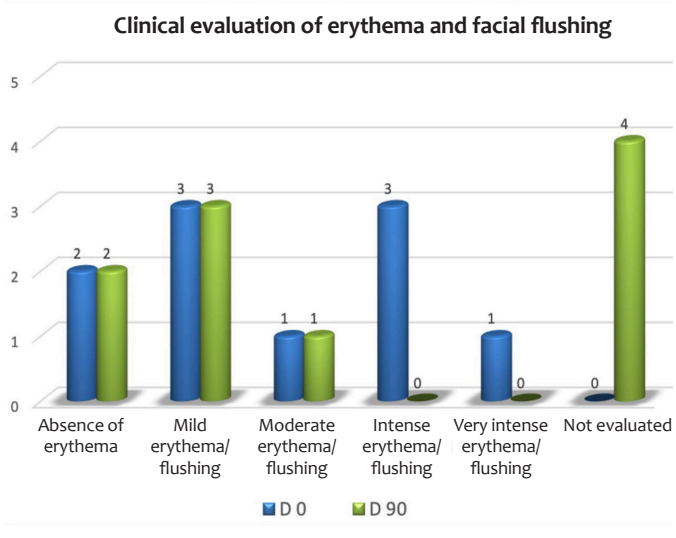


Figure 3: Before BT application and after 30 days

Table 1: Facial flushing triggers

Flushing triggers	Patients	
	Yes (%)	No (%)
Heat	80	20
Cold	60	40
Physical activity practice	60	40
Consumption of hot drinks	20	80
Consumption of alcoholic beverages	40	60
Emotional stress	70	30
Consumption of spicy foods	20	80
Sun exposure	90	10
Use of medications	20	80
Use of cosmetics	60	40
Premenstrual period	10	90
Others	10	90

Facial flushing triggers



Graphic 1: Clinical evaluation of erythema and facial flushing before TB application and after 90 days

Table 2: Studies that used BT to treat flushing and persistent facial erythema

Author	N.	Country	Treated area	Toxin used	Dilution / final concentration	N of points per area	Distance between points	Dose per point/ total dose	Results (erythema improvement)	Complications	Duration of effect	Follow up
Yuraitis M *et al.*, 2004[12]	1	USA	Malar	BT type A	100U in 5ml SF 0.9%/ 2U/0.1ml	⋆	1cm	⋆/ 10U (per area)	Satisfactory (after 2 weeks)	⋆	⋆	2 weeks /1 month
Kranendonk SK *et al.*, 2005[15]	1	USA	Unilateral malar	BT type A	⋆/ 4U/0.1ml	4 points	1cm	2U/ 8U total	Unsatisfactory	Yes (upper lip drop one week after application)	⋆	⋆
Alexandroff AB et al., 2006[16]	2	UK	Unilateral face	BT type A (ONA)	100U in 5ml SF 0.9%/ (2U/0.1ml)	⋆	1cm	⋆/ 10U total	Unsatisfactory (no improvement after 6 weeks)	⋆	⋆	⋆
Oh YJ *et al.*, 2011[13]	15	Korea	Unilateral face	BT type B	1ml BT-B in 0.1ml de NaHCO 8.4%	10-15 points	1cm	⋆/ 682U	Unsatisfactory (after 1, 4 e 8 weeks)	No	-	1, 4 and 8 months
Dayan SH *et al.*, 2012[17]	13	USA	Malar	BT type A (ONA)	100U in 7ml SF 0,9%/ (1.4U/0.1ml)	⋆	0,5cm	0,7U/ 8-12U per area	Satisfactory (after 1 week)	No	3 months	⋆
Park KY *et al.*, 2015[18]	2	South Korea	Malar, chin and forehead	BT type A (ONA)	50U in 2,5ml SF 0.9%/ (2U/0/1ml)	⋆	1cm	⋆/ 40-50U total ⋆⋆	Satisfactory (after 1 week)	No	4 months	1 week/3 months
Bloom BS *et al.*, 2015[19]	25	USA	Forehead, nose, malar and chin	BT type A (ABO)	300U in 3ml SF 0.9%	⋆	⋆	⋆/ 15-45U (mean dose: 25U)	Satisfactory ⋆⋆⋆	No	3 months	1, 2, 3 months
Eshghi G *et al.*, 2016[20]	24	Iran	Malar	BT type A	⋆	⋆	1cm	1U / 30U per area	Satisfactory (between week 2 e 3)	No	⋆	1 month
Bharti J *et al.*, 2018[11]	⋆	India	⋆	BT (type ⋆)	⋆/ 1U/0.1ml	⋆	0,5cm	0,5U/ ⋆	Satisfactory (after 1 a 2 weeks)	⋆	3-4 months	4-5 months
Antonio CR *et al.*, 2018[3]	1	Brazil	Forehead, nose, malar and chin	BT type A (ONA)	100U in 8ml SF 0,9%/ (1.25U/0.1ml)	10 points	0,5cm	0,625U /5-7,5U per area	Satisfactory (after 2 weeks and performed a second application)	⋆	⋆	14 days/24 days/ 2 months
Silva LC *et al.*, 2018[21]	6	Brazil	Malar	BT type A	100U in 5ml SF 0.9%/ (2U/0.1ml)	⋆	0,5cm	0,2-0,5U / 6-15U per area	Satisfactory (in the first 3 months)	⋆	6 months	1, 2, 3, 6 months
Kim MJ *et al.*, 2019[22]	23	South Korea	Unilateral malar	BT type A ⋆⋆⋆⋆	⋆/ 1U/0.1ml	30 points	1cm	0,5U/ 15U	Satisfactory (after 4 e 8 weeks)	No	⋆	2, 4, 8, 12 weeks
Al-Niaimi F *et al.*, 2020[23]	20	England, Denmark and Russia	Bilateral malar	Pulsed dye laser + BT type A (ABO or ONA) ⋆⋆⋆⋆⋆	500U in 5ml (ABO)/ 10U/0.1ml and 100U/ 2.5ml (ONA)/ 4U/0.1ml	⋆	⋆	⋆/2050U per area (ABO) and 10-20U per area (ONA)	Satisfactory	Yes (Moderate purpura in a patient lasting 10 days)	⋆	2 weeks/3 and 9 months

SF 0,9% - sodium chloride at 0,9%; NaHCO 8,4% - sodium bicarbonate at 8,4%

⋆ Not reported; ⋆⋆ Two BT applications were performed one week apart; ⋆⋆⋆ 15/25 patients had improvement in erythema scores at 1, 2 and 3 months after treatment; ⋆⋆⋆⋆ Prabotulinumtoxin A; ⋆⋆⋆⋆⋆ Three pulsed dye laser sessions were performed, followed by the application of BT at intervals of four to six weeks

DISCUSSION

The therapeutic arsenal to treat rosacea aims at controlling vascular inflammation. Topical medications such as metronidazole, azelaic acid, and, more recently, ivermectin reduce erythema related to vascular inflammation, as well as the group of oral cyclins. However, they have minor effects on erythema caused by permanently dilated superficial vessels.[7] Vasoconstrictor drugs, such as brimonidine, which acts as an alpha-adrenergic agonist, promote transient effects on facial erythema (9 to 12 hours) with reports of a rebound effect.[8] Some oral drugs, such as non-steroidal anti-inflammatory drugs, antihistamines, clonidine, and beta-blockers, have off-label use to control flushing in rosacea, with variable results and presence of adverse events.[9] According to the ROSCO 2019 panel, topical alpha-adrenergic modulating agents and oral beta-blockers were discouraged due to limited scientific evidence to treat flushing.[10]

BT use was suggested in the search for other alternatives to treat flushing and facial erythema. Its mechanism of action is not yet fully understood. Among the hypotheses is the inhibition of the release of the neuropeptides associated with vasodilation and inflammation, such as substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and acetylcholine (ACh) from the presynaptic vesicle.[5]

In a recent study, Choi et al. demonstrated through in vivo tests that the mechanism of botulinum toxin in rosacea treatment involves blocking the mast cells degranulation through the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins cleavage. Therefore, it proposed that BT targets the rosacea's neurogenic inflammatory component and also has direct inhibitory effects on mast cells.[5] Its effect in reducing the size of noticeable pores has also been reported. Its therapeutic benefit is possibly explained by blocking acetylcholine directed to the hair's erector muscles, decreasing pore size, and muscarinic receptors located in the sebaceous glands.[11]

Yuraitis and Jacob published the first report on intradermal BT type A as an effective treatment for facial erythema in 2004.[12] The authors reconstituted BT-A with 5 ml of isotonic saline for a final dilution of 2 IU by 0.1 ml. The application was performed at points 1 cm apart, in a total of 10 UI of BT in each treated region. The study observed a satisfactory result within two weeks after application, and the patient returned one month later to continue treatment in other areas. However, not all BT serotypes are effective in treating rosacea. An open, double-blind, split-face study, conducted in 2011 in Korea, aimed to assess BT--B's effectiveness in treating facial flushing. Fifteen individuals participated in the study, receiving the application of 682 units of BT-B on one side of the face, and saline solution on the other side, as a control. However, after evaluating the erythema index between the two treated sides, the BT-B injection side showed no significant decrease in erythema compared with the control side.[13]

According to the literature, there are no explicit criteria for treatment dilution, dose, and frequency, considering the different presentations of BT and each author's experience. A 2019 review analyzed 30 articles on the use of BT to treat facial flushing and rosacea. The dose of BT applied ranged from 1 UI to 6 UI for each cm^2 of treated area, and the number of sessions varied from 1 to 3 with different time intervals between them. All articles had satisfactory results.[14] Table 2 presents a literature review on the studies that used BT to treat flushing and persistent facial erythema with dilutions, doses, complications, duration, follow-up time, and results.[3,11-13, 15-23] In the present study, we opted for clinical observation of erythema after exposure to a LED red light mask (with heat emission) to standardize the stimulus since the heat was one of the triggers most reported by patients. Our series found satisfactory results, with few adverse events in the 1:1 BT dilution and a total dose ranging from 25 U to 35 U per patient.

Our limitations include the small sample size, the lack of a control group to compare the results and a long-term follow--up, and the fact that this was an open-label study. More extensive, randomized, blinded, placebo-group studies are needed for standardization and consensus on the ideal dose, technique, and treatment duration.

CONCLUSION

The intradermal application of BT can be considered a therapeutic alternative to control rosacea's erythema and facial flushing without a rebound effect or systemic repercussion. There is no consensus in the literature regarding the best dilution, number of points, dose, and frequency of application in these cases. The protocol performed (standard dilution 1:1 [1 U per 0.01ml]) generated good clinical results without significant adverse events. ●

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AUTHORS' CONTRIBUTION:

Jaqueline Barbeito de Vasconcellos ORCID 0000-0002-9726-0719

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

Isabele Oliveira Santos ORCID 0000-0002-2263-3736

Preparation and writing of the manuscript; critical literature review; critical revision of the manuscript.

Daniela Alves Pereira Antelo ORCID 0000-0001-8203-1772

Statistical analysis; approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.