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Botulinum Toxin for the Treatment of Refractory Erythema and Flushing of Rosacea

Kui Young Park[a] Moo Yeol Hyun[a] Se Yeong Jeong[b] Beom Joon Kim[a]
Myeung Nam Kim[a] Chang Kwun Hong[a]

[a]Department of Dermatology, Chung-Ang University College of Medicine, and [b]GoodDay Skin and Laser Clinic, Seoul, South Korea

Key Words
Botulinum toxin · Erythema · Flushing · Rosacea · Refractory

Abstract
Background: Persistent erythema and severe rosacea flushing can cause significant physical discomfort and emotional stress to patients. Currently, no satisfactory treatments are available. ***Methods:*** We report two cases of refractory flushing and erythema of rosacea that were successfully treated with intradermal botulinum toxin injections. ***Results:*** Good cosmetic results were achieved for both patients. The side effects during and after treatment were mild pain and localized bruising; these symptoms resolved within several days without further treatment. ***Conclusion:*** Intradermal botulinum toxin injection may be an effective treatment for refractory erythema and rosacea flushing that deserves further study in a larger patient population.

Introduction

Rosacea is a chronic inflammatory skin disorder with various clinical symptoms, including transient and permanent erythema, inflammatory papules and pustules, phymatous changes and ocular signs and symptoms [1]. Treatment of erythematotelangiectatic rosacea with severe facial flushing and persistent erythema remains challenging despite some successes with β-adrenergic blockers, clonidine (α-adrenergic agonist), naloxone (opiate antagonist), ondansetron (serotonin antagonist) and endoscopic thoracic sympathectomy [2–6].

Around the world, botulinum toxin has become one of the most frequently requested products in cosmetic rejuvenation since its initial approval for treatment of strabismus, hemifacial spasms and blepharospasms. After years of clinical successes and demonstrated safety for use in the upper face, botulinum toxin treatment has expanded to include increasingly complicated indications [7]. A recent report showed that botulinum toxin could decrease the intensity and duration of erythema and rosacea flushing [8].

We report two cases of refractory erythema and rosacea flushing treated with intradermal botulinum toxin injections.

Case Reports

Patient 1

A 36-year-old Korean woman presented with facial flushing and erythema that had persisted for over 2 years (fig. 1a); her symptoms were provoked by heat, sun exposure, stress, spicy food and cosmetics. Although she was treated with oral agents (minocycline, antihistamine, carvedilol, methylprednisolone), topical

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E-Mail karger@karger.com
www.karger.com/drm

Beom Joon Kim, MD
Department of Dermatology, Chung-Ang University Hospital
224-1 Heukseok-dong, Dongjak-ku
Seoul 156-755 (South Korea)
E-Mail beomjoon@unitel.co.kr

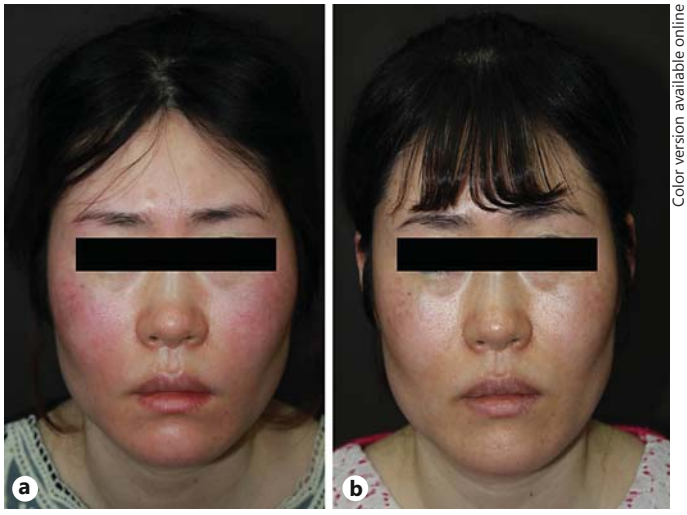

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Fig. 1. a Pronounced erythema and flushing on the whole face. **b** Marked improvement of the lesions after two rounds of intradermal botulinum toxin injections.

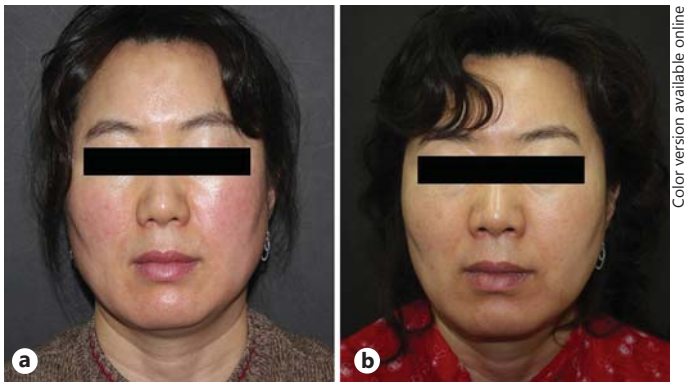

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Fig. 2. a Prominent erythema and flushing on both cheeks. **b** Marked improvement of the lesions after two rounds of intradermal botulinum toxin injections.

agents (tacrolimus cream, metronidazole gel) and medical skin care, satisfactory improvement was not achieved.

The patient received two treatments of intradermal botulinum toxin injections at 1-week intervals. Each vial of onabotulinumtoxinA, which contained 50 U of *Clostridium botulinum* toxin type A with human serum albumin and sodium chloride (botulinum toxin A, purified neurotoxin complex; Allergan, Campbell, Calif., USA), was reconstituted with 2.5 ml of sterile saline to achieve a concentration of 2 U/0.1 ml. A lidocaine-based topical anesthetic cream (EMLA; AstraZeneca, London, UK) was applied 1 h before treatment. A 30-gauge insulin syringe was used for the injection. The injection points were staggered 1 cm apart to cover the entirety of the erythematous lesions of the face. The toxin was injected vertically at a 90° angle. The total dose of botulinum toxin in two treatments was 50 U. In session 1, 15 U in each cheek and 3 U in each chin and the supra-eyebrow area were injected. One week after session 1, the erythema was much improved but still remained, thus additional injections were done. In session 2, 5 U in each cheek and 2 U in each chin and the supra-eyebrow area were additionally injected. The dose of botulinum toxin was chosen in reference to the study by Dayan et al. [8] and decided by experience of the clinician. It was preferred to inject the total dose dividing two or three times, because too much dosing in one time can make the patient uncomfortable and nervous. By 1 week after the second treatment, a good esthetic result was achieved (fig. 1b), and the patient did not report any major side effects; she only experienced mild pain during the treatment and localized bruising afterward, which spontaneously disappeared after 1 week.

Patient 2

A 49-year-old Korean woman presented with erythematous telangiectatic patches and flushing on the face that had persisted for 3 years (fig. 2a). Four months prior to her visit, she underwent 585-nm-pulsed dye laser therapy for erythema at a clinic, but did not see satisfactory improvement. She also took various oral medications, such as propranolol, carvedilol, steroids and oral contraceptives, but none of these drugs resolved her erythema and flushing.

The patient received two treatments of intradermal botulinum toxin injections at 1-week intervals. A topical EMLA cream was applied 1 h before treatment and a 30-gauge insulin syringe was used for the injections. The injection points were staggered 1 cm apart to cover the erythematous lesions of her face, and the injection procedure was the same as in patient 1. The total dose of botulinum toxin used was 40 U – 15 U in the first treatment and 5 U in the second treatment for each cheek. By 1 week after the second treatment, a good cosmetic result was achieved (fig. 2b), and the patient experienced only mild pain during the treatment. Three months after the final treatment, the lesion remained in an improved state.

Discussion

Although recent reports have questioned the safety of botulinum toxin, 25 years of therapeutic use and over 20 years of cosmetic use have yielded an impressive record of safety and efficacy when applied appropriately by experienced injectors [9, 10]. Seven different serotypes of botulinum toxin have been identified, but type A is most frequently used because of its favorable side effect profile and consistent clinical efficacy [11, 12].

Several recent reports demonstrate the possible action of botulinum toxin for facial erythema and flushing. In a case series of 17 patients with Frey syndrome who received botulinum toxin A injections to affected areas, all patients experienced complete regression of gustatory sweating and flushing. The effects persisted for at least 7 months, with low to negligible recurrence rates [13]. The clinical results were substantiated with corresponding decreases in cutaneous blood flow, as measured using laser Doppler

flowmetry [14]. Botulinum toxin works as a neuromodulator at the neuromuscular junction. Chemical denervation by botulinum toxin appears to interfere with normal acetylcholine signaling pathways and can provide symptomatic relief to patients with severe facial flushing [15].

In the cases reported here, we achieved satisfactory results for both patients, who both voluntarily returned for repeat treatment after 4 months. Because of the growing evidence supporting the efficacy of botulinum toxin dermatological treatment, we call for an effort to optimize treatment protocols and to run clinical trials with larger sample sizes that confirm its efficacy. Furthermore, we did not compare the effects of treating with intradermal botulinum toxin injections alone with those of a combination therapy that includes intradermal botulinum toxin injections and other treatment combinations; further studies that incorporate control groups and comparison treatments are required.

Conclusions

In conclusion, intradermal botulinum toxin injection may be an effective and safe therapy for patients with refractory erythema that deserves further study. No single optimal treatment has been indicated for rosacea, therefore intradermal botulinum toxin injection may be considered a reasonable addition to the therapeutic options for treating these conditions, especially when other established therapies have failed.

Disclosure Statement

The authors declare no conflicts of interest. There were no funding sources.

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