Received: 26 June 2020 | Revised: 2 July 2020 | Accepted: 5 July 2020

DOI: 10.1111/dth.13976

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

# Pulsed dye laser followed by intradermal botulinum toxin type-A in the treatment of rosacea-associated erythema and flushing

Firas Al-Niaimi[1,2] | Ekaterina Glagoleva[3] | Elena Araviiskaia[4]

[1]Department of Dermatology, University Hospital of Aalborg, Aalborg, Denmark

[2]Skin Clinics, London, UK

[3]KomMod Clinic, Saint Petersburg, Russian Federation

[4]Federal State Budgetary Educational Institution of Higher Education "Academician I. P. Pavlov First St. Petersburg State Medical University of Ministry" of Healthcare of the Russian Federation, Saint Petersburg, Russian Federation

**Correspondence**
Firas Al-Niaimi, Department of Dermatology University Hospital of Aalborg, Aalborg, Denmark.
Email: firas55@hotmail.com

## Abstract

Rosacea is a common inflammatory skin disease characterized by erythema, episodes of flushing, and inflammatory lesions. It typically affects the face and is more prevalent among fair skin individuals affecting women more than men. Various treatments are available for rosacea with light-based therapies commonly used in the management of erythema. The use of intradermal botulinum toxin type-A has been reported to be beneficial in the treatment of rosacea-associated erythema and flushing with good results and a low side-effect profile. In this article, we present our experience on the successful combination of both pulsed dye laser and intradermal botulinum toxin type-A in erythema and flushing in 20 rosacea patients. In addition to subjective improvement, we measured the degree of erythema using a 3D Antera camera in order to quantify our results. We demonstrated high efficacy and satisfaction rate with this combined approach and a low side-effect profile. To our knowledge, the combination of laser and intradermal botulinum toxin in the management of rosacea has not been previously reported.

**KEYWORDS**

Antera, botulinum toxin, erythema, flushing, pulsed dye laser, rosacea

## 1 | INTRODUCTION

Rosacea is a common inflammatory skin disease with a higher prevalence among lighter skin individuals affecting women more than men.[1] It typically affects the centrofacial areas with fixed erythema being a common feature.[1,2] The exact pathophysiological mechanism behind rosacea is unclear with a complex multifactorial interplay in susceptible individuals.[2,3] Vascular factors with increased vascularity and vasomotor dysregulation alongside aberrant neuro-inflammatory signaling appear to be key factors in the symptom presentation of rosacea.[3] Traditionally, rosacea was classified based on subtype morphology and included: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, and ocular subtype.[4] More recently, the new consensus has included fixed centrofacial erythema as the only diagnostic criterion with additional symptoms subclassified as major and minor criteria.[5] Flushing is a troublesome symptom that is particularly difficult to treat and is a major symptom in the new classification.

Treatment of rosacea depends on the severity and phenotype presentation and may include lifestyle adjustments, topical treatments, and systemic therapy.[1,4,5] Lifestyle advice on trigger avoidance and appropriate use of skincare regimens is increasingly being recognized with cosmeceuticals playing a role in barrier function and hydration. Light-based treatments are particularly effective for the erythema and vascular component with the pulsed dye laser (PDL) and intense pulsed light widely researched in this field.[6-8]

More recently, the use of intradermal botulinum toxin type-A (BoNTA) in rosacea has gained much interest particularly as a treatment for the flushing.[9,10] Several reports have highlighted the different approaches and techniques used with a high safety margin and patient satisfaction.[11-14] In this article, we present our experience with a novel combined approach of PDL treatment followed by

  

intradermal injections of BoNTA for the treatment of both the vascular component as well as additional symptoms of flushing, pruritus and burning sensation. All our patients had marked results and a high satisfaction with a low adverse effects rate.

In this article, we report the safety and effectiveness of reducing refractory erythema, flushing and telangiectasias associated with rosacea using the combination of PDL and intradermal BoNTA.

## 2 | PATIENTS AND RESULTS

A total of 20 patients were treated with this combination across the dermatology centers of all authors over the last 18 months. While the authors have treated many more with this combination the results described herein relate to a standardized protocol and a prospective evaluation of outcomes over the aforementioned period. The primary outcome was to determine a reduction in the severity and frequency of flushing and erythema in the treated patients. Secondary outcome was an improvement or reduction in the symptoms of pruritus and burning sensation as well as an increase in patient satisfaction scores. All patients had a consultation prior to the treatment detailing the nature of the treatment with explanation about the laser procedure including mechanism of action, recovery and potential side-effects in addition to explanation on the mechanism of BoNTA and its recovery time or potential side-effects. Informed consent was obtained from all patients prior to treatment. Treated patients were not on any concurrent topical or systemic therapy—other than skincare products—for at least 4 weeks prior to the first treatment. Patients with moderate-to-severe erythema and flushing were treated with this approach.

Standardized photographs were taken prior to and post treatments in addition to erythema quantification measurement using Antera 3D camera (Miravex Limited, Ireland). The Antera 3D camera uses multidirectional illumination and computer-aided reconstruction of the skin surface. The erythema concentration is derived from the spatial and spectral analysis of the acquired image data through illumination of LEDs with different wavelengths.[15] Quantification of reduction in erythema is of particular importance in standardization and elimination of subjective bias. In addition, erythema and flushing severity scores were measured based on the Clinician's Erythema Assessment Grading Scale on a scale from zero to five (0 = no erythema; 5 = severe erythema) prior to and post treatment at follow-up. A 3-month follow-up was performed which was followed by a final follow-up at 9-month.

Prior to treatment the skin was prepared through adequate removal of make-up and the use of a non-irritating cleanser. Topical retinoids or alpha-hydroxy acids were discontinued 48 h prior to treatment. Contra-indications to treatment included an ongoing active tan, pregnancy, lactation, history of facial keloid scarring, and hypersensitivity to previous BoNTA treatments. All patients were diagnosed with rosacea by dermatologists with predominance of ETR subtype and symptoms of flushing, burning sensation, and pruritus.

The protocol for laser treatment with the PDL (Vbeam, Candela, Massachusetts) used a single pass over the treated areas on the face using sub-purpuric settings in the range of 7 to 10 mm spot size, pulse duration of 3, 6, or 10 ms, and fluences ranging from 7 to 10 J/cm$^2$. The selected parameters varied among patients and was based on the skin type, amount of chromophore, skin response, and anatomic area treated. Purpura was not a desirable outcome and sub-purpuric parameters were adjusted based on the tissue response. Immediately post treatment intradermal BoNTA injections were administered in the areas affected by flushing in the cheeks only with typically a 1 cm interval between injection sites. The decision to limit the BoNTA to the cheeks is to minimize any unwanted functional compromise of facial muscles. The BoNTA used was abobotulinum (Dysport, IPSEN, UK) in a 5 mL dilution of 500 units using typically 20 to 50 units per cheek or onabotulinum (Botox, Allergan, USA) at 2.5 mL dilution in 100 units with doses ranging from 10 to 20 units per cheek. A 30-gauge needle was used with an insertion intradermally. The total dose varied between patients given the variation in severity and extent of the erythema and flushing. Post-treatment care consisted of cold compress with icepacks and the application of a light-based moisturizer suitable to rosacea skin.

A total of three treatments were performed with an interval of 4 to 6 weeks and post treatment measurements were performed minimum 2 weeks post the third treatment to allow for post treatment

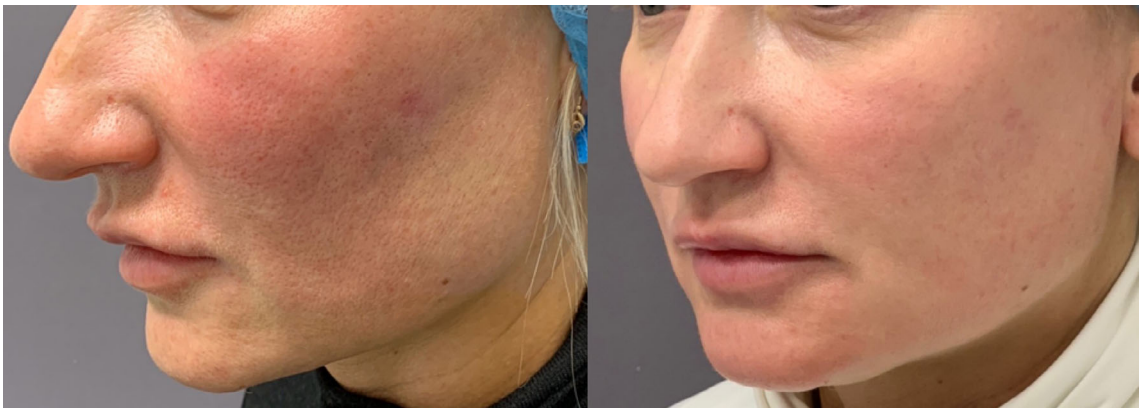

**FIGURE 1** Reduction in erythema before and after PDL plus intradermal BoNTA injections for the cheeks

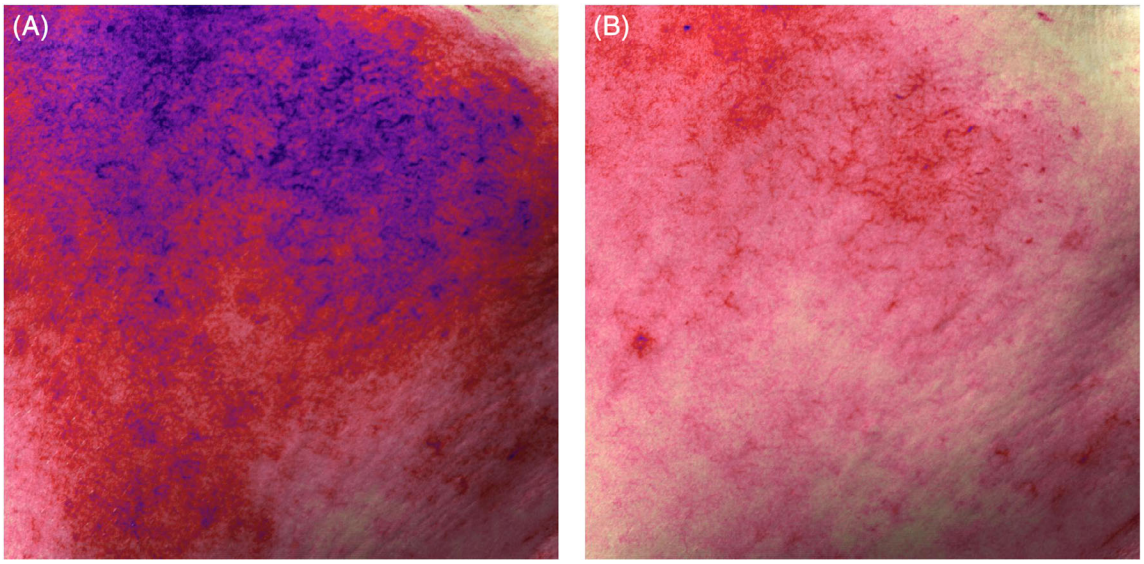


**FIGURE 2** A,B, Quantitative reduction in erythema with reduced spectral uptake after three treatments measured by the 3D Antera camera

erythema to subside. All patients experienced improvement in the erythema, telangiectasia, flushing, pruritus, and symptoms of burning sensation. Patients experienced high satisfaction with the treatment with minimal side-effects beyond expected reactive erythema and edema for few days post laser treatment (Figure 1). Only one patient experienced areas of mild purpura lasing 10 days with no residual sequelae. Objective erythema measurement showed improvement too in a quantifiable fashion with a marked decrease in erythema spectral uptake (Figure 2). Follow-up at 3 and 9 months showed sustained improvement in reduction of erythema with few patients experiencing a resurgence of flushing symptoms albeit with less severity compared to prior to treatment commencement.

## 3 | DISCUSSION

The exact pathophysiology of rosacea remains unclear but is likely to be the result of an interplay of neurovascular mechanisms and innate immune dysregulation.[1,3,16] Several phenotypic subtypes exist and it is possible that different mechanisms are implicated in each subtype, although most patients present with a degree of erythema with or without episodes of flushing. Current treatments depend largely on the clinical presentation, symptoms, and subtype.[5]

Treatments for the vascular component of rosacea—telangiectasia and erythema—is currently largely based on topical or light-based therapies. Topical therapy in the form of alpha-adrenergic receptor agonists provide symptomatic temporary relief and their use is limited by rebound effects in some patients.[17,18] PDL is largely considered the gold-standard treatment for telangiectasia and erythema of rosacea with downregulation of vascular endothelial growth factors and angiogenesis.[19] Improvements in sensitive skin symptoms is possibly achieved through substance P reduction.[20] Interestingly, other markers elevated in the neurogenic inflammation of rosacea such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) appear not be affected by PDL. A limitation of PDL—and other light-based therapies—is the suboptimal control of the intermittent flushing episodes experienced by rosacea patients despite a demonstrable reduction in erythema in most cases.[21]

The use of intradermal BoNTA in the management of rosacea has been a subject of growing interest with several studies reported on its efficacy and low side-effect profile.[10-12] Botulinum toxin is derived from *Clostridium botulinum* and is widely used in dermatology for its muscle relaxant effect through the inhibition of acetylcholine (Ach) release in presynaptic vesicles of the neuromuscular junction of peripheral nerve endings.[22] Furthermore, it has been shown that Ach plays a role in vasodilatation of vessels since this is mediated through the cholinergic effects of the autonomic sympathetic nervous system.[23] Additional effects are observed through modulation of various neuropeptides implicated in the neurovascular mechanisms of rosacea such as substance P, VIP, and CGRP.[24] In fact, VIP and CGRP appear to play an increasingly recognized role in the neurovascular regulation implicated in rosacea symptoms contributing to the episodes of flushing, pain and burning sensation in rosacea patients.

The above mentioned neuropeptides interact with transient receptor potential vanilloid (TRVP) and transient receptor potential ankyrin (TRPA) receptors under the influence of "triggers" such as ultraviolet light, alcohol or environmental stimuli.[25] The associated presence of symptoms such as burning sensation and pruritus alongside flushing is indicative of neurogenic inflammation beyond simple vascular hyperreactivity. Further evidence has pointed to the role of mast cells in cathelicidin-induced inflammation.[26] Cathelicidin is an antimicrobial peptide and cutaneous serine protease capable of inducing inflammation in rosacea through activation by kallikrein.[27] BoNTA has shown to have mast cell stabilizing effects (the latter expressing SNARE proteins that are the target of Ach) with reduction in histamine release in rosacea patients further supporting its role in symptom reduction in neurogenic rosacea.[26]

Various BoNTA brands and dilutions have been used in rosacea with no conclusive demonstrative superiority of a particular type or dilution. Some authors hypothesized that a higher dilution and a longer-acting brand might offer advantages in terms of physical spread therefore maximizing the effects in the intended treated area. No increased risk of side-effects were noted in those studies. We agree with this and our experience corroborate these findings hence the 5 mL dilution used in the abobotulinum toxin cases ($n$ = 10). We did not observe any difference between the two different neurotoxin types and achieved a high satisfaction rate from all treated patients. Our interval for treatments was based on the common interval for PDL and we believe this is appropriate for BoNTA too as similar intervals have been reported in the literature. We purposefully chose the intradermal BoNTA to be delivered post PDL as the reverse would have increased the risk of toxin dispersion through the laser pulsation and the ensuing edema.

Over the years, we have observed that flushing is a challenging symptom to treat and while a significant reduction in erythema and telangiectasia is possible with light-based approaches, control of flushing episodes remained a challenge. Systemic treatments such as beta-blockers offered symptomatic relief only and are not free from side-effects.[28] With this in mind we looked to explore the added value of combination therapy with the notion that PDL will control the erythema and BoNTA to control the symptoms of flushing, pain and burning symptoms mediated by the neuropeptides CGRP and VIP. The synergistic effects lead to a reduction of both the vascular and neurogenic inflammation in our patients and we noticed an improvement in reduction of flushing at a level not observed previously when using the PDL alone in comparable parameters and clinical endpoints. We observed marked and sustained reduction in the flushing which gradually weaned in a time fashion coinciding with the loss of biologic activity of the neurotoxin. Despite this, the intensity, frequency and severity of the flushing did not match the pre-treatment levels, a mechanism likely explained through the synergistic effect of the PDL coagulating and treating many vessels that could potentially dilate. Further evidence for the synergism is the lack of demonstrable reduction in the flushing in the PDL-treated areas alone (nose, central forehead, and chin) despite reduction in erythema. As explained earlier, the decision to limit the intradermal BoNTA injections to the cheeks was made to minimize and potential unwanted adverse effect from functional compromise. Furthermore, an objective reduction in both visible telangiectasia as well as background erythema was obtained through our imaging system.

We observed a reduction in the symptoms of painful burning sensation and pruritus with sustainment at 9-month follow-up. This is likely to be the combined effect of reduction in neuropeptides action and modulation of the innate immune system. It has been previously reported that PDL can reduce both substance P and demodex count and this may have contributed to our observation.[20,29] Of note, Substance P is less implicated in flushing compared to Ach and VIP.

In conclusion, we observed a synergistic benefit from combining the PDL with BoNTA injections with a reduction in both the erythema and flushing grading scores as well as a drop in the erythema index measurement using our 3D camera analysis. Limitation of our study was the relative small number of participants and the lack of control group though our intention was a proof-of-concept observation of a treatment combination increasingly used but to date has not been published.

We propose that the combination of PDL followed by intradermal BoNTA injections in patients with rosacea and symptoms of flushing, burning sensation and pruritus is safe and effective with a synergistic effect compared to either treatment performed individually.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ORCID

*Firas Al-Niaimi* https://orcid.org/0000-0002-0684-4322

## REFERENCES

1. Crawford GH, Pelle MT, James WD. Rosacea: I. etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol*. 2004;51:327-341.
2. Tan J, Berg M. Rosacea: current state of epidemiology. *J Am Acad Dermatol*. 2013;69(6) Suppl. 1:S27-S35.
3. Schwab VD, Sulk M, Seeliger S, et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc*. 2011;15:53-62.
4. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society expert committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
5. Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol*. 2018;78(1):148-155.
6. Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. *J Am Acad Dermatol*. 2004;51(4):592-599.
7. Handler MZ, Bloom BS, Goldberg DJ. IPL vs PDL in treatment of facial erythema: a split-face study. *J Cosmet Dermatol*. 2017;16(4):450-453.
8. Butterwick KJ, Butterwick LS, Han A. Laser and light therapies for acne rosacea. *J Drugs Dermatol*. 2006;5(1):35-39.
9. Dayan SH, Pritzker RN, Arkins JP. A new treatment regimen for rosacea: onabotulinum toxin A. *J Drugs Dermatol*. 2012;11(12):e76-e79.
10. Yuraitis M, Jacob CI. Botulinum toxin for the treatment of facial flushing. *Dermatol Surg*. 2004;30(1):102-104.
11. Park KY, Hyun MY, Jeong SY, Kim BJ, Kim MN, Hong CK. Botulinum toxin for the treatment of refractory erythema and flushing of rosacea. *Dermatology*. 2015;230(4):299-301.
12. Dayan SH, Ashourian N, Cho K. A pilot double-blind, placebo-controlled study to assess the efficacy and safety of incobotulinum toxin a injections in the treatment of rosacea. *J Drugs Dermatol*. 2017;16(6):549-554.
13. Forbat E, Ali F, Al-Niaimi F. Non-cosmetic dermatological uses of botulinum neurotoxin. *J Eur Acad Dermatol Venereol*. 2016;30:2023-2029.
14. Bloom BS, Payongayong L, Mourin A, Goldberg DJ. Impact of intradermal abobotulinum toxin A on facial erythema of rosacea. *Dermatol Surg*. 2015;41:9-16.
15. Linming F, Wei H, Anqi L, et al. Comparison of two skin imaging analysis instruments: the VISIA from canfield vs the ANTERA 3D CS from Miravex. *Skin Res Technol*. 2018;24(1):3-8.
16. Gerber PA, Buhren BA, Steinhoff M, Homey B. Rosacea: the cytokine and chemokine network. *J Investig Dermatol Symp Proc*. 2011;15:40-47.

17. del Rosso JQ. Topical a-agonist therapy for persistent facial erythema of rosacea and the addition of oxmetazoline to the treatment armamentarium: where are we now? *J Clin Aesthet Dermatol*. 2017;10:28-32.
18. Fowler J Jr, Jackson M, Moore A, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2013;12:650-656.
19. Menezes N, Moreira A, Mota G, Baptista A. Quality of life and rosacea: pulsed dye laser impact. *J Cosmet Laser Ther*. 2009;11(3):139-141.
20. Lonne-Rahm S, Nordlind K, Edstrom DW, et al. Laser treatment of rosacea: a pathoetiological study. *Arch Dermatol*. 2004;140:1345-1349.
21. van Zuuren EJ, Fedorowicz Z, Carter B, et al. Interventions for rosacea. *Cochrane Database Syst Rev*. 2015;2015(4):CD003262.
22. Tighe AP, Schiavo G. Botulinum neurotoxins: mechanism of action. *Toxicon*. 2013;67(1):87-93.
23. Holowatz LA, Thompson CS, Minson WL, et al. Mechanisms of acetylcholine-mediated vasodilatation in young and aged human skin. *J Physiol (London)*. 2005;563(3):965-973.
24. Peters EM, Ericson ME, Hosoi J, et al. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. *J Invest Dermatol*. 2006;126:1937-1947.
25. Choi JE, di Nardo A. Skin neurogenic inflammation. *Semin Immunopathol*. 2018;40:249-259.
26. Choi JE, Werbel T, Wang Z, Wu CC, Yaksh TL, di Nardo A. Botulinum toxin blocks mast cells and prevents rosacea like inflammation. *J Dermatol Sci*. 2019;93(1):58-64.
27. Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity. *J Investig Dermatol Symp Proc*. 2011;15(1):12-15.
28. Logger JGM, Olydam JI, Driessen RJB. Use of beta-blockers for rosacea-associated facial erythema and flushing: a systematic review and update on proposed mode of action. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2020.04.129. [Epub ahead of print].
29. Ertaş R, Yaman O, Akkuş MR, et al. The rapid effect of pulsed dye laser on demodex density of facial skin. *J Cosmet Laser Ther*. 2019;21(3):123-126.

**How to cite this article:** Al-Niaimi F, Glagoleva E, Araviiskaia E. Pulsed dye laser followed by intradermal botulinum toxin type-A in the treatment of rosacea-associated erythema and flushing. *Dermatologic Therapy*. 2020;e13976. https://doi.org/10.1111/dth.13976