A Randomized Controlled Pilot Study: Combined 595-nm Pulsed Dye Laser Treatment and Oxymetazoline Hydrochloride Topical Cream Superior to Oxymetazoline Hydrochloride Cream for Erythematotelangiectatic Rosacea

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Background and Objectives: We evaluated if oxymetazoline therapy combined with 595-nm pulsed dye laser (PDL) will be more beneficial than topical oxymetazoline alone for the improvement of erythematotelangiectatic rosacea.

Study Design/Materials and Methods: This was a randomized, controlled, prospective clinical trial approved by an independent Institutional Review Board, which enrolled 34 patients with moderate to severe clinical erythema (CEA) into a two-arm study of PDL with concomitant oxymetazoline cream (Arm 1) and oxymetazoline cream alone (Arm 2). Patients in Arm 1 were treated with 3 monthly laser sessions, which were started after 1 month of topical oxymetazoline cream. Thirty subjects continued with the study, and 25 subjects (Arm 1: 14, Arm 2: 11) completed the 6-month follow-up. With photographic comparison to baseline images, efficacy endpoints were based on clinical on-site grading by both the investigator and the patient, using the grading tools for CEA, Global Aesthetic Improvement (GAI) assessment, vessel size improvement, and subject self-assessment. These scales were assessed at baseline and/or at each clinical follow-up at 1, 2, 3, and 6 months. Subject satisfaction as well as post-treatment immediate response and treatment-associated pain scores were also evaluated.

Results: Statistically significant improvement in CEA was seen in both arms at the 1-, 2-, and 3-month post-baseline visits ($P < 0.01$). Only Arm 1 presented statistically significant improvement in CEA ($P < 0.001$) at 6 months post baseline with a mean score of 1.6 (almost clear-mild) compared with 3.2 at baseline. Arm 1 showed significantly greater mean vessel size improvement at 3 months ($P < 0.01$) and 6 months ($P < 0.05$) post baseline compared to Arm 2. Significantly greater improvement ($P < 0.05$) in the investigator GAI score was reported at the 2- and 6-month follow-ups compared with Arm 2. Subject GAI scores showed statistically significant greater improvement in Arm 1 compared with Arm 2 at both the 3- and 6-month follow-ups ($P < 0.01$). There were no complications or long-term effects associated with PDL or topical oxymetazoline treatments.

Conclusion: The prospective trial verifies a safe, enhanced clinical outcome with the combination of PDL therapy and topical oxymetazoline for the treatment of erythematotelangiectatic rosacea patients. Lasers Surg. Med. © 2021 The Authors. *Lasers in Surgery and Medicine* published by Wiley Periodicals LLC.

Key words: pulsed dye laser; oxymetazoline; rosacea

INTRODUCTION

Rosacea, a chronic inflammatory skin disorder, is characterized by centro-facial erythema and transient

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episodic flushing due to UV exposure, temperature variation, alcoholic beverages, and exercise. The spectrum of clinical features includes telangiectasias and papular/pustular lesions [1]. With an estimated global prevalence between 4%–6% and 1.5%–3.5% in the outpatient dermatological population, quality of life assessments have shown that rosacea significantly impacts self-perception, emotional status, grooming, and social interactions, with worsening measures in patients with increasing erythema severity [2]. The erythema and telangiectasias can be particularly challenging to treat as topical therapies are often transient in the duration of effect, and laser therapy typically requires multiple sessions.

Vascular-specific lasers are the mainstay for treating superficial blood vessels, which are the underlying pathologic lesion that causes prominent erythema. The newer generation 595-nm pulsed dye laser (PDL) with longer pulse durations, higher energies, and incorporated skin cooling allows for safer, nonpurpuric, and effective therapy of the erythema and telangiectasias of rosacea [3–5]. Potassium titanyl phosphate (KTP), intense pulsed light (IPL), and Nd:YAG have also been shown to be effective [3,6–9].

Vascular dysregulation may also be managed with the use of topical adrenergic receptor agonists for cutaneous vasoconstriction of the smooth muscle bearing subcutaneous arteries and small distal arterioles [10,11]. FDA-approved options include topical brimonidine and oxymetazoline. Though capillaries do not contain smooth muscle, the activity of such agents on the smooth muscle of superficial and deep vascular plexus reduces overall erythema. As a potent vasoconstrictor with high selectivity for the α1A-adrenoreceptor and partial selectivity for the α2A-adrenoreceptor, oxymetazoline was investigated in two phase 3 vehicle-controlled 29-day REVEAL trials [12]. Pooled analysis showed that the treatment group achieved a statistically greater reduction in facial erythema by day 29 (13.6% vs. 6.0%) with minimal adverse effects and subnanomolar serum concentrations [12,13].

In a prior retrospective review, Suggs et al. [14] showed that moderate-severe rosacea had significantly greater improvement in both erythema and telangiectasias when 595-nm PDL therapy was used in combination with oxymetazoline. This dual therapy approach achieved a greater clinical outcome in more severe phenotypes and was shown to be well tolerated. These outcomes were recently confirmed in a study that evaluated the safety and tolerability of combined oxymetazoline cream with one of four different energy-based therapies, including two PDL systems, a KTP laser, or IPL [6].

In this randomized study, we evaluated a potential enhanced effect of combined oxymetazoline therapy with 595-nm PDL versus topical oxymetazoline only for the purpose of improving erythematotelangiectatic rosacea.

METHODS

Study Design and Patient Selection

This was a randomized, controlled, prospective clinical trial approved by an independent Institutional Review Board. Eligible participants were enrolled at a private dermatologic surgery practice in either Charlotte, NC or Houston, TX. Inclusion criteria were male or female subjects ages 18–75 years with Fitzpatrick skin types I–IV and a baseline score of at least 3 (moderate) on the Clinical Erythema Assessment (CEA) and Subject Self-Assessment (SSA) grading scales [15,16].

Exclusion criteria included pregnancy, autoimmune and connective tissue disorders, disorders of immunosuppression or use of immunosuppressive medications, active cancer or significant concurrent illness (such as cardiac or neurological), and history of skin cancer, including the presence of malignant or premalignant lesions in the areas to be treated.

After obtaining informed consent, each subject was randomly assigned to receive either oxymetazoline therapy combined with three monthly 595-nm PDL treatments (Arm 1) or oxymetazoline therapy only (Arm 2). Thirty-four subjects were enrolled. Follow-ups were conducted at 1-, 2-, 3- and 6-month post baseline visit.

Treatment Protocol

Once-daily application of oxymetazoline hydrochloride cream, 1% (oxymetazoline; RHOFADE®; Allergan, Irvine, CA, USA) was initiated on Day 1 and continued throughout the 6-month trial (Fig. 1). Following 4 weeks of oxymetazoline therapy and a 3-day washout period, subjects in Arm 1 received the first of three monthly (±1 week) PDL (Vbeam® Prima; Candela Medical,

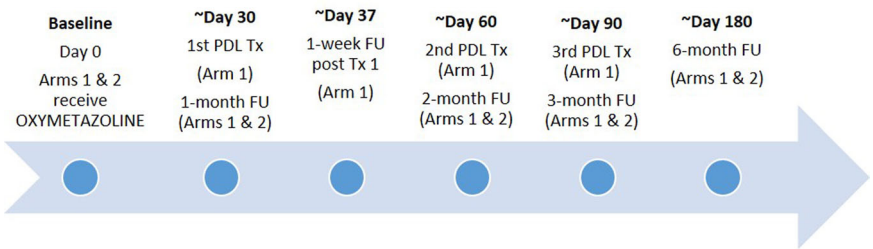


Fig. 1. Study visits flowchart. Baseline assessments were performed on Day 0. Following 4 weeks of oxymetazoline therapy and a 3-day washout period, subjects in Arm 1 received three PDL treatments at 3–5 weeks intervals.

Marlborough, MA) treatments. Prior to PDL treatment, topical anesthesia was offered (EMLA AstraZeneca Pharmaceuticals LP, Wilmington, DE; or benzocaine–lidocaine–tetracaine 20%–6%–6%) and removed after 30–60 minutes. Parameter settings were optimized for the 3×10 spot size to treat linear telangiectasias and for the 11–15 mm spot sizes to treat diffuse erythema until the desired clinical endpoints of immediate vessel blanching or subtle bluish graying with subsequent erythema (nonpurpuragenic) were observed (Table 1). Contact cooling was utilized for 17 treatments (36%) and dynamic cooling for 30 treatments (64%) with the following settings: 30 ms spray / 20 ms delay (n = 28 treatments) or 20 ms spray / 20 ms delay (n = 2). Treatment-associated discomfort and treatment responses were recorded immediately after treatment. Oxymetazoline cream was applied after the PDL treatment and patients continued with the daily application until the next washout period.

Assessments

Prior to each PDL treatment and at each clinical follow-up, faces were cleansed, and clinical photographs were captured by the Visia® Skin Analysis system (Canfield Scientific, Fairfield, NJ) for standardized magnification, lighting, and positioning.

Efficacy endpoints were based on clinical on-site grading by both the investigator and the patient, using the following grading tools, assessed at baseline and/or at each clinical follow-up at 1, 2, 3, and 6 months post-baseline:

(1) Investigator Clinical Erythema Assessment (CEA) [15]: a five-category scale ranging from 0 (clear skin with no signs of erythema), 1 (almost clear; slight redness), 2 (mild erythema; definite redness), 3 (moderate erythema; marked redness) to 4 (severe erythema; fiery redness);
(2) Subject Self-Assessment (SSA) [16]: a five-category scale ranging from 0 (clear of unwanted redness), 1 (Nearly clear of unwanted redness), 2 (Somewhat more redness than I prefer), 3 (More redness than I prefer), and 4 (completely unacceptable redness).

Follow-Up Assessments

(3) Investigator and Subject Global Aesthetic Improvement (GAI): a five-category scale ranging from 0 (Excellent improvement), 1 (Good improvement), 2 (Moderate improvement), 3 (Slight improvement), and 4 (No change);
(4) Investigator assessment of improvement in vessel size: a five category scale ranging from 0 (76%–100% improvement [excellent]), 1 (51%–75% improvement [marked]), 2 (26–50% improvement [moderate]), 3 (1%–25% improvement [mild]), and 4 (no response);
(5) Subject Satisfaction Scale: a five category scale ranging from 0 (Very Satisfied), 1 (Satisfied), 2 (No Opinion), 3 (Dissatisfied), and 4 (Very Dissatisfied).

Safety Endpoints

(1) Arm 1, Immediate Treatment Response: assessment of purpura, edema, erythema, blistering, hyperpigmentation, and hypopigmentation immediately after each PDL treatment.
(2) Arm 1, Numerical Response Scale for rating pain after each PDL treatment: an eleven-category scale ranging from 0 (no pain) to 10 (worst pain imaginable);
(3) Arm 1 and 2, reporting of frequency, type, and severity of any adverse event throughout the course of the study.

Statistical Analysis

The following statistical tests were used to compare intra-arm values to baseline and to compare inter-arm values (Arm 1 vs. Arm 2):

(1) Wilcoxon signed-rank test for paired data (intra-arm baseline to follow-up) for investigator CEA and for the subject SSA.
(2) Wilcoxon rank-sum test (Mann–Whitney U test) for unpaired data for the investigator and subject GAI and vessel improvement between study cohorts.

TABLE 1. PDL Treatment Parameters

Spot size	Fluence range (J/cm^2)	Pulse duration (ms)	# pulses per treatment (Mean ± SD)	No. of treatments with contact cooling	No. of treatments with dynamic cooling	N (total)
11	7.5–8	6, 10	554	1	0	1
11.5	7.25	6	707	1	0	1
12	6.25–7.5	3, 6	252 ± 29	0	3	3
12.5	6.75–7.25	6	586 ± 174	3	0	3
13.5	6.75	6	355	1	0	1
15	4.5–7.5	1.5, 3, 6, 20	293 ± 111	11	21	32
15, 12	6.75	3	225	0	1	1
15,	5–6.75	1.5, 3	199 ± 26			
3×10	11–16	20-40	19 ± 5	0	5	5
Total				17	30	47

The results are expressed as mean ± standard deviation and $P \leq 0.05$ is considered statistically significant.

RESULTS

Thirty-four patients were enrolled (Fig. 2) and randomized to treatment arms (Arm 1, $n = 18$; Arm 2, $n = 16$). One subject in the combined therapy Arm 1 withdrew from the study prior to the 1-month follow-up. Three subjects in Arm 2 withdrew from the study prior to the 1-month follow-up: one subject could not comply with study visits, one subject requested withdrawal, and one subject experienced breakouts, pustules, increased redness, and burning with topical oxymetazoline cream and withdrew from the study. These four subjects are not included in the baseline demographics (Table 2). Of the 30 subjects who continued with the study, 25 subjects (Arm 1, $n = 14$; Arm 2, $n = 11$) completed the 6-month follow-up (Fig. 2). There was no significant difference ($P = 0.61$) in investigator assessments of erythema severity (CEA score of 3.2 for both Arm 1 and Arm 2) or in subject assessments ($P = 0.66$; SSA score of 3.5 for Arm 1 and 3.6 for Arm 2) at baseline between the two study cohorts. Figures 3–5 provide examples of improvement in CEA in the two clinical arms.

TABLE 2. Baseline Characteristics for Study Cohorts Arm 1 and Arm 2 (n = 30 subjects at 1-month post-baseline)

	Total ($n = 30$)	Arm 1 ($n = 17$)	Arm 2 ($n = 13$)
Males	7	4	3
Females	23	13	10
Mean age ± SD (years)	45 ± 11	44 ± 12	46 ± 9
(Age range)	(26–61)	(26–61)	(29–60)
Fitzpatrick skin type I	1	0	1
Fitzpatrick skin type II	19	10	9
Fitzpatrick skin type III	8	6	2
Fitzpatrick skin type IV	2	1	1

A total of 47 PDL treatments were administered to the subjects in Arm 1. Most treatments (68%, 32/47) were performed using only the larger 15-mm spot size (Table 1). Pretreatment topical anesthetic was applied for 49% (23/47) of treatments. Treatments were well tolerated with a mean pain score of 4.5 ± 2.2.

Investigator Assessments

Investigator assessments for CEA, GAI, and vessel size improvement are shown in Table 3. Statistically significant improvement in CEA compared with baseline was seen in both arms at the 1-, 2-, and 3-month post-baseline visits ($P < 0.01$). Notably, only Arm 1 presented statistically significant improvement in CEA ($P < 0.001$) at 6 months post baseline with mean score of 1.6 (almost clear-mild) compared with 3.2 at baseline. Arm 1 showed significantly greater mean vessel size improvement at 3 months (1.8, $P < 0.01$) and 6 months (1.6, $P < 0.05$) post baseline compared to Arm 2 (score of 3.1 at both the 3- and 6-month follow-ups). Significantly greater improvement ($P < 0.05$) in the investigator GAI score was reported at the 2-month follow-up and at the 6-month follow-up of Arm 1 (good-moderate, 1.2) compared to Arm 2 (moderate-slight, 2.5).

Subject Assessments

SSA scores and GAI scores are shown in Table 4. SSA scores were significantly improved compared with baseline at all study visits after the first PDL treatment for

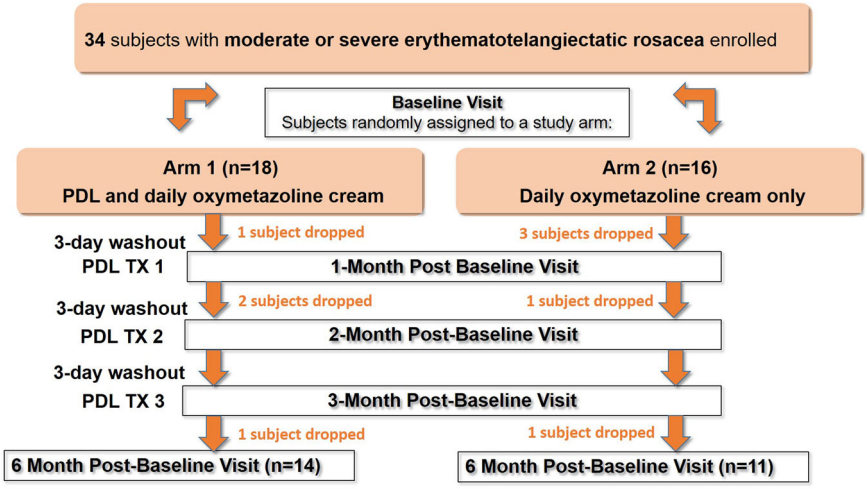


Fig. 2. Consortium diagram randomization scheme. One subject in the combined therapy Arm 1 withdrew prior to the 1-month follow-up. Three subjects in Arm 2 withdrew prior to the 1-month follow-up: one subject could not comply with study visits, one subject requested withdrawal and one subject experienced skin reaction to topical oxymetazoline cream and withdrew. Of the 30 subjects who continued with the study, 25 subjects (Arm 1, n = 14; Arm 2, n = 11) completed the 6-month follow-up. PDL, pulsed dye laser; TX, treatment.

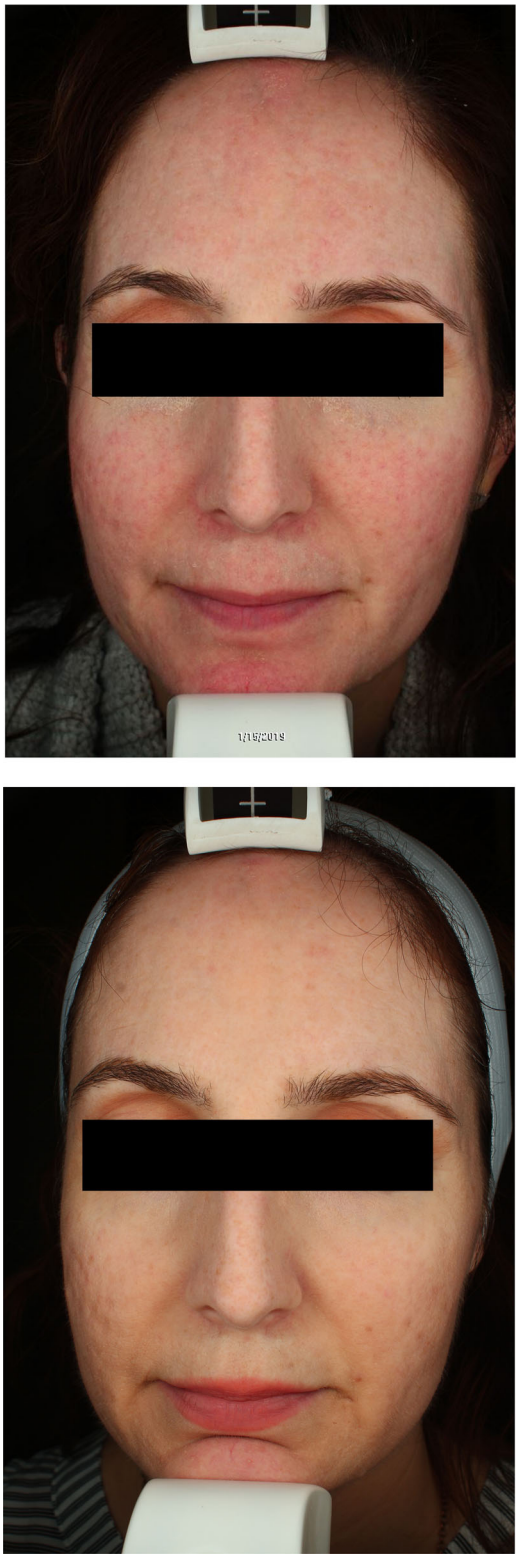


Fig. 3. Baseline and 6-month post-baseline: patient treated with PDL and topical oxymetazoline and subsequent two-grade improvement in CEA score (3–1). CEA, clinical erythema assessment; PDL, pulsed dye laser.

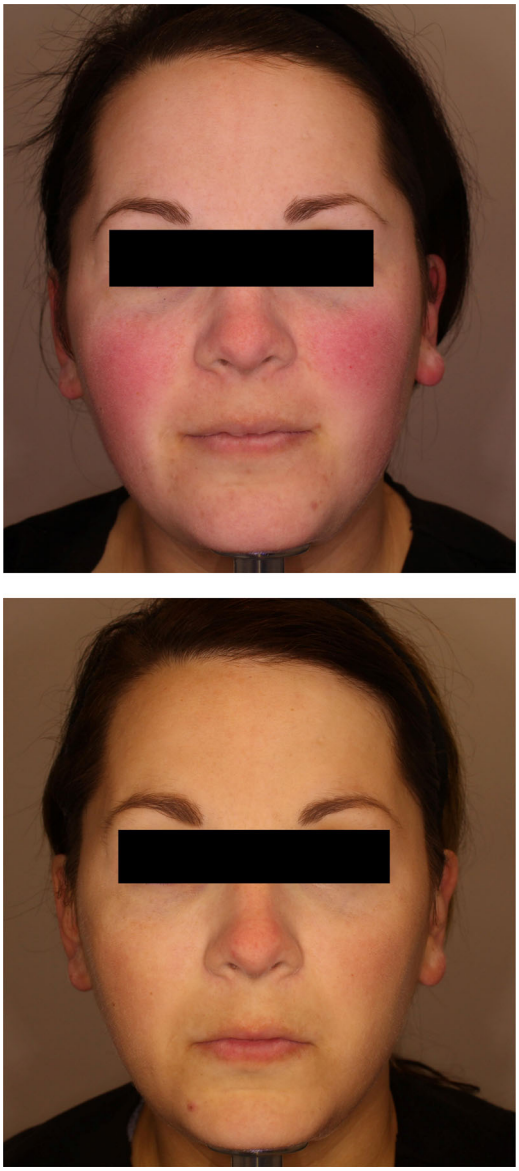
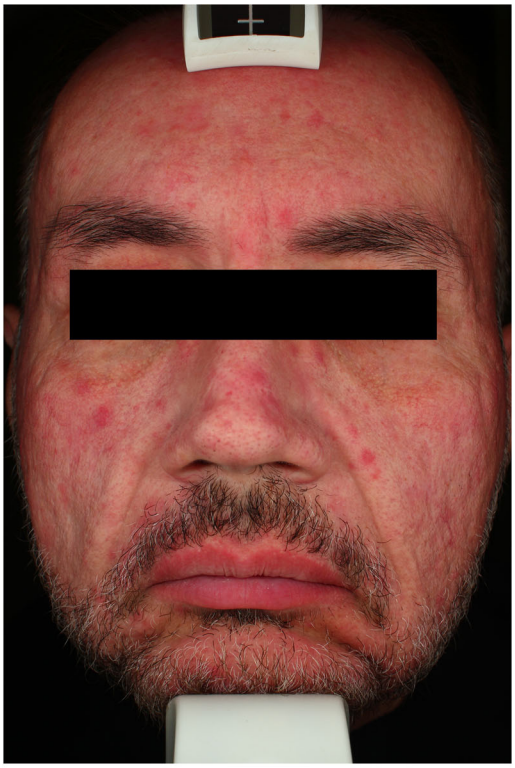


Fig. 4. Baseline and 6-month post-baseline: patient treated with PDL and topical oxymetazoline and subsequent three-grade improvement in CEA score (3-0). CEA, clinical erythema assessment; PDL, pulsed dye laser.

Arm 1 ($P < 0.01$) and at all study visits for Arm 2 ($P < 0.01$). There was no significant difference between study cohorts. Subject GAI scores showed statistically significant greater improvement in Arm 1 compared with Arm 2 at both the 3- and 6-month follow-ups ($P < 0.01$).

Subject satisfaction with combined PDL and topical treatment outcome was high (85%) with 64% "Very Satisfied" and 21% "Satisfied" for Arm 1 at the 6-month follow-up. None of the Arm 2 subjects were "Very Satisfied" with oxymetazoline cream only; 64% of subjects were "Satisfied" after 6 months of continuous topical monotherapy.



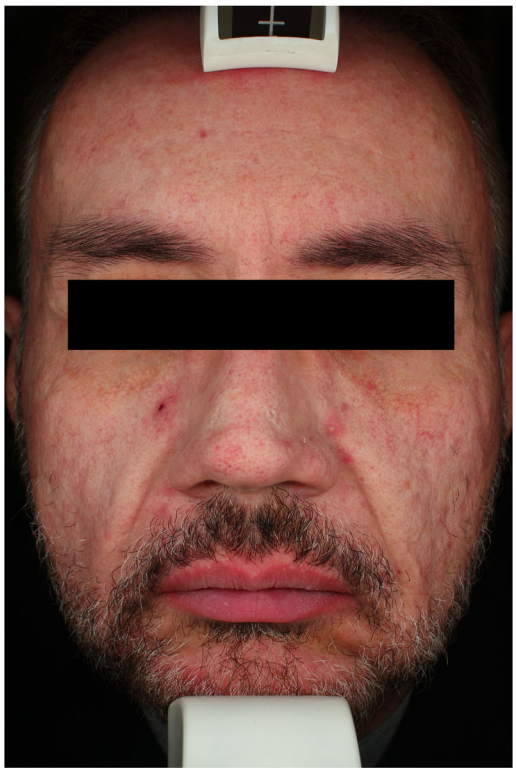


Fig. 5. Baseline and 6-month post-baseline: patient treated with topical oxymetazoline only and subsequent three-grade improvement in CEA score (4-1). CEA, clinical erythema assessment.

TABLE 3. Investigator Assessments by Study Visit

Study arm	Baseline	1-month visit (1st PDL)	2-month visit (2nd PDL)	3-month visit (3rd PDL)	6-month visit
Clinical Erythema Assessment (CEA)					
Arm 1	3.2	2.6[a]	2.5[a]	2.0[b]	1.6[b]
Arm 2	3.2	2.6[a]	2.0[a]	2.3[a]	2.4
Investigator Vessel Improvement Scale					
Arm 1	_	3.4	2.4	1.8[c]	1.6[d]
Arm 2	_	3.2	2.7	3.1	3.1
Global Aesthetic Improvement (GAI) Scale					
Arm 1	_	2.5	2.3[d]	1.7	1.2[d]
Arm 2	_	2.7	1.4	2.5	2.5

[a]$P \leq 0.01$—Wilcoxon signed rank test for paired data (Intra-Arm comparison to baseline).
[b]$P \leq 0.001$—Wilcoxon signed rank test for paired data (Intra-Arm comparison to baseline).
[c]$P \leq 0.01$—Wilcoxon rank sum test (Mann–Whitney U test) for unpaired data (Inter-Arm comparison).
[d]$P \leq 0.05$—Wilcoxon rank sum test (Mann–Whitney U test) for unpaired data (Inter-Arm comparison).

TABLE 4. Subject Assessments by Study Visit

Study arm	Baseline	1-month visit (1st PDL)	2-month visit (2nd PDL)	3-month visit (3rd PDL)	6-month visit
Subject Self-Assessment (SSA) Score					
Arm 1	3.5	3.3	2.7[a]	2.1[a]	1.4[a]
Arm 2	3.6	3.0[a]	2.3[a]	2.3[a]	2.2[a]
Global Aesthetic Improvement (GAI) Scale					
Arm 1	_	2.6	1.9	1.2[b]	0.7[b]
Arm 2	_	2.9	2.4	2.6	2.1

[a]$P \leq 0.01$—Wilcoxon signed rank test for paired data (Intra-Arm comparison to baseline).
[b]$P \leq 0.01$—Wilcoxon rank sum test (Mann–Whitney U test) for unpaired data (Inter-Arm comparison).

Safety Evaluation

There were no complications or long-term effects associated with PDL treatments. Transient mild to moderate erythema (87%, 41/47) appeared immediately following PDL treatments and resolved spontaneously. Mild edema occurred with 51% of treatments (24/47) and mild to moderate purpura with 30% (14/47) of treatments. There was one mild case of prolonged edema and erythema after the first PDL treatment that had recovered without intervention at the 1-week follow-up. Mild blistering (4%) appeared after two treatments. No dyschromia was noted.

The use of topical oxymetazoline was associated with two cases of mild dryness (2/30 subjects, 7%) that occurred within the first month of use and resolved spontaneously. One subject (3%) experienced a tingling sensation after applying oxymetazoline cream, which improved after 1 month of continued use. One subject (3%) experienced papules within the first month of oxymetazoline cream, which improved after several weeks of applying topical SOOLANTRA® (ivermectin; Galderma Laboratories L.P., Fort Worth, TX, USA) cream, 1%.

DISCUSSION

Combination treatments with energy-based devices and topical medications have been shown to enhance clinical outcomes compared to single treatment modalities, and in certain cases and applications, to provide a better result with fewer treatments. In particular, PDLs have been used in combination with topical aminolevulanic acid for the treatment of actinic damage, topical rapamycin, and imiquimod for the treatment of port-wine stains, and topical timolol for the treatment of infantile hemangiomas, to name a few [17–23]. Oxymetazoline is an α_{1A}-adrenoceptor agonist for the treatment of persistent facial erythema, which targets vessels with smooth muscle activity.

A recent study with PDL alone, utilizing the 15 mm spot size, demonstrated an average improvement in rosacea of $53.9\% \pm 2.6\%$ (mean $\pm$ standard error of the mean) with four monthly treatments [5]. Linear vessels were first treated using the 3×10 mm elliptical spot at a fluence of $15\,J/cm^2$ and a 40 milliseconds pulse duration. Then diffuse redness was treated over the entire face with a 15 mm diameter circular beam, a pulse duration of 3 milliseconds, and increasing average fluences over the four treatments starting at $6.25\,J/cm^2$ for the first treatment and averaging $6.97\,J/cm^2$ for the final treatment. Improvement at 2 months after the final treatment ranged from 6.6% to 86.7% on the 11-point scale (0%–100% in 10% increments).

Other studies have investigated the efficacy of combining PDL therapy with oxymetazoline treatment. The use of combined oxymetazoline applied 5 minutes prior to PDL treatment and daily thereafter showed persistent vascular shutdown 7 days after irradiation, though clinical trials and further elaboration of *in vivo* mechanism is needed to explain these findings [24]. Suggs et al. [14] first reported on the treatment of erythematotelangiectatic rosacea with PDL treatment and topical oxymetazoline, showing that 55% of patients (17/31) improved by least one grade CEA improvement and 41% of patients achieved at least 50%–75% clearance of telangiectasias after an average of 4 months of topical therapy with an average of two sessions of PDL. Notably, in patients with moderate to severe CEA at baseline, 69% of patients (11/16) showed more than 2-grade improvement in erythema and 100% achieved more than 2-point improvement in telangiectasia clearance [14]. These results guided our recruitment of the moderate to severe rosacea phenotype in this study, though patients with mild disease may benefit from this treatment approach.

We report on the first randomized, baseline-controlled prospective trial supporting the safety and benefit of combined topical oxymetazoline and PDL compared with topical oxymetazoline alone. This study demonstrated greater improvement in CEA in the dual therapy arm following 6 months of topical oxymetazoline and three PDL treatments compared with the topical oxymetazoline-only cohort. Vessel size also improved significantly in the dual treatment arm, and treatment outcome was associated with greater patient satisfaction. Treatment-associated adverse events and side effects were minimal and comparable to expected sequelae, with no effects leading to patient dropout. No clinical worsening was noted during the study.

Recently, a prospective interventional trial showed that oxymetazoline can be safely combined with PDL, KTP, and IPL energy-based therapy to reduce facial erythema in patients with moderate to severe persistent facial erythema associated with rosacea [6]. All subjects received 2 monthly energy-based treatments and once-daily oxymetazoline. Energy-based treatment was administered at baseline (day 1), and oxymetazoline was initiated on day 3. One-grade or greater erythema improvement on the 5-point validated CEA scale was observed in 20 (45.5%) patients before the application of oxymetazoline on day 3. Once-daily application of oxymetazoline was continued through day 27, with an oxymetazoline washout prior to and after the second energy-based treatment on day 29. Predose assessments showed improvement in 26 (60.5%) patients on day 31 and by 38 (88.4%) patients at 6 hours after oxymetazoline dosing. On day 56, 30 (68.2%) patients showed improvement prior to the application of oxymetazoline, and 39 (90.7%) patients showed improvement at 6 hours posttreatment. Clinical scores of telangiectasia improvement also occurred across all energy-based devices [6]. These results are supported by our study, which provides further confirmation of the enhanced effect with the combined therapy compared to topical oxymetazoline alone.

In this study, we also utilized the novel large spot (up to 15 mm), higher energy (12 J maximum, compared with the 8 J predecessor) PDL used by Bernstein et al. [5], which was effective in treating the erythema and telangiectasia in rosacea patients. Although the same PDL was used in both studies, it is difficult to compare the improvement in rosacea, as the assessment scale differed from the CEA scale used in the combined therapy studies. There were also differences in study design. Four PDL treatments were performed with only the 15 mm spot size to address the diffuse redness in the PDL study, while three treatments were administered in the current study with a range of spot sizes. Moderate or severe rosacea at baseline diagnosis was a study inclusion criterion in the current study, while not reported in the PDL alone study. Patients reported mild edema, mild to moderate erythema, and mild to moderate purpura, aligning with the post treatment effects reported in this study, and,

therefore, validating the use of this new-to-market device in this study [5].

Timing of topical oxymetazoline initiation prior to or after energy-based therapy has been variable throughout the studies mentioned herein. We opted for starting application 1 month prior to laser treatment due to clinical improvements seen by early clinical trials and long-term monitoring studies on the efficacy of oxymetazoline monotherapy [6,12,13,25]. A three-day washout period was instituted prior to PDL treatment, which is supported by partial recovery of vasodilation at 48 hours in mouse models and the calculated effective half-life of 18 hours in pharmacokinetic studies (~3.75 days for 97% elimination) [13,26]. Recently, a mouse model with optical imaging and flow experiments demonstrated that oxymetazoline has effects on both venular and arteriolar vasoconstriction and vasodilation that varies between 5 and 60 minutes post application [24]. Moreover, this study by Kelly et al. [24] showed persistent vascular shutdown after treatment with combined PDL and oxymetazoline therapy, supporting our findings [24]. Further *in vivo* studies are needed to better understand how application times of oxymetazoline may be improved to augment results with energy-based devices.

Needless to say, there is a complex interplay between topical adrenergic agonists and their receptors, with oxymetazoline showing a number of off-target activities, such as 5-hydroxytryptamine (5-HT) receptor activity that may affect the overall clinical effect [24,27]. Oxymetazoline has also been shown to combat UVB-induced erythema and inflammation, which has been known to be a cause of rosacea [26]. The regeneration of vessels after energy-based therapy is an important barrier to therapeutic efficacy that must be overcome, and topical therapy provides a safe option. Brimonidine has been shown to suppress choroidal endothelial cell proliferation by blockage of vascular endothelial growth factor (VEGF) and interleukin-6, and a similar mechanism may suppress neovascularization by oxymetazoline after laser therapy [28]. Topical rapamycin and axitinib have been shown to be effective in suppressing PDL-induced angiogenesis in rodent models by inhibition of the AKT/mTOR/P70S6K pathway [29,30]. Short-duration application of these agents after laser treatment may be worthy of studies in the future.

Limitations exist in our study. Despite the statistical significance we achieved for many of our endpoints, this study could not achieve appropriate power for randomization due to clinic closures during the early phase of the COVID-19 pandemic. Optical coherence tomography would provide an enhanced understanding of the vascular targets and depths, optimal laser settings, and timing of action of the topical therapies, which would promote overall understanding and optimize use. As we have mentioned, there are several topical treatments that may be considered. Future studies would benefit from an energy-based treatment group only, to determine the incremental gain of topical therapy, as cost-effectiveness is an important consideration in patient care.

The prospective trial verifies a safe, enhanced clinical outcome and possible synergistic response to PDL and topical oxymetazoline, which may be due to persistent vascular shutdown, overall reduction of inflammatory and neurogenic mediators, or inhibition of vascular regeneration or neovascularization. Further studies to examine other applications and combination therapies are warranted and likely to be safe.

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