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The effectiveness of flashlamp-pumped pulsed dye laser in conjunction with topical imiquimod treatment for rosacea

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ABSTRACT

Rosacea is a chronic dermatosis with no cure. Our goal was to evaluate if the combination of flashlamp-pumped Pulsed Dye Laser (PDL) treatment with topical imiquimod could improve therapeutic outcomes. Fourty patients diagnosed with rosacea and aged between 16 and 53 years were assigned for three different types of treatment: i) PDL-only, ii) imiquimod-only, and iii) PDL + imiquimod. The PDL test sites received a single treatment with the VBeam laser (λ = 595 nm; spot size = 7 mm; t_p = 1500 msec) at a dosage of 10 J/cm^2 with cryogen spurt duration (30 msec) and the delay time (20 msec). For the test sites of PDL + imiquimod and imiquimod-only, the patients applied imiquimod topically to the test sites once a day for 1 month. Patients were followed-up at 1, 3, and 6 months. The primary efficacy was measured with a DermoSpectrometer. Patients were also monitored for adverse effects. Pair-wise analysis showed statistically significant differences between the blanching responses for the PDL + imiquimod and PDL-only and imiquimod-only treatments ($p<0.005$). Transient hyperpigmentation was noted in 5% (n=2) and 20% (n=8) of patients in the PDL + imiquimod and PDL-only treatment, respectively. Hyperpigmentation resolved spontaneously within 6 months. Permanent hypopigmentation or scarring was not observed. Superior blanching responses were obtained when using PDL + imiquimod than PDL-only or imiquimod-only treatment for rosacea. A larger number of patients are required to support the results of this study.

Key words: Laser Therapy; pulsed dye lasers; imiquimod; rosacea; flashlamp-pumped Pulsed-Dye Laser (PDL).

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Pulsed dye laser and imiquimod treatment of rosacea
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Introduction

Rosacea is a common skin disorder that presents a variety of clinical manifestations primarily localized on the central part of the face.[1,2] This disorder is divided into four main subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. Persistent centrofacial redness is a characteristic feature of the erythematotelangiectatic form of rosacea. Whereas, papulopustular disease presents acne-like inflammatory papules and pustules in the same distribution. The phymatous form of rosacea may demonstrate skin thickening and facial distortion. Ocular rosacea, which often presents redness of eye, irritation, or pruritus and hordeola. Nonpharmacological interventions such as avoidance of flushing triggers, sun protection, gentle skin care, and the use of cosmetic products may be useful for the management of cutaneous manifestations of rosacea regardless of the clinical subtype. Biophotonic therapy have also been used for patients with rosacea-related flushing; however, data on the treatment effects remain limited.[3-6]

The development of lasers to destruct selective blood vessels offers an alternative choice for the clinical management of patients with rosacea. Various lasers have been utilized for this purpose; however, the flashlamp-pumped Pulsed Dye Laser (PDL) has achieved the best clinical results with a low incidence of adverse effects.[7-11] Yellow light produced by the PDL is preferentially absorbed by Hemoglobin (Hb), which allows more selective destruction of the dilated ectatic capillaries in the upper dermis. Through selective photothermolysis, PDLs offering wavelengths from 585 to 600 nm in conjunction with Cryogen Spray Cooling (CSC) are now available.

Angiogenesis inhibitors have been derived from different sources, such as natural products, monoclonal antibodies, and cleaved proteins, which contain a variety of chemopreventive compounds. These compounds exert antiangiogenic and chemopreventive properties through various mechanisms. One such component is imiquimod, which is a topical immune response modifier agent that inhibits the proliferation of new blood vessels.[12-16]

The purpose of this study was to inhibit the vascular hyperactivity of rosacea blood vessels after PDL therapy by using imiquimod as an antiangiogenic agent. The primary efficacy measurement involved the quantitative assessment of blanching responses. The safety was also assessed for each treatment site by searching for any adverse effects, such as dyspigmentation or scarring.

Materials and Methods

The Chang Gung Memorial Hospital's Institutional Review Board (IRB) in Taipei, Taiwan, gave its approval to the study protocol. Each patient (or legal guardian) consented to participate in the trial by signing the IRB-approved permission form. In this study, 40 rosacea patients treated between September 2016 and March 2020—16 men and 24 women—were reviewed. All of the subjects were Asian, and their ages ranged from 16 to 53. Charts were used to extract data on the following variables: sex, age, kind of rosacea, number of treatments, time between treatments, and results of treatments. The inclusion criteria for the participants were as follows: i) participants who had rosacea suitable for comparison testing, namely those with rosacea of width larger than 20 cm^2, and ii) participants in good health as recorded by medical history. The following exclusion criteria were used: i) history of photodermatoses or skin cancer, ii) concurrent using of known photosensitizing drugs, iii) pregnancy/lactation, and iv) any related therapy within the previous 3 months on the selected rosacea test sites.

Upon enrollment, patients had three test sites measuring 3 cm^2 marked on their rosacea lesions. By using computer-generated randomization, the three sites were assigned to three different types of treatment: i) PDL-only, ii) imiquimod-only, and iii) PDL + imiquimod. The PDL test sites received a single treatment through the VBeam laser (λ= 595 nm wavelength; spot size = 7 mm; t_p = 1500 sec) at a dosage of 10 J/ cm^2 with cryogen spurt duration of 30 msec and the delay time of 20 msec (Candela, Wayland, MA, USA).[17-25] Imiquimod cream (5% w/w; Aldara, 3M Health Care Limited, Leicestershire, UK) was purchased. Patients were provided with imiquimod cream for the duration of the study. For the PDL + imiquimod and imiquimod-only test sites, patients were instructed to apply a thin layer of topical imiquimod to the test sites once a day for 1 month after PDL treatment. Photographs were taken under standardized conditions for the film, light source, and exposure before and after treatment.

Following PDL therapy, patients were checked on at 1,

3, and 6 months. DermoSpectrometer (Cortex Tech., Hadsund, Denmark) measurements of the primary efficacy of blanching reactions were used for the quantitative evaluation. At each subsequent visit, the hemoglobin (Hb)-index was determined for the three test locations of each patient using the blanching responses. For vascular lesions, the quantitative treatment outcome was obtained using a DermaSpectrometer. The two specific wavelengths of light that light emitting diodes emit are 568 nm and 655 nm. The levels of oxyhemoglobin and melanin can then be determined by measuring the amount of green (568 nm) and red (655 nm) light that is absorbed and reflected, respectively.[26] The differences between the mean blanching response for the three test sites were then assessed, and a paired sample test analysis was performed. There existed a possibility that blood could be compressed out of the skin during the DermoSpectrometer measurements, which would result in a bias in the hemoglobin index measurement. Therefore, care was taken during each measurement to ensure that the device was in gentle contact with the surface of skin without the application of pressure to the test site.

Patients were also closely monitored for the incidence of any adverse effects. The safety was evaluated for each treatment by the occurrence of any blistering, scabbing, erosion, abnormal wound healing, scarring, dyspigmentation as well as allergy to imiquimod cream. Scarring was defined as a permanent hypertrophic, atrophic, or depressed skin texture on the test sites. Dyspigmentation (hyperpigmentation or hypopigmentation) was defined as a transient or permanent change in the skin color. Which was resolved within 1 year of post-treatment at the test sites compared with the adjacent normal skin.

Results

The Hb-indices blanching responses were assessed prior to PDL treatments as well as 1, 2, 3, and 6 months later for each of the treatment sites: i) PDL-alone, ii) imiquimod only, and iii) PDL + imiquimod. The means shown in Table 1 are the average values across the 40 study participants. The hemoglobin indices assessed with the DermoSpectrometer at each subsequent visit showed that the PDL + imiquimod treatment had better blanching responses than the PDL-only treatment. The hemoglobin index did not decrease with imiquimod as the sole therapy. On the imiquimod-only therapy, no blanching reactions or PDL-induced blood vessel disruption were seen (Table 1).

Paired sample testing revealed that the blanching responses of the PDL + imiquimod test sites were statistically significant compared with the responses from PDL-only treatment ($p<0.005$). At 6 months, there occurred some revascularization of the rosacea test sites that underwent the PDL + imiquimod and PDL-only treatments. However, according to the Hb-indices measured 1 and 3 months after PDL treatment (Table I), the rosacea test sites treated with PDL + imiquimod underwent less revascularization [mean value of 1.25 (6.79 – 5.54)] compared with the test sites treated with PDL-only [mean value of 2.61 (12.46 – 9.85)].

The safety was evaluated for each treatment by assessing the occurrence of blistering, scabbing, erosion, abnormal wound healing, scarring, and dyspigmentation, or allergy to imiquimod cream. Transient hyperpigmentation was noted in 5% (n = 2) and 20% (n = 8) of patients in the PDL + imiquimod and PDL-only treatment groups, respectively. In both test sites, hyperpigmenta-

Table 1. Mean hemoglobin (Hb)-indices of the blanching responses of test site in the rosacea patients.

	(A) PDL-only (n = 40)	(B) Imiquimod-only (n = 40)	(C) PDL# Imiquimod (n = 40)
Pre-PDL+	22.61 ± 4.29	22.61 ± 4.29	22.61 ± 4.29
1 Month	9.85 ± 2.31	22.12 ± 4.07	5.54 ± 1.24*
2 Months	10.37 ± 2.45	22.35 ± 4.53	5.87 ± 1.64*
3 Months	11.62 ± 2.57	22.56 ± 4.73	6.64 ± 1.72*
6 Months	12.46 ± 2.85	22.58 ± 4.78	6.79 ± 1.47*

*#Pre-PDL values represent the mean hemoglobin (Hb)-indices for all the patients (n = 40) according to the measurement on the test sites of each group before and after treatment. *p<0.005.*

tion in all the patients was resolved without further medical treatment within 6 months. Swelling, pain, abnormal wound healing, or scarring were not observed in any of the test sites. One patient reported very minor symptoms of itching and burning on the PDL + imiqui-

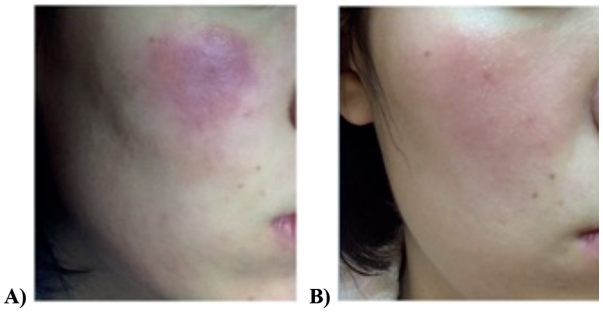

Figure 1. A) Twenty-six-year-old Asian female with rosacea of the right cheek; B) Condition of the patient 6 months after receiving two treatments at an energy density of 11 J/cm^2. Significant blanching was observed on the side of the rosacea receiving PDL-LT + imiquimod treatment.

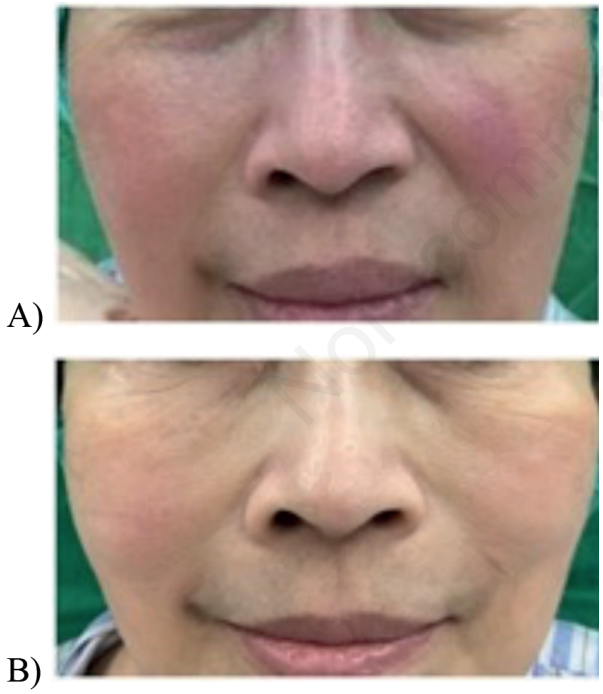

Figure 2. A) Fifty-three-year-old Asian female with rosacea of the bilateral cheek and nose; B) Condition of the patient 1 year after receiving two treatments of PDL + imiquimod at an energy density of 10 J/cm^2. The result was evaluated as an excellent blanching response.

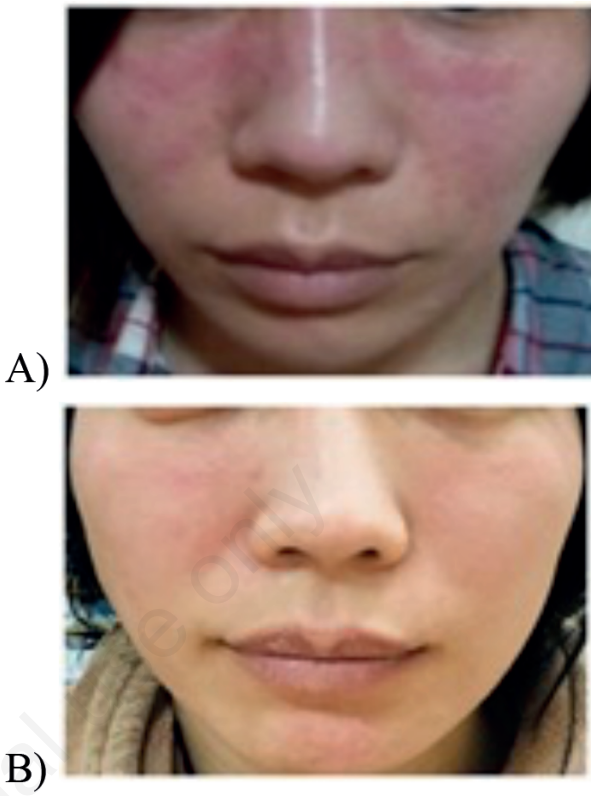

Figure 3. A) Twenty-four-year-old Asian female with rosacea of the right cheek; B) Condition of the patient 6 months after receiving one treatment of PDL + imiquimod at an energy density of 10 J/cm^2. The result was evaluated as an excellent blanching response.

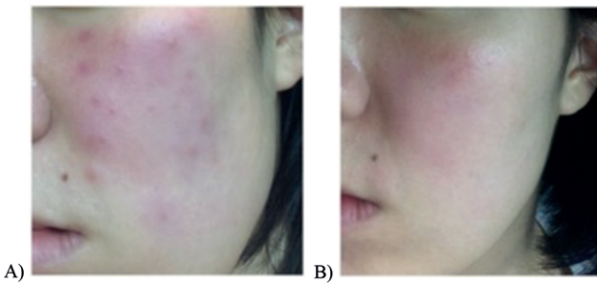

Figure 4. A) Twenty-seven-year-old Asian female with papulopustular rosacea of the left cheek; B) Condition of the patient 6 months after receiving one treatment at an energy density of 11 J/cm^2. A reduction was achieved in the colonization of the bacterium and ultimately in the number of active inflammatory lesions, which decreased post-inflammatory erythema. Significant blanching was observed on the side of the rosacea receiving PDL-LT + imiquimod treatment.

mod and imiquimod-only test sites 1 week after beginning topical imiquimod treatment. However, this patient could accomplish the 1-month course of topical imiquimod application without any disruption in the daily treatment regimen for the following 3 weeks. The symptoms appeared to be assessed as a minor allergic reaction. In our final assessment, all the patients treated with PDL + imiquimod displayed excellent blanching response (Figure 1-4).

Discussion

Rosacea is a common disorder of face that is most frequently observed in fair-skinned individuals (Fitzpatrick skin phototypes I and II). The prevalence of rosacea is difficult to assess due to its variable clinical manifestations and the wide ranges of varieties of skin disorders with similar clinical features. Estimates of the incidence of rosacea in fair-skinned populations range from 1% to 10%.[27-29] Similarly, the occurrence of rosacea is not uncommon in Asian with fair skin type. Rosacea occurs in people with darker skin complexions; however, it is less frequently diagnosed in such populations.[30-34] In general, adults over the age of 30 are the primary age group affected by rosacea, and the disorder occurs more frequently in female than in male.[27,35] However, the vast majority of patients affected with phymatous rosacea are adult males. In adolescents, rosacea is often mistaken for acne vulgaris in this population. On the other hand, rosacea rarely occurs in children. Children may exhibit all subtypes except the phymatous form, and symptoms may persist till adulthood.[3,36,37]

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The pathways that lead to the development of rosacea are not well understood.[4,5] Proposed contributing factors include vascular dysfunction, ultraviolet damage, abnormalities in innate immunity, and inflammatory reactions to cutaneous microorganisms. Increased blood flow has been detected in the skin of some patients. These observations suggest a role for vascular hyperreactivity in the pathogenesis of this disorder[6,34,38] Dysregulation of thermal mechanisms has also been proposed as a contributing factor to flushing associated with rosacea.[39] The pathways that may lead to neurovascular dysregulation. One theory proposes that the activation of transient receptor potential vanilloid 1 and ankyrin 1 receptors found on primary sensory neuron endings as well as keratinocytes by triggers of rosacea (e.g., extremes of temperature and spices) may stimulate the release of vasoactive peptides that exacerbate rosacea.[31] Histopathological findings from erythematous facial skin in erythematotelangiectatic rosacea usually indicate the dilation of superficial blood vessels and a low grade perivascular lymphohistiocytic inflammatory infiltrate with occasional plasma cells. Solar elastosis is also often present.[40]

The central hypothesis of our research is that the combination of PDL to induce rosacea blood vessel injury and imiquimod (to prevent blood vessel angiogenesis and recanalization after laser treatment) would improve blanching of rosacea.[18,25-27] Through selective photothermolysis, PDL destroys blood vessels of subsurface rosacea skin. PDL treatment of rosacea induces hypoxia, edema, and inflammation in the upper dermis. Inflammatory cells migrate into the treated area secreting cytokines, which are potent up-regulators of proangiogenic factors. It also stimulates procollagen production secondary to the nonlethal heating of dermal perivascular tissues, which is postulated to alter local cellular metabolism. In addition, for papulopustular rosacea, the bactericidal effect can be induced by high power laser energy. Furthermore, for papulopustular rosacea, the PDL emits visible light that is absorbed primarily by oxyhemoglobin and decreases post-inflammatory erythema, thus reducing the colonization of the bacterium and the number of active inflammatory lesions (Figure 4).[41,42]

From a histopathological point of view, blood vessels are located at a depth of 250-750 msm in rosacea. The time delay before the cold front produced by CSC reaches the most superficial layer of the pathological vessels is on the order of 100 msec. Based on this theory, CSC duration of 30 msec has been set to permit selective photothermolysis on the rosacea blood vessels. Temperature in the most superficial skin layer is reduced from 30 to -10°C, the spatial distribution of cooling remains localized in the epidermis.[18,22-24] On the other hand, protection of epidermis from thermal injury produced by melanin light absorption at clinically relevant wavelengths can be effectively achieved while using CSC. Meanwhile, prevention of exacerbation factors (triggers of flushing) such as extremes of temperature for recurrent rosacea can be achieved.

Imiquimod, a topical immune response modifier, prevents neovascularization, which can hasten the devel-

opment of this illness. The production of cytokines that prevent angiogenesis (interferons, IFN-α,β,γ, IL-10, IL-12, and IL-18) is one of imiquimod's antiangiogenic actions, as well as increase in endogenous angiogenesis inhibitors locally (IFNs, IP10, TSP-1, and TIMP) while down regulating factors that promote angiogenesis (MMP-9 and bFGF) and inducing endothelial apoptosis.[14-16]

According to the hemoglobin indices determined for 40 patients by using a DermoSpectrometer (Table 1), more favorable blanching responses of rosacea were observed on the test sites treated with PDL + imiquimod than on the test sites treated with PDL-only ($p<0.005$). The enhanced blanching responses obtained on the test sites treated with PDL + imiquimod were maintained up to more than 6 months after treatment. Although some rosacea revascularization occurred, the test sites treated with PDL + imiquimod displayed better long-term blanching responses than the test sites treated with PDL-only. As expected, for the test sites treated with imiquimod-only, no drug-induced rosacea blanching was observed.

The risks of PDL treatment are as follows: swelling, discomfort and pain, erosion, crusting, abnormal wound healing, scarring, and skin dyspigmentation. The possible risks of topical imiquimod include redness of skin, swelling, itching/burning, peeling, flaking, scabbing, crusting, blistering, ulceration, and acute allergic reaction. Transient hyperpigmentation was noted in 5% (n=2) and 20% (n=8) of patients in the PDL + imiquimod and PDL-only groups, respectively. The lower incidence of hyperpigmentation in the PDL + imiquimod group may possibly be due to the chemopreventive properties of the imiquimod itself. In both treatment sites, hyperpigmentation was resolved without medical intervention in all the patients within 6 months. Permanent hypopigmentation or scarring was not observed. One patient appeared a minor allergic reaction to topical imiquimod, which was resolved smoothly.

Conclusions

The results of our study demonstrated that superior blanching responses were obtained over time when using the combination of PDL + imiquimod than when using PDL-only or imiquimod-only for the treatment of rosacea. The combination of PDL + imiquimod treatment was found to be safe. Although the PDL + imiquimod approach is compelling, clinical validation in large numbers of rosacea patients are required to further support and clarify the results of this study.

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Conflict of interest: The Authors declare no conflict of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: The Ethics Committee of Chang Gung Memorial Hospital approved this study (102-3062B). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. All patients participating in this study signed a written informed consent form for participating in this study.

Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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