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ORIGINAL ARTICLE

Prospective Comparison of Dual Wavelength Long-Pulsed 755-nm Alexandrite/1,064-nm Neodymium:Yttrium-Aluminum-Garnet Laser versus 585-nm Pulsed Dye Laser Treatment for Rosacea

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Background: Rosacea treatments including oral/topical medications and laser therapy are numerous but unsatisfactory. **Objective:** To compare the effectiveness of the dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser (LPAN) with that of 585-nm pulsed dye laser (PDL) for rosacea. **Methods:** This was a randomized, single-blinded, comparative study. Full face received four consecutive monthly treatments with LPAN or PDL, followed-up for 6 months after the last treatment. Erythema index was measured by spectrophotometer, and digital photographs were evaluated by consultant dermatologists for physician's global assessment. Subjective satisfaction surveys and adverse effects were recorded. **Results:** Forty-nine subjects with rosacea enrolled and 12 dropped out. There were no significant differences between LPAN and PDL in the mean reduction of the erythema index (p=0.812; 3.6% vs. 2.8%), improvement of physician's global assessment (p=1.000; 88.9% vs. 89.5%), and subject-rated treatment satisfaction (p=0.842; 77.8% vs. 84.2%). PDL showed more adverse effects including vesicles than LPAN (p=0.046; 26.3% vs. 0.0%). No other serious or permanent adverse events were observed in both treatments. **Conclusion:** Both LPAN and PDL may be effective and safe treatments for rosacea. **(Ann Dermatol 28(5) 607~614, 2016)**

-Keywords-
Alexandrite, Lasers, Neodymium, Rosacea

INTRODUCTION

Rosacea is a chronic cutaneous disease characterized by facial flushing, persistent facial redness, telangiectasia, papules and pustules. It can affect the cheeks, nose, eyes, forehead and chin[1-3]. Since the face is the predominant site of involvement, rosacea has a psychosocial impact on a patient's life[3,4].

The etiopathogenesis of rosacea is not fully understood and rosacea is considered to a multifactorial disease[5-7]. Factors including neuroinflammatory mechanisms, abnormalities in the congenital immune system, ultraviolet radiation, microorganisms such as *Demodex folliculorum* and *Helicobacter pylori*, dermal matrix degeneration an environmental factors, as well as changes in vessel and vascular regulation appear influential[3,6-9].

There are numerous treatment options for rosacea, such as topical metronidazole, azelaic acid, tacrolimus, systemic antibiotics and isotretinoin. However, any treatment must be for an extended time and treatment efficacy is commonly based on anecdotal evidence[10-12]. These medications are limited in that topical and systemic agents con-

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trol rosacea but do not cure it[13].

The most effective laser for treatment of facial telangiectasia and erythema is the pulsed dye laser (PDL). It has been used to treat vascular lesions for decades. Diffuse redness can be treated with nonpurpuragenic parameter, which is very tolerable to patients[14-16]. Recently, various laser devices have become available to treat rosacea. But their comparative effectiveness is not clear. The 755-nm long-pulse Alexandrite laser has proven effective to treat vascular diseases refractory to PDL because of the relatively short penetration depth of PDL (about 1.2 mm). The Alexandrite laser can penetrate 50%～75% deeper into the skin than the PDL[17-20]. Microsecond neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is less painful and less risky than traditional millisecond Nd:YAG laser devices, and is effective for cutaneous vascular lesions[15,21].

We used the dual wavelength long-pulsed 755-nm alexandrite/microsecond 1,064-nm Nd:YAG laser (LPAN) to improve treatment efficacy, taking advantage of the synergy between alexandrite and Nd:YAG laser. The aim of this study is to compare the effectiveness of the LPAN with that of 585-nm PDL for rosacea.

MATERIALS AND METHODS

Trial design

This was a randomized, single-blinded, comparative study conducted at a single academic institution with a 1:1 allocation ratio. This study was approved by the Institutional Review Board at Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea (IRB no. KBSMC 2013-01-200). All patients provided written informed consent. This study was conducted in accordance with the CONSORT statement[22].

Subject selection

Eligible subjects were ≥18 years of age with Fitzpatrick skin types III-V, and a clinical diagnosis of rosacea with erythematotelangiectatic or papulopustular subtype. All patients underwent baseline laboratory examination with serum complete blood count, total calcium, phosphorus, fasting glucose, total protein, albumin, globulin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransaminase, blood urea nitrogen, creatinine, uric acid, total cholesterol and urinalysis.

Study exclusion criteria included severe phymatous or ocular rosacea, any other concurrent skin condition affecting the face, history of keloid, history of photosensitive disease, treatment with oral isotretinoin during the 6 months prior to the study, any oral medication or treatment that could affect facial erythema during the month prior to the study, history of alcohol abuse, and pregnant or lactating women.

Randomization

Randomization was achieved by determining the treatment laser for each subject number before assigning any subject with a subject number. Each subject was treated with the same laser every month for four consecutive treatments.

Intervention

After informed consent was obtained, the subjects were randomly assigned to treatment with LPAN or PDL in form of a person-by-person comparison. Before the treatment, all makeup was removed and each subject's face was cleansed with a mild soap. Half of the total subjects were treated with the dual wavelength long-pulsed 755-nm alexandrite/microsecond 1,064-nm Nd:YAG laser (Clarity®; Lutronic Inc., Seoul, Korea) using fluence 30 J/cm^2 with a spot size of 10 mm and pulse width of 12 ms for the alexandrite laser and fluence 3.0 J/cm^2 with a spot size of 10 mm and pulse width of 0.5 ms for Nd:YAG laser. The others were treated with the 585-nm, long-pulsed PDL (Cynergy®; Cynosure Inc., Westford, MA, USA) using fluence 7 J/cm^2 with a spot size of 10 mm and pulse width of 6 ms for PDL. The entire area of the face was treated with two passes with at least 15% overlap for the Alexandrite and PDL lasers, and with six passes for the microsecond 1,064-nm Nd:YAG laser. Each subject received the treatment by a single operator using an identical technique.

Primary outcome

The primary outcome was the mean reduction of the erythema index measured by a spectrophotometer from baseline to 2-weeks and 6-months after the completion of the treatment protocol. A Dermatospectrometer spectrophotometer (Cortex Technology Inc., Hadsund, Denmark) was used to quantify erythema. Three measurements on a total of seven sites (two sites on each side of the cheek: upper cheek [malar area, 2 cm below midpupillary line] and lower cheek [6 cm below midpupillary line], and three sites on the nose: nasal tip and each side of nasal ala) were performed at baseline and at each follow-up visit, and the mean value of the measurements was used as the erythema index in the analysis.

Secondary outcomes

The secondary outcomes included: (1) the proportion of physician's global assessment and (2) subjective satisfaction assessment; the procedure-associated (3) pain

scores and (4) adverse effects. Color digital photographs of the full face were taken under the fixed position and same conditions (light source, room, and camera) using a Dermavision digital imaging system (Optobiomed Inc., Gangwon, Korea) at baseline, and 2 weeks and 6 months after the last treatment. The physician's global assessment was evaluated by two blinded consultant dermatologists based on the cross parallel image between baseline and 2 weeks after the last treatment photographs, and the cross parallel image between baseline and 6 months after the last treatment photographs using the following grading system: 1=worsening, 2=no change, 3=improved (<50%), and 4=much improved (50%~100%). All patients completed a questionnaire that assessed their subjective satisfaction of treatment using the following grading system: 1=no change or worsening, 2=poor, 3=fair, 4=good, and 5=excellent 6 months after the last treatment. The procedure-associated pain scores after each treatment were assessed using a 10-point visual analogue scale, and any procedure-associated adverse effects, such as erythema, cursts, pigmentary change, vesicles, dryness, itching, tightening sense and scar, during the study were recorded.

Statistical methods

Continuous variables were expressed as mean with standard deviations. The χ^2 test was used to determine whether there was significant difference in variables expressed by frequency or proportion between subjects receiving LPAN and PDL. The independent t-test was performed to examine differences in continuous variables between subjects receiving LPAN and PDL treatment. The paired t-test was performed to compare the erythema index between baseline, 2 weeks and 6 months after the last treatment. All analyses were performed using the IBM SPSS Statistics ver. 22.0 software (IBM Co., Armonk, NY, USA). Statistical significance was considered when p-value was <0.05.

RESULTS

Progression of the subjects throughout the study is presented in Fig. 1. After evaluating 54 subjects for inclusion, 49 subjects with rosacea were enrolled. Twelve subsequently dropped out. Eleven were lost before last follow-up and one subject treated with the PDL dropped out reporting post-treatment worsening. Thirty seven subjects completed the trial; they were Fitzpatrick skin phototypes III (n=2), IV (n=30) and V (n=5). Baseline demographics and clinical characteristics of subjects are summarized in Table 1. At baseline, there were no differences in demographics and clinical characteristics between the subjects treated with the LPAN and PDL.

Erythema index measured by spectrophotometer was significantly reduced at 2 weeks after four treatments for both LPAN and PDL, with a mean difference of 7.9% ($p<0.001$; 95% confidence interval [CI], −11.4 to −4.34) and 5.3% ($p<0.001$; 95% CI, −8.44 to −2.09), respectively. Six months after the last treatments (last follow-up), the reduction of erythema index was maintained, with a mean dif-

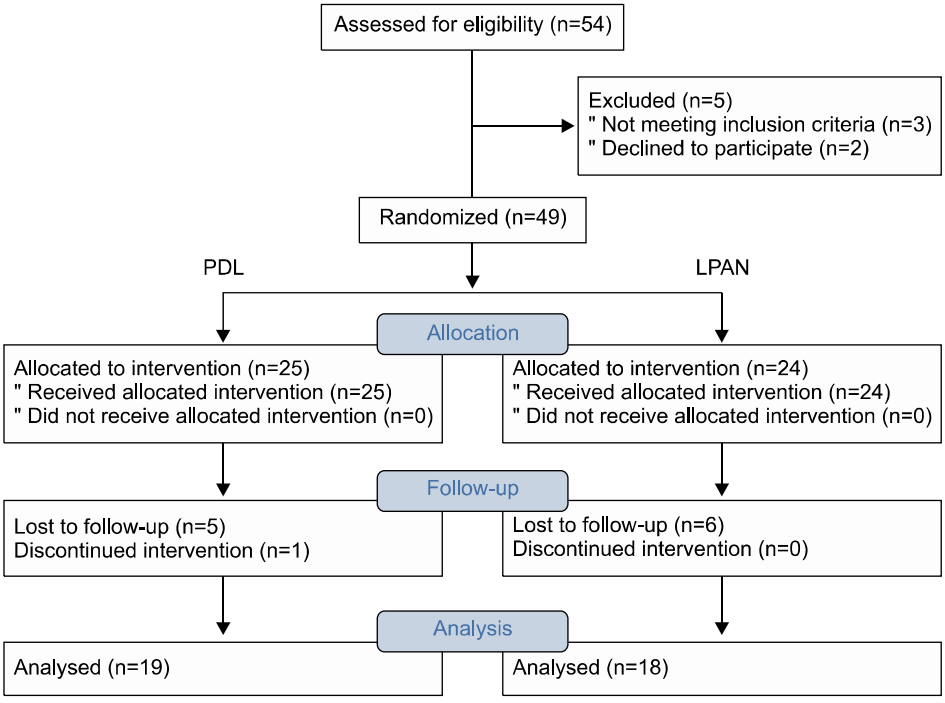

Fig. 1. Flow diagram according to CONSORT guidelines showing the flow of subjects in the trial. PDL: 585-nm pulsed dye laser, LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium: yttrium-aluminum-garnet laser.

Table 1. Demographics and clinical characteristics of the study subjects

Characteristic	PDL (n=19)	LPAN (n=18)	*p*-value
Age (yr)	48.6±11.3	49.9±12.8	0.733
Male	11 (57.9)	8 (44.4)	0.413
Rosacea duration (yr)	11.0±15.4	7.5±9.7	0.416
Rosacea severity			0.384
Mild	11 (57.9)	14 (77.8)	
Moderate	4 (21.1)	3 (16.7)	
Severe	4 (21.1)	1 (5.6)	
Baseline erythema index	18.1±3.8	17.3±2.3	0.433

Values are presented as mean±standard deviation or number (%). PDL: 585-nm pulsed dye laser, LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser.

Table 2. Erythema index results with pairwise comparisons between time periods

	Before treatment	Short-term follow-up	Long-term follow-up	Between baseline and short-term follow-up		Between baseline and long-term follow-up	
				Difference in means	*p*-value	Difference in means	*p*-value
LPAN	17.3±2.3	16.0±2.6	16.7±2.4	1.36±1.23	<0.001	0.63±1.16	0.035
PDL	18.1±3.8	17.2±4.2	17.6±3.4	0.96±1.20	0.003	0.51±1.70	0.206

Values are presented as mean±standard deviation. LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium: yttrium-aluminum-garnet laser, PDL: 585-nm pulsed dye laser. Short-term follow up: 2-week after the last treatment, long-term follow up: 6-month after the last treatment.

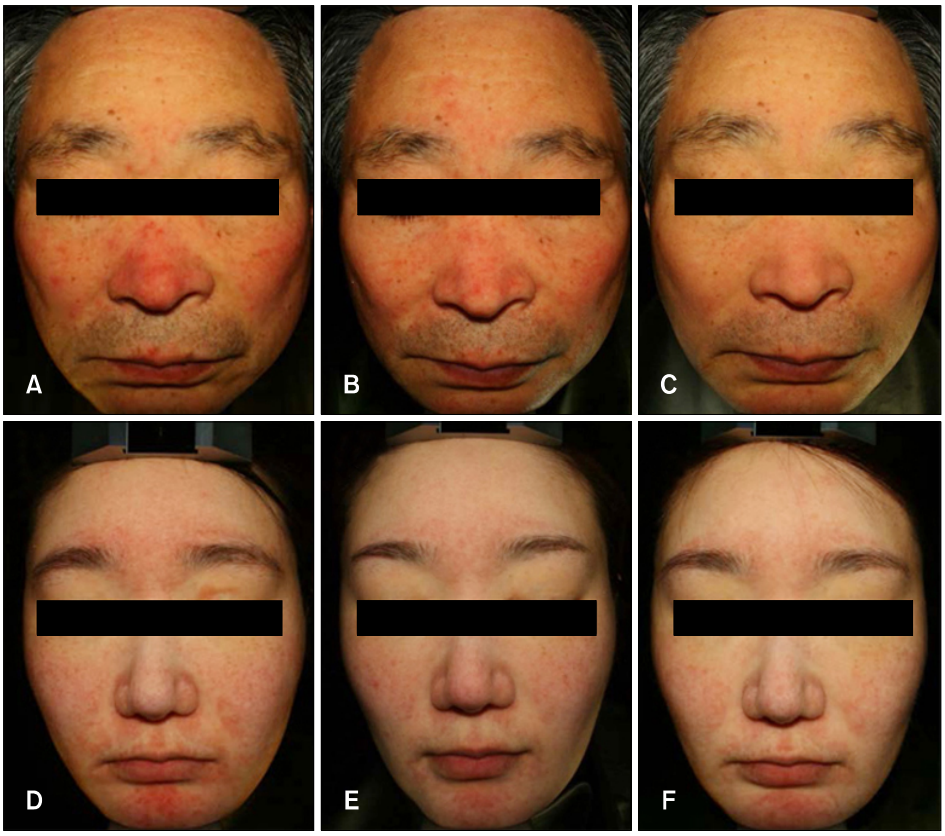

Fig. 2. (A~C) Male patient. (A) Before treatment, (B) at 2 weeks after four 585-nm pulsed dye laser (PDL) treatments, (C) at 6 months after last treatment. (D~F) Female patient. (D) Before treatment, (E) after four PDL treatments, (F) at 6-month after final treatment.

ference of 3.6% (p=0.035; 95% CI, −6.93 to −2.82) for LPAN and 2.8% (p=0.206; 95% CI, −7.31 to 1.69) for PDL (Table 2). When comparing the mean reduction of erythema index in both lasers, the mean change was comparable, and there were no statistical differences 2 weeks after the last treatments (p=0.313) and 6 months after the last treatments (p=0.812). Fig. 2 and 3 are photographs of subjects at baseline, and 2 weeks and 6 months after the last treatment.

The proportion of the physician's global assessment from baseline to 2 weeks and 6 months after the treatments are presented in Table 3. Two weeks after treatments, the proportion of improved or much improved varied (p=0.025) by treatment, with PDL showing a proportion of 68.4%, compared with 50.0% for LPAN. However, the proportion of improved or much improved increased during follow-up, with no statistical differences between LPAN and PDL 6 months after the treatments (p=1.000; 88.9% vs. 89.5%).

Subject satisfaction assessments after the treatments are presented in Fig. 4. There was no significant difference in the proportion of good or excellent between LPAN and PDL (p=0.842; 77.8% vs. 84.2%).

The treatment-related adverse effects are summarized in Table 4. Most subjects noted mild erythema after the both laser treatments (66.7% for LPAN and 52.6% for PDL). It

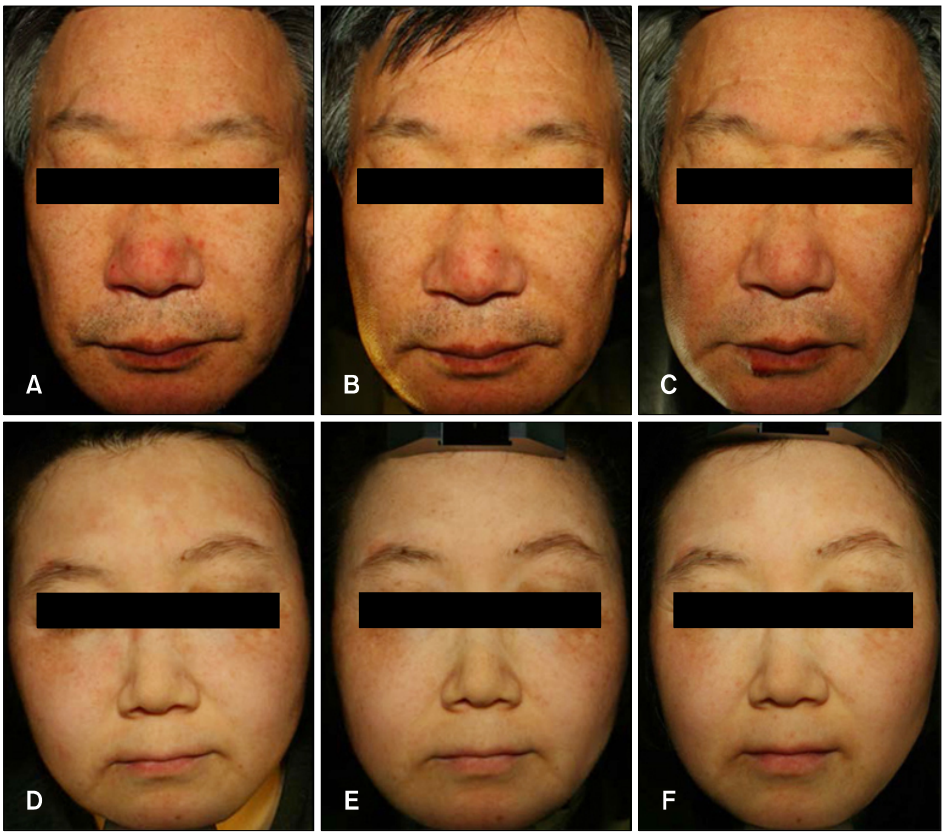

Fig. 3. (A∼C) Male patient. (A) Before treatment, (B) at 2 weeks after four dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser (LPAN) treatments, (C) at 6 months after last treatment. (D∼F) Female patient. (D) Before treatment, (E) after four LPAN treatments, (F) at 6 months after final treatment.

Table 3. Proportion of the physician's global assessment

Physician's global assessment	LPAN (n=18)		PDL (n=19)	
	Short-term follow-up	Long-term follow-up	Short-term follow-up	Long-term follow-up
Worse	3 (16.7)	1 (5.6)	6 (31.6)	2 (10.5)
No change	6 (33.3)	1 (5.6)	0	0
Improved	7 (38.9)	8 (44.4)	9 (47.4)	7 (36.8)
Much improved	2 (11.1)	8 (44.4)	4 (21.1)	10 (52.6)

Values are presented as number (%). LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium: yttrium-aluminum-garnet laser, PDL: 585-nm pulsed dye laser. Short-term follow up: 2-week after the last treatment, long-term follow up: 6-month after the last treatment.

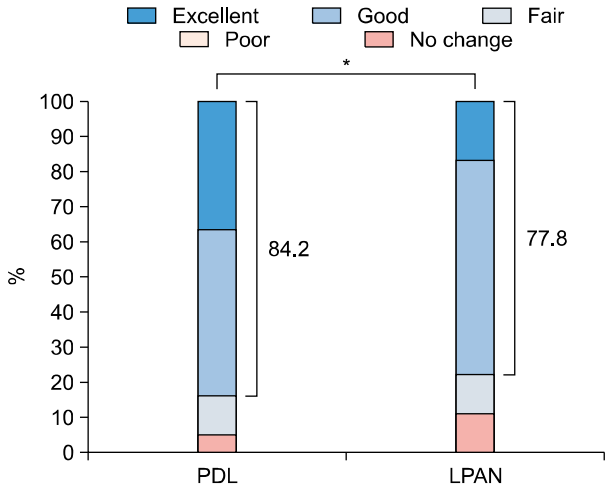

Fig. 4. Subjective satisfaction assessment for the treatments. *No significant difference in the proportion of good or excellent between both treatments (p=0.842). PDL: 585-nm pulsed dye laser, LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser.

faded within 2 weeks. Skin tightening and itching sense were also noted in many cases. Pain scores were not significantly different (p=0.108), with LPAN at 2.44 and PDL at 3.42. Although serious or permanent adverse events were not observed, adverse effect such as vesicles (26.3%) was significantly more observed in PDL than in LPAN (p=0.046). Post-therapy hyperpigmentation was observed in one subject per each laser group.

DISCUSSION

Our study compared the effectiveness of two lasers for rosacea treatment and resulted in several important findings. Firstly, both LPAN and PDL treatments reduced erythema index measured by spectrophotometry from baseline. There was no statistical difference in mean change of erythema index between both lasers. The reduced erythema index was maintained until 6 months after the final treatments. Secondly, in physician's global assessment, PDL showed high proportion of subjects with more than 50% improvement at short-term follow-up, but there was no significant difference between LPAN and PDL at long-term follow-up. Thirdly, in subject satisfaction assessment, both lasers were similarly rated. Fourthly, the adverse effects of erythema were frequent but well tolerated in both treatment groups. Subjects receiving PDL showed more significant adverse effect such as vesicles than those receiving LPAN. Lastly, serious or permanent adverse events were not observed in both treatment groups. Collectively, our results suggest that both the LPAN and PDL can be effective and safe modalities for the treatment of rosacea and facial erythema.

Table 4. Adverse effects

Adverse effect	LPAN	PDL	p-value
Erythema	12 (66.7)	10 (52.6)	0.385
Crusts	2 (11.1)	6 (31.6)	0.232
Hyperpigmentation	1 (5.6)	1 (5.3)	1.000
Vesicles	0 (0.0)	5 (26.3)	0.046
Dryness	4 (22.2)	3 (15.8)	1.000
Itching sense	6 (33.3)	3 (15.8)	0.269
Tightening sense	4 (22.2)	6 (31.6)	0.714

Values are presented as number (%). LPAN: dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium:yttrium-aluminum-garnet laser, PDL: 585-nm pulsed dye laser.

Deeper penetration by the longer wavelength of the LPAN is possible explanation for its effectiveness. With the longer wavelength of 755-nm and 1,064-nm lasers can penetrate greater depth and deeper tissues can be targeted. Also, longer wavelength laser beams are able to penetrate dilated capillary walls more effectively.[19] The latter study compared the long-pulsed PDL and long-pulsed Alexandrite laser in patients with port wine stain; both laser devices effectively reduced the erythema index as measured by erythema reflectance spectrometry. Say et al.[23] reported that long-pulsed Nd:YAG is a safe and effective modality for vascular and inflammatory lesions of rosacea with high fluence of 100 to 160 J/cm^2, 15 to 20 ms pulse width and 2 to 3 mm spot size. In a double-blind randomized controlled trial comparing microsecond Nd:YAG laser and nonpurpuragenic PDL for treatment of diffuse facial erythema, PDL showed a better effect than microsecond Nd:YAG, but microsecond Nd:YAG laser produced less pain than PDL.[15] In another study with hidradenitis suppurativa patients, through ablation of hair follicles and selective photothermolysis, long-pulsed Nd:YAG was an effective modality for inflammatory lesions.[24] It seems that Alexandrite and PDL have synergistic effect on treatment of rosacea. This remains to be conclusively verified.

This study adds to the existing literature on treatment of rosacea and facial erythema with laser. In our study, all subjects with rosacea ceased the any medication such as minocycline, doxycycline, isotretinoin, topical tacrolimus, or topical metronidazole at least 1 month prior to the study (for isotretinoin, at least 6 months prior to the study). However, in about half of all subjects, therapeutic effects were maintained for 6 months after the laser treatments without any medication. To our knowledge, this study is the first using LPAN laser for rosacea comparing to traditional nonpurpuragenic PDL.

In this study, the reduction of erythema index was well maintained at the long term follow-up. Interestingly, the physician's global assessment of long term follow-up seemed to be better compared to that of short term. The latter was evaluated at two weeks after the last treatment and that period was thought to be an acute phase of post laser irradiation, which occurring healing and remodeling process of target tissue. Thus the physician's global assessment at the short term follow-up may be due to transient redness which is laser induced flushing or microvascular purpura.

Concerning adverse effects, Alam et al.[15] reported that Nd:YAG laser had a lower risk of unintentional bruising than PDL, and PDL showed purpuric macules during laser treatment. In other studies using microsecond Nd:YAG settings, pain and adverse effects were less than traditional millisecond settings.[15,21] Although a non-purpuragenic parameter was used in this study, subjects receiving PDL showed more significant complications, such as vesicles, than those receiving LPAN. In light of this finding, LPAN seems to be a safer treatment than PDL in treatment of rosacea.

There are several limitations in the general application of the study findings. Firstly, as with all studies comparing two devices, there is no way to be absolutely certain that the settings were comparable, since those have different parameters and laser settings. Secondly, because the spectrophotometer measured only small spots, erythema index might not reflect the entire severity of rosacea or facial erythema. Thirdly, in subjects receiving LPAN treatments, it is difficult to determine the effect of each laser separately. Fourthly, all the subjects were of Korean with darker skin types, which may limit the generalizability of the study.

In conclusion, this study demonstrates that both the LPAN and PDL are very effective and tolerable treatments for rosacea. The LPAN treatment may be an alternative modality for rosacea when conventional PDL devices cannot be used. Future studies with split-face comparison, various laser settings, and comparison of long-pulsed alexandrite and PDL are necessary to establish the optimal treatment devices and settings for rosacea treatment.

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