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The Comparison of the Efficacy and Safety of Q-Switched Potassium Titanyl Phosphate Laser and Long-Pulsed Neodymium-Doped Yttrium Aluminum Garnet Laser in the Treatment of Erythematotelangiectatic and Papulopustular Rosacea

Eritemotelenjektatik ve Papülopüstüler Rozasea Tedavisinde Q-Anahtarlı Potassium Titanyl Phosphate Lazer ve Uzun Atımlı Neodymium-Doped Yttrium Aluminum Garnet Lazerin Etkinliği ve Güvenilirliğinin Karşılaştırması

Abstract

Objective: The best laser for patients with erythematotelangiectatic rosacea is still a controversial topic. The efficacy and safety of Q-switched potassium titanyl phosphate (KTP) and long-pulsed neodymium-doped yttrium aluminum garnet (IpNd:YAG) lasers were compared in the treatment of erythematotelangiectatic and papulopustular rosacea.

Methods: Thirty patients aged 16-70 years who had multiple telangiectasias on both sides of the face and a diagnosis of stage 1-2 rosacea were included in a split-face, double-blinded, randomized clinical trial. Lasers were applied to two different sides of the face for four sessions at one-month intervals. The number of papules and pustules were investigated before treatment and at each visit. The erythematotelangiectatic rosacea severity scores, thickness of telangiectasias, clinician's assessment of treatment response, patient satisfaction, and adverse effects were examined.

Results: In the third and fourth months, the number of papules on the side treated with IpNd:YAG laser was significantly lower than the other side. In the fourth month, the mild or severe erythematotelangiectatic rosacea score rate was significantly lower on the side treated with IpNd:YAG laser. The clinician's assessment was similar for both treatments.

Conclusion: We recommend IpNd:YAG laser for erythema and Q-switched KTP laser for thin and superficial telangiectasias for the highest treatment efficacy.

Keywords: Erythema, lasers, purpura, rosacea, solid-state, telangiectasias

Öz

Amaç: Eritemotelenjektatik rozasealı hastalar için en iyi lazer halen tartışmalı bir konudur. Q-anahtarlı potassium titanyl phosphate (KTP) ve uzun atımlı neodymium-doped yttrium aluminum garnet (IpNd:YAG) lazerlerin eritemotelenjektatik ve papülopüstüler rozasea tedavisinde etkinliği ve güvenilirliği karşılaştırıldı.

Yöntemler: Yüzünün her iki yanında çok sayıda telanjiektazileri olan ve evre 1-2 rozasea tanısı bulunan 16-70 yaşları arasında 30 hasta yarım-yüz, çift-kör, randomize klinik çalışmaya alındı. Lazerler yüzün iki farklı yanına bir aylık aralıklarla 4 seans uygulandı. Tedavi öncesinde ve her takipte papül ve püstül sayısı araştırıldı. Eritemotelenjektatik rozasea şiddet skoru, telanjiektazi kalınlığı, klinisyenin tedavi yanıtını değerlendirmesi, hasta memnuniyeti ve yan etkiler incelendi.

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Submitted/Geliş Tarihi: 29.11.2017
Accepted/Kabul Tarihi: 12.01.2018

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Turkish Journal of Dermatology published
by Galenos Publishing House.

Öz

Bulgular: Üçüncü ve dördüncü aylarda, IpNd:YAG lazer ile tedavi edilen taraftaki papüllerin sayısı diğer tarafa oranla anlamlı oranda daha düşük idi. Dördüncü ayda hafif veya şiddetli eritemotelenjektatik rozasea skor oranı IpNd:YAG lazer ile tedavi edilen tarafta anlamlı oranda daha düşük idi. Klinisyenin değerlendirmeleri her iki tedavi için benzer idi.

Sonuç: En yüksek tedavi etkinliği için eritemde IpNd:YAG lazeri, ince ve yüzeysel telenjektazilerde Q-anahtarlı KTP lazeri önermekteyiz.

Anahtar kelimeler: Eritem, lazerler, purpura, rozasea, katı hal, telenjektaziler

Introduction

In early stages of rosacea, long-term and persistent telangiectasias may be accompanied by confluent and persistent erythema (1). In some cases, only diffuse persistent erythema is seen. No single laser type is effectively used in the treatment of all cutaneous vascular lesions. The most common laser is long-pulsed neodymium-doped yttrium aluminum garnet (IpNd:YAG) with a wavelength of 532 nm and 577-600 nm for vascular lesions and 1064 nm for deeper tissues (2-4). Other lasers in clinical use include argon-ion laser, pulsed potassium titanyl phosphate (KTP), laser diode and continuous wave IpNd:YAG laser with the capability of coagulation and flash lamp pumped pulsed-dye laser (PDL) and long PDL. The safest light sources for facial telangiectasias are KTP (532 nm, 585 nm), PDL (595 nm), and intense pulsed light (IPL) (520-1200 nm) (3).

KTP laser (532 nm, 585 nm) is essentially a type of Nd:YAG that produces green light with a half wavelength and enhanced or doubled frequency (5). Thus, it is very effective for telangiectasia and erythema treatment (3). However, its low wavelength is a disadvantage preventing penetration into deeper vascular tissues. Since this wavelength is absorbed by both hemoglobin and melanin, it is preferred for superficial and thin vessels (5). Although not causing purpura may seem to be an advantage, not being able to penetrate deeper into the tissues and restrictions regarding skin phototypes 3 or greater present as disadvantages (2,5).

At conservative doses with a spot size of 1.5-3 mm and efficient cooling fans, IpNd:YAG laser (1064 nm) offers a highly safe treatment profile in rosacea. IpNd:YAG laser is absorbed non-specifically by tissue proteins and bio-molecules (6). Another advantage of this laser is its deep penetration capability of 5 mm and poor absorption by two skin chromophores, hemoglobin and melanin. However, it may cause a wide thermal damage zone and scarring. Furthermore, it creates more thermal coagulated tissue than other lasers (6).

The best laser for patients with erythemotelangiectatic rosacea (ETR) is still controversial. To achieve better efficacy and a higher penetration depth, IpNd:YAG laser has been suggested for vascular lesions (7). In this study, we aimed to compare the efficacy and safety of 585 nm Q-switched KTP laser and 1064 nm IpNd:YAG laser in the treatment of ETR and papulopustular rosacea (PPR). We investigated the clinical effects of these lasers separately on diffuse erythema, telangiectasias, papules, and pustules.

Methods

Thirty patients aged 16-70 years having two or more telangiectasias on both sides of the face and a diagnosis of

stage 1 or 2 rosacea were included in a split-face, double-blinded, randomized clinical study in our department between January 2016 and January 2017. The study was approved by the İstanbul Medipol University, Medical Device Clinical Research Ethics Committee (approval number: 10840098-604.01.01-E.41020), and all the patients provided written informed consent. Q-switched KTP and IpNd:YAG lasers were applied separately to the randomly selected sides of the face over four sessions at one month intervals. The inclusion criteria were having minimum two linear or radiating telangiectasias on the malar or perialar regions of the face. Patients with a history of keloids, platelet functional disorder or cardiovascular, pulmonary, renal or psychological diseases were excluded. Other exclusion criteria were having sunbathed or taken drugs that cause photosensitization such as isotretinoin and acitretin within the last six months, having undergone cosmetic procedures such as laser or chemical peeling within the last three months, being pregnant, breastfeeding, or having a photosensitive or Koebner-positive dermatological disease. Furthermore, patients with telangiectasias of greater than 4 mm or stage 3 or 4 rhinophymatous- or granulomatous-type rosacea were excluded from the study.

We recorded demographic data including age, sex, skin phototype, rosacea clinical subtype, duration of disease, and previous treatments. We investigated the presence of facial erythema, lesions including telangiectasia, papules and pustules, and the number of lesions before treatment and at each visit using a digital dermoscopy device (FotoFinder®). The side of face for KTP or Nd:YAG laser treatment was determined through the heads or tails method. A local anesthetizing cream containing topical lidocaine and prilocaine (Emla®) was applied to both sides one hour before each session. The face was cleaned using physiologic serum and dried. All patients were advised to apply SPF 50+ sunscreen every four hours. In addition, a topical moisturizer containing panthenol and provitamin B5 (Bepanthol, Bayer®) was recommended twice a day for three days after each session. The patients were asked not to wash their face for more than twice a day.

The two lasers had the following characteristics: Q-switched KTP laser (585 nm) 1.5-2 joule/cm², 3 mm spot size, 2 hertz (Fotona QX MAX® 25W, 2-6 mm, TwinLight 220A, Slovenia) and IpNd:YAG laser (1064 nm) 90-110 joule/cm², 15 ms, 4 mm, 1.5 hertz with a 5% overlap (Fotona XP max®, Twinlight 220A, Slovenia). The target dose of KTP laser was determined to be that which would not cause the formation of bulla or epidermal damage, but the vessel would resemble a pale maroon-cherry bruise in a string shape. For IpNd:YAG laser, the target dose was that which resulted in the complete disappearance of the trace of the vessel. Dynamic Cryo 5

(level 4, Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany) was used to cool the skin during both laser procedures. We limited the maximum laser pass to 3 for IpNd:YAG laser until the disappearance of telangiectasia on the malar area or ala nasi. After half face was treated with one laser, the other half was treated using the other laser on the same day.

The patients were photographed by the same digital camera (Nikon®) from a fixed distance before treatment and at every session. The photographs were evaluated and compared by two independent investigators through a computer-based analysis at every month. Clinical assessments were made according to two different scoring systems via a digital dermoscopy device (FotoFinder®) before treatment and after each session. The erythema and telangiectasia scores were interpreted on a four-point scale: 0: none, 1: mild, 2: moderate, and 3: severe. The telangiectasia thickness was recorded in mm using the same device. Telangiectasias were classified into four different groups by diameter: 0-0.25 mm, 0.25-0.50 mm, 0.50-0.75 mm, and 0.75-1.00 mm. At the end of the study, we also examined the change in telangiectasia thickness. The ETR severity score was assessed as 0: no visible erythema or presence of minimal residual erythema/telangiectasia, 1: mild (presence of minimal erythema or telangiectasia on the central face or spread), 2: moderate (presence of marked erythema or telangiectasia on the central face or spread), 3: severe (presence of pronounced red or violet erythema or telangiectasia on the central face or spread).

The clinician assessed patients' treatment response under four categories: bad (<30% improvement), poor (30-60% improvement), good (60-85% improvement), and very good ($\geq 85\%$ improvement). Patient satisfaction was scored on a four-point scale from 1 least satisfied to 4 very satisfied. A visual analog scale (0-10) was used for pain analysis. Adverse effects; e.g., erythema, infection, scar, hypopigmentation, hyperpigmentation, and purpura were recorded. The patients were asked to complete the Turkish version of the Dermatological Life Quality Index (DLQI) comprising 11 questions on their social and emotional status, daily activities, sexual life, cognitive function, and symptoms one month before and after the study. The responses were scored on four-point scale, the total varying between 0 and 44 (8).

Six months after the last session, all patients were invited for a follow-up appointment, in which the presence of $\geq 20\%$ clinical deterioration in the half-face ETR scores was considered clinical recurrence.

Results

After two months into treatment, two patients dropped out due to adverse effects. Thus, the study was completed with 15 male (53.6%) and 13 female (46.4%) patients. The mean age was noted as 38.64 ± 13.33 (range: 22-67). Twenty patients (71.4%) had ETR and 8 (28.6%) had PPR. The mean duration of disease was calculated as 13.71 ± 8.68 years. Nineteen patients (67.9%) had skin phototype 2 and 9 (32.1%) phototype 3.

Papules

The number of papules on the facial side with IpNd:YAG laser was significantly lower than the side treated with

Q-switched KTP laser only at months 3 ($p=0.034$) and 4 ($p=0.034$) ($p<0.05$). The pre-treatment and post-treatment clinical photographs of a patient with PPR treated with IpNd:YAG laser on the right side are given in Figure 1a. As shown, there was a significant decrease in the number of papules after treatment.

Pustules

The number of pustules on the side treated with Q-switched KTP laser was similar at all visits ($p>0.05$). However, on the side treated with IpNd:YAG laser, there was a statistically significant decrease in the number of pustules at months 2 ($p=0.034$), 3 ($p=0.034$) and 4 ($p=0.034$) compared to month 1 ($p<0.05$).

Facial Erythema

Although no significant difference was noted in the rate of facial erythema on the side treated with Q-switched KTP ($p>0.05$), a significant decrease was found after treatment with Nd:YAG laser at months 3 ($p=0.001$) and 4 ($p=0.001$) compared to month 0 ($p<0.01$). The rate of moderate erythema score was statistically significantly lower in IpNd:YAG laser side compared to the other side at month 4 ($p=0.007$; $p<0.01$).

Facial Telangiectasias

No significant difference was seen in the rate of facial telangiectasias and telangiectasia scores in any of the visits ($p>0.05$). The pre-treatment and post-treatment clinical photographs of a patient with facial telangiectasias treated with KTP on the left side are presented in Figures 1b. There was a significant decrease in the number of telangiectasias after treatment. For the side treated with IpNd:YAG laser, the decrease in telangiectasia scores was only significant at months 2, 3 and 4 compared to month 0 ($p<0.01$); however,



Figure 1. The (a) pre-treatment and post-treatment (month 4) photographs of a patient with papulopustular rosacea treated with long-pulsed neodymium-doped yttrium aluminum garnet laser on the right side. (b) The pre-treatment and post-treatment photographs of a patient with facial telangiectasias treated with Q-switched potassium titanyl phosphate laser on the left side

for Q-switched KTP laser, these scores were significant at all visits ($p < 0.05$).

Telangiectasia Thickness

On the side treated with IpNd:YAG laser, the mean telangiectasia thickness at month 1 was measured as 0.50-0.75 mm or 0.75-1.00 mm at a higher rate compared to the other treatment side ($p = 0.039$; $p < 0.05$). Moreover, the mean telangiectasia thickness was measured as 0-0.25 mm or 0.25-0.50 mm at month 4 at a significantly lower rate on the side treated with IpNd:YAG laser than the other side ($p = 0.035$; $p < 0.05$) (Figure 2).

ETR Score

The ETR scores of both treatment sides were similar at months 0, 1 and 2 ($p > 0.05$). However, the rate of a moderate ETR score on the side treated with IpNd:YAG laser was statistically lower than the other side at month 3 ($p = 0.026$; $p < 0.05$). Moreover, the rate of a mild or severe ETR score was statistically significantly lower on the side treated with IpNd:YAG laser than the other side ($p = 0.007$; $p < 0.01$) (Table 1). While the decrease in ETR scores at months 2 ($p = 0.010$), 3 ($p = 0.001$) and 4 ($p = 0.001$) on the side treated with IpNd:YAG were all significant compared to month 0 ($p < 0.05$), for the Q-switched KTP side, there was a significant decrease only at months 3 and 4 ($p = 0.002$ and 0.001 , respectively; $p < 0.01$).

Clinician’s Assessment and Patient Satisfaction

The clinician’s assessment of clinical improvement was similar for both sides at all months ($p > 0.05$). The patient satisfaction was significantly higher for the side treated with IpNd:YAG laser than the other side at months 2 and 4 ($p = 0.008$ and 0.008 , respectively; $p < 0.01$).

Visual Analog Scale

The visual analog scale scores for pain were significantly higher on the side treated with IpNd:YAG laser than the other side at all months ($p = 0.001$; $p < 0.01$).

Dermatology Life Quality Index

Although the Dermatology Life Quality Index (DLQI) scores were similar for both sides at month 0 ($p > 0.05$), they were significantly lower on the side treated with IpNd:YAG laser than the other side at month 4 ($p = 0.004$; $p < 0.01$).

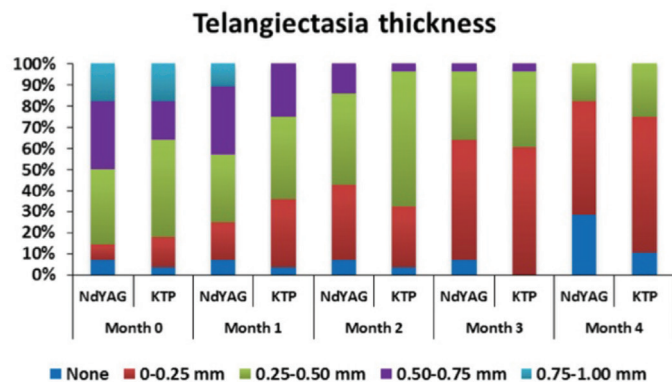


Figure 2. The distribution of telangiectasia thickness
Nd:YAG: Neodymium-doped yttrium aluminum garnet laser, KTP: Potassium titanyl phosphate

Adverse Effects and Follow-Up

Adverse effects were similar for both laser applications at all visits ($p > 0.05$). Following the IpNd:YAG and KTP treatments, hyperpigmentation was seen in three patients each, edema in 3 and 2 patients, transient purpura in 1 patient and 6 patients, erythema in 2 patients and 1 patient, and atrophy in 2 patients and 1 patient, respectively. Of the three patients that developed atrophy, two dropped out after the second session. Atrophy was reported on both sides in one patient

Table 1. The assessment of the erythematotelangiectatic rosacea scores in erythematotelangiectatic rosacea patients

IpNd:YAG Q-switched KTP	n (%)	n (%)	^a p
None/minimal	0 (0)	2 (7.1)	0.480
Mild	5 (17.9)	1 (3.6)	
Moderate	4 (14.3)	7 (25)	
Severe	11 (39.3)	11 (39.3)	
Very severe	8 (28.6)	7 (25)	
None/minimal	1 (3.6)	1 (3.6)	0.854
Mild	3 (10.7)	2 (7.1)	
Moderate	5 (17.9)	7 (25)	
Severe	13 (46.4)	13 (46.4)	
Very severe	6 (21.4)	5 (17.9)	
None/minimal	2 (7.1)	0 (0)	0.166
Mild	5 (17.9)	5 (17.9)	
Moderate	7 (25)	10 (35.7)	
Severe	13 (46.4)	9 (32.1)	
Very severe	1 (3.6)	4 (14.3)	
None/minimal	3 (10.7)	0 (0)	0.026*
Mild	7 (25)	5 (17.9)	
Moderate	13 (46.4)	17 (60.7)	
Severe	5 (17.9)	5 (17.9)	
Very severe	0 (0)	1 (3.6)	
None/minimal	10 (35.7)	3 (10.7)	0.007**
Mild	5 (17.9)	9 (32.1)	
Moderate	11 (39.3)	11 (39.3)	
Severe	2 (7.1)	5 (17.9)	
Very severe	0 (0)	0 (0)	
Month 0-month 1	0.883	0.869	
Month 0-month 2	0.010*	0.181	
Month 0-month 3	0.001**	0.002**	
Month 0-month 4	0.001**	0.001**	

IpNd:YAG: Long-pulsed neodymium-doped yttrium aluminum garnet laser, KTP: Potassium titanyl phosphate
^aWilcoxon signed-rank test
 * $p < 0.05$, ** $p < 0.01$

and on the IpNd:YAG laser side in the other patient. The recurrence rates were similar for both applications ($p>0.05$).

Statistical Analysis

NCSS 2007 (Kaysville, Utah, USA) was used for statistical analysis. In addition to qualitative statistical methods (mean, standard deviation, median, frequency, rate, minimum, and maximum), the Wilcoxon signed-rank test was used to compare the quantitative data. Furthermore, the qualitative data was compared using Wilcoxon signed-rank and McNemar tests. The significance was evaluated at $p<0.05$.

Discussion

Rosacea is characterized with a variety of vascular changes including flushing, persistent erythema, telangiectasias, papules, pustules, and granulomatous nodules (1). Vascular instability and passive vascular dilatation cause ETR, leakage of fluid and inflammatory mediators into the dermis leading to PPR (9). Laser application is considered beneficial for the treatment of pathogenetic pathways of rosacea in several ways such as through the destruction of small vessels, ablation of vascular anomalies, reorganization, remodeling of dystrophic dermal connective tissue, and interruption of the release of inflammatory mediators (10). In this study, despite slight differences, the overall efficacy of both lasers was found similar.

Laser treatment guidelines do not include precise data about the laser preference in the presence of polymorphic lesions including telangiectasia, diffuse persistent erythema, papules, and pustules in patients with early-stage rosacea. Different laser types with different wavelengths; e.g., KTP (532 nm), IpNd:YAG (1064 nm), IPL (500-1200 nm), and PDL (585 nm-595 nm) target hemoglobin that leads to vessel destruction (2,5,9-12). KTP laser is effective for especially superficial vascular lesions due to its lower wavelength. However, although KTP allows for a slower, gentler heating, coagulation, and collapse of the vessel, it is not effective for deeper vessels (13). If high doses of energy are used to increase the penetration depth, this may cause bulla, scars, and depigmentation. These side effects can be minimized by decreasing fluency or increasing pulse duration. Due to lower melanin absorption with IpNd:YAG lasers, there is less concern for epidermal damage or post-inflammatory hyperpigmentation; thus, they are safer to use in patients with darker skin (14).

In recent years, not only erythema and telangiectasias but also inflammatory lesions; e.g., papules and pustules have been shown to improve after vascular laser treatments such as Nd:YAG laser as a result of a possible immune tissue response to light absorption (15). One theory for the higher success of IpNd:YAG in the treatment of PPR lesions of rosacea is that it destroys the follicular unit affected by *Demodex* mites that induce perifollicular inflammation in PPR (15,16).

IpNd:YAG laser has also been increasingly preferred in long-pulsed durations to enhance its efficacy in the neighboring vessels of erythematous tissues and reduce adverse including scarring and purpura. Satisfying beneficial outcomes were reported in previous two studies that evaluated IpNd:YAG laser (7,15). Almost 50 percent of the patients with ETR or PPR, good to excellent improvement was achieved. Clinical

improvement was better in the ETR patients than PPR patients and hypopigmented atrophic scars were only reported in two patients (15).

Despite being a subtype of IpNd:YAG, KTP laser has a half wavelength allowing it to efficiently penetrate into superficial telangiectasias (1,4,13,17). Our results confirmed the better destruction capability of Q-switched KTP laser for superficial vessels in ETR patients. Interestingly, we did not observe the complete destruction of telangiectasias but there was a remarkable decrease in their thickness. In particular, the thinnest telangiectasias (0-0.25 mm and 0.25-0.50 mm) were measured at a higher rate in the KTP laser application at month 4, which confirms its advantages. However, KTP laser was not as successful as IpNd:YAG laser in removing macular erythema and inflammatory rosacea lesions. In previous studies, controversial results have been reported concerning the comparative clinical efficacy of KTP and other vascular lasers; e.g., PDL (18-22). KTP laser has also been reported to be very safe when used in combination with topical retinaldehyde (21). Previous studies have similarly reported the scar risk of KTP laser to be lower than IpNd:YAG laser (23). However, contrary to previous studies that reported no undesirable adverse effects such as purpura and crusting, we observed transient purpura accompanied with mild crusting in six patients on the side treated with Q-switched KTP (585 nm) laser, probably due to the higher wavelength of the laser mode. In this study, purpura continued for 12 days, which may have resulted in lower patient satisfaction at month 2 for the side treated with KTP laser.

It has been reported that IpNd:YAG laser has advantages in the treatment of inflammatory lesions (2,7,14,15,23,24). In this study, the decrease in the number of pustules following IpNd:YAG laser treatment was remarkable. The deeper penetration capability of IpNd:YAG provides desirable results for not only deeper and thicker telangiectasias but also erythema. Thicker telangiectasias may increase tissue temperature, risk of tissue damage, and pain intensity. Atrophy observed in two patients treated with IpNd:YAG laser supports this idea. However, the similar rates of adverse effects of both lasers result in practitioners tending to equally use either laser for vascular lesions. However, in this study, the patients reported IpNd:YAG laser to be more painful. Thus, we think that the pain factor of IpNd:YAG laser may have negatively affected patient satisfaction at month 1. However, the remarkably successful removal of inflammatory lesions by IpNd:YAG laser in PPR patients may have resulted in better patient satisfaction and lower DLQI scores.

To our knowledge, there is no report on the results of a split-face clinical comparative study on the efficacy of IpNd:YAG and Q-switched KTP lasers for rosacea. In this study, we evaluated not only the improvement of erythema and telangiectasias but also the number of inflammatory lesions in rosacea patients. We also examined the change in telangiectasia thickness as an important objective criterion for vascular laser studies.

Study Limitations

The effect of different laser parameters such as influence, spot size, pulse duration for each laser type on the results was not examined in this study.

Conclusion

Although IpNd:YAG laser had certain advantages including greater efficacy in facial erythema, higher patient satisfaction, and better quality of life parameters, the overall efficacy of both lasers was similar according to the ETR scores. The clinician's assessment, adverse effects, and follow-up records demonstrated similar results. Thus, we recommend the use of IpNd:YAG laser predominantly for facial erythema and Q-switched KTP laser for thin and superficial telangiectasias (7,17,23). Since we did not observe a distinct objective difference between the two laser treatments, further studies should be undertaken to investigate the effects of vascular lasers with different parameters on the main clinical features and particular signs of rosacea.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Medipol University, Medical Device Clinical Research Ethics Committee (approval number: 10840098-604.01.01-E.41020).

Informed Consent: Informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.Ü., Concept: P.Ü., M.Ö., Design: P.Ü., M.Ö., Data Collection or Processing: P.Ü., A.B., Analysis or Interpretation: P.Ü., Literature Search: P.Ü., A.B., Writing: P.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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