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Comparative effectiveness of purpuragenic 595 nm pulsed dye laser versus sequential emission of 595 nm pulsed dye laser and 1,064 nm Nd:YAG laser: a double-blind randomized controlled study

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Abstract

Introduction: Erythematotelangiectatic rosacea is a common condition in Caucasians. The most frequently used lasers to treat this condition are pulsed dye laser (PDL) and neodymium:yttrium-aluminum-garnet laser (Nd:YAG). This study compares the treatment efficacy of purpuragenic PDL with that of sequential emission of 595 nm PDL and 1,064 nm Nd:YAG (multiplexed PDL/Nd:YAG).
Methods: We performed a prospective, randomized, and controlled split-face study. Both cheeks were treated, with side randomization to receive treatment with PDL or multiplexed PDL/Nd:YAG. Efficacy was evaluated by spectrophotometric measurement, visual photograph evaluation, the Dermatology Quality of Life Index questionnaire, and a post-treatment questionnaire.
Results: Twenty-seven patients completed the study. Treatment was associated with a statistically significant improvement in quality of life ($p < 0.001$). PDL and multiplexed PDL/Nd:YAG modalities significantly reduced the erythema index (EI; $p < 0.05$). When comparing the degree of EI reduction, no differences were observed between the two treatment modalities. PDL was associated with a higher degree of pain and a higher percentage of purpura. Multiplexed PDL/Nd:YAG modality was associated with fewer side effects and greater global satisfaction, and 96.3% of the patients would recommend this treatment to a friend.
Conclusions: Both laser modalities are efficacious in the treatment of erythematotelangiectatic rosacea. The multiplexed PDL/Nd:YAG modality was preferred by the patients.

Keywords: pulsed dye laser, Nd:YAG, effectiveness, rosacea treatment

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Introduction

Erythematotelangiectatic rosacea is a common condition in Caucasians, affecting up to 10% of the population (1). The most frequent locations are the nose, bilateral cheeks, the chin, and the forehead (2). The most frequently used laser to treat this condition is pulsed dye laser (PDL). One can also use intense pulsed light (IPL), and more recent studies have shown the efficacy of microsecond neodymium:yttrium-aluminum-garnet (Nd:YAG) (3–11). Studies have suggested that a combination of multiple wavelengths in the treatment of vascular lesions could provide additional efficacy and reduction in purpura (12, 13). Multiplexed PDL/Nd:YAG is a laser modality that corresponds to a 595 nm pulsed dye laser fired milliseconds before a 1,064 nm Nd:YAG laser beam, and some authors have suggested that this multiplexed PDL/Nd:YAG modality is efficacious for treating recalcitrant rosacea (14). The advantages of combining both laser modalities have been attributed to the ability of PDL in transforming oxyhemoglobin into methemoglobin before the Nd:YAG laser fires. PDL was reported to enhance Nd:YAG laser absorption in vascular structures by a factor of three to five, which allows the use of lower fluences, thus reducing the risk of side effects (15). This study compares the effectiveness of purpuragenic PDL with that of multiplexed PDL/Nd:YAG (595 nm/1,064 nm).

Methods

We performed a prospective, randomized, and controlled split-face study in which the unit of randomization was the individual facial side of each patient.

Subjects were selected from the Department of Dermatology at Vila Nova de Gaia and Espinho Central Hospital from September to December 2015. Inclusion criteria were patients with a diagnosis of erythematotelangiectatic rosacea, older than 18, and with no other relevant comorbidities. All patients were naive to laser treatment or had had their last laser treatment more than 1 year prior. Exclusion criteria were the presence of inflammatory papules, pustules, or vesicles and facial telangiectasias greater than 2 mm in diameter. None of the patients had a history of photosensitivity, nor were any treated with a known photosensitizing medication in the prior month. Twenty-nine patients were initially included and 27 patients completed our study. Only patients that completed the study were included in the statistical analysis.

All subjects provided written informed consent. All the procedures described in this study were in accordance with national and institutional ethical standards and were approved in advance by local ethical review committees.

Study devices

One laser device (Cynergy with Multiplex, Cynosure, Westford, MA, USA) with two different modalities (purpuragenic 595 nm PDL vs. multiplexed PDL/Nd:YAG) was used for the two arms of the study. The PDL settings were fluence of 6.0 J/cm², spot size of 7 mm, pulse duration of 0.5 ms, dynamic cooling device (DCD) level 3 of 5, and one pass with an overlap of 10%. The multiplexed PDL/Nd:YAG settings were PDL fluence of 7.0 J/cm², Nd:YAG laser fluence of 35 J/cm², spot size of 7 mm, pulse duration of 10 ms for PDL and 15 ms for Nd:YAG laser (long-delay), DCD level 3 of 5, and one pass with

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minimal overlap in order minimize the risk of thermal injury. These settings were standard company settings for the treatment of erythematotelangiectatic rosacea. When the nose was affected, we used the same randomization as the malar region. Other affected regions were treated with the last laser used. Only one pass was used (if areas were missed during the treatment, we did not retreat those areas).

Randomization protocol

The left or right side of each patient's face was randomized to a treatment modality using a random number generator. Each given assignment was sealed in an opaque, sequentially numbered envelope given to the patient by one investigator (MAC).

Study procedures

Each cheek received treatment with either PDL or either multiplexed PDL/Nd:YAG at 3- to 4-week intervals. After each treatment session, a questionnaire (Supplementary material 1) was delivered to the patient and returned at the following visit. Visual analog scales were used to rate pain (1 to 10), degree of purpura (expressed in %), and global satisfaction (expressed in %). The Dermatology Life Quality Index (DLQI) questionnaire (16) was completed in order to evaluate improvement in quality of life (QoL), standard digital photographs were taken, and erythema quantification with a spectrophotometer was obtained at baseline, before each session, and 1 month after the last treatment. Adverse events reported by the patient or observed by the investigator were recorded.

Topical skin procedures

The face was gently cleansed with chlorhexidine gluconate 0.2% before treatment. All patients applied broad-spectrum SPF 50 sunscreen immediately after each treatment and were instructed to use sunscreen daily.

Blinding

Patients were unaware of which cheek received which laser modality. Both laser treatments were performed in the same room by a different investigator (NM). The investigator taking the spectroscopy measurements (MAC) was blinded regarding allocation and did not assist in the laser treatments.

Photographs

After removing all makeup, digital single-lens reflex (SLR) photographs were obtained of the face from the front, and the right and left lateral positions. A third independent investigator (PV) evaluated the photographs taken and rated the improvement in erythema on a four-grade scale as previously described by Karsai et al. (9): Grade 1 was defined as clearance of less than 10% of the redness, Grade 2 as clearance of 10 to 50% of the redness, Grade 3 as clearance of 51 to 90% of the redness, and Grade 4 as clearance of more than 90% of the redness.

Spectrophotometer

A Mexameter MX 18 (Courage + Khazaka, Germany) quantified the erythema index (EI) from both sides of the face at three points: Point A = 2 cm below the midpupillary line, Point B = 4 cm below the midpupillary line, and Point C = 6 cm below the midpupillary line (Fig. 1). Three measurements were obtained at each point, and a mean was recorded. In order to compare efficacy between both lasers, the mean EI difference (mean EI after the third treatment minus mean EI at baseline) was calculated for both lasers. All measurements were performed in the same office at a controlled room temperature of 20°C and patients were instructed to avoid hot beverages (e.g., coffee or tea) prior to the observation.

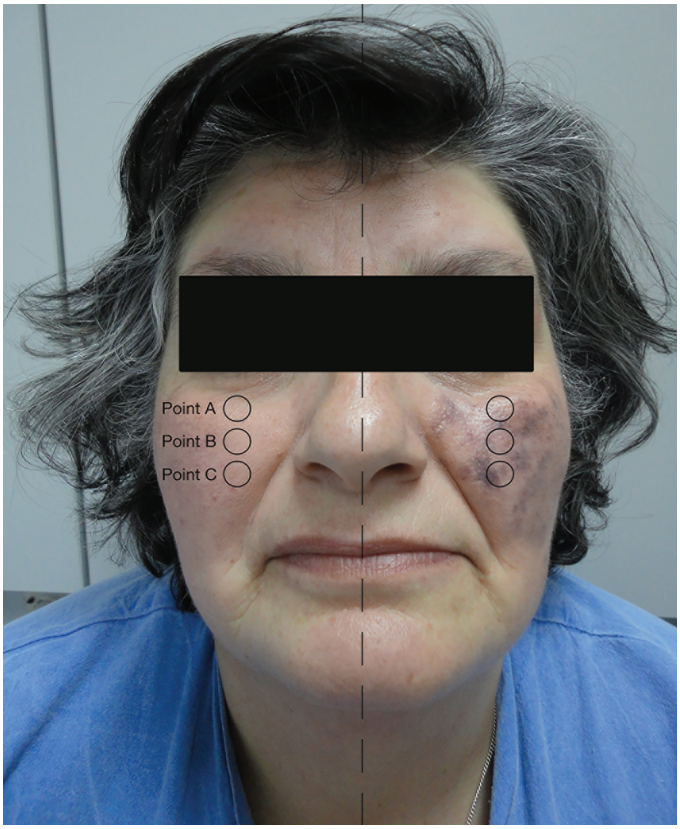

Figure 1 | Spectrophotometry measurement points and result immediately after treatment (left side treated with multiplexed PDL/Nd:YAG and right side with PDL).

Statistical analysis

Statistical analysis was conducted in SPSS version 24.0 (SPSS Inc., USA). Descriptive statistics and a *t*-test (unpaired and paired, two-tailed) were used when appropriate. Repeated-measures analysis of variance (ANOVA) were conducted to compare means at the data collection points. The results were considered statistically significant at $p < 0.05$.

Results

Twenty-nine patients were initially enrolled in the study. Two female patients dropped out after the first treatment because of unacceptable purpura that interfered with work and excessive pain during the treatment, respectively. The remaining 27 patients completed all three treatment sessions and a follow-up visit. Of these, 63.0% were females (17 out of 27 cases) and 37.0% were males (10 out of 27 cases). The mean age was 52.9 ± 15.9 years and no differences were observed between sexes (57.8 ± 17.0 years in males vs. 50.0 ± 14.9 years in females; $p = 0.224$). The proportion of patients older than 30 was 88.9% (24 out of 27 cases).

The DLQI, photograph evaluation, spectrophotometer meas-

urements, and patient questionnaire are presented in Table 1.

Overall, we observed a statistically significant reduction in DLQI in our study ($p < 0.001$). The reduction in DLQI occurred after just one treatment, with a reduction of mean DLQI of 6.15 to 3.30 ($p < 0.001$). Further reduction was observed between the reported DLQI after the second treatment (3.30 vs. 1.74; $p = 0.018$) and third treatment (1.74 vs. 1.22; $p = 0.001$).

As assessed by visual photograph evaluation, mean improvement in erythema was maximum after just one treatment (mean clearance of 10 to 50%) in both laser modalities and did not improve with further treatments.

EI was significantly reduced at Points B and C with multiplexed PDL/Nd:YAG modality ($p = 0.002$ and $p = 0.007$, respectively) and with PDL modality ($p = 0.004$ and 0.005, respectively). At Point A, both lasers failed to demonstrate a significant reduction in EI ($p = 0.585$ and $p = 0.287$, respectively). When we compared the mean EI difference (EI after third treatment – EI at baseline) between the two lasers, we did not observe a statistical difference in the three measurement points (Point A: $p = 0.231$; Point B: $p = 0.674$; Point C: $p = 0.966$).

PDL was associated with a higher degree of pain (mean value) in all treatment sessions when compared to multiplexed PDL/Nd:YAG modality (5.93 ± 2.9 vs. 5.11 ± 2.6 after the first session; 5.89 ± 2.4 vs. 5.0 ± 2.5 after the second session; 5.33 ± 2.9 vs. 5.04 ± 3.0 after the third session). PDL modality was also associated with a higher reported pain score (mean value) in the first 3 days after treatment (3.41 ± 3.0 vs. 3.41 ± 3.0 after the first session; 2.89 ± 2.7 vs. 1.74 ± 2.0 after the second session; 2.44 ± 3.2 vs. 1.67 ± 2.2 after the third session). Side effects were significantly more common with PDL after every session, and purpura was the most common side effect. The most frequently reported side effect with multiplexed PDL/Nd:YAG was edema. When patients were asked to classify the purpura in the 1st week after each treatment, PDL was associated with a higher percentage of purpura than multiplexed PDL/Nd:YAG (63.70 ± 21.3 vs. 20.74 ± 27.2 after the first session; 51.92 ± 24.2 vs. 26.15 ± 27.1 after the second session; 57.41 ± 27.7 vs. 27.0 ± 25.1 after the third session). The percentage of purpura after PDL as reported by the patient decreased after each session of treatment, despite not achieving statistical significance ($p = 0.063$). Multiplexed PDL/Nd:YAG achieved a superior global satisfaction score (%) than PDL (56.15 ± 27.7 vs. 46.54 ± 26.2 after the first session; 61.85 ± 27.7 vs. 59.26 ± 23.2 after the second treatment; 67.8 ± 22.2 vs. 61.85 ± 20.0 after the third session). In both laser modalities, global satisfaction increased significantly after each session ($p = 0.046$ and $p = 0.001$). At the end of the study, when patients were asked if they would recommend this treatment to a friend with the same condition, 96.3% would recommend multiplexed PDL/Nd:YAG modality and 70.4% would recommend PDL modality.

Discussion

We studied the efficacy of two laser modalities, PDL and multiplexed PDL/Nd:YAG, in the treatment of erythematotelangiectatic rosacea in a consecutive series of 27 patients. Because every patient received both modalities, we believe our study represents the most appropriate method to compare these two treatment modalities. The evaluation of efficacy combining the use of visual assessment, spectrophotometer measurements, the DLQI, and the patient questionnaire makes our study the most complete comparison between these two treatment modalities. To our knowledge, no previous study of rosacea has attempted a spectrophotometric comparison between these two laser modalities.

An important point that must be highlighted in our study is that different investigators performed visual assessment (PV), spectro-

Table 1 | **Description of Dermatology Life Quality Index (DLQI), photograph evaluation, spectrophotometer measurements, and patient questionnaire.**

	Baseline	First treatment	Second treatment	Third treatment	*p* value
Cases (*n*)	29	27	27	27	
DLQI (mean ± *SD*)	6.15 ± 4.9	3.30 ± 3.5	1.74 ± 1.6	1.22 ± 1.2	0.001
Photographic erythema improvement (mean %)					
Multiplexed PDL/Nd:YAG	10–50	10–50	10–50	10–50	–
PDL	10–50	10–50	10–50	10–50	–
Spectrophotometer erythema index (mean ± SD)					
Multiplexed PDL/Nd:YAG at Point A	526.7 ± 127.9	537.3 ± 111.4	542.1 ± 97.2	537.0 ± 103.9	0.585
Multiplexed PDL/Nd:YAG at Point B	591.9 ± 96.9	559.0 ± 113.0	559.7 ± 111.2	537.7 ± 93.6	0.002
Multiplexed PDL/Nd:YAG at Point C	520.1 ± 119.7	509.2 ± 95.2	498.1 ± 116.7	465.7 ± 114.6	0.007
PDL at Point A	534.7 ± 113.2	526.4 ± 106.1	550.6 ± 85.4	525.9 ± 91.5	0.287
PDL at Point B	585.6 ± 99.4	575.4 ± 85.0	563.2 ± 85.1	537.6 ± 97.8	0.004
PDL at Point C	520.5 ± 95.5	497.0 ± 91.3	494.3 ± 96.3	465.2 ± 99.9	0.005
Pain during treatment (0 to 10)					
Multiplexed PDL/Nd:YAG	–	5.11 ± 2.6	5.0 ± 2.5	5.04 ± 3.0	0.948
PDL	–	5.93 ± 2.9	5.89 ± 2.4	5.33 ± 2.9	0.253
Pain during first 3 days (0 to 10)					
Multiplexed PDL/Nd:YAG	–	1.59 ± 2.0	1.74 ± 2.0	1.67 ± 2.2	0.894
PDL	–	3.41 ± 3.0	2.89 ± 2.7	2.44 ± 3.2	0.202
Side effects observed (*n*, %)					
Multiplexed PDL/Nd:YAG	–	4 (14.8)	7 (25.9)	9 (33.3)	–
PDL	–	15 (55.6)	15 (55.6)	13 (48.1)	–
Purpura in first week after treatment (0 to 100%)					
Multiplexed PDL/Nd:YAG	–	20.74 ± 27.2	26.15 ± 27.1	27.0 ± 25.1	0.122
PDL	–	63.70 ± 21.3	51.92 ± 24.2	57.41 ± 27.7	0.063
Global satisfaction with treatment (0 to 100%)					
Multiplexed PDL/Nd:YAG	–	56.15 ± 27.7	61.85 ± 27.7	67.8 ± 22.2	0.046
PDL	–	46.54 ± 26.2	59.26 ± 23.2	61.85 ± 20.0	0.001
Recommendation of this treatment to a friend (n, %)					
Multiplexed PDL/Nd:YAG	–	22 (81.5)	23 (85.2)	26 (96.3)	–
PDL	–	17 (63.0)	19 (70.4)	20 (70.4)	–

SD = standard deviation, PDL = pulsed dye laser, Nd:YAG = neodymium:yttrium-aluminum-garnet laser.

photometer measurement (MAC), and laser treatment (NM), and that PV and MAC were blinded to which side of the face received PDL or multiplexed PDL/Nd:YAG modality.

Similar to previous studies (1, 2), our study population had a predominance of females (63.0%), and 88.9% of the patients were older than 30.

Our baseline DLQI index (6.15) is in line with previous studies, demonstrating that our study population is comparable in terms of the DLQI (16). As demonstrated in previous studies (17–20), our patients had a significant improvement in QoL, reflected by the statistical reduction in the DLQI. Interestingly, the improvement in QoL was achieved after the first treatment, but it continued to improve significantly after the second and third sessions of treatment. Because our patients received both treatment modalities, we cannot specify whether the improvement in QoL was attributed more to PDL or multiplexed PDL/Nd:YAG. Despite this limitation, we can conclude that both treatment modalities significantly improved QoL. Further studies are needed to evaluate QoL improvement with multiplexed PDL/Nd:YAG modality.

Visual photograph evaluation did not differ in the two laser modalities. Maximum improvement (10 to 50% clearance) was obtained after one session and did not improve with further treatments. Because different scales have been used to evaluate improvement of erythema, the comparison between studies is troublesome. Despite these difficulties, a previous study reported a higher degree of clearance (mean clearance of 10 to 50% with PDL and mean clearance of 51 to 90% with multiplexed PDL/Nd:YAG), although this study only evaluated telangiectasias of the nose (9).

Both laser modalities significantly reduced EI at two of the three points evaluated. The lack of statistical significance at Point A may be attributed to a lesser degree of involvement in this area and consequently to a reduced improvement in erythema in this location. EI reduction had already been demonstrated in PDL and IPL (10), but not with multiplexed PDL/Nd:YAG or with long-pulsed Nd:YAG laser. We did not observe differences when comparing the degree of EI reduction between the two laser modalities, suggesting that both treatment modalities have similar efficacy.

Our study reported more side effects with PDL than with multiplexed PDL/Nd:YAG modality. As previously reported, purpura induced by PDL is a major outcome problem for patients (3, 9, 10, 17, 19, 21–23). As expected, PDL was associated with a higher degree of purpura than multiplexed PDL/Nd:YAG, although this side effect decreased after the second and third sessions. PDL was also associated with more pain during the treatment and in the following 3 days when compared to multiplexed PDL/Nd:YAG. Edema was the most common side effect with multiplexed PDL/Nd:YAG modality. Multiplexed PDL/Nd:YAG modality achieved higher global satisfaction by patients in each session, and more patients would recommend this treatment modality to a friend with the same condition. Interestingly, global satisfaction significantly increased for both laser modalities after each session. To our knowledge, this improvement in global satisfaction had not been described previously.

We are aware that our study has a limited number of participants. Nevertheless, we included a consecutive series of patients, and the number of participants in our cohort is actually higher when compared to most previous studies (3, 9, 17, 21–23). Between-subject variations were minimized by our study design, in which split-face comparison was used within the same subjects. Taking into account that these laser modalities have proved efficacy in treating erythematotelangiectatic rosacea, we did not include split-face subjects with a no-treatment control. Although split-face comparisons within the same patient reduces variability, we acknowledge that our study design may have not overcome all variances due to the small sample size. Spectrophometric measures have been described as liable and they depend on room temperature and cutaneous vascular tone (21, 23). In order to reduce this variability, all measurements were performed at controlled room temperature.

We conclude that both laser modalities are efficacious in the treatment of erythematotelangiectatic rosacea. Despite demonstrating similar efficacy, multiplexed PDL/Nd:YAG modality was associated with fewer side effects and a higher satisfaction rate by patients. Taking these results into account, we believe the choice between both modalities must be individualized and discussed with patients.

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