Treatment of Previously Treated Facial Capillary Malformations: Results of Single-Center Retrospective Objective 3-Dimensional Analysis of the Efficacy of Large Spot 532 nm Lasers

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BACKGROUND Current treatment of facial capillary malformations (CM) has limited efficacy.

OBJECTIVE To assess the efficacy of large spot 532 nm lasers for the treatment of previously treated facial CM with the use of 3-dimensional (3D) image analysis.

PATIENTS AND METHODS Forty-three white patients aged 6 to 59 were included in this study. Patients had 3D photography performed before and after treatment with a 532 nm Nd:YAG laser with large spot and contact cooling. Objective analysis of percentage improvement based on 3D digital assessment of combined color and area improvement (global clearance effect [GCE]) were performed.

RESULTS The median maximal improvement achieved during the treatment (GCE^{max}) was 59.1%. The mean number of laser procedures required to achieve this improvement was 6.2 (range 1–16). Improvement of minimum 25% (GCE25) was achieved by 88.4% of patients, a minimum of 50% (GCE50) by 61.1%, a minimum of 75% (GCE75) by 25.6%, and a minimum of 90% (GCE90) by 4.6%. Patients previously treated with pulsed dye lasers had a significantly less response than those treated with other modalities (GCE^{max} 37.3% vs 61.8%, respectively).

CONCLUSION A large spot 532 nm laser is effective in previously treated patients with facial CM.

The authors have indicated no significant interest with commercial supporters.

Facial cutaneous capillary malformations (CM) also known as port-wine stains (PWS) affect approximately 1 to 300 newborns.[1] If untreated, they do not regress and significantly affect quality of life.[2] The development of several devices that deliver pulsed light that can be absorbed by hemoglobin has revolutionized the treatment of CM. Pulsed dye lasers (PDL) are currently regarded as a first-line treatment option. However, total clearance is hardly ever achieved, and a proportion of patients are resistant to this therapy.[3] Frequency-doubled, 532 nm Nd:YAG laser also known as KTP (K [potassium] titanyl phosphate) is generally regarded as a secondary treatment option (Table 1).[4,5] Intense pulsed light sources of nonlaser light are regarded as secondary[5] or even tertiary alternatives.[4] Other options are less effective or associated with a higher risk of induction of atrophic hypopigmented scars. That includes Nd:YAG 1,064 nm, alexandrite 755 nm, or diode 800 to 940 nm. They may be used in darker skin patients and/or for deep and resistant CM. Argon 488 to 514 nm, krypton 520 to 530 nm, and copper bromide/copper vapor 578 nm lasers are first-generation lasers, which are currently rarely used. Before the era of laser selective vessel coagulation (1980s), less specific methods such as radiotherapy, cryotherapy, electrocoagulation, and carbon dioxide lasers were used. They should not be considered an option

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TABLE 1. Hemoglobin (Vascular) Selective Lasers for the Treatment of Capillary Malformations

Laser/Light Source	*Wavelength*	*Spot Sizes*	*Pulse Duration*	*Energy Density (J/cm²)*	*Epidermal Cooling*	*Comments*
PDL	585–595 nm (yellow)	Up to 10 mm	0.45–50 ms	5–24	Spray cooling	First-line option for I-III skin phototypes
KTP						
Small spot	532 nm (green)	1 mm with scanner	2–25 ms	3–45	Available for some devices (spray or contact)	Second-line option for treatment of superficial capillary malformations in I-III skin phototypes. Penetrates up to 1 mm.
Large spot long pulse		5–10 mm	30 ms	6–12	Yes (contact)	New large spot KTP devices have deeper penetration (up to 4 mm) than small dot KTP.
Large spot short pulse		5–10 (12) mm	3–10 ms	7–11.5	Yes (contact)	
IPL	500–1,200 (noncoherent)	Rectangular up to 10–400 mm	Various	Various	Integrated with modern devices (contact)	Modern devices with contact cooling can be regarded as an alternative option for superficial lesions. Large variety of systems makes this group heterogenous.
Nd:YAG	1,064 nm (infrared)	Usually up to 6 mm but 18 mm possible	3–300 ms	Up to 600	Integrated with some devices (contact, spray, or cold air)	Deeper penetration of up to 5 mm for large spot and high energy. Suitable for thick hypertrophic (nodular) purple lesions. High energy required for coagulation—high risk of atrophic scars.
Alexandrite	755 nm (infrared)	Up to 18 mm	3–80 ms	Up to 90	Integrated with some devices	Deep penetration (2.5–5 mm) but high melanin absorption. Suitable for thick hypertrophic (nodular) purple lesions.

TABLE 1. (Continued)

Laser/Light Source	*Wavelength*	*Spot Sizes*	*Pulse Duration*	*Energy Density (J/cm²)*	*Epidermal Cooling*	*Comments*
Diode	800–983 nm (infrared)	Up to 15 mm	10–150 ms	Up to 500	Different systems	Deep penetration. Data on its efficacy for PWS are limited. Commonly used for hair removal.
Argon	488–514 nm (blue)	1 mm (scanners available)	50–200 ms up to continuous	8–12	None	First generation of vascular laser. Used mostly in 1980s and 1990s. Currently mostly not used/available for dermatological applications. High risk of atrophic scars.
Krypton	521–530 nm (green), 568 (yellow)	1 mm		16		
Copper bromide/ copper vapor	578 nm (yellow)	1 mm (scanners available)		For 50 ms should not exceed 15 J/cm² to diminish the risk of scars		

KTP lasers were subdivided into 3 groups characterized by different spot size and pulse duration.
IPL, intense pulsed light; KTP, K (potassium) titanyl phosphate; PDL, pulsed dye laser; PWS, port-wine stain.

nowadays. There are a growing number of patients who have already been treated but did not achieve satisfactory results and seek other treatment options.

Several factors influence the efficacy and safety of laser therapy. The main factor is wavelength. This should be optimized to target hemoglobin as selectively as possible. It should also be able to penetrate the skin sufficiently enough. Other parameters such as spot size (laser beam diameter), pulse duration, and epidermal cooling are also crucial for effective and safe treatment (Table 1). Recently, the new device based on frequency-doubled, 532 nm Nd:YAG laser, characterized by a spot size of up to 12 mm and short pulse length, was introduced and has proven its efficacy in nontreated facial CM.[6,7] Although the light source is using the "classic" KTP laser technology, it provides a larger spot diameter that facilitates deeper energy penetration and warrants even distribution along vessels, reducing the cooling effect of blood flow. An average improvement in previously untreated facial CM obtained with this new approach was 70.4%.[7]

Several different approaches were used for the evaluation of CM treatment outcomes. Most of them were based on subjective scales. In the authors' previous report, they proposed an objective method of 3-dimensional (3D) assessment of both color and area for their method of evaluation.[7] Objective analysis of digital photography was already used in some studies but was limited by the analysis of 2-dimensional (2D) methods of area measurements. This is especially important for the assessment of the face with its complex 3D shape. Three-dimensional imaging has already been proposed to evaluate the area and volume of CM in 1 study, but this was not connected to the analysis of the lesion color.[8] Several methods can be used to objectively measure color changes after treatment, that is, reflectance spectrophotometry, tristimulus colorimetry, and analysis of digital or digitalized photographs.[9–12] The first 2 techniques are suitable to analyze the color change in a selected point of the larger area. Choosing this point can make a difference, as different regions may have different color and may respond differently to laser treatment.[13] To overcome this problem, analysis of 2D digital or digitalized photographs was proposed in 1995 by Ion

and coworkers. In this method, an average color of a whole selected area is used.[9,11] This approach may be limited by the existence of shadows on complex 3D surfaces. However, measuring the color with this technique was found to be superior to the subjective methods of analysis.[10]

Patients and Methods

The authors performed a single-center, retrospective study, which included all consecutive patients with previously treated facial CM who attended to their clinic between January 2013 and October 2016. These patients were treated by 3 physicians (B.K., M.R., and K.O.). All patients had "common" facial CM (PWS) not associated with any rare syndromes or variants, for example, PWS Proteus type, PWS CLOVES type, Rhodoid nevus, segmental angioma serpiginosum, and angiokeratoma.[14,15]

The study was approved by the institutional review board. Only patients who had 3D photographs performed before and after the treatment and had at least 1 single procedure were included in the study. This led to the exclusion of 3 adult patients who did not have the appropriate photographic documentation for unknown reasons. Forty-three white patients were enrolled into further analysis (23 females and 20 males), aged from 6 to 59 (mean 30.4; SD 10.7). All patients, except for 1 child (Age 6) and 1 adolescent (Age 17), were adults. All patients had Phototype II or III. Eight patients had minor residual atrophic scars after previous treatment.

Patients currently tanned or with the history of sun and/or ultraviolet exposure within 1 month before the procedure date were asked to return after at least 4 weeks of careful sun protection. All patients were treated with large spot, frequency-doubled, 532 nm Nd:YAG laser with contact cooling provided by sapphire glass (Excel V; Cutera Inc., Brisbane, CA). No other treatment of CM was preferable and used at that time in the authors' practice. Variable settings were used with the fluencies ranging from 8 to 11,5 J/cm^2, pulse duration ranging from 4 to 9 ms, and spot size ranging from 5 to 10 mm according to the judgment of the physician. The highest available spot size for the preset fluence and time was preferable. Local anesthetic (tetracaine and lidocaine ointment for 30 minutes before the procedure) was used on 1 patient. This patient was a child. Cooling the treated skin surface with a cold pack was used for 20 to 30 minutes after each procedure. Patients were asked to use post-treatment emollient for 7 days, avoid sun exposure, and use topical preparations with sun protection factor of 50+. The minimal interval between treatments was 4 weeks.

Three-dimensional images were taken with the use of Vectra XT under standardized conditions according to the manufacturer guidelines for the acquisition of facial images. The device was standing in the same room and placed throughout the entire study. The room had no windows and had stable artificial lights and a stable temperature of 22°C.

Image analysis was performed with the use of Vectra XT preinstalled image software as described previously.[7] Briefly, lesions were outlined manually by one of 2 investigators (B.K. or M.R.) using adequate magnification whenever necessary. Options of "selected surface area (cm^2)" and "selected area average color (described with L*a*b* coordinates)" were used for further analysis. Whenever possible, the healthy skin of the symmetric area served as a control for color evaluation. In other cases (lesion covering 2 sides of the face), the skin adjacent to the lesion was used. The difference between the color of the lesion and healthy skin (ΔT) was calculated according to the following equation:[9,11]

$$\Delta T = \left[(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2\right]^{1/2}.$$

To establish the improvement of the color of the lesion after treatment clearance effect, (CE) was calculated as follows:

$$CE = (1 - \Delta T \text{ after the treatment} / \Delta T \text{ before the treatment}) \times 100\%.$$

Reduction of the area (A%) of the lesion was calculated as a percentage difference between the area (A) before and after the treatment:

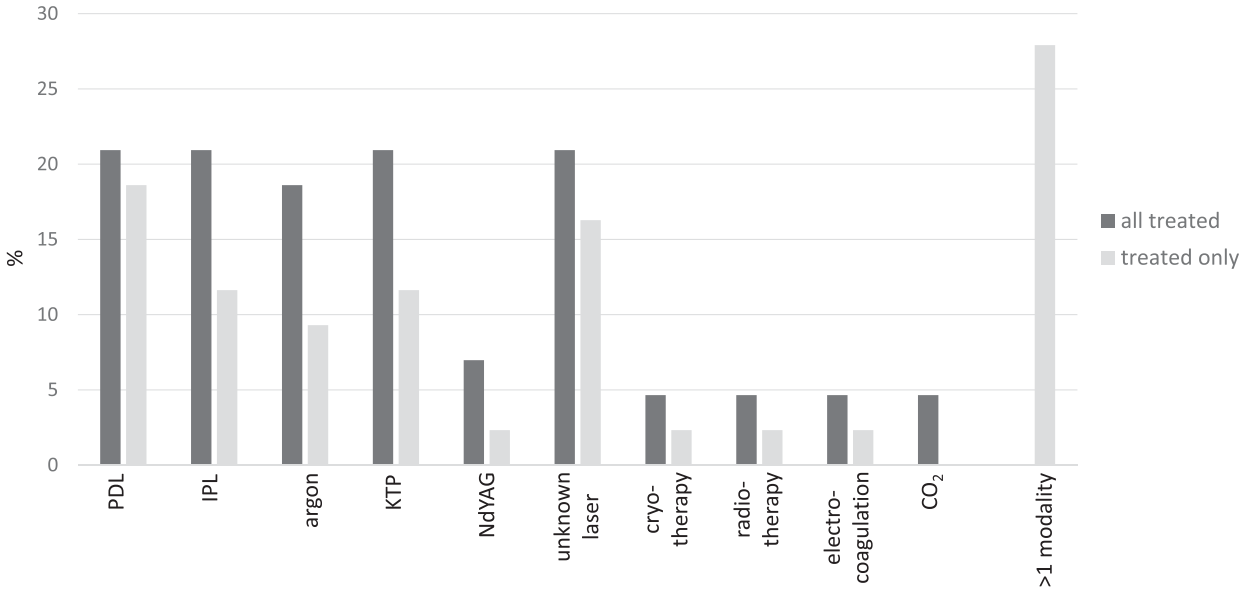

Figure 1. Previous treatment modalities used before the study. Dark gray bars represent the percentage of all patients who had been treated with the indicated method, regardless if they were treated with the other one or not. Light gray bars show the percentage of patients who were exclusively treated with the indicated modality and the subgroup treated with more than 1 modality. PDL, pulsed dye laser; IPL, intense pulsed light; argon, argon laser; KTP, small dot (<5 mm) K (potassium) titanyl phosphate laser (532 nm); Nd:YAG, 1,064 nm; CO_2, carbon dioxide laser (10,600 nm).

$$A\% = (1 - A \text{ after the treatment} / A \text{ before the treatment}) \times 100\%.$$

Finally, to combine the A% with the CE, the global clearance effect (GCE) was calculated as follows:

$$GCE(\%) = A\% \times 100 + ([100 - A\%] \times CE)/100.$$

The maximal GCE observed throughout the treatment of patient was defined as GCE^{max}. The number of patients achieving the GCE^{max} of minimum 25% (GCE25), 50% (GCE50), 75% (GCE75), and 90% (GCE90) during the treatment was calculated. For safety evaluation, patients were asked to report a presence and longevity of erythema, edema, and bruises, as well as an appearance of blistering and/or crusting. Patients were asked to come for unscheduled visits or send a photograph immediately if blistering and/or crusting appeared for clinical evaluation and exclusion of secondary bacterial or herpes simplex infection. The skin was assessed for the presence of scars before the treatment and on each visit thereafter.

Statistical analysis was performed with Statistica 12.0 software (StatSoft). Quantitative variables were characterized with mean, standard deviation or median, quartiles, and ranges after testing normality with the Shapiro–Wilk test. Significance of differences among 2 groups of variables was tested with the Mann–Whitney test. The Student *t* test was used for comparison between 2 related groups. The χ^2 test was used to compare discrete variables (with Yates correction when needed and with Cochran and Fisher tests).

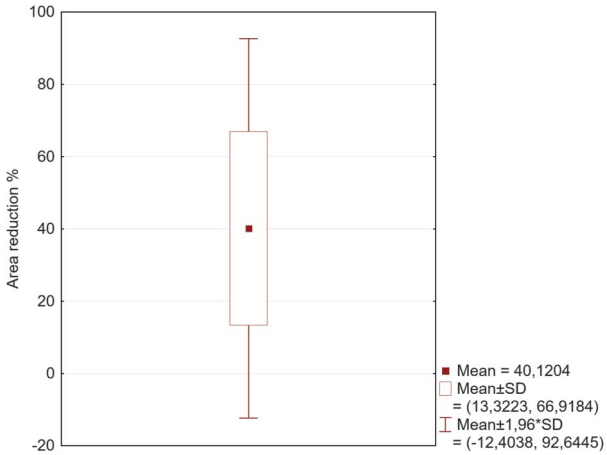

Figure 2. Reduction of the area of facial capillary malformation during the treatment calculated with 3-dimensional image analysis.

All *p*–values <.05 were considered statistically significant.

Results

Treatment modalities used before the study for individual patients are summarized on Figure 1. The number of treatment sessions with large spot 532 nm laser performed on these patients varied from 1 to 18 (median 7). The mean percentage reduction of the area of CM from the baseline to the last observation was 40.1% (SD 26.5; Figure 2). The median maximal improvement achieved during the treatment (GCE^{max}) was 59.09% (n = 43) (Figure 3A,B). Improvement of minimum 25% (GCE25) was achieved by 88.4% of patients, GCE50 by 65.1%, GCE75 by 25.6%, and GCE90 by 4.6% (Figure 4).

The treatment modality used before this study had an influence on the improvement rate (Figure 5). Patients who have been previously treated with PDL responded significantly worse than those who have not (GCE^{max} 37.3% and 60.3%, respectively; Figure 6A). Two-thirds of the previously PDL-treated patients achieved a response of minimum 25% (GCE25), and one-third of patients improved more than 50% (GCE50). This was significantly less than in the group of patients treated with other modalities (Figure 7A). By contrast,

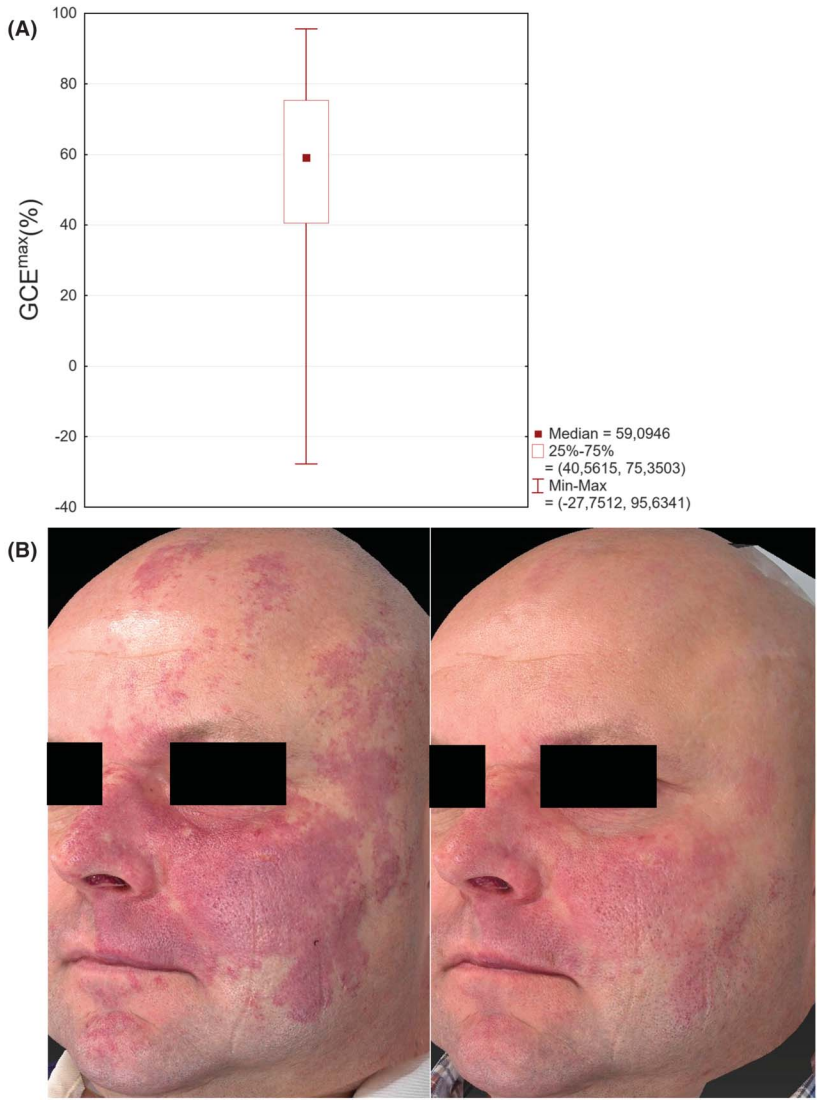

Figure 3. (A) Maximal improvement (%) achieved in 43 patients defined as maximal global clearance effect (GCE^{max}). Median, quartiles, and ranges are presented. (B) An example of the patient with a GCE of 63.0% representative of the median GCE^{max} calculated for all patients (59.72%; n = 43).

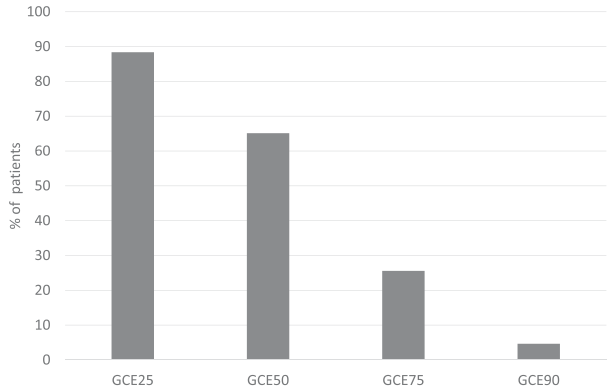

Figure 4. Percentage of patients who have achieved a maximal improvement of ≥25% (global clearance effect [GCE] 25), ≥50% (GCE50), ≥75% (GCE75), and ≥90% (GCE90); *n* = 43.

patients who have been previously treated with argon laser achieved better results (GCE^{max} 72.5%) than those who have not (GCE^{max} 55.6) (Figure 6C). Similarly, patients previously treated with radiotherapy, cryotherapy, or electrocoagulation had a significantly more favorable outcome than those not treated (GCE^{max} 75.6% and 57.3%, respectively; Figure 6E).

One patient's CM worsened during the treatment (GCE^{max} −27.8). This patient had only 1 treatment session and had been treated with PDL previously. Two additional patients got worse after the first session but improved further during the treatment, achieving GCE^{max} of 60.1% and 48.2% after 9 and 6 procedures, respectively. One of these patients had been treated with PDL previously (80 sessions) and the other with an unknown laser.

All patients experienced edema lasting for up to 4 days and not longer than 7 days. Bruising was usually present and lasted for 7 to 14 days. Crusting and/or blistering was present in a minority of patients and only focally, preferentially near the nose–cheek transitional skin or on the lateral angle of the eye. No new scaring was noticed. No secondary skin infections were observed.

Discussion

Lasers have already been used for the treatment of facial CM for more than 30 years. However, most of the patients achieve only partial improvement regardless of the device used. Suboptimal or no clearance prevails in 20% to 46% and 14% to 40% of patients, respectively.[16] Thus, most of the previously treated patients seek for new alternatives. The mechanism behind the resistance to laser treatment is complexed and in great part related to limitations of the process of selective photocoagulation. No laser technique is fully selective, and all of them do not only target hemoglobin but also other absorbers. The light wavelength determines the depth of penetration and the ratio between absorption of photons by melanin,

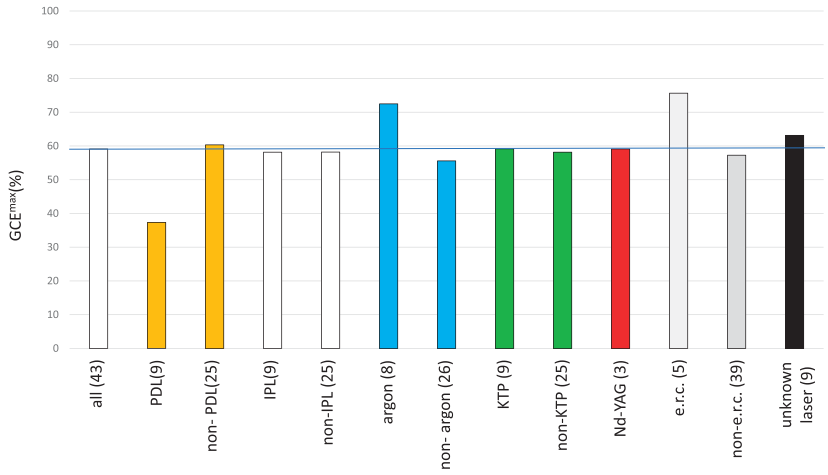

Figure 5. An overview of the influence of previous treatment on the expected improvement rate measured as global clearance effect (GCE^{max}) %. The number of patients for each group is shown in brackets. The blue line indicates the average GCE^{max} for all 43 patients. PDL, pulsed dye laser; IPL, intense pulsed light; argon, argon laser; KTP, small dot (<5 mm) K (potassium) titanyl phosphate laser (532 nm); Nd:YAG, 1,064 nm; e.r.c., electrocoagulation, radiotherapy, and cryotherapy groups shown together—representing nonlaser techniques.

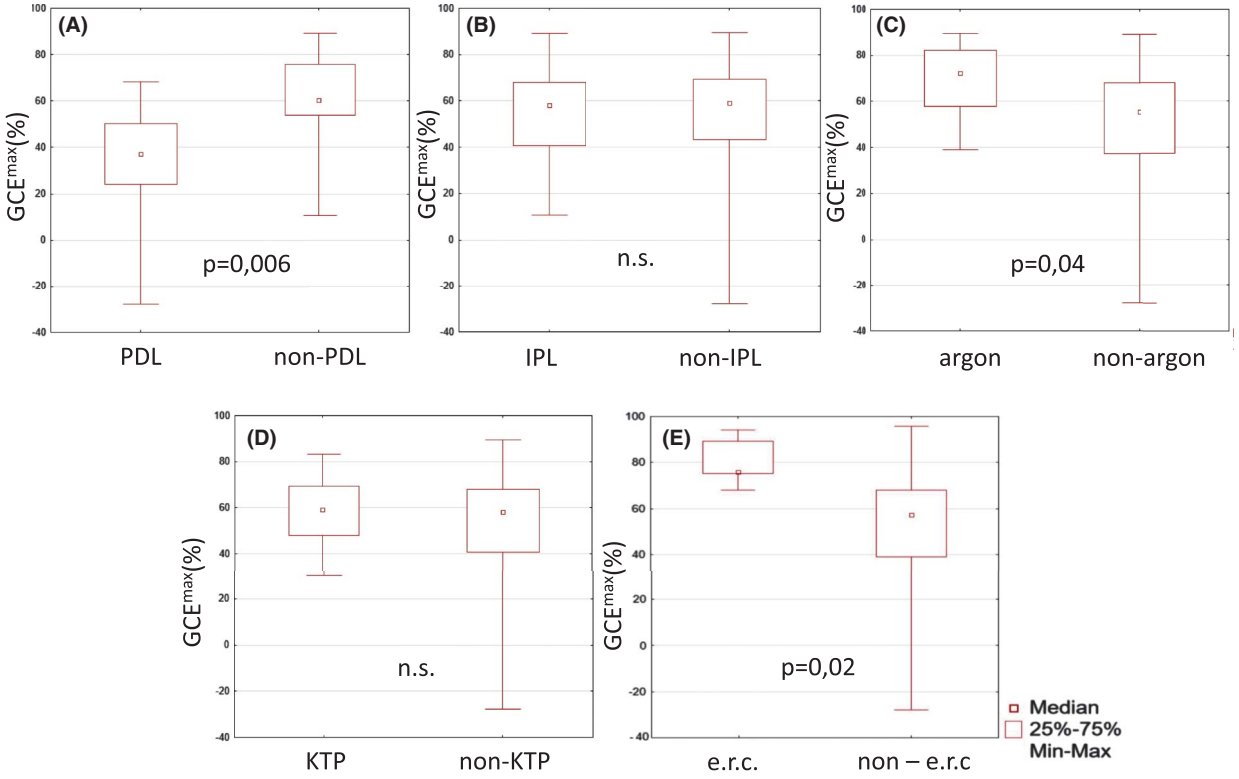

Figure 6. (A-E) Detailed comparison of the influence of previous treatment on the expected improvement rate measured as global clearance effect (GCE^{max}) %. Patients previously treated with pulsed dye laser (PDL) do not respond statistically as good as patients not treated with PDL. By contrast, patients previously treated with argon laser or a nonlaser method (e.r.c., electrocoagulation, radiotherapy, cryotherapy) had statistically higher GCE^{max} than those treated with other modalities. (C and E) Median, quartiles, and ranges are shown. IPL, intense pulsed light; KTP, small dot (<5 mm) K (potassium) titanyl phosphate laser (532 nm). n.s.; not significant. $p \geq .05$.

hemoglobin, and water. Shorter wavelengths such as 532 nm are closer to the peak absorption for hemoglobin but are also strongly absorbed by melanin and were believed to not penetrate sufficiently enough to close CM vessels that are located within papillary or even in the reticular layer of the dermis. This assumption was supported by clinical observations of the relatively lower efficacy of old devices based on 532 nm lasers and the higher risk of side effects.[17–27] However, devices used in those studies had a small (<5 mm, usually 1 mm) laser beam diameter (spot size), and some of them had no integrated cooling system to prevent epidermal heating. Recent experimental evidence indicates that photons of the 532 nm laser effectively reach the deep dermis and even the subcutis tissue layer. Also, 532 nm green light provides more complete intraluminal photocoagulation and more extensive damage to the blood vessel wall compared with 595 nm light.[28] This concept was proved in 2013 by Reed and colleagues by finding vascular damage at 4-mm depth on histopathological section in patients treated with large spot 532 nm lasers.[6] Recently, the authors were able to prove that the 532 nm laser with a spot size of up to 12 mm with contact cooling and pulse duration within a millisecond range can be effective in previously untreated facial CM and had a good safety profile.[7] In the previous report, the authors have shown that only 23.7% of patients did not reach an improvement of >50% (GCE50) and that >75% of improvement (GCE75) was achieved in 38.6% of cases, which is among the best result reported in the literature so far.[16] In this article, the authors have shown that this system can also be effectively used in previously treated facial CM. Forty-three patients included in this study were, in their subjective opinion, opposed to further therapy or not satisfied with the improvements and sought alternative treatment. The degree of improvement obtained in the cohort of patients was related to the previously employed treatment modality. The worst effect was

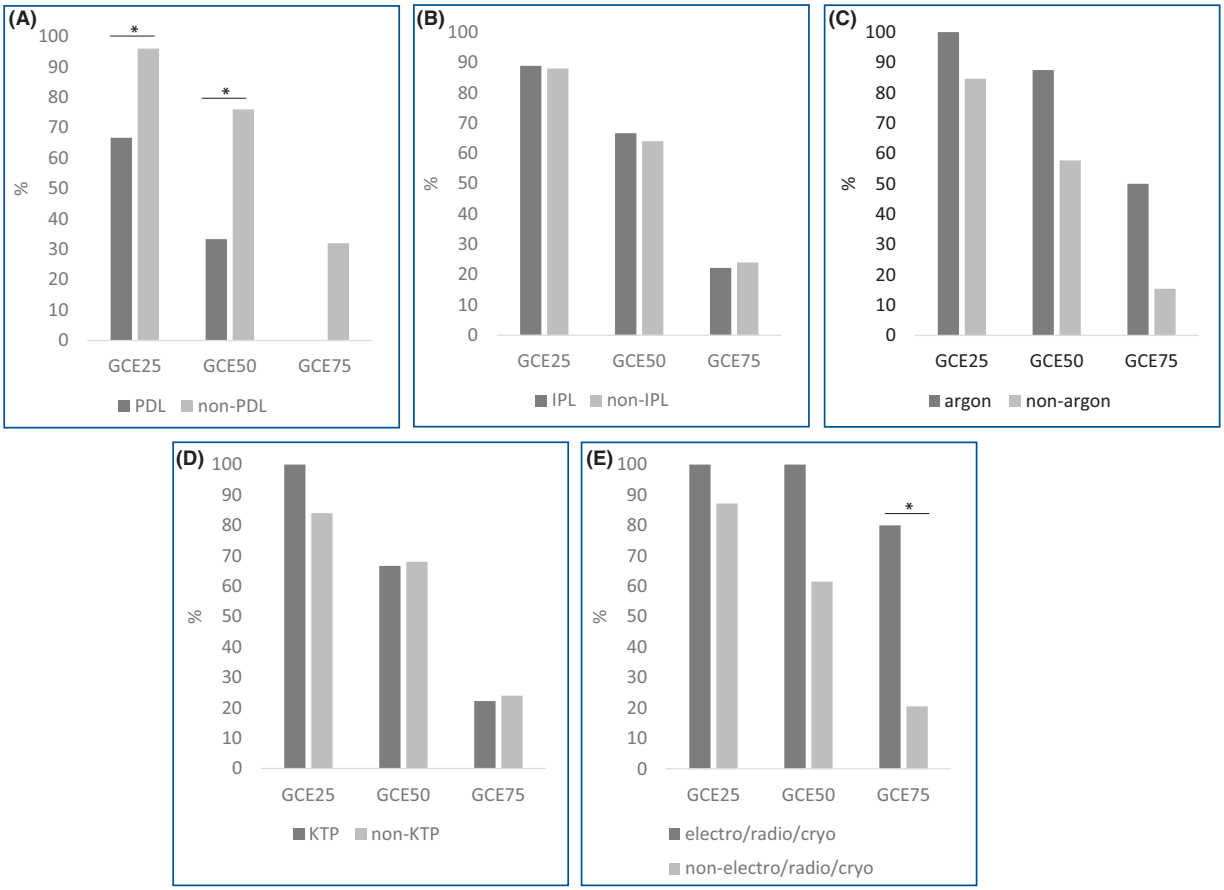

Figure 7. (A-E) Percentage of patients who have achieved maximal improvement of ≥25% (global clearance effect [GCE] 25), ≥50% (GCE50), ≥75% (GCE75), and ≥90% (GCE90) in subgroups previously treated with different lasers. Patients treated with pulsed dye laser (PDL) have statistically less chance to achieve GCE25 and GCE50 (A). Patients previously treated with a nonlaser method, e.r.c. (electrocoagulation, radiotherapy, cryotherapy), have a statistically higher rate of GCE75 response (E). IPL, intense pulsed light; KTP, small dot (<5 mm) K (potassium) titanyl phosphate laser (532 nm). *$p < .05$.

seen in patients who have previously undergone PDL therapy. This subgroup had a significantly lower rate of GCE25 and GCE50 responses, and no patient obtained GCE75 (Figure 7A). The authors were not surprised that patients previously treated with the "gold standard" PDL improved less than those treated with other methods. Most of the previously PDL-treated patients (6 of 9) had more than 20 sessions with PDL (Table 2). There is a well-documented plateau in the response to PDL reported in the literature. It is usually achieved between 6 and 12 sessions of PDL. Thus, one could not expect further improvement in these patients after additional PDL. All except 1 have achieved improvement after large spot 532 nm laser.

The best response was seen in patients previously treated with old techniques not related to selective photocoagulation: radiotherapy, cryotherapy, and electrocoagulation. Eighty percent of these patients may expect to achieve at least 75% of improvement (GCE75) and that is statistically more than patients not treated with this method (Figure 7E). It is important to note that although these modalities are no longer recommended for CM treatment, patients with residual lesions after such procedures seek for more efficient treatment and that is why the authors have included them into their analysis.

Figures 6D and 7D show that patients previously treated with "old" small spot KTP lasers can benefit from the "new" large spot KTP equipped with contact cooling used in this study. This subgroup of patients have obtained a median GCE^{max} of 59.13%, and all of them have reached GCE25. This is in accord with the hypothesis that the wavelength cannot be judged as a sole parameter determining the final outcome of laser

TABLE 2. Characteristic of the Subgroup of Patients Previously Treated With PDL

Patient No.	*Sex*	*Phototype*	*Age*	*No. of Previous PDL Sessions*	*Other Treatments*	*GCE^{max} %*	*Initial Worsening After First Session*	*No. of Large Spot 532 nm Laser Sessions*
1	F	2	18	80	—	60.98	Yes	11
2	M	2	41	4	—	68.18	No	12
3	M	2	6	6	—	29.5	No	6
4	M	2	34	Not known	—	50.44	No	5
5	M	3	27	≈20	—	24.05	No	4
6	F	2	25	>30	—	−27.8	Yes	1
7	M	2	18	>30	—	22.18	No	1
8	M	2	31	>30	—	43.37	No	3
9	F	2	11	>20	IPL	37.35	No	13

GCE^{max}, maximal global clearance effect; IPL, intense pulsed light; PDL, pulsed dye laser.

treatment (Table 1). This should also change the current assumption of the limited efficacy of KTP lasers found in some of the current guidelines.[16] Thus, large spot KTP 532 nm lasers should be considered as a different method than small spot KTP 532 nm lasers in terms of efficacy.

Improvement rates of 25%, 50%, and 75% were commonly used in previous studies on CM treatment regardless the method of efficacy assessment. Subjective assessment was usually based on Physician Global Assessment (PGA).[29] This scale rates 0% to 25% improvement as "poor improvement," 26% to 50% as "moderate improvement," 51% to 75% "significant improvement," and "cured" as 76% to 100% improvement. Most of the studies that try to objectively evaluate the efficacy were following the same levels. By following this point threshold, the authors made it possible to compare the results with other studies (Figure 7). The authors have used the scale of GCE25, GCE50, GCE75, and GCE90. Physicians and authorities are familiar with Psoriasis Area And Severity Index (PASI) 50, PASI 75, and PASI 90 terms, and they are currently the main end points for the evaluation and comparison of different psoriasis treatment. The authors have transferred this approach into the evaluation of CM treatment in their previous report[7] and followed it hereby.

A worsening of the GCE^{max} after the first treatment in 3 of 43 patients could be related to neoangiogenesis caused by trauma recovery, which could be mostly seen on the periphery of the coagulation spot. Initially, the authors commonly avoided overlap of spots during the first session to reduce the risk of overtreatment and to prevent possible scaring. Currently, the authors prefer to make some overlaps (10%–20%) during the first session, and they do not see the paradoxical worsening after initial treatment. Two of 3 patients who worsened after the first procedure had been previously treated with >30 sessions of PDL (Table 2). This could be another risk factor for an initial worsening. However, the authors believe that such deteriorations should not exclude further treatment, as the 2 patients who continued therapy improved after the second session.

Analysis of the combined 3D-measured area and color assessment used in this study could become a standard method for objective comparison of new methods of treatment. It was shown previously that objective analysis of the efficacy of treatment of CM gives slightly lower rates of improvement than subjective methods.[10] Thus, the median maximum improvement obtained in the cohort of white patients with previously treated facial CM that reached 59.09% clearly shows that these patients can benefit from new large spot 532 nm lasers. Side effects were transient and included bruising, edema, and erythema, and rarely focal crusting.

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