Retrospective Single Center Study of the Efficacy of Large Spot 532 nm Laser for the Treatment of Facial Capillary Malformations in 44 Patients With the Use of Three-Dimensional Image Analysis

Bartłomiej Kwiek, MD, PhD [1,2*] Michał Rożalski, MD,[2] Cezary Kowalewski, MD, PhD,[1] and Marcin Ambroziak, MD[2]

[1]*Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland*

[2]*Klinika Ambroziak, Warsaw, Poland*

Objective: We wanted to asses the efficacy of large spot 532 nm laser for the treatment of facial capillary malformations with the use of three-dimensional (3D) image analysis.

Study Design and Methods: Retrospective single center study on previously non-treated patients with facial capillary malformations (CM) was performed. A total of 44 consecutive Caucasian patients aged 5–66 were included. Patients had 3D photography performed before and after and had at least one single session of treatment with 532 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser with contact cooling, fluencies ranging from 8 to 11.5 J/cm^2, pulse duration ranging from 5 to 9 milliseconds and spot size ranging from 5 to 10 mm. Objective analysis of percentage improvement based on 3D digital assessment of combined color and area improvement (global clearance effect [GCE]) were performed.

Results: Median maximal improvement achieved during the treatment (GCE^{max}) was 70.4%. Mean number of laser procedures required to achieve this improvement was 7.1 (ranging from 2 to 14)). Improvement of minimum 25% (GCE 25) was achieved by all patients, of minimum 50% (GCE 50) by 77.3%, of minimum 75% (GCE 75) by 38.6%, and of minimum 90% (GCE 90) by 13.64.

Conclusion: Large spot 532 nm laser is highly effective in the treatment of facial CM. 3D color and area image analysis provides an objective method to compare different methods of facial CM treatment in future studies. Lasers Surg. Med. 49:743–749, 2017. © 2017 Wiley Periodicals, Inc.

Key words: 532 nm; Nd:YAG; KTP; port-wine stain; capillary malformation; 3D

INTRODUCTION

Laser treatment is a gold standard procedure for cutaneous capillary malformation (CM). There are several types of devices that deliver pulse light that can be absorbed by hemoglobin which may be used with pulse dye lasers (PDL) being currently the first line option [1]. However, total clearance is hardly ever achieved and a proportion of patients is resistant to this therapy [2]. The degree of improvement depends on several factors. Lesion localization is one of the most important among them [3]. Facial CM are among the most common and the most difficult to treat.

Lasers other than PDL and non-laser sources of intense pulsed light (IPL) have also proven their efficacy in CM. One of these other options are devices based on frequency-doubled, 532 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser. The number of studies showing the efficacy of 532 nm lasers is limited. Most of them were performed with tools that generate small spot size with up to 2–4 mm diameter and/or long pulse width [4–7]. Lately, the new device with a spot size of up to 12 mm and short pulse length was introduced and proven its efficacy on small group of patients [8].

Assessment of the efficacy of CM treatment is usually based on subjective methods of patients or physician's judgment. This makes comparison of the results of different studies difficult or even impossible. Objective analysis of digital photography was used in some studies but results can be influenced by the usage of two-dimensional (2D) methods of area measurements. This is especially important for the assessment of the face with its complex three-dimensional (3D) shape. 3D imaging has already been used to evaluate an area of CM in one study but was not connected to the analysis of the lesions

Abbreviations: A, area; CE, clearance effect; CM, capillary malformation; GCE, global clearance effect; GCE^{max}, maximum GCE; IPL, intense pulsed light; Nd:YAG, neodymium-doped yttrium aluminum garnet; PASI, (psoriasis area and severity index); PDL, pulse dye laser; SD, standard deviation; 2D, two-dimensional; 3D, three-dimensional

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

*Correspondence to: Bartlomiej Kwiek, MD, PhD, Department of Dermatology and Immunodermatology, Medical Uniwersity of Warsaw, Koszykowa 82A street, 02-008 Warsaw, Poland.
E-mail: bartlomiej@kwiek-dermatolog.pl

Accepted 4 April 2017
Published online 22 April 2017 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.22681

color [9]. Objective analysis of the color change during CM has been used with the use of different techniques, including reflectance spectrophotometry, tristimulus colorimetry, and analysis of digital or digitalized photographs [10–13]. Analyzing two dimensional (2D) photographs is difficult because of shadows on complex 3D surfaces, but already measuring the color with this technique was found to be superior to the subjective methods of analysis [11].

Devices for standardized 3D pictures of face and/or neck has been introduced and are commercially available. Here, we propose to use such a tool for the objective assessment of facial CM treatment. It was the aim of the study to assess the efficacy of large spot, frequency-doubled, 532 nm Nd:YAG with the use of 3D image analysis.

PATIENTS AND METHODS

We performed one center, retrospective study that included all consecutive patients with previously untreated facial CM that came to our clinic between January 2013 and June 2016 and who were treated by two physicians (B.K. and M.R.). The study was approved by Institutional Review Board. Only patients who had 3D photographs performed before and after and had at least one single procedure were included into the study. This has led to exclusion of six patients who did not have proper photographic documentation: four children below age of 4 (from technical reasons), and two adults from unknown reasons. A total of 44 Caucasian patients were enrolled into further analysis (27 females and 17 males), aged from 5 to 66 (mean 31; SD 16.3). Most of patients (37) had skin phototype II according to Fitzpatrick scale and five had phototype I and four patients had phototype III. Patients currently tanned or with the history of sun and or ultraviolet exposure within 1 month prior to the procedure were asked to come after more than 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 (ExcelV®; Cutera Inc., Brisabane, CA). No other treatment for CM was preferable and used at that time in our practice. Variable setting were used with the fluencies ranging from 8 to 11.5 J/cm^2, pulse duration ranging from 5 to 9 milliseconds and spot size ranging from 5 to 10 mm according to the judgment of the physician, with no overlap of radiated fields. The highest available spot size for the preset fluence and time was preferable. Local anesthetic (tetracaine and lidocaine ointment for 30 minutes prior to the procedure) was used in 2 out of 44 patients. Cooling with a cold pack was used for 20–30 minutes after each procedure. Patients were asked to use post treatment emollient for 7 days (Cicalfate®; Avene, France), avoid sun exposure and use topical preparations with sun protection factor 50+. Minimal interval between treatments were 4 weeks.

3D images were taken with the use of Vectra® XT in standardized condition according to the manufacturer guidelines for the facial images. The device was standing in the same room and place throughout the whole study. The room had no windows and had stable artificial lights and stable temperature of 22°C.

Image analysis was performed with the use of Vectra®XT preinstalled image software. Lesions were carefully outlined on the 3D color images with the use of sufficient magnification by one observer (BK). Lesions that had extended to the neck, scalp, and/or eye brows has been marked till the jaw line and/or the hair line (Fig. 1). Selected surface area (cm^2) and selected area average color (described with $L^*a^*b^*$ coordinates) were used for further analysis. Whenever possible, healthy skin of symmetric area served as control for color evaluation. In other cases, (lesion covering two sides of the face) 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 [10,12]:

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

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

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

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

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

Finally, to combine the $A\%$ with the CE the Global CE (GCE) was calculated as follow:

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

Maximal GCE observed throughout the treatment of patient was defined as GCE$^{\max}$. The rate of the patients achieving GCE$^{\max}$ of minimum 25% (GCE 25), 50% (GCE 50), 75% (GCE 75), and 90% (GCE 90) during the treatment were calculated. For safety evaluation, patients were asked to report a presence and longevity of erythema,

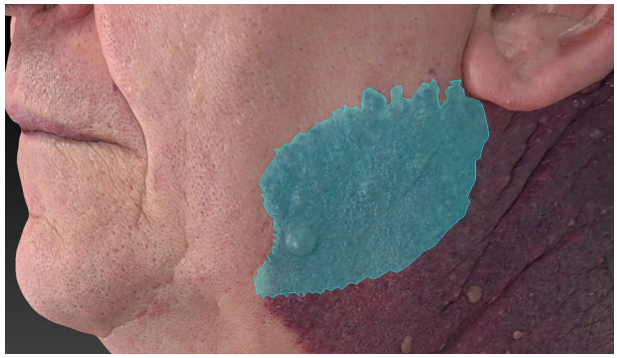

Fig. 1. Manual marking of facial capillary malformation on 3D images for area and color evaluations. Lesions were marked following their natural boarders using 3D image and adequate magnification. Lesions that extended beyond the face (to the neck or scalp) were outlined till the hair line or the jaw line.

edema, and bruises as well as an appearance of blistering and/or crusting or secondary bacterial or herpes infections. Skin was assessed for the presence of scars on each visit.

Statistical analysis was performed with Statistica 12.0 software (StatSoft). Quantitative variables were characterized with mean, standard deviation or median, quartiles, and range after testing normality with Shapiro–Wilk test. Significance of differences among two groups of variables was tested with Mann–Whitney test. Student's test was used for comparison between two related groups. Chi-squared (χ^2) test was used to compare discrete variables. Correlations were calculated according to Pearson or Spearman test. All P values <0.05 were considered to be statistically significant.

RESULTS

Number of treatment sessions performed in our patients varied from 2 to 14 (Fig. 2). Mean percentage reduction of the area of CM from the baseline to the last observation was 49.22% (SD 23.97) and was achieved on the eight visits on average (ranging from 2 to 14). Median maximal improvement achieved during the treatment (GCE^{max}) was 70.4% ($n=44$) (Fig. 3A and B). Mean number of laser procedures required to achieve this improvement was 7.1 (SD 2.9). Mean total number of procedures was 7.8 (SD 3.2). Improvement of minimum 25% (GCE 25) was achieved by all patients, GCE 50 by 77.3%, GCE 75 by 38.6%, and GCE 90 by 13.64% ($n=44$; Fig. 4). CM improved along with the number of procedure (Fig. 5A). Patients who had received not more than three procedures had significantly lower GCE than those who had undergone four to six procedures (42.44% vs. 58.83%; $P<0.001$; Fig. 5B). Patients who had undergone more than six treatment sessions improved more than those who had four to six procedures. However, this difference was on the border to become statistically significant (67.19% vs. 58.83%; $P=0.05$). When the cohort of 22 patients who had not achieved 75% improvement (GCE% <75%) until 4–6 visit but have been treated longer (>6 treatment) were analyzed, a significant improvement was seen along with the increased number of sessions (Fig. 6). In these patients GCE^{max} augmented from 53.79% between 4 and 6 session to 67.49% after more than six treatments ($P<0.001$). Average number of additional laser treatments to obtain this additional 13.7% of improvement was 3.1.

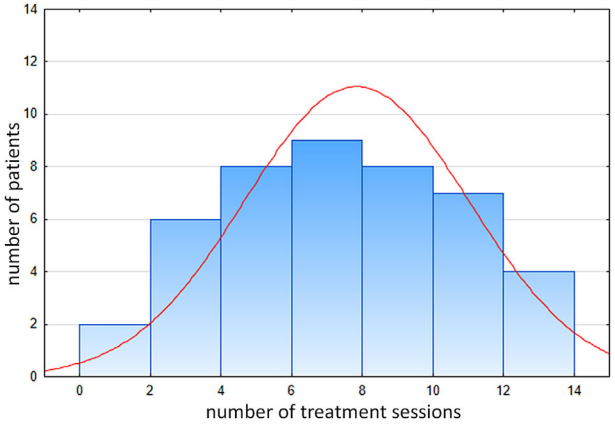

Fig. 2. Total number of laser sessions per patient.

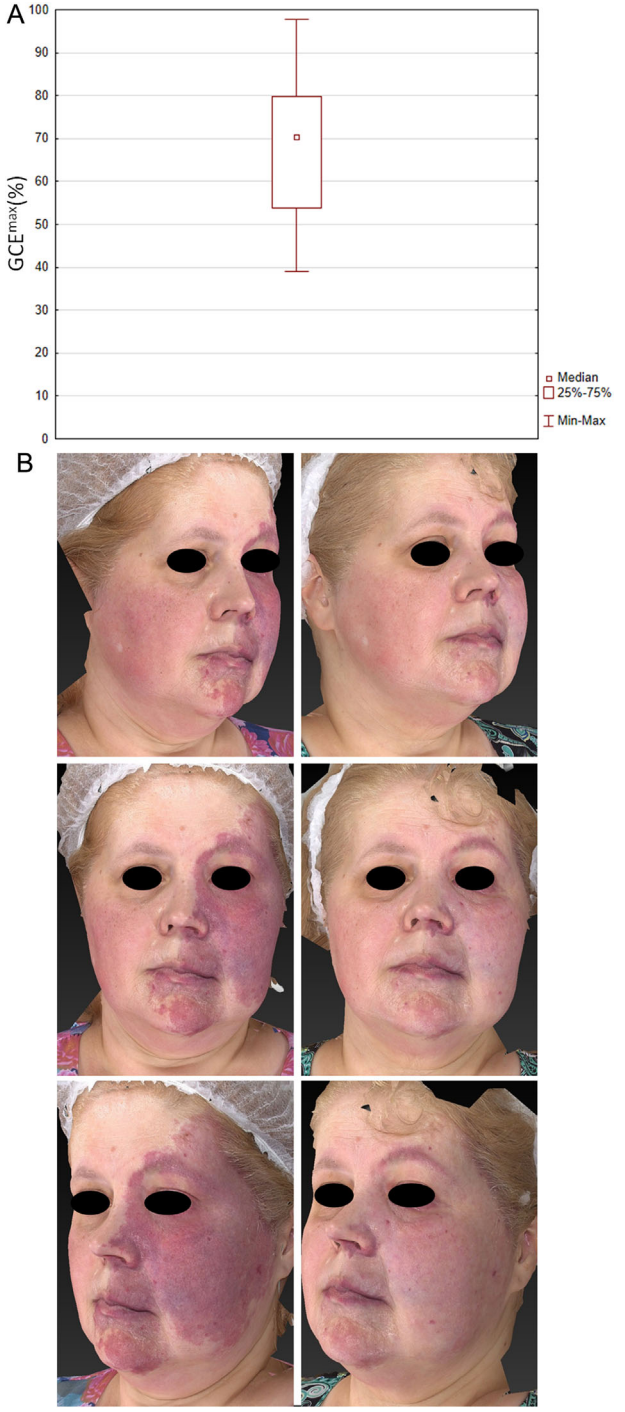

Fig. 3. **A**: Maximal improvement (%) achieved in 44 patients defined as maximal global clearance effect (GCE^{max}). Median, quartiles and ranges are presented. **B**: An example of the patient with GCE^{max} of 68.72% representative for the median GCE^{max} calculated for all patients (70.4%; $n=44$).

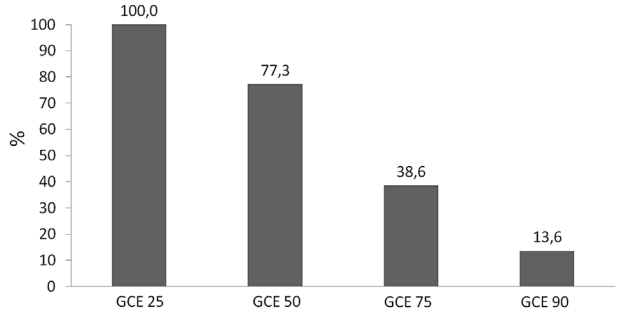

Fig. 4. Percentage of patients who have achieved maximal improvement of >25% (global clearance effect [GCE] 25), ≥50% (GCE 50), ≥75% (GCE 75), and ≥90% (GCE 90). $n = 44$.

We have not found statistically significant differences in the GCE^{max} rate between patients with different phototypes (data not shown). We were also not able to find significant differences in GCE^{max} when patients were divided according to affected dermatomes. The number of

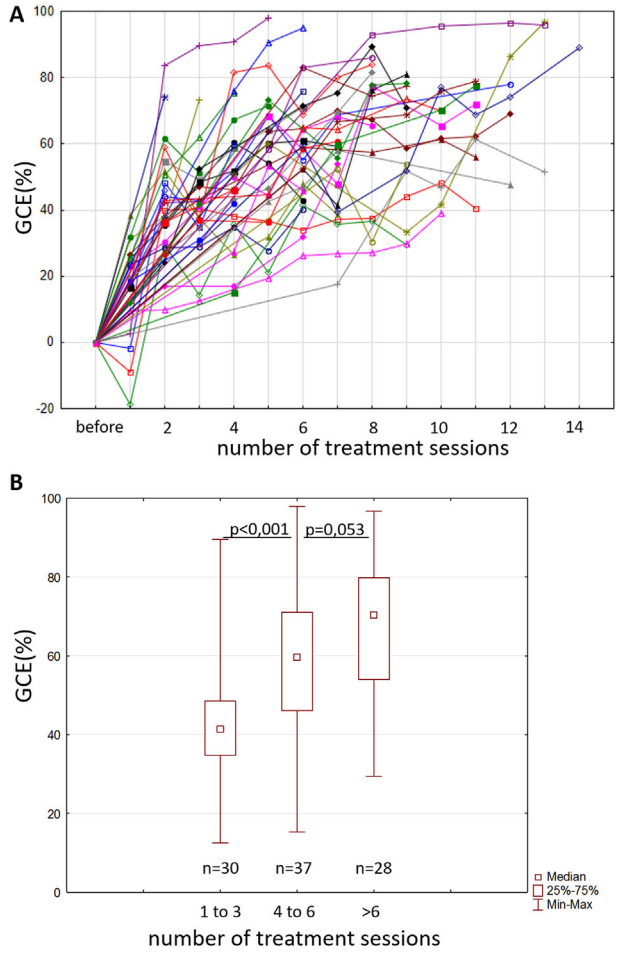

Fig. 5. **A**: Improvement of facial capillary malformations defined as global clearance effect (GCE) % during the treatment in all patients ($n = 44$). **B**: GCE% shown for patients with different number of laser sessions.

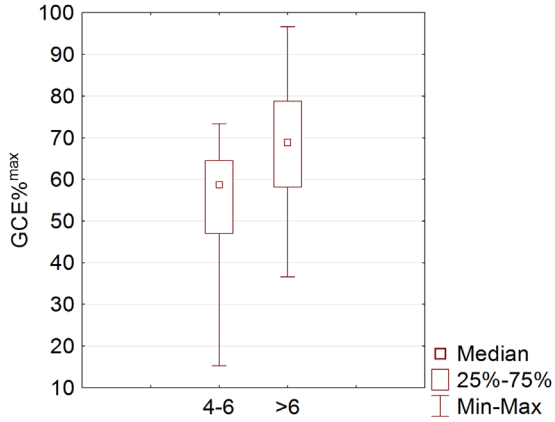

Fig. 6. Analysis of a subgroup of "slow-responders": patients who did not achieve 75% of improvement (GCE 75) between four and six visits. Prolonged treatment in this group (>6) resulted in additional 13,7% improvement. $n = 22$; $P < 0.001$.

patients achieving GCE 90 was higher than expected (3 vs. 1.36) in the group of patients who had no V2 dermatome involvement but this did not reach statistical significance ($P = 0.08$).

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

DISCUSSION

It was believed that shorter wavelengths, like 532 nm, penetrate more superficially (hardly through the epidermis) and thus compromise the effect on thicker CM. Recent experimental evidence are opposing this concept and indicate that photons of the 532-nm laser effectively reach deep dermis and even the subcutis tissue. A 532 nm light provides more complete intraluminal photocoagulation and more extensive damage to the blood vessel wall compared with 595 nm light [14].

Median improvement of facial CM obtained in our group of patients (GCE^{max}) has reached 70.4%. This indicates that this method can be judged as first line treatment for facial CM together with PDL lasers for previously untreated patients with fair skin, however, direct comparison in prospective study would be conclusive.

We were not able to show lower efficacy in phototype III patients however this subgroup was not high in number (9.9%) and most of our patients had phototype II (79.5%).

It was interesting for us to answer a following question: how many patients will achieve improvement of minimum 50%, 75%, and 90% as well as how many patients will not respond to treatment and will have their improvement rate of less than 25%. Values of 25%,

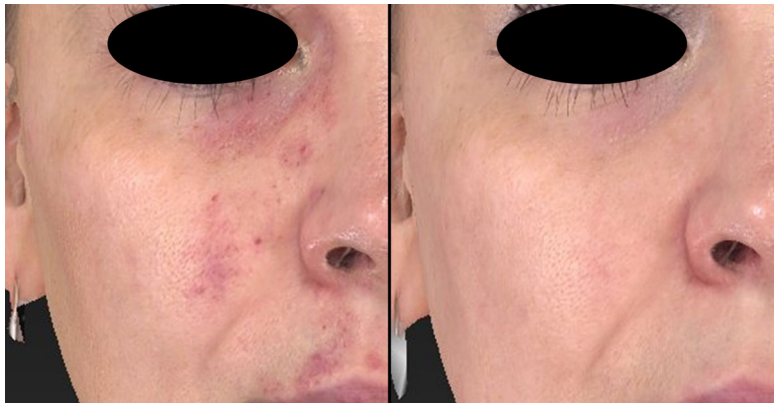

Fig. 7. Improvement >90% (global clearance effect ≥90%—GCE 90) after five treatment sessions.

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) [15]. This scale rates 0–25% improvement as "poor improvement," 26–50% as "moderate improvement," 51–75% "significant improvement," and "cure" as 76–100% improvement. Most of the studies that try to objectively asses the efficacy were following the same thresholds. We have followed this threshold points to make it possible to compare the results and added the improvement of >90% as we believe that this is a kind of improvement that can be regarded as "cured" or "cleared" (Fig. 7). We have chosen the presentation of the results in the way that is well established in the studies on psoriasis treatment. Physicians and authorities are familiar with PASI (psoriasis area and severity index) 50, PASI 75, PASI 90 terms and they are currently the main endpoints for the evaluation and comparison of different psoriasis treatment. We have transferred this approach into the evaluation of CM treatment. We have found that that all patients have experienced improvement of minimum 25% (GCE 25) and most of the patients (77.3%) achieved at least 50% of clearance (GCE 50). GCE 90 was achieved in 6 out of 44 patients (13.6%) and this seems to be related with distribution of the lesion. Less patients with V2 dermatome involvement than expected experienced 90% improvement, however, this finding did not reach statistical significance. Although we were not able to find statistically significant correlations between

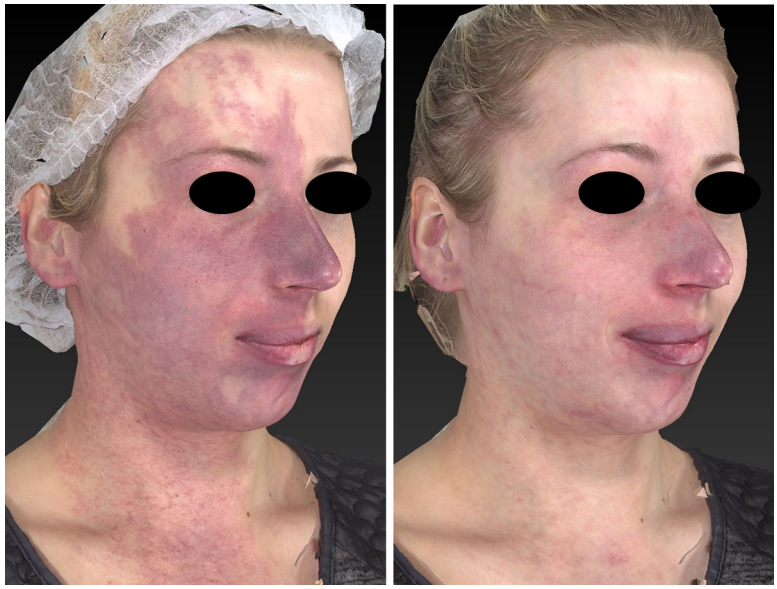

Fig. 8. Region dependent grade of response to treatment. Global clearance effect (GCE) for this two pictures is 53.3%. However, almost total clearance is seen on the upper forehead and temporal area, partial clearing on the lateral part of the cheek and lower forehead, and only minor improvement on the central part of the face and nose.

dermatomal localization of CM and efficacy there seem to be areas which are more resistant to treat but do not follow dermatomal distribution. We have found that the central part of the cheek and nose respond only partially in majority of patients. In opposite, forehead and lateral parts of face were more prone to clear (Fig. 8) which is similar to previous observations obtained with PDL lasers [16–18].

After proving that large spot 532 nm laser with contact cooling is an effective approach to previously not treated facial CM in all Caucasian patients, it was intriguing for us: when should we stop the treatment and how many sessions are required to maximize the effect? It is clear that patients will benefit more from 4 to 6 sessions of treatment than from 1 to 3 (Fig. 5B). Further treatment (>6 sessions) seems to bring additional improvement for some patients as shown on diagrams for individual patients (Fig. 5A). The analysis of all patients who underwent >6 treatments revealed that they improved better than those with 4–6 sessions but this was on the boarder of significance ($P = 0.05$). Looking at the rapidity of a response of individual patients, one can see that there are fast responders who will achieve their GCE 75 after 4–6 sessions (Figs. 5A and 7). Some of these patients stop their treatment when they reach satisfying result and this group is affecting global analysis presented on Figure 5B. To better address the question about the necessity of longer treatment, we have examined the subgroup of patients who have not achieved GCE 75 after 4–6 sessions (Fig. 6). When GCE^{max}% was compared between 4 and 6 and >6 visits treatment points in this slow responders cohort a significant improvement of additional 13.7% was observed ($P < 0.001$).

We have found the large spot, 532 laser treatment with contact cooling to be safe. Most of side effects were transient (bruising, edema, and erythema). Atrophic scars were present in a single patient and were not noticed by a patient himself.

Analysis of combined 3D measured area and color assessment used for the first time in our study could become a standard method for objective comparison of new methods of treatment. Before such studies are available one can only indirectly compare large spot 532 nm laser with other tools. It was shown previously that objective analysis of the efficacy of treatment of CM gives slightly worse results than subjective methods [11]. Thus, the median maximum improvement obtained in our cohort of previously untreated facial CM reached 70.4% has to be considered as one of the best results available in the literature [1,16,19]. Most of the studies conducted on the efficacy of laser treatment for CM included patients with different distribution of skin lesions. It was previously shown that regions such as neck and upper chest are responding better to the treatment than other areas, while distal extremities respond poorer. Reports that included such patients cannot be directly compared with our study designed to assess the efficacy of the facial CM treatment.

CONCLUSION

Results of our study indicate that large spot 532 nm laser is an effective option for the treatment of facial CM and can be used as a first line regimen for previously non-treated facial CM in patients with type I–III skin phototypes. Objective assessment of the efficacy with 3D image analysis can be helpful in future studies to directly compare different methods of facial CM treatment.

ACKNOWLEDGMENT

We would like to thank Jakub Szczupak for careful review of our manuscript.

REFERENCES

1. Adamic M, Pavlovic MD, Troilius Rubin A, Palmetun-Ekback M, Boixeda P. Guidelines of care for vascular lasers and intense pulse light sources from the European Society for Laser Dermatology. J Eur Acad Dermatol Venereol 2015;29(9):1661–1678.
2. Savas JA, Ledon JA, Franca K, Chacon A, Nouri K. Pulsed dye laser-resistant port-wine stains: Mechanisms of resistance and implications for treatment. Br J Dermatol 2013;168(5): 941–953.
3. Nguyen CM, Yohn JJ, Huff C, Weston WL, Morelli JG. Facial port wine stains in childhood: Prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. Br J Dermatol 1998;138(5):821–825.
4. Woo WK, Jasim ZF, Handley JM. Evaluating the efficacy of treatment of resistant port-wine stains with variable-pulse 595-nm pulsed dye and 532-nm Nd:YAG lasers. Dermatol Surg 2004;30(2 Pt 1):158–162; discussion 162.
5. Lorenz S, Scherer K, Wimmershoff MB, Landthaler M, Hohenleutner U. Variable pulse frequency-doubled Nd:YAG laser versus flashlamp-pumped pulsed dye laser in the treatment of port wine stains. Acta Derm Venereol 2003;83(3):210–213.
6. Pence B, Aybey B, Ergenekon G. Outcomes of 532 nm frequency-doubled Nd:YAG laser use in the treatment of port-wine stains. Dermatol Surg 2005;31(5):509–517.
7. Chowdhury MM, Harris S, Lanigan SW. Potassium titanyl phosphate laser treatment of resistant port-wine stains. Br J Dermatol 2001;144(4):814–817.
8. Reddy KK, Brauer JA, Idriss MH, et al. Treatment of port-wine stains with a short pulse width 532-nm Nd:YAG laser. J Drugs Dermatol 2013;12(1):66–71.
9. Frigerio A, Bhama PK, Tan OT. Quantitative three-dimensional assessment of port-wine stain clearance after laser treatments. Lasers Surg Med 2013;45(10):633–638.
10. Rah DK, Kim SC, Lee KH, Park BY, Kim DW. Objective evaluation of treatment effects on port-wine stains using $L^*a^*b^*$ color coordinates. Plast Reconstr Surg 2001;108(4):842–847.
11. Szychta P, Al-Nakib K, Anderson W, Stewart K, Quaba A. Quantitative method for evaluation of aesthetic results after laser treatment for birthmarks. Lasers Med Sci 2013;28(6):1567–1572.
12. Ion LE, Kavouni A, Scheepers H, Percival N. Objective evaluation of treatment effects on port-wine stains. Plast Reconstr Surg 2002;110(2):712–713.
13. Lister T, Wright P, Chappell P. Spectrophotometers for the clinical assessment of port-wine stain skin lesions: A review. Lasers Med Sci 2010;25(3):449–457.
14. Wang B, Landaverde H, Milner T. Laser photocoagulation of port-wine stain blood vessels: Three-dimensional Monte Carlo/finite element simulation with realistic vessel geometry. Lasers Surg Med 2013;45(Suppl 25):39–39.
15. Currie CL, Monk BE. Can the response of port-wine stains to laser treatment be reliably assessed using subjective methods? Br J Dermatol 2000;143(2):360–364.

16. Shi W, Wang J, Lin Y, et al. Treatment of port wine stains with pulsed dye laser: A retrospective study of 848 cases in Shandong Province, People's Republic of China. Drug Des Devel Ther 2014;8:2531–2538.
17. Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol 993;129(2):182–188.
18. Yu W, Ma G, Qiu Y, et al. Why do port-wine stains (PWS) on the lateral face respond better to pulsed dye laser (PDL) than those located on the central face? J Am Acad Dermatol 2016;74(3):527–535.
19. Faurschou A, Olesen AB, Leonardi-Bee J, Haedersdal M. Lasers or light sources for treating port-wine stains. Cochrane Database Syst Rev 2011;9(11):CD007152.