**LONG TERM TREATMENT PWS REQUIREs DUAL THERAPY INCLUDE INDUCTION AND MAINTENANCE**

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Bulleted statements:

**What’s already known about this topic?**   
The method of evaluating the effectiveness of treatment of Port Wine Stain capillary malformations has been so far mainly based on the subjective assessment of color and surface changes. It was based mainly on visual inspection, but this is not a reliable method for clinicians, because it makes it difficult to accurately assess and compare the effects of treatment. In our study, for objective image analysis, we used a 3D digital photograph, which was taken with the Vectra1 XT camera (Canfield Scientific, NJ) under standard conditions, in accordance with the guidelines of the face image manufacturer.

**What does this study add?**   
The results of our research allowed us to develop and implement a new scheme for the treatment of Port Wine Stain capillary malformations with 532nm laser therapy in the Ambroziak Clinic and in several facilities in Poland.

**What are the clinical implications of this work?**   
Through objective evaluation of the efficacy of the treatment with 3D image analysis we recommend for intensive treatment up to 9 visits and maintenance sessions twice a year.

**Summary**

**Background**

Laser treatment of port wine stains (PWS) has proven its efficacy but complete clearance is hardly ever achieved.

**Objectives**

This study aims to determine the optimal long-term approach for PWS treatment using a 532 nm large spot laser.

**Methods**

The study included Fifty-five Caucasian patients aged 6 to 59 underwent 2 to 37 laser sessions. 3D photography was performed before and after treatment with a 532 nm Nd:YAG laser with large spot and contact cooling. The percentage improvement based on 3D digital images assessment of colour and area was retrospectively analysed for all patients. Using the same method, a prospective study was conducted for patients who stopped treatment for more than 4 years.

**Results**

The median maximal improvement (GCEmax) achieved during the series of laser treatment was 63.61%. The first two laser procedures had a median maximal improvement of 31.19%, while the first 5,10,15 and 20 laser procedures had 49.84%, 58.01%, 60.13%, and 60.17%, respectively. Lesions not treated for more than 4.5 years worsened by 24.67 GCE percentage points on average, but improved after additional treatment.

**Conclusion**

Analysis indicates that large spot 532 nm laser is highly effective in the treatment of PWS. The first five laser procedures have higher efficacy, and improvements start plateauing around the 9th visit. The correlation between time groups and treatment efficacy could be explained by the exacerbation of PWS over time, indicating bi-annual treatment is needed to counteract deterioration. Patients who have not received treatment for a few years can experience worsening, but this can be reversed with reintroduction of laser treatment.

**Introduction**

Port wine stains (PWS) are the most common capillary malformations of the skin, affecting about 0.3-0.5% of infants. They are characterized by the dilatation of skin capillaries and post-capillary venules and can occur anywhere on the body, with the face and neck being the most common locations. PWS are present from fetal life and persist for a lifetime, gradually darkening and thickening if left untreated (1, 2). Vascular lasers are the considered the standard treatment for PWS, with pulse dye laser (PDL) being the first-line option. However, recent studies suggest that the large spot laser 532 nm is similarly effective in patients with lighter skin phototypes(3, 4). Early treatment of PWS is considered particularly effective in new-borns or infants and should be the primary treatment strategy for PWS (2, 5, 6). However, many older children and adults remain untreated or have received incomplete treatment(7). The standard PWS laser treatment with PDL or 532nm spot laser requires a series of treatments to achieve the maximum possible effect. In most cases, this is a significant but not complete improvement ranging from 29% to 59% (3, 5, 7, 8, 9), varying between patient population and assessment method. The outcome of the PWS treatment depends, among other things, on the Fitzpatrick phototype of the skin, the location of the lesion, the history of previous treatment[BK1] [GU2] and the type of vascular pattern in dermoscopy. The latter is mainly related to the depth of the enlarged vessels. Adequate laser setting, treatment protocol and schedule may also influence the outcome(4, 5, 9, 10, 11). For the PDL laser, the appearance of a plateau after a series of 6-12 treatments is well documented and further treatment appears to be of little or no benefit[BK3] [MP4] (7, 12, 13, 14) [BK5]. Our previous short- and medium-term studies show that a similar treatment response pattern occurs with the large spot 532nm laser and maximal response is present after 7 laser sessions in previously untreated PWS(15), but detailed data is not available.

**Materials and methods**

In our study, we analysed data from the treatment of PWS with frequency doubled Nd:YAG 532 nm laser characterized by a large spot (up to 12 mm in the retrospective study and up to 14 mm in the prospective study), a short pulse and contact cooling by sapphire glass (Cutera Excel V and Cutera Excel V plus ; Cutera Inc, Brisbane, CA, USA). Patients had 3D photography performed before and after treatment. Treatment setting, pre and post laser procedures were performed as described previously (16, 17, 18, 19). We used objective 3D digital photography with the Vectra1 XT (Canfield Scientific, NJ) to analyse images under standard conditions according to the facial image manufacturer guidelines. During the measurements, we considered the change in lesion area (cm2) and the change in mean colour (represented by L\*a\*b coordinates). Whenever possible, healthy skin from a symmetrical region served as a control for colour evaluation. In cases where this was not feasible, we measured the colour of skin adjacent to the lesion(3). Based on those 3D digital assessment, we calculated percentage described as global clearance effect (GCE) (3)

|  |  |
| --- | --- |
| Demography | |
| gender | M – 25, F – 30 |
| age | 6-59 (mean 36,71) |
| location | Face - 52, Neck - 3 |
| previous treatment | 56% YES, 44% NO |

Table 1

We conducted a retrospective analysis of patients treated in our clinic between 2012 and 2022. This cohort overlapped with the patients who were reported in our previous studies(3, 7, 8), but for our current analysis we only included patients who had at least two digital 3D images available from two consecutive visits which resulted in 55 PWS and 412 images that were subjected to further analysis. The analyzed cohort included both previously treated and never treated Caucasian patients aged 6 to 59 with Fitzpatrick phototype I-III, who had undergone 2 to 37 sessions of 532nm large spot laser treatment for facial, neck or trunk PWS (Table 1). We used Python's programming environment, including Pandas, Matplotlib, and SciPy frameworks to generate our statistics and graphs. The primary objective of our statistical analysis was to establish if treatment effects reach a plateau, and when. Our secondary goal was to find out if untreated PWS worsen over time and determine how long it takes for PWS to start deteriorating when left untreated. Throughout the research we’ve decided to use alpha-level of 0.05. Due to limited data, we often bucketed together sessions. For our first objective we grouped together visits based on the visit number (eg. one bucket for sessions 3rd to 5th). To ensure robustness we applied bucketing based on our clinical experience, and applied multiple different groupings, all resulting in similar and significant (p-value <0.05) results. We used Student's t-tests to compare any two means of the bucketed sessions. For our secondary objective, we’ve also grouped the sessions, this time based on time elapsed between two consecutive sessions. As previously, we’ve compared the means using Student's t-tests and applied multiple groupings to ensure robustness. Furthermore, for our second objective we’ve also used chi-squared test to establish a correlation between time elapsed between two consecutive visits and PWS worsening between those same two visits. We’ve applied chi-squared on expected and observed frequencies of PWS’s categorical data, where categorical data consisted of PWS worsening between visits (True/False) and time elapsed (bucketed). As previously, this has been done multiple times using different groupings to ensure robustness.

**Results:**

Our study aimed to confirm the hypothesis that a plateau of maximal response exists after a certain number of laser procedures, beyond which further improvement is not seen. We plotted the relationship between mean percentage improvement (GCE) relative to the start of treatment [BK10] [GU11] and the number of laser sessions [Fig1]. We found that after around the ninth session, the improvement slowed down, and GCE plateaus and oscillates around the height reached around the ninth session.

Chart, line chart

Description automatically generated

*Figure 1, The mean percentage improvement of PWS (GCE%) in relation to number of laser sessions. Treatment plateau is achieved on average around the 9th laser session, after which the improvement oscillates around the reached height. The blue lines mark the 2nd and 5th sessions, which have clear gradual increases in GCE. The orange line marks the 9th session, around which the plateau is reached. The fluctuations/instability of the graph can be explained by limited data, since there are few patients who had more than 15 visits.*

To statistically find the plateau, we grouped visits into buckets based on visit number and compared the means between each bucket. We grouped visits into [1-2, 3-5, 6-9, and 10+] buckets and found that sessions up to around ninth still bring a significant improvement (multiple different buckets were applied). Therefore, somewhere around 9th session a plateau is reached [Fig2]. [BK13?]

Chart, bar chart

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*Figure 2, Comparison of mean improvement (GCE%) [BK14] - between bucketed treatment sessions shows the treatment is still significantly effective up to around the 9th session, after which the plateau is reached, and the further treatment stops being effective.*

To confirm our clinical observations that discontinuation of 532nm large spot laser treatment causes relapse, we examined the intervals between visits and their impact on disease worsening. We grouped visits based on time elapsed between two visits and plotted a graph relating mean percentage improvement (GCE) between visits and time groups[Fig3]. Based on the graph and our clinical experience we believe the improvement achieved during a single session of treatment is lost after around 180 days, although the exact number may vary.

Chart, line chart

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*Figure 3, The improvement achieved during any given single session of treatment is lost after around 180 days break [BK16] [GU17] . Mean objective improvement based on 3D area, and colour assessment in-between any consecutive visits reach up to 10% when the assessment is performed for up to 180 days post-treatment and drops dramatically thereafter. This results in a complete loss of improvement and even worsening when two consecutive visits are spread for a longer period of time like 270 days.*

To find the time after which the PWS worsens, we have compared the means of separate buckets of visits (buckets based on time in-between visit)[Fig4]. We found that after around 180 days there is a significant worsening of PWS, which matches our clinical experience. Furthermore, there is some evidence (p-value<0.1) of even longer breaks having even further negative effect, but further research based on more data will be required. We have also used the chi-squared test in the Materials and Methods section to prove a relationship between the length of intervals and the amount of negative clearance.

Chart, waterfall chart

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Figure 4, A comparison of mean total clearance between bucketed treatment sessions shows that treatment effectiveness gets significantly worse for breaks longer than 180 days, with mean clearance in-between visits becoming negative for buckets with 180 days+. The figure showcases that the only two consecutive means that differ significantly (p-value <0.05) are means for buckets after and before 180 days, with shorter breaks having no significant effect on the treatment's efficacy.*

We found that worsening of PWS caused by long-lasting break in the treatment may be reversed by reintroduction of the treatment. To further solidify our hypothesis that PWS worsens over time when not treated, we have selected patients who completed a full course of treatment and ceased treatment when further improvement in their PWS was not achieved after several laser sessions. These patients have not been treated for more than four years, allowing us to more strongly support our hypothesis that PWS worsens over time if not treated. Three out of five selected patients agreed to our suggestion of a 3D image evaluation and additional treatment. Analysis of the images post-break indicated that their PWS had gotten remarkably worse in relation to their last session(Fig 5A). Their GCE compared to the their last session worsen by 24.67 percentage points, demonstrating the drastic effect a break in treatment can have on PWS (Fig. 5B). Patients [BK21] were able to recover most of previous treatment’s progress within one session. Of the three patients, two fully recovered in one session, while the third person recovered 23 absolute percentage points of GCE in a single session (Fig. 5A) [BK22] [BK23]

*Patient 1*

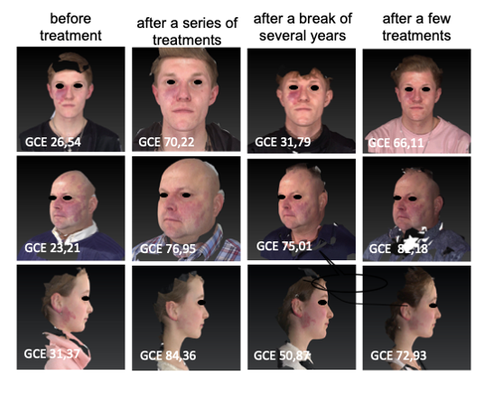
*Patient 2*

*Patient 3*

Obraz zawierający wykres

Opis wygenerowany automatycznie

*Figure 5A*



Obraz zawierający wykres

Opis wygenerowany automatycznie

*Figure 5B*

*Figure 5. The worsening of PWS caused by a long break from treatment can be reversed by re-introduction of the treatment. The figure and pictures present data of 3 patients who have taken 4.5+ year break from treatment. The pictures show absolute GCE measurement of patients' PWS before and after induction treatment as well as absolute GCE post-treatment break and after treatment has been re-introduced. The graph shows the mean GCE of the aforementioned 3 patients.*

**Discussion**

Previous studies have demonstrated that a large spot 532 nm laser with contact cooling is effective in PWS treatment of Caucasian patients. In the previous study we’ve recorded the median maximum improvement (GCEmax) of 70.4% in previously untreated and 59,09% [BK24] (8) in previously treated PWS. In this study, the GCEmax value was 62.69%, which is lower than in the preceding studies, most likely due to filtering down to patients who had at least two laser treatments documented with 3D photography in succession. In our current work we have shown a GCEmax value of 59.1%, which is slightly worse than in previous studies. Historically, the efficacy of PWS treatment has been measured subjectively by a doctor employing a “one-view” approach(20) and a limited grading system. This method, however, is not sensitive enough to detect even minor changes. An objective measure of 3D color and area assessment gives accurate results on continuous percentage scale, which is particularly necessary when examining factors influencing the final outcome of the treatment(21). Treatment of PWS with laser requires multiple sessions to achieve a complete result, making traditional subjective techniques of efficacy evaluation inadequate for the detection of minor percentage improvements between treatments - especially in the later stages of the treatment when the maximum improvement is close to being achieved. Use of objective and accurate efficacy assessments ensures a close look at the reality of treatment scheduling and its effect on the clinical result.

There are number of studies suggesting that early treatment of PWS within the first weeks and months of life can alter the course of the disease and result in better treatment outcomes(22). However, the majority of our patients have not received early treatment or have received no treatment at all. Given the cost to the patient, it is important to limit the number of procedures to necessary minimum. Monitoring the treatment with objective 3D photography may help to find the plateau for individual patients, as our data has shown that it occurs around the 9th laser session [BK25]. To achieve the best outcome in the shortest time, and to avoid a worsening of lesions due to intervals longer than 6 months between sessions, it is important to plan the treatment and keep the intervals short, even less than one month, as this has no effect on single session efficacy. This will not reduce treatment costs, but will help to accomplish what we propose to call 'induction therapy' (Fig. 6). Simultaneously it seems not feasible to further intensively treat the patient as a clear plateau in GCE% was found in current study.

Maintenance Treatment  
A laser session at least every 6 months to prevent reoccurrence of PWS

Regenerative Treatment  
3 laser sessions. Each 4-8 weeks apart, till plateau is reached

Induction Treatment  
9 laser sessions. Each 4-8 weeks apart, till plateau is reached

*Figure 6, To achieve the best therapeutic results in treating Port Wine Stain vascular malformations, we recommend inductive treatment - 9 laser sessions every 4-8 weeks (at a minimum of every 6 months). We also suggest maintenance treatment - at least one laser session every 6 months to prevent disease reoccurrence. If maintenance therapy is neglected, we recommend initiating a regenerative treatment - 3 laser sessions every 4-8 weeks, followed by a return to maintenance therapy.*

Our findings that disease relapses after treatment cessation for more than 180 days and tends to further worsen within months or even years has led us to propose [BK26], a maintenance therapy concept (Fig. 6). The natural course of PWS treatment leads to a slow but continuous progression of lesion thickening and darkening. Our observations suggest that laser treatments can only temporarily and partially reverse these symptoms. Therefore, to maintain optimal treatment effectiveness, it is advised to have non-intensive maintenance therapy that includes at least two laser sessions annually.

In cases where maintenance treatments are not possible or feasible for the patient, relapse can be significant as reflected in our four-year plus follow up. Such patients may benefit from 1-3 recovery sessions with a short 4-8 week interval and then can switch to a maintenance regimen. Drawing from our previous research, we have established that the large 532 nm dot laser is an effective treatment for facial CM and can be used as first-line therapy in patients with phototypes types I - III. Through objective evaluation of efficacies of the treatment utilizing 3D image analysis, we suggest intensive treatments of up to nine visits and maintenance sessions twice a year.

**Acknowledgments**

**not applicable**

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**Supporting Information**

not applicable

**Figure Legends for most Original Articles**