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Is it better to reduce the intervals between pulsed dye laser treatments for port wine stains in children? Laser Doppler Imaging based study

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ABSTRACT

Background: Pulsed Dye Laser (PDL) is the treatment of choice of Port Wine Stains (PWS). Laser Doppler Imaging (LDI) has been used to evaluate the effectiveness of this treatment. In a previous study, we demonstrated that LDI allows an objective evaluation. The purpose of this study is to investigate if reducing the delay between two laser sessions could improve the clinical outcome.

Method: This prospective study was conducted from September 2015 to November 2017. Three Laser sessions were performed every month in twenty patients with PWS. The PWS response was assessed by LDI after each session and at the end of the third one. The present study was compared to the first one.

Results: The LDI confirmed the efficacy of PDL treatment with an average blanching rate of 26.7 %. The response is statistically significant after each session. When we compare both studies, there is an average decrease in vascularization of 0.42 for the first study and 0.50 for the present one.

Conclusion: This study allows us to validate the use of LDI for the numerical evaluation of PDL effect on PWS in children. However, we cannot confirm that reducing the interval between laser sessions could improve therapeutic outcomes.

Levels of Evidence: Treatment Study

Level II (Prospective Comparative Study)

Contents

Port wine stains (PWS) are congenital vascular malformations characterized by ectatic capillaries in the upper dermis. Their diameter ranges from 10 to 150 microns. PWS occurs in 0.3% to 0.5% of neonates [1]. They are macular, pink to red at birth, and tend to darken progressively to purple over time due to the invasion of surrounding tissue: this may potentially result in disfigurement [2].

Pulsed Dye Laser (PDL) is the gold standard for the treatment of PWS [3]. The response to laser treatment depends on several parameters that

Abbreviations: CHUV, University Hospital Center of the Canton of Vaud; PWS, Port wine stains; PDL, Pulsed Dye Laser; LDI, Laser Doppler Imaging; ROI, Region of interest; APU, Arbitrary Perfusion Units.

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include the patient's age, the location of the PWS, the fluence used, and the interval between sessions. All these variables can affect the efficacy of laser treatment.

Several laser-based techniques have been developed for assessing the microcirculatory blood perfusion. Non-invasive assessment methods can be used to obtain the perfusion values and evaluate changes in PWS perfusion after successive laser treatments [4]. The current Laser Doppler Imaging system (Aïmago® EasyLDI) used for our study, developed by the biomedical optic laboratory of the Federal Polytechnic Institute of Lausanne, belongs to the third generation of LDI [5]. A red diode laser scans the designed area in a non-contact technique. The incident light is picked up and reflected back by the red blood cells within the dermal microvasculature. A Doppler effect occurs due to a frequency shift caused by the scatter of the moving red blood cells relative to the fixed light source from the LDI machine. This shift is picked up by a photo detector of the Doppler machine that re-collects the scattered light and correlates the scatter to the movement and velocity of the red blood cells in the dermal microvasculature. It generates two-dimensional color-coded images that correspond to the spatial distribution of tissue perfusion. A computer attached to the imager can then calculate the mean perfusion units or flux values in the region of interest (ROI) [6]. The images were analyzed by means of the “Easy LDI Studio” (v1.0-v1.2). LDI can provide a “digital photograph” of the PWS surface under examination as well as the corresponding “Doppler photograph” that reflects skin perfusion.

In our previous paper published in 2015, we performed three PDL sessions at 2 months' intervals on twenty young patients and evaluate the treatment efficacy with LDI technology. We were able to show that LDI could be used to objectively validate the efficacy of the PDL treatment of infantile PWS. It also showed that the effect obtained after each treatment fades over time [5].

In order to improve PDL treatment outcomes, two options were available: increasing the fluence of the laser at the risk of creating skin burns, or reducing the interval between two successive treatments. The purpose of the current study is to evaluate whether a reduction of the interval between two laser sessions from 8 to 4 weeks could improve the PWS clearance and thus the clinical outcome.

1. Methods

This prospective study was approved by The Board of Ethics of our hospital and conducted from September 2015 to November 2017 in the Department of Pediatric Surgery of the CHUV. We obtained parental verbal and written informed consent for all our patients. Laser treatments have been performed for about 25 years in our department and are covered by insurance policies dedicated to congenital malformations

The criteria for inclusion in the present study were almost identical to those of the first study [5]: presence of a PWS as defined by the International Society for the Study of Vascular Anomalies [7]; patient age ranging from 8 months to 9 years at the beginning of the PDL treatment; skin phototype I, defined according to Fitzpatrick's criteria [8]; and no previous laser treatment.

1.1. Treatment protocol

Laser treatments were performed using PDL, specifically the 595-nm V-beam. In the case of PWS in infants, we used a 7mm spot size, 1.5 ms pulse width and energies of 7-10 J/cm2 without cooling. The initial flow of the laser was set at 7 J/cm^2 and in the absence of complications it was raised by 0.5 J/cm2 at each new session. The clinical endpoint was determined by the presence of purpura over the treatment area. When treating periorbital skin, an intraocular metallic eye shield was placed under the eyelids to avoid the risk of retinal lesions. The eyes were always protected, regardless of the location of the angioma, in order to avoid retinal damage [9]. Laser sessions were performed every 4 weeks. After the parents had accepted the indication for laser treatment; which is mainly cosmetic; they were given the dates for four laser sessions at intervals of 4 weeks. If a session could not take place, the patient was excluded from the study. The procedure takes place under general anesthesia. Local anesthesia was not an option because of the young age of the patients, the discomfort associated with the procedure and the extent of the surfaces to be treated.

The choice to treat young children is based on previous studies that have demonstrated that early treatment is more effective [10,11,12].

In addition, it has been established that considerable psychological impairment can be avoided if children are treated before school age and before they have to interact with many other children [13].

1.2. LDI protocol

L-Doppler images were made before and after each of the four treatment sessions. The perfusion of PWS lesions and contralateral normal skin was determined. A fourth and last imaging session was performed at the end of the study in order to evaluate the efficacy of the third PDL session. The same two experienced surgeons who had conducted the first study performed the laser treatment as well as the LDI measurements. In order to minimize handling biases, the measurement of the healthy skin was taken only once before the first treatment, as we had observed in the course of the first study that this value differed from one session to another, was operator dependent, and could be a source of analysis error. The images were analyzed by means of the “Easy LDI Studio” (v1.0-v1.2), a program that allows quantitative arbitrary perfusion units (apu) measure of the vascularization of the PWS. The apu is a unit of measurement of values of vascularization for each patient, based on a comparison of healthy skin (the standard) with that of the PWS [5].

1.3. Data analysis

The statistical analysis was done by the center for primary care and public health of the Lausanne University. The value of vascularization of the PWS (ipsilateral side) before and after treatment was divided by the value of vascularization of the healthy skin (on the contra lateral side). Blanching rate was calculated by comparing the pre-treatment values with the post-treatment ones (i.e. values before the first session vs those after the last session), using the Wilcoxon signed-rank test, as the vascularization did not follow a normal distribution. The same test was used to compare vascularization between each treatment session. A threshold alpha = 0.05 was chosen for statistical significance.

The data were analyzed by comparing each individual’s pre-treatment and post- treatment findings and then by comparing these with those of the first study. Mann-Whitney tests were used to compare the present study to the first one [5].

2. Results

Twenty untreated patients clinically diagnosed with PWS were recruited for the present study. This group was composed of 11 girls and 9 boys. Patient age at the first treatment ranged from 8.16 months to 8.2 years, with an average of 2.65 years. The median was 12.7 months.

PWS were located on the face in 13 cases, on extremities in four cases and on the trunk in three cases. The patient skin types according to the Fitzpatrick Skin Type were type I in all children. They underwent four PDL treatment sessions under general anesthesia, even when the two possibilities of anesthesia (local or general) are offered, the older patients choose the general one. No serious adverse events were noted. No complications related to the laser treatment itself, such as

Table 1
Patient distribution

Patient	Age (days)	Sex	PWS localization
1	352	F	Right front
2	294	M	Left cheek
3	865	F	Midfront
4	302	M	Trijumeau 2
5	350	M	Left cheek
6	2425	F	Right arm
7	897	F	Left cheek
8	245	F	Trijumeau 1
9	394	F	Right leg
10	3000	F	Right Knee
11	1173	F	Midfront
12	673	M	Right thorax
13	253	M	Left hemiface
14	321	M	Trunk
15	3116	M	Right cheek
16	298	F	Right temple
17	412	M	Right temple
18	322	F	Right thorax
19	1646	M	Right thumb
20	2071	F	Right front

pigmentation change, infection, scarring, or atrophy, were observed during this study. The records of these 20 patients are summarized in (Table 1).

The results of the present study were analyzed on the basis of the values before and after each treatment, divided by the values of healthy skin taken only once at the beginning of the first session in the part closest to the treatment area. The evolution of individual values between the first and the last measurement showed a statistically significant decrease after each treatment, and vascularization was reduced in all the children (Fig. 1). At the end of the three sessions, there was an average clearance of 26.7% with a standard deviation of 13.51%. Median clearance was about 25.76%. Port-wine stains cleared in all patients as illustrated in Fig. 2.

3. Discussion

PDL is currently the gold standard therapy for PWS treatment. Laser (Light Amplification by Stimulated Emission of Radiation) therapy is based on the principle that tissues absorb light. Depending on its chosen wavelength, laser will have several different effects on the tissue, such as thermal, cutting, chemical or mechanical. In cases of PWS, early intervention is recommended in order to reduce their psychological effect

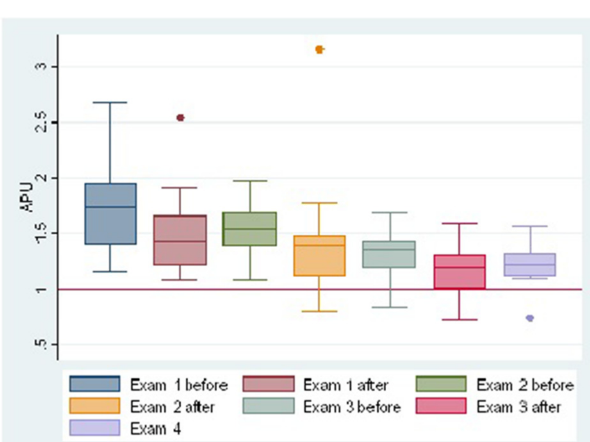

Fig. 1. Evolution of vascularization after three treatments.

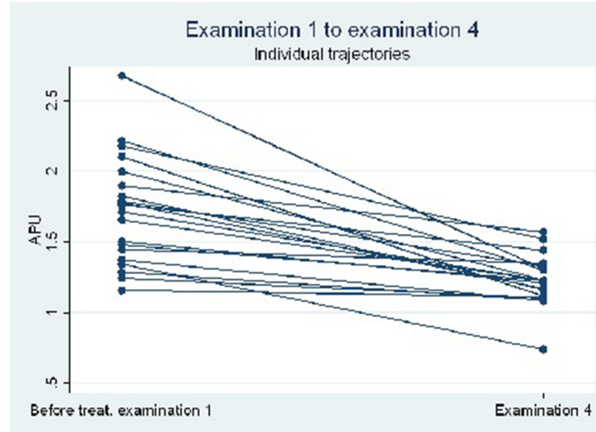

Fig. 2. Individual trajectories before the first visit and at the end of the treatments.

and avoid hypertrophy with age. The mechanism of PDL is selective photothermolysis: the expected effect is a thermal coagulation of the wall of the vessels and surrounding dermis. The optimal wavelength to target oxygenated hemoglobin is 595 nm. At that wavelength, light penetrates the skin easily, has limited melanin absorption and is well absorbed by blood vessels [3]. The beginning of the treatment, its frequency and its parameters vary considerably from one team to another. In standard clinical practice, a PDL treatment needs to be repeated several times. Laser parameters can be modified, such as the fluence (J/cm^2) of the laser beam, the diameter (mm) of the light bundle, the duration (ms) of the impulse, the cooling of the skin, and the time interval between each session. Generally, the effect of the treatment decreases over time [14]. It is recognized that early treatment in infancy may improve clinical outcome because the skin is thinner, thus allowing for better penetration of the laser beam. It is therefore recommended that patients with PWS should be referred for pulsed-dye laser treatment during early infancy [12].

The objective of the PDL treatment is to fade the lesion, to avoid age-related changes such as malformation darkening and hypertrophy and to reduce the aesthetic disfigurement.

In order to improve PDL treatment outcomes, we can vary PDL parameters such as fluence settings, spot size, pulse duration, dynamic cooling and the interval between sessions.

For this study, we chose to evaluate the interval between two successive treatments. We considered that this interval should be short enough to reduce spontaneous revascularization, but long enough to allow the recovery of the skin and the disappearance of the purpura which is the endpoint of the laser treatment. Our work was thus based on the hypothesis that reducing the interval between laser sessions to 4 weeks might improve PWS blanching. Several studies examining the effect of changing PWS parameters on its effectiveness can be found in the literature [15], including the interval between treatments. This last parameter was objectively either evaluated by spectrophotometer measurements [16] or visual and chromameter evaluation [17] To our knowledge, our study is the first to use the LDI technology as an objective method of assessing the effect of reducing the interval between two sessions.

As described in the chapter results, giving PDS treatment at one-month intervals did not result in any adverse effects or skin complications, as this was one of the potential concerns beforehand.

The results of this study do confirm quantitatively the effectiveness of PDL for the treatment of PWS in children. As expected, the flow within the vascular capillary malformation was partially reestablished during the interval between two consecutive treatments. Blanching rate and color improvement were statistically significant after each treatment, and the final results show a median clearance of 25.8% at the end of the three planned sessions with a last record before the 4th session. This compares favorably with the blanching rates of PWS with PDL treatment found in the literature, which range from 1.38% to 66.68% [18].

However it compares less favorably with the results of our previous study, where the median clearance was about 56%. It seems that reducing the interval between treatments to 4 weeks does not lead to a better result.

A comparison of the results of our two studies shows that there is no significant statistical difference between the two groups. (Prob > z = 0.6073), but that the results are somewhat better in the first study. PWS clearance after each treatment is objectively superior in the first study. The results after all treatments show an average decrease of 0.42 for the first study and 0.50 for the second, which is statistically insignificant. Individual trajectories for both studies are presented in Fig. 3. The results reported in the second study appear to be more homogeneous at the beginning and after the third treatment (Fig. 4).

A closer comparison of both studies reveals that in the first study there was a great disparity in the values of healthy skin measured before each treatment. The ratio of the apu value of the angioma area to the healthy area was therefore very different in comparison to this present study. This can have a major effect on the results, which must therefore be interpreted with caution. With this in mind, and in order to avoid bias attributed to healthy skin area, this value of comparison was taken only once before the first treatment for each patient. We tried to minimize the variables for the treatment and applied a single setting and the same treatment protocol for all patients. In our opinion, this may explain the non-statistical results of this study. A randomized study with children assigned to a 4-week and a 6-week group will be required to draw more precise conclusions.

There were some obvious limitations to this study, including the small number of enrolled children, the variability of the treated areas and the differences in age. The patient is shown in red on the graph in Fig. 3 is the one with the best clinical outcome, but this is not reflected on the curve (Fig. 5) These remarks confirm the important role of experienced surgeons in the visual assessment that remains a reliable way to evaluate the evolution of capillary malformation. Another factor that can be taken into account is the impact on these young children of a general anesthesia every 4 weeks.

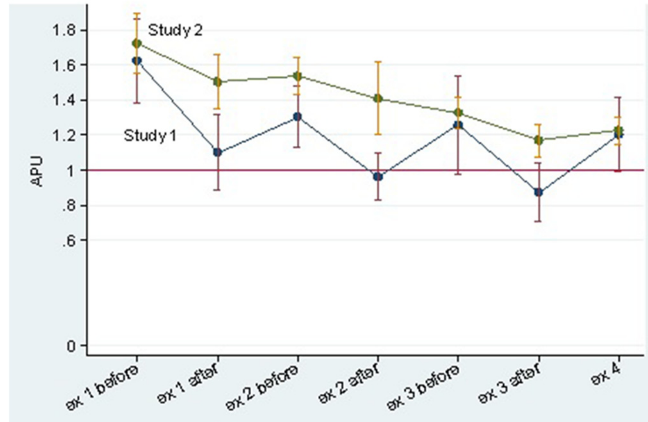

Fig. 4. Summary of treatments in both studies.

4. Conclusion

This prospective study has indeed allowed us to validate the standard clinical practice of using non-invasive technology, LDI, to provide numerical information on the positive effect of PDL on PWS in children (Fig. 6). However, we cannot yet confirm our hypothesis that reducing the interval between laser sessions could improve therapeutic outcomes.

The optimal treatment regime with PDS with regard to many variables, including the treatment interval and timing has still not been conclusively determined.

A randomized study with a larger population would be the next step in assessing the best way to treat these visible malformations that have an undeniable psychological impact.

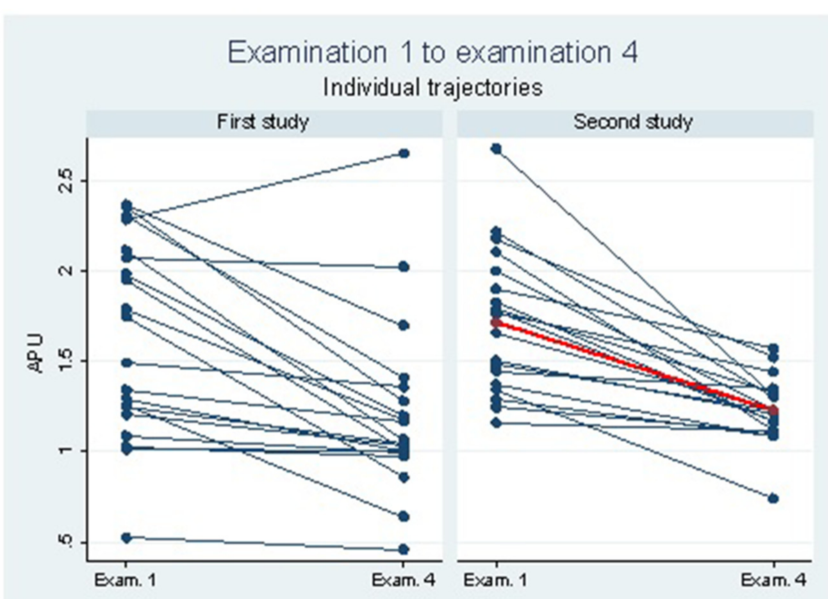

Fig. 3. Individual trajectories in both studies.

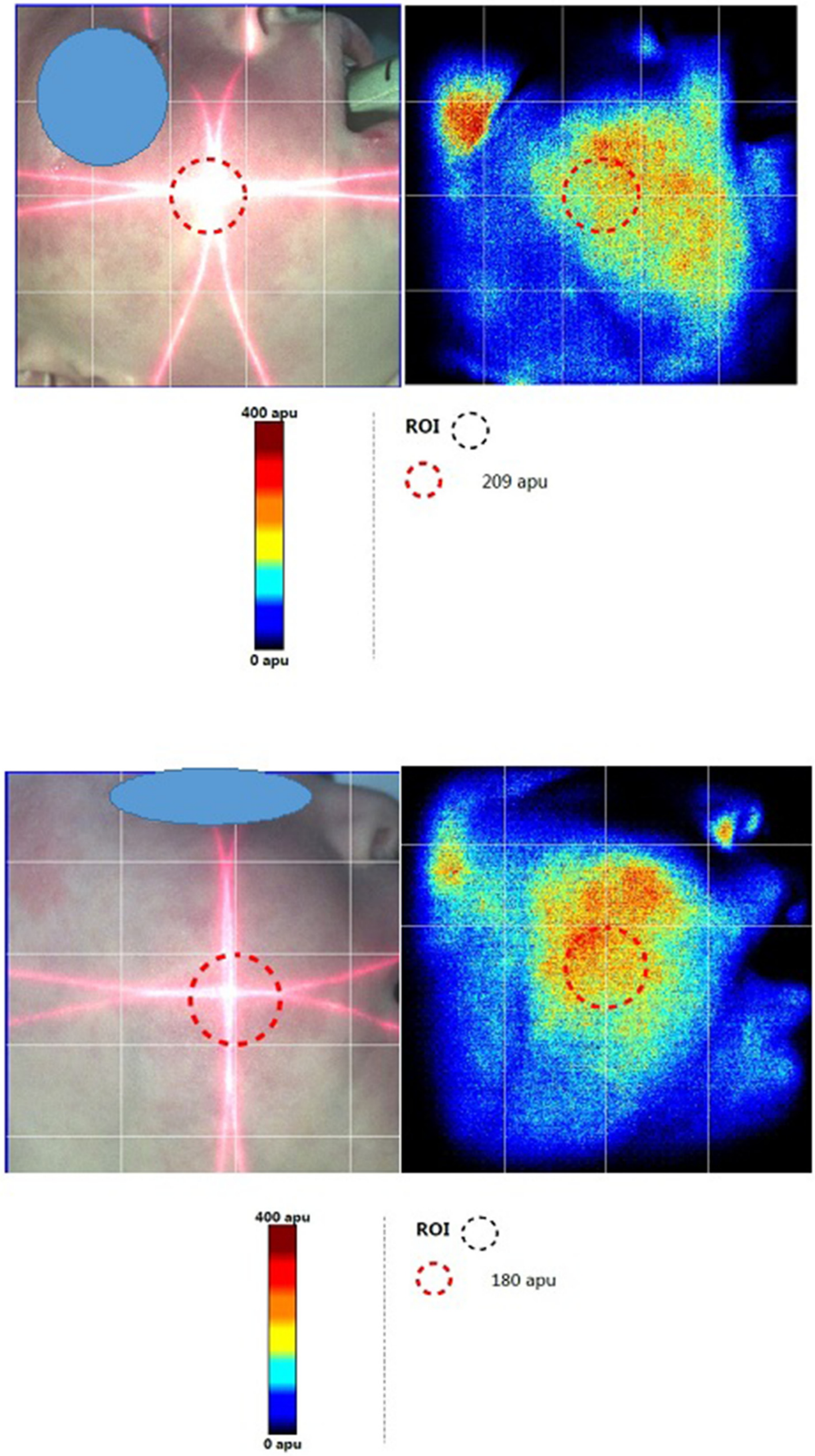

Fig. 5. Illustration of the contrast between clinical appearance and APU value.

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Fig. 6. Illustration of the effectiveness of PDL therapy in clearing PWS. Abbreviations: APU, Arbitrary Perfusion Units; ROI, Region of interest

Declarations of interest

None

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