Journal of Pediatric Surgery 50 (2015) 1388–1392

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Assessment of the role of LASER-Doppler in the treatment of port-wine stains in infants☆

Tessa Mermod [a], Oumama El Ezzi [a], Wassim Raffoul [b], Paolo Erba [b], Anthony de Buys Roessingh [a,*]

[a] Department of Pediatric Surgery, University Hospital Center of the Canton of Vaud (CHUV), Lausanne, Switzerland
[b] Department of Plastic and Hand surgery, University Hospital Center of the Canton of Vaud (CHUV), Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 28 August 2014
Received in revised form 22 December 2014
Accepted 24 December 2014

Key words:
Angioma
Doppler
LASER

ABSTRACT

Background: Port-wine stains (PWS) are malformations of capillaries in 0.3% of newborn children. The treatment of choice is by pulsed dye LASER (PDL), and requires several sessions. The efficacy of this treatment is at present evaluated on the basis of clinical inspection and of digital photographs taken throughout the treatment. LASER-Doppler imaging (LDI) is a noninvasive method of imaging the perfusion of the tissues by the microcirculatory system (capillaries). The aim of this paper is to demonstrate that LDI allows a quantitative, numerical evaluation of the efficacy of the PDL treatment of PWS.

Method: The PDL sessions were organized according to the usual scheme, every other month, from September 1, 2012, to September 30, 2013. LDI imaging was performed at the start and at the conclusion of the PDL treatment, and simultaneously on healthy skin in order to obtain reference values. The results evidenced by LDI were analyzed according to the "Wilcoxon signed-rank" test before and after each session, and in the intervals between the three PDL treatment sessions.

Results: Our prospective study is based on 20 new children. On average, the vascularization of the PWS was reduced by 56% after three laser sessions. Compared with healthy skin, initial vascularization of PWS was 62% higher than that of healthy skin at the start of treatment, and 6% higher after three sessions. During the 2 months between two sessions, vascularization of the capillary network increased by 27%.

Conclusion: This study shows that LDI can demonstrate and measure the efficacy of PDL treatment of PWS in children. The figures obtained when measuring the results by LDI corroborate the clinical assessments and may allow us to refine, and perhaps even modify, our present use of PDL and thus improve the efficacy of the treatment.

Port-wine stains (PWS) are congenital, low-flow vascular malformations of the skin. They are caused by dilation of capillaries whose diameter ranges from 10 to 150 μm. They are present at birth, and their diameter remains stable throughout life. Their color, however, changes over time from red to purple as the skin thickens [1,2]. They can invade and deform mucous membranes, the lips in particular. Depending on their localization, PWS can be accompanied by various syndromes. Sturge–Weber syndrome is characterized by cerebral nervous system and ocular anomalies associated to a PWS in the area of ophthalmic (V1) and maxillary (V2) trigeminal nerve (Fig. 1). Glaucoma is not always present at birth. The child may develop neurologic problems such as epilepsy and cognitive deficits caused by the presence of abnormal blood vessels on the brain surface, the loss of nerve cells and calcification of underlying tissue in the cerebral cortex. Klippel–Trenaunay syndrome (Fig. 2) usually affects one lower limb and it is characterized by the presence of a capillary malformation associated to bone and/or soft tissue overgrowth and superficial or deep venous system anomalies of the affected limb [3]. Bleeding angiokeratomas can affect the skin area interested by the capillary malformation. Intrapelvic extension with presence of sub mucosal venous varicosities leading to rectal bleeding is extremely rare [3]. Capillary malformations of the median line in the face are very common: they are commonly defined as nevus simplex, salmon patch, and angel kiss. They often discolor spontaneously within the first 1 or 2 years of life. They do not need to be investigated for underlying malformations.

The standard treatment for PWS is the pulsed dye LASER (PDL) [4,5]. LASER (Light Amplification by Stimulated Emission of Radiation) therapy is based on the principle that tissues absorb light. The light is produced by any kind of electrical, chemical energy or by another LASER. It will be amplified in a "gain medium", liquid for the PDL. This process of amplification is called "pumping". The final wavelength, determined by the gain medium, will defined the target of the LASER. The tissue may have different interaction with the beam, such as refraction of light, absorption, diffusion and/or transmission. The PDL itself produces a mechanical effect (photothermolysis) on vessels at a chosen

☆ Ethical approval given by the Faculty of Medicine of the University of Lausanne, Switzerland (CER: 271/11).

* Corresponding author at: Service de chirurgie pédiatrique, Centre Hospitalier Universitaire Vaudois (CHUV), CH −1011 Lausanne, Switzerland. Tel.: +41 21 314 31 26; fax: +41 21 314 30 76.
E-mail address: anthony.debuys-roessingh@chuv.ch (A. de Buys Roessingh).

http://dx.doi.org/10.1016/j.jpedsurg.2014.12.022
0022-3468/

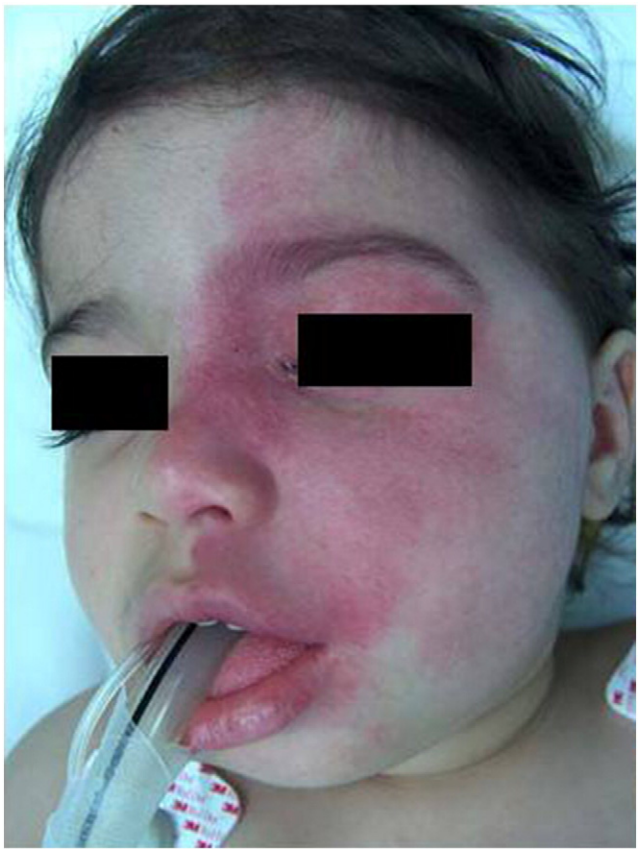


Fig. 1. The Klippel-Trenaunay syndrome.

wavelength of 595 nm. This effect will close the microcirculation of small blood vessels diminishing by this way the color (red) of the capillary malformation, becoming less visible.

In standard clinical practice, a PDL treatment must be repeated several times, at least three, with an interval of 6 weeks to 2 months between each session, in order to be effective and to cover the entire affected surface. The procedure may take place under general anesthesia, if necessary depending of the child's age, and metal lenses must be worn to protect the eye and avoid the risk of retinal lesions. Several 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 pulse, the cooling of the skin, and the time interval between each session.

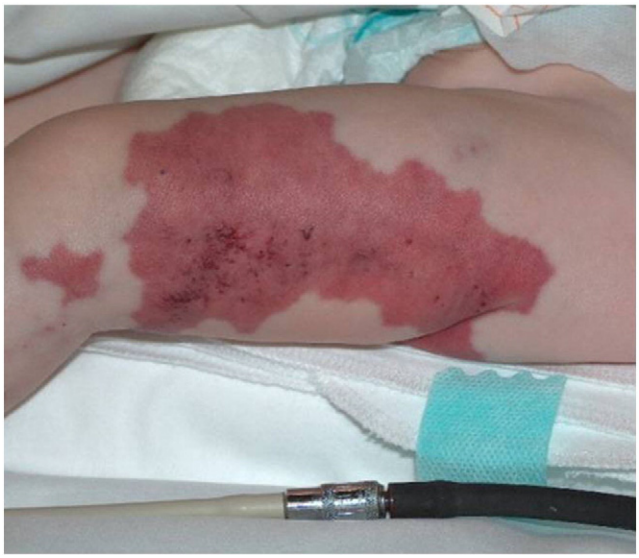


Fig. 2. Port-wine stain of the cheek, before the first treatment and after three.

Up to now, the success of a PDL treatment has been evaluated subjectively by clinical inspection and on the basis of digital photographs which show the progressive discoloring of the PWS as the treatment progresses. In order to be effective, the LASER must create a type of purpura lesion that disappears within 10 to 15 days, thus discoloring the port-wine stain. Talking with the patient's parents before a LASER session helps to determine whether the previous session was effective. At the same time, inspection of the skin by trained observers will determine whether there has in fact been a discoloration of the PWS. The knowledge of experienced personnel, used to dealing with this problem, is necessary to decide a possible modification of the PDL parameters, for instance its fluence or the length of the interval between two sessions.

Imaging by LDI is a new technology that allows the numerical measurement of cutaneous microcirculation. It makes it possible to translate in numbers the efficacy of PDL treatment on blood microcirculation. LDI uses the interaction of light and mobility of erythrocytes to visualize perfusion in the microcirculatory system. It produces not only a “digital photograph” of the surface of the skin under examination, but also a “Doppler photograph” that reflects tissue perfusion.

The aim of this paper is to show that LDI can be used to validate the current treatment of infantile PWS by PDL, quantify its efficacy, and even refine it by modifying certain parameters of our clinical procedure, in particular the fluence or the interval of time between each session.

1. Method

This prospective study was carried out over a period of 13 months, from September 1, 2012, to September 30, 2013, in the Department of Pediatric Surgery of the CHUV, where PDL therapy has been practiced for more than 15 years. All LASER treatments were performed under general anesthesia.

The criteria for inclusion in the study were: the presence of a PWS as defined by the International Society for the Study of Vascular Anomalies [6]; the age of the children at the time of the start of the PDL treatment (from 12 months to 6 years of age); a skin phototype I, II or III, defined according to Fitzpatrick's criteria [7]. The criteria for exclusion were as follows: contraindication of a general anesthesia; refusal by the parents (or the child) to participate in the study; skin phototype IV, V or VI.

Our PDL had a wavelength of 595 nm, with 0.45 to 40 ms duration of pulsation. We set our duration of pulsation to 1.5 ms. The initial flow of the laser was set at 7 J/cm^2 and raised by 0.5 J/cm^2 at each new session. The diameter of the laser handpiece was 7 mm. Cooling of the treated zone was set at zero. We followed the usual clinical protocol and performed three PDL sessions at 2 months' intervals.

The LDI (Aïmago® EasyLDI) used for our study belongs to the third generation of L-Doppler, developed by the biomedical optic laboratory of the Federal Polytechnic Institute of Lausanne (EPFL). It was approved in Switzerland for its planned use within our study (evaluation of microcirculation) [8–10]. It uses a camera that makes 7 × 7 cm (912 × 900 pixels) area at 4 Hz, and its 808 nm wavelength is set so as to be absorbed by HbO_2 and deoxyhaemoglobine. The resulting images appear as numerical photographs. The distance between the subject and the device is defined by a beam of light, and it is important to position the device perpendicularly to the area to be photographed (Fig. 3).

L-Doppler images were made before and after each of the three treatment sessions, one of the area of the lesion, and another of the contralateral healthy skin, in order to allow a comparison of the measurements for each individual patient. 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 images were analysed with the “EasyLDI Studio” (v1.0-v1.2), a program that allows a quantitative [apu] measure of the vascularization of the PWS. The [apu] is a unit of measurement

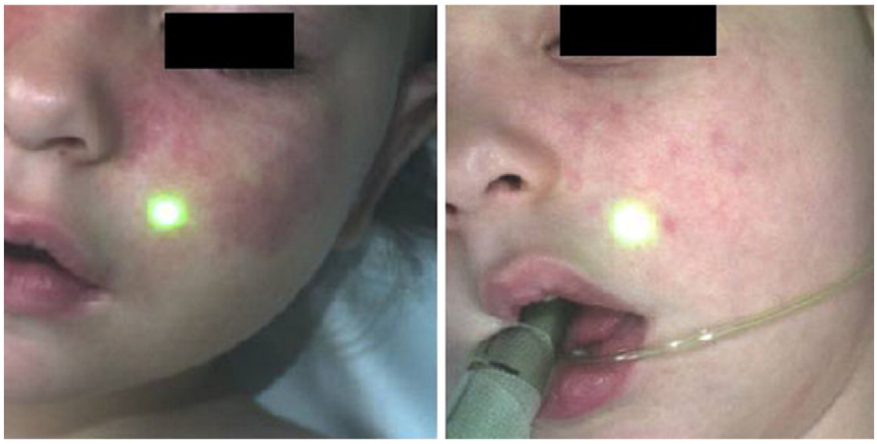


Fig. 3. The outline of the study.

that provides values of vascularization for each patient by comparing healthy skin (the standard) with that of the PWS.

The statistical analysis was done by the University Institute of Social and Preventive Medecine (IUMSP): 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 controlateral side). This gives a value >1 if vascularization is greater in the area of the PWS area, and <1 if vascularization is greater in the area of the healthy skin.

On each of the three visits, vascularization before and after treatment was compared 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.

2. Results

Our results are based on a sample of 20 children (eleven girls and nine boys) who presented with a PWS. They all had a skin photopype I. Their ages were as follows: five 1-year-olds, one 2-year-old, six 3-year-olds, two 4-year-olds, five 5-year-olds and one 6-year-old. Sixteen patients presented a facial PWS, and four a PWS on a lower member. There were associated syndromes in three children: two Sturge–Weber syndromes, and one Klippel–Trenaunay syndrome.

All parents agreed to participate in the study. The outline of the study is presented in Table 1. There were no complications linked to the anesthesia or to any other procedures of the study. Following the PDL procedure, two children (one girl and two boys) developed blisters after sessions 1 and 2, but these resolved spontaneously.

2.1. Global results

The data shown in a box plot (Table 2) show how the median vascularization decreased after each treatment. Vascularization observed during the fourth visit is globally weaker than before the treatments. Already after two sessions, median vascularization of the PWS (ipsilateral side) had been reduced to practically the same level as that of the healthy area (median value close to 1). After the third treatment, vascularization of the PWS was even weaker than that of the healthy area.

When we observed the vascularization of the PWS during the intervals between treatments, we noted that in spite of a global tendency to revascularization between treatments (Table 3), the level of vascularization of the affected ipsilateral side grew ever closer to that of he healthy contralateral side.

2.2. First visit

Median vascularization (p50) was 1.62 before treatment, and 0.98 after. Before treatment, the PWS side showed a 62% higher vascularization than the healthy side. After the treatment, this had been reduced to 2%. The IQR indicates the interquartile range. This difference is statistically significant according to the Wilcoxon test ($z = 3.920$; $p < 0.001$). Vascularization was reduced in all children after the initial treatment.

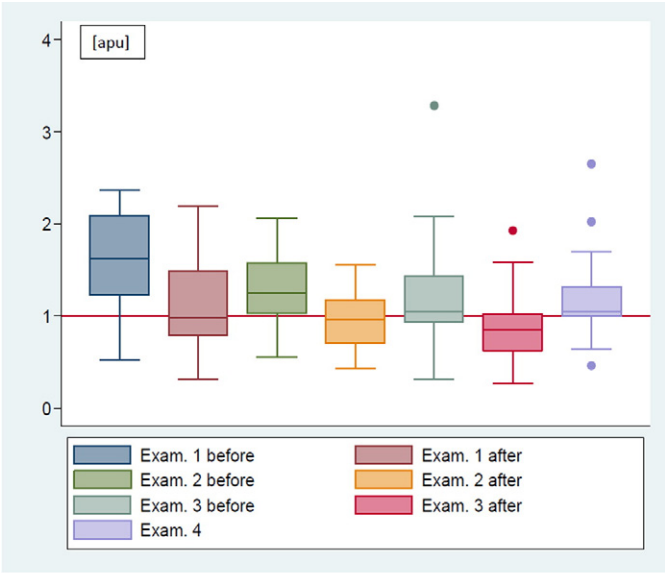
2.3. Second visit

Median vascularization was 1.25 before treatment, and 0.96 after. Before treatment, the PWS side showed a 25% higher vascularization

Table 1
The outline of the study.

	Examination 0	Examination 1	Examination 2	Examination 3	Examination 4
	Initial consultation	Treatment 1	Treatment 2	Treatment 3	Final examination
Information's study	X				
Signature/consent		X			
Case					
history		X			
Anamnesis		X	X	X	X
Vital signs before general anesthesia (T°, Blood pressure, heart rate, respiratory rate, saturation)		X	X	X	X
Local medical examination (color, blisters, itch, erythema)		X	X	X	X
Treatment (pulsed dye laser)		X	X	X	
L-Doppler imaging (before/after treat)		X	X	X	X
Survey of adverse events (AE)			X	X	X

Table 2
Evolution of the vascularization after three treatments.



[apu] is a unit of measurement that provides values of vascularisation for each patient by comparing healthy skin (the standard) with that of the port wine stain PWS.

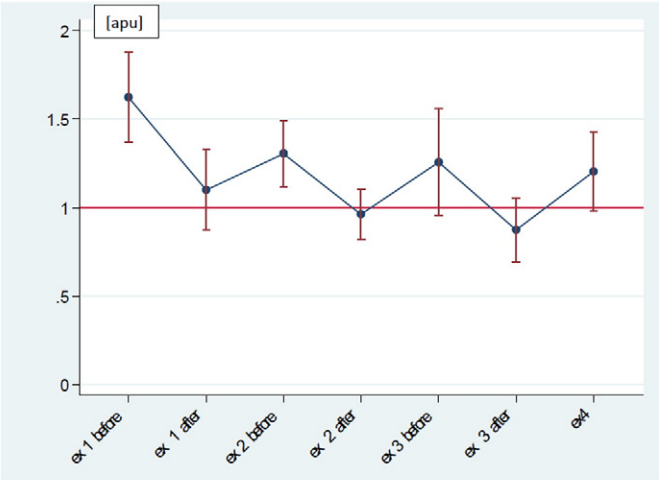
than the healthy side. After the treatment, this had been reduced to 4%. This difference is statistically significant according to the Wilcoxon test ($z = 3.920$; $p < 0.001$). Vascularization was reduced in all children after treatment.

2.4. Third visit

Median vascularization was 1.05 before treatment, and 0.85 after. This difference is statistically significant according to the Wilcoxon test ($z = 3.920$; $p < 0.001$). Vascularization was reduced in all children after treatment.

Statistics established according to the Wilcoxon test are identical for the three sessions: following each, vascularization was reduced (the test results reflect the number of subjects where vascularization was reduced or increased, and not the scope of the change).

Table 3
Revascularization between the treatments (2 months).



[apu] is a unit of measurement that provides values of vascularisation for each patient by comparing healthy skin (the standard) with that of the port wine stain PWS.

2.5. Evolution between the start of the first treatment session and the final consultation

Median vascularization of the PWS was 1.62 before the first treatment session and 1.06 at the final consultation (visit 4). This means that it was 62% higher than that of the healthy side at the start of the treatment, and 6% higher at the end of the treatment, i.e. a median reduction of 56%. This difference is statistically significant according to the Wilcoxon test ($z = 3.920$; $p < 0.001$) (Table 4).

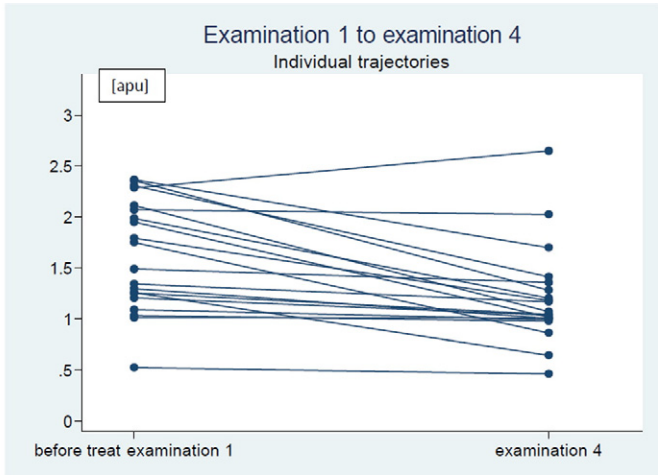
Globally, in all the children, vascularization of the capillary malformation was reduced between the first and the third PDL treatments. An individual analysis of each patient provides the following information: in nine patients (001AC, 002AD, 003AY, 005CM, 007CA, 010HE, 015ME, 016NS, 019SM), vascularization of the PWS was drastically reduced (a 60 to 108% improvement); in another nine patients (004BL, 006CA, 008FA, 009GE, 011KH, 012MC, 014MT, 017PL, 018RC), it was moderately reduced (5 to 28.5%); in one patient (020PO), vascularization was practically unchanged (0.1%); and in the last patient (013MM), it increased by 37%.

3. Discussion

This prospective study shows that LDI imaging makes it possible to confirm the efficacy of PDL treatment of PWS by providing numerical values for the results. On the first visit, median vascularization of the PWS before the first treatment was higher than that of healthy skin by 62%, and by only 2% after this treatment, and by 6% after the third treatment, i.e. a median reduction of 56%. This confirms that PDL reduces microcirculation by closing the capillary networks. The stability of the percentage of devascularization after each treatment can be explained by the fact the laser flow was increased by 0.5 J/cm^2 for the second treatment and again for the third.

The PDL treatment was performed on the entire surface of the PWS. One must remember that it is impossible to treat the whole surface of the PWS uniformly in one session because the laser beam is circular and works in spots. Consequently, a homogeneous treatment requires that the laser beam is applied with regularity to the area treated at each session and then be redirected between the spots during the other sessions.

Table 4
Results before the first visit and after treatment.



variable	N	p50	iqr	min	max
vasc1before	20	1.62	0.87	0.52	2.37
vasc1after	20	1.06	0.32	0.46	2.65

[apu] is a unit of measurement that provides values of vascularisation for each patient by comparing healthy skin (the standard) with that of the port wine stain PWS.

As regards the percentage of revascularization between each treatment session, we noted that on the second visit, perfusion of the ipsilateral side was 25% greater than that of the controlateral side (and 4% lower after the second treatment). Vascularization was thus 27% higher than at the end of the first treatment (from minus 2 to 25%). However, this value is very relative, when one considers that the impact of the laser not only causes closure of the treated vessels (photothermolysis), but also induces spasms in the adjacent vessels (thermal effect).

As far as vascularization is concerned, we noted a reduction between the values before the first treatment and before the second, the percentage of vascularization compared to that of the healthy skin having gone from 62 to 25%. The flow within the vascular capillary malformation was partially reestablished during the interval between two treatment sessions, which is why treatment needs to be repeated. We consider that since the effect of PDL appears to decrease over time, with a lower percentage of devascularization after each treatment, a stronger laser flow may be necessary for each consecutive treatment in order to increase its efficacy. The interval between two treatment sessions should be short enough to allow an efficacious thermolysis of the whole area and reduce spontaneous revascularization, while also allowing the recovery of the skin and the disappearance of purpura.

On the third visit, vascularization of the PWS was 5% higher than that of the healthy areas, and after the third treatment, it was 15% lower. Between the 2nd and 3rd treatment sessions, vascularization had increased by 9%, a lesser increase than between the 1st and 2nd sessions, when it had reached 27%. This is owing to the fact that the strength of the PDL flow was increased by 0.5 J/cm^2 after the first and second sessions. Reperfusion of the capillary vascular malformation does indeed occur during the intervals between sessions, but it decreases to the point where vascularization becomes equal to that of healthy skin.

An individual analysis of each patient shows that eighteen responded positively to the treatment, one did not respond, and one even suffered an increase in vascularization after the three laser sessions. According to several studies [4,5,11], various factors can explain the variations in patients' response to treatment: (1) the intensity of the color of the PWS before treatment plays an essential role in the response to PDL. The darker the red color, the more difficult it is to obtain a response to PDL, because the wavelength of 595 nm is linked to the red chromophore and not to the purple one. It is therefore advisable to treat the children at a young age, if possible already after 1 year of age or even 6 months, since the younger the child, the more monochromatic the red color, and the better the response. With time, the PWS tends to more deeply infiltrate the skin, and its color changes from red to purple. As the child ages, the red increasingly turns purplish, and the response to PDL will be less satisfactory. This decision should however be weighed against the risk of burning a younger child, whose skin is finer and more sensitive to the heat produced by the use of a laser. (2) For our study, we endeavored to limit the age of the children (from 12 months to 6 years of age) and chose skin phototypes I. (3) The anatomical localisation of the PWS also seems to play a role in the response to a laser treatment. The response is good on the neck, and less satisfactory on the members, especially the lower members, or on the cheeks, where the skin is thicker. The histological depth and diameter of the capillary vessels of the lesion decidedly play a major role: capillaries with a smaller diameter and more deeply seated respond less well to a PDL treatment [12].

The LDI is a useful machine in standard clinical practice. It provides us with a better knowledge of microcirculation [13]. This allows us to refine and improve treatment by modifying the PDL parameters and the length of the intervals between sessions in order to adapt to each individual case. This is a point on which we intend to pursue our research with a larger pannel of patients. Nevertheless, its use is not very practical, as the machine is large and unwieldy. The precision of the images depends on the skill of the operator, and this complicates its use for a study which spans several years. After the images have been made, they must then, in a second stage, be analyzed in order to provide information on the percentage of vascularization. This makes it impossible to have useful and immediate data during a PDL treatment session.

In conclusion, this study has allowed us to validate the standard clinical practice by giving us numerical information on the response to the PDL treatment of PWS. The use of LDI provides an additional and helpful evaluation of the standard clinical treatment of port-wine stains, even though its use requires a fairly long learning process, it is operator dependent, and cannot provide immediate data during treatment.

Acknowledgment

The authors are grateful to Annette Wagnière for reviewing the English text and the University Institute of Social and Preventive Medecine (IUMSP) at the CHUV for the statistical analysis (Dr Pierluigi Ballabeni).

References

[1] Mulliken JB, Glowacki J. Hemangioma and vascular malformations in infants and children: a classification based on endothelial characteristics. J Plast Reconstr Surg Nurs 1982;69:412–22.
[2] Kelly KM, Choi B, McFarlane S, et al. Description and analysis of treatments for port-wine stain birthmarks. Arch Facial Plast Surg 2005;7(5):287–94.
[3] Natterer J, Joseph JM, Denys A, et al. Life-threatening rectal bleeding with Klippel–Trenaunay syndrome controlled by angiographic embolisation and rectal clip. J Pediatr Gastroenterol Nutr 2005;42:581–4.
[4] Stier MF, Glick SA, Hirsch RJ. Laser treatment of pediatric vascular lesions. Port wine stains and hemangiomas. J Am Acad Dermatol 2007;58(2):261–85.
[5] Burns A, Navarri J. Role of laser therapy in pediatric patients. Plast Reconstr Surg 2009;124(1):82e–92e.
[6] Moure C, Reynaert G, Lehmman P, et al. Classification of vascular tumors and malformations: basis for classification and clinical purpose. Rev Stomatol Chir Maxillofac 2007;108:201–9.
[7] Sachdeva S. Fitzpatrick skin typing: applications in dermatology. Indian J Dermatol Venereol Leprol 2009;95:93–6.
[8] Erba P, Espinoza D, Koch N, et al. Flux Explorer: a new high-speed LASER Doppler imaging system for the assessment of burn injuries. Skin Res Technol 2012;18(4):456–61.
[9] Leutenegger M, Martin-Williams E, Harbi P, et al. Real-time full field LASER Doppler imaging. Biomed Opt Express 2011;2(6):1470–7.
[10] Serov A, Steinacher B, Lasser T. Full-field LASER-Doppler perfusion imaging and monitoring with an intelligent CMOS camera. Opt Express 2005;13(10):3681–9.
[11] Zaid F, Handley J, Handley JM. Treatment of pulsed dye LASER resistant port wine stain birthmarks. 2007;57(4):677–82.
[12] Motley RJ, Lanigan SW, Katugampola GA. Videomicroscopy predicts outcome in treatment of port-wine stains. Arch Dermatol 1997;133:921–2.
[13] Chen JK, Ghasri P, Aguilar G, et al. Overview of clinical and experimental treatment modalities for port wine stains. J Am Acad Dermatol 2012;67(2):289e–304e.