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ORIGINAL ARTICLE

Laser use in infantile hemangiomas, when and how

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ABSTRACT: Infantile hemangiomas (IHs) are proliferating embrional tumors which can stem from placented tissue and are constituted by endothelial cell hyperproliferation. The management of the IHs is always challenging for all the specialists because of the heterogeneous behavior of these lesions. The factors leading to an aggressive position are essentially these: the prevention or reduction of aesthetic risks, the prevention or treatment of ulcerated hemangiomas, the prevention or impairment of functional risks and pain, and the removal of life-threatening risks. The treatment of vascular lesions is one of the mostly sought and performed cutaneous laser procedures, and in the field of IH treatments the more used laser devices certainly are pulsed dye lasers. Early laser therapy is able to reduce the possibility that the lesion will reach its full size, preventing several complications, connected to the hemangioma's growth, and providing psychological relief for pediatric patients and their parents.

KEYWORDS: infantile hemangiomas (HI), laser therapy, pulsed dye laser (PDL), vascular lesions

Introduction

Hemangiomas

The classification of the vascular lesions can be made according to the onset of their appearance, separating them in congenital and acquired lesions. Congenital vascular lesions are set up by hemangiomas, constituted by endothelial cell hyperproliferation, and true vascular malformations, with normal endothelial cell turnover and vessel wall ectasies; this last group contains capillary malformations (port-wine stain (PWS)), venous malformations, arterial malformations, arteriovenous malformations, and lymphatic malformations. The field of the acquired vascular lesions includes forms characterized by various degrees of blood vessel ectasia as leg vein anomalies, venous lake, pyogenic granuloma, spider angiomas, cherry angiomas, and telangiectasias. Infantile hemangiomas (IHs) are proliferating embrional tumors which can stem from placented tissue; an interesting theory suggests that the hemangiomas originate from embolized placental cells to the fetus inside utero, a perfect place where these cells are able to lie and grow. This theoretical model is endorsed by the fact that the chorionic villus sampling can increase the risk for hemangioma up to 10 times in comparison to children of women who have not received this procedure. With this diagnostical technique, a fetal trophoblast is moved from placenta, inducing a placental embolization and a maternofetal transfusion. Another fact that advances this theory is given by the presence of GLUT-1 and other placental antigens, like the Lewis Y antigen, uniquely expressed in hemangiomas, and completely absent in other vascular

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malformations and tumors. After the birth the vascular endothelial rests, groups of embryonic cells, continue proliferating faster, if compared with what happens inside healthy blood vessels. With the time, in the postnatal phase, the growth of hemangioma is guaranteed by an imbalance of the up-regulated vascular endothelial growth factors and the down-expressed angiogenetic inhibitors. Hemangiomas, the most common benign tumors in childhood, have a prevalence estimated up to 10–12% in Caucasian infants, whereas they are less common in African and Asian children; the incidence is three times higher in women and especially in premature infants, because a lower gestational age and a lower birth weight are associated with the tumor development. The cutaneous hemangiomas can lie on the head and trunk in the most part of cases, 60%, only on the trunk in 25% of cases whereas the extremities are involved in 15% of cases. These vascular lesions are often superficial, 50–60%, but they occur also as mixed ones, 25–35%, or rarely as deep ones, about 15% of cases. Moreover, not only the soft tissue (cutis, subcutis, mucosa, submucosa) can be involved but the solid parenchymal organs (liver) and viscera, aerodigestive, and urogenital tracts may be affected too with relevant consequences. Despite a single lesion is the most common event among the children, it can happen that several hemangiomas develop in the meantime or at different times, the patient presenting a case of hemangiomatosis (1–3). The clinical history and the physical examination are usually enough for the diagnosis of the IHs, but other examinations can prove to be useful for the physicians; not so much the biopsy but the color-coded duplex sonography, which can show the lesion's presence and the details regarding its evolution phase, its potential complications, and other features. The magnetic resonance imaging and the computed tomography are so precious to exhibit details of lesions localized into the most critical topographic regions (4). The IHs are typically described for their common behavior; although they are by nature heterogenous, it is possible to predict their evolution, which is divided into four stages. The tumors are usually not present at birth, appearing immediately afterward, the first precursor lesion can coincide with an area of telangiectasia or an erythematous patch. During the initial phase, the lesion protrudes from the skin, infiltrating the surrounding tissues or being sharply demarcated, with a light reddish color. The second stage is given by a proliferation phase, during which the hemangioma increases its size, having an exophytic or endophytic subcutaneous growth, with a quick pace; the pathologist can see endothelial cell hyperplasia, mast cells, lobules, and a prominent basement membrane. The first 6–8 months of the patient's life are normally occupied by this proliferative period, even if deeper and larger lesions can need 12–24 months for developing. The third phase is named maturation one, the proliferation tends to stop, and the hemangioma reduces its dimensions and the color, which becomes no more red but grey in some parts; in this period, the histology changes too, showing large veins with a single-layer endothelium and it is not rare in the occurrence of ulcerations. The fourth and last period is the regression phase, during which the surface is flattened, grey, and the lesion is divided into smaller segments before disappearing. This last stage is usually achieved by the sixth birthday. The hemangioma completes the involution without any clinical traces in 50% of cases, in the other 50% it is possible to find residual changes like fibrofatty tissues, scarrings, or simply telangiectasias, wrinklings, and dyspigmentations; the smallest hemangioma easily heals without residuals, whereas the largest ones often leave significant changes. Despite the well-defined phases that describe the IH appearance, it is difficult to predict the length of a specific phase or the possible occurrence of functional impairments and complications (5,6).

Discussion

When they have to be treated

The management of the IHs is always challenging for all the specialists, dermatologists, plastic surgeons, and pediatrics; it is due to the heterogeneous behavior of the hemangiomas which shows a clear succession of stages but not always with the same duration. Also the potential appearance of aesthetic complications, functional impairments, and life-threatening events is hard to predict. The physicians have to balance between two different and opposite positions: a conservative one and an aggressive one. Because quick changes of the lesion are possible and frequent, the specialist has to be always ready to take a decision in one sense. Many IHs do not require any treatment, but only an active nonintervention based on a close observation of the patient made through periodical visits; this approach is due to the probability of a spontaneous and unproblematic involution of the lesion. It is very important to educate the patient's parents, who seek a treatment or an active intervention

often moved by a sense of guilt, and by the information received from the environment. This education helps them to better understand that the "wait and see" approach is the best one for that specific case. The dermatologist should closely monitor the hemangioma through measurements and photographs, not only with the aim to check the situation but also to provide the parents with an emotional support. The factors leading to an aggressive position are essentially these: the prevention or reduction of aesthetic risks, the prevention or treatment of ulcerated hemangiomas, the prevention or impairment of functional risks and pain, and the removal of life-threatening risks. The disfigurement, the aesthetic prejudice, and the consequent psychological stress in parents and patients when they grow up can justify the decision to initiate a treatment. Hemangiomas localized in areas likely to scar like nose, ear, lip, perioral and glabellar regions, medial cheek, as well as thick and large lesions of the face and the scalp have to be treated. The same active approach has to be followed in cases of exophytic, sessile, pedunculated hemangiomas appearing with a major dermal component because they regress with significant skin alterations and mainly fibrofatty tissues. Nasal tip hemangioma (Cyrano nose) can compromise not only the aesthetic appearance of the patient but also his self-esteem when he grows up. Another indication to treat comes from the ulcerated hemangiomas, which constitute 15–25% of all IHs. The ulceration, typically occurring 2–3 months after the birth, is very problematic because it is potentially complicated by infections, bleedings, and always painful for the patients, who could have difficulties in the movements. With the experience the dermatologist becomes able to anticipate this event, recognizing those hemangiomas with high risk to ulcerate: large segmental hemangiomas with a superficial component located on sites as neck, perineum, lips, and anogenital area. The hemangiomas must be treated also when they limit some important functions. Eyelid, periorbital and intraorbital, can hamper the orbit, leading to amblyopia, and through the compression of the eyeball to anisometropy and astigmatism; in some rare cases, it is possible to arrive to an optic atrophy due to the compression of the optic nerve. IHs that occurred in the ears can often cause hypertrophy of the ear growth, cartilage destruction, as well as foreclosure, ear infections, and deafness. Perioral and labial localizations may interfere with the suction, the food intake, and lead to lip deformations, abnormalities of the jaw, and irregular dental structures. All the large segmental hemangiomas must be considered to be treated because they can limit and decrease the first movements of the infant. The last and most important indication to treat such lesions is given by the necessity to remove the life-threatening complications. Airway hemangiomas have to be suspected in every case of neonates presenting noisy breathing, hoarse cry, and stridor; segmental hemangiomas, mainly those on the jaw, are often associated with these airway hemangiomas. In these cases, the cooperation among dermatologists, pediatrics, and otolaryngologists allows to achieve the best results as regards the management of these high-risk patients.

All the treatments

When the treatment is needed, the choice of the best one can depend on many factors, that the dermatologists must take into consideration the anatomic location, the size, the depth, the phase of the lesion, the age of the patient, the physician's experience, and the availability of a particular therapeutical approach. The procedures that let the physicians treat the IHs are several. (Table 1): they can be systemic or local, physical, mechanical, or chemical. The mechanical approaches to hemangiomas as the compression, the ligation, and the embolization are no longer used for the numerous lesions' recruitments. The field of physical procedures not only contains techniques no longer used for their side effects like the X-ray therapy (mutagenicity and carcinogenicity), techniques with controversial, modest results like the cryotherapy, but also effective and safe techniques like laser therapies. Surgery can be seen from two different points of view: early surgery and late surgery. Early surgery

Table 1. Several different approaches to infantile hemangiomas

Approach	Local	Systemic
Mechanical	Compression	–
	Ligation	
	Embolization	
Physical	Cryotherapy	–
	X-ray therapy	
	Laser therapy	
	Surgery	
Chemical	Topical steroids	Steroids
	Imiquimod	β-blockers
	Topical β-blockers	Interferon alpha (2A and 2B)
	Intralesional steroids	Vincristine

can have a relevant role during the proliferative phase for not drug-responding hemangiomas, for function-impairing hemangiomas, and for hemangiomas complicated by ulcerations and persistent bleedings. Late surgery can be useful to repair the cutaneous residua, typically observed after the hemangioma regression: dyspigmentations, fibrofatty tissues, scarrings, and wrinkles. The main risk correlated with the surgical management is the induction of a posthealing scarring, especially in such young children who start moving by their own and who can have a problematic cicatrization. The chemical approach, surely the most used by the dermatologists and the pediatrics, is mainly formed by different local and systemic drug therapies. The topical therapy contemplates the application on the lesion of potent steroids, clobetasol, or imiquimod, but these therapies are not deprived of side effects like cutaneous atrophy, striae, crusting, and ulceration, and mainly there are no clinical trials supporting their uses for hemangiomas, not having yet provided evidence of a good benefit/risk ratio. Recently, also the topical β-blockers have been inserted in this therapeutical field, showing some effectiveness only for small, superficial hemangiomas. Intralesional therapy with steroids, triamcinolone, can reveal efficacy but only for small tumors in the proliferative phase and with the cost of several side effects as bleeding, skin atrophy, and necrosis. Systemic therapy is surely the category of treatments more used for the IH management. Interferon alpha is indicated for hemangiomas, being an antiangiogenic drug, able to reduce the endothelial cells' proliferation through a downregulation of bFGF; but this agent is not so appreciated for the potential appearance of significant neurologic side effects, spastic displegia in 20% of patients, and also for flulike symptoms (fever and muscle aches), hematological and hepatic effects (neutropenia and higher level of transaminases), and depressive syndrome. Another antiangiogenic agent is vincristine, which works through the interference with mitotic microtubules and the apoptosis induction; it can be characterized, as happened with many chemotherapeutic drugs at high doses, by the potential presence of fatigue, constipation, abdominal pain, alopecia, immunosuppression, neuropathy, and hematological toxicity. The steroids (prednisolone, prednisone) have been the principal effective treatments since 1960 when they have been tested for this kind of vascular lesions for the first time. They certainly are efficacious if given during the early part of the proliferative stage, within 1–4 months of life. The main restriction to their employment is derived from the several and frequent side effects suffered by the treated patients: gastrointestinal irritability, gastroesophageal reflux, weight gain, cushingoid appearance, hypertension, delayed growth, adrenal suppression, immunosuppression, insomnia, irritability, acne, hair growth, and osteoporosis; even a case of hypertrophic cardiomyopathy has been described by Leaute-Lebraze et al. (7) The French author was the first to note the effectiveness of β-blockers for treating hemangiomas; the propranolol drug was casually chosen to contrast the hypertrophic cardiomyopathy and the tachycardia induced by a steroid-based therapy employed for an IH of the nose. Since that promising moment the oral β-blockers became the first-line therapy for the IHs, working through a vasoconstriction which implies the apoptosis of endothelial cells and the downregulation of vascular endothelial growth factors. Despite the initial and justified enthusiasm for this kind of drugs, several side effects have emerged with the time and a more diffuse use: wheezing, insomnia, agitation, and nightmares; the most relevant effects, which can limit or exclude its use in a part of patients with hemangiomas, surely are the hypoglycemia, hypotension, and bradycardia.

The role of lasers, when and how

The treatment of vascular lesions is one of the mostly sought and performed cutaneous laser procedures; data from the literature and the clinical experience confirm the relevant role of lasers in the congenital vascular lesion treatments (8–13). Naturally, all the benefits and the advantages that come from the use of these nonablative vascular lasers are connected to the exact clinical diagnosis, the experience of the physician, the choice of the adequate laser, and of the parameters to be used according to the features of that single clinical case. The application of laser technology in dermatologic field was started in the early 1960s by Dr Goldman. Goldman and the other first employers used ruby laser, and argon and carbon dioxide continuous wave lasers; between these argon laser developed a primary role as successfully lightening and removing some vascular lesions as PWS and hemangioma, but only with the cost of a high risk of scarrings and permanent dyspigmentations. Dermatological laser treatment was completely changed in 1983, thanks to the introduction of the selective photothermolysis theory by Anderson and Parrish, which defines how to localize thermal injury to the target tissue, minimizing the damage to surrounding areas by choosing the adequate wavelength of light that the chromophore inside the target tissue will

absorb. In the case of vascular lasers, the intended chromophore is mainly intravascular oxyhemoglobin and less deoxyhemoglobin and methemoglobin. Hemoglobin shows absorption peaks in the blue, green, and yellow bands of light (418, 542, and 577 nm) as well as in the near-infrared part of the spectrum (700–1100 nm), so laser devices emit wavelengths near these peaks to treat vascular lesions and to achieve a photomechanical and a photothermal damage of the target tissue. In the field of IH treatments, the more used laser devices certainly are pulsed dye laser (PDL), and in minor mode neodymium:yttrium-aluminum-garnet laser (14) and potassium titanyl phosphate laser (15).

Before beginning the laser therapy, a discussion with the parents should take place to examine the number of sessions estimated necessary and the possible outcome; sharing photographs of other treated patients with the parents can be extremely useful to give them more realistic expectations of outcomes. Once they agree with the decision of starting a laser treatment, they provide a detailed personal history of their son (clinical manifestations, health conditions, previous medications) and sign an informed consent. The young patients are usually treated receiving a range of five to seven treatments at two to six weekly intervals, depending on the current phase; growing hemangiomas are treated at 2–3-week intervals to avoid the regrowth between the sessions, while more stabilized lesions are normally treated at 4–6-week intervals. After several years of experience in the laser therapy, the authors have adopted Dermobeam 2000 (DEKA-M.E.L.A., Calenzano, Italy) as PDL device. We prefer these settings: wavelength of 595 nm, fluence of 5–6.5 J/cm^2, pulse duration of 0.5–1.5 ms, and spot size of 10 mm. Cooling device is always used during each laser session. Some hours before starting the treatment, patients are administered a few drops of sedative drug, diazepam (Valium 5 mg/mL, La Roche, Basilea, Switzerland), to reduce the agitation and the movements of the newborn. Parents are instructed to avoid sun and cosmetics during the immediate postprocedural periods and to apply cool compresses, emollient creams, and sunscreens until complete reepithelization. The daily application of cool wraps is prior to prevent the appearance of vesicles and blisters. An antibiotic ointment, gentamicin (Gentalyn 30 g 0.1, Schering Plough, Kenilworth, NJ, USA), is also applied to the target areas for 7 days after each laser session, avoiding potential cutaneous infections and crustings. Photographs are taken with a Canon digital camera and a polarized flash (Anthology system, DEKA-M.E.L.A.) before and after each treatment, 6 and 12 months after the final treatment. The pictures have been standardized using the same camera, shooting setting, twin flash, ambient light, and chin holder to guarantee the same distance and to observe in the best way the results achieved.

Our choice always falls on PDL, which is considered the best tool to treat this kind of lesion by the most important laser practitioners. PDLs are often employed to treat IHs for three different indications: erasing the residual vascular changes after involution like telangiectasia, accelerate healing in ulcerated hemangiomas, and the proliferative stage of IH. PDL has shown how it can be useful in reducing pain, preventing infections and bleedings by facilitating the reepithelization of the ulcerated hemangioma. Although it is considered always efficacious for the first two aims, it is still controversial its exact role during the proliferative phase of the hemangioma's growth. Not so much is known about the real mechanism triggering hemangioma regression induced by the laser, and it is hard to think that it can be simply explained by the vascular occlusion as in other lesions; also because in the early and proliferative stages there are no significant vascularization and thus the chromophore lacks. The tissue reaction to the laser treatment is not only described by a microvascular destruction but with a more presumable induction of apoptosis secondary to an inflammation process. The lesions should be ideally treated when they appear only through a precursor as early macular stain within the first weeks of age; the most skillful laser practitioners recommend the treatment of an early macular lesion with the aim to halt or reduce the growth. Also using low-dose parameters it is possible to diminish the growth, preventing potential complications; unfortunately, this ideal approach is often not possible because it is rare that the dermatologists visit the patients at such an early phase, and when the newborn arrives to a specialized center his lesion is already easily entered into a proliferative phase; for this reason, we recommend a dermatological visit and an active intervention as soon as possible. An early laser approach is not only more effective and successful (FIGS. 1A,B, 2A–C) but also more easily manageable for the physicians who have a newborn as patient; the treatment of the youngest newborn in comparison to an older boy is more advantageous to do, because this kind of patient requires less physical restrictions and their movements are more easily limited. Another advantage of a precocious laser therapy is due to the size of the hemangioma; smaller lesion dimensions means a reduced number of necessary

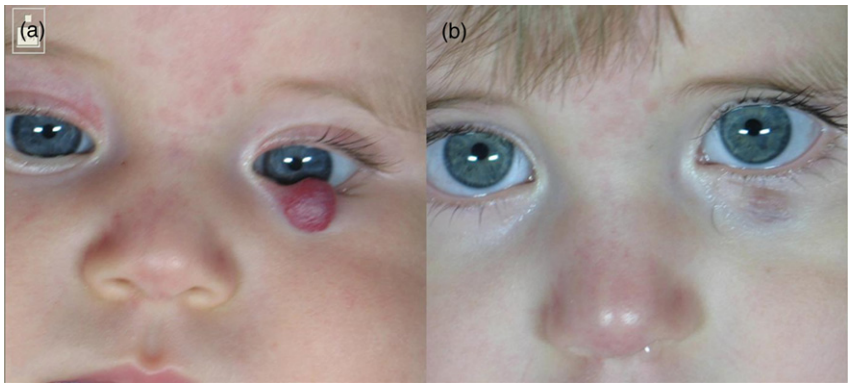

FIG. 1A. **(a) A newborn with hemangioma localized on the lower eyelid; it was able to induce a marked strabismus. (b) After four treatments with pulsed dye laser, there was no more lesion and neither strabismus.**

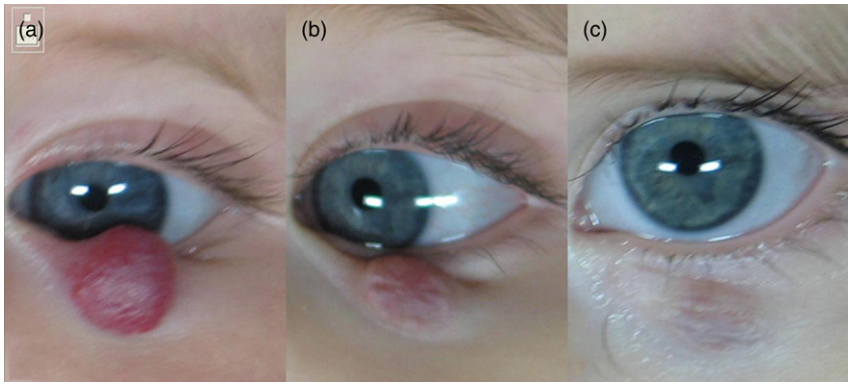

FIG. 2. **A particular of the same patient in FIG. 1. (a) At baseline. (b) After two pulsed dye laser (PDL) treatments. (c) After the fourth and final PDL treatment.**

FIG. 3. **(a) Hemangioma disfiguring the right cheek at baseline. (b) Only through three pulsed dye laser (PDL) sessions the lesion disappeared.**

sessions to contrast the growth of this vascular congenital lesion. It implies a lower loss of time and money for the patient's parents, because the number of sessions can be fewer; moreover, these economical and time savings can be considered as a valid tool to build up the compliance of the parents to these treatments, which show their efficacy not immediately at the first sessions. An early therapy has also another relevant meaning because it is able to limit and minimize the psychological distress and the somatopsychic rebound due to the presence of a large, disfiguring lesion often placed in visible areas (FIGS. 3A,B, 4A,B). The benefits guaranteed not only to the patient but mainly to the parents, who seek an emotional support, are easily understandable. Before the introduction of such laser technique, a more diffuse "wait and see" policy was much better explainable because the other effective approaches were often accompanied by many significant side effects; today the dermatologists can hold a tool which is not only very successful in selected cases, but also completely safe and free of unpleasant side effects. In the past, the laser systems to treat the IHs were victims of a

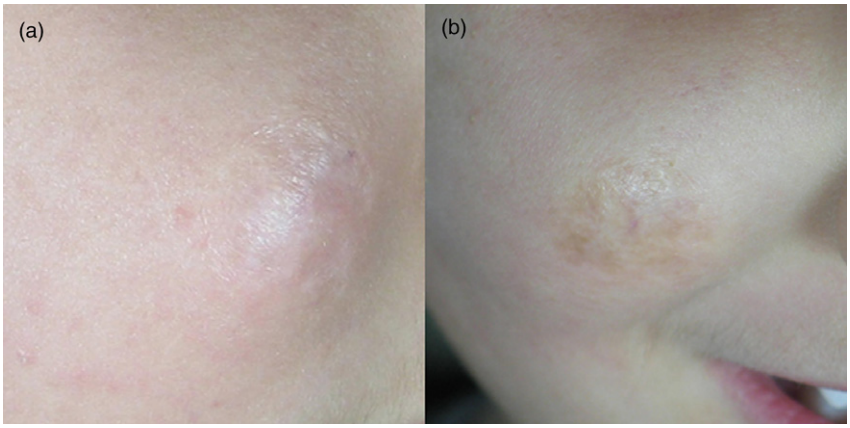

FIG. 4. **(a) A particular of the FIG. 3B, disappearance of the lesion. (b) The same treated area with a transient hyperpigmentation due to sun exposure.**

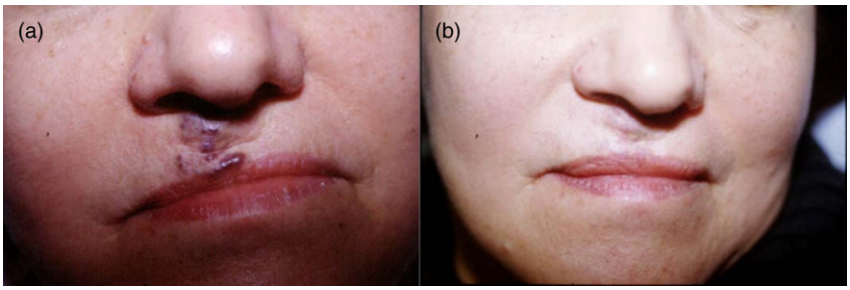

FIG. 5. **(a) Hemangioma of the perioral area at baseline. (b) The lesion was treated using neodymium:yttrium-aluminum-garnet laser only with a remarkable delay at adult age. The modest results with scarrings, due to this delay, are easily observable.**

diffuse prejudice from the physicians who showed some suspicions about the real efficacy of this technique. An overreporting of adverse outcomes, due to the lack of an advanced laser technology and the delay of treatment (FIG. 5A,B), has worsened the judgment of many pediatrics and dermatologists in front of this laser application. Nowadays, the optimization of the laser devices, the settings, and the parameters has permitted a safe employment of higher fluencies, better targeting the deeper structures (16,17). The choice of longer pulse widths and wavelengths and the use of cooling devices have let the dermatologists to use higher fluencies with faster and complete results and less epidermal damages (FIGS. 1B, 2C, 3B) (18–21).

Conclusions

Early laser therapy is able to reduce the possibility that the lesion will reach its full size; in this way it can prevent several complications connected to the hemangioma's growth and provide psychological relief for pediatric patients and their parents during the first years of life. For these reasons, we suggest an early laser intervention given the minimal risks associated and a high percentage of success.

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