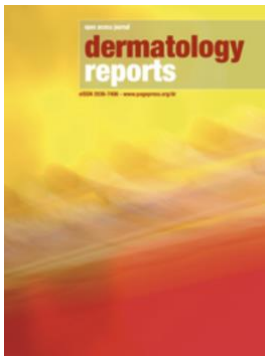

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Treatment of keloids with pulsed dye laser in a pediatric population

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Abstract

Several studies confirmed the role of Pulsed Dye Laser (PDL) in successfully treating keloids. To our knowledge, this is the first study conducted entirely in children (<14 years old).

Case notes and photographic records of 16 pediatric patients with keloids treated with PDL at our centre between 2012 and 2019 were reviewed. The red tone of the lesion before the first treatment, number of sessions, clinical improvement, and the evaluation of the satisfaction of patients have been reported.

An excellent clearance has been achieved in 7 out of 16 (43.8%) cases, a good-moderate clearance in 7 patients (43.8%), and a slight clearance in 2 patients (12.4%). No patients detected absent or low results. A total of 13 out of 16 patients (81.2%) were satisfied. Lesions of higher red-tone grades were able to take advantage of multiple treatment sessions.

PDL is an effective treatment of keloids in the pediatric population, characterized by a good safety profile and high satisfaction. We observed good results treating the active remodeling lesions with a higher red tone. These data have to be confirmed with further studies in a larger set of pediatric patients.

Introduction

An injury of the skin does not always lead to a normal, smooth skin surface. Occasionally, the skin reacts with a proliferation of fibrous tissue. When this reaction is overzealous, the result is a hypertrophic scar or keloid.[1] By definition, hypertrophic scars do not overpass the boundaries of the original wound, keloids extend beyond. Keloids have a functional, aesthetic, or psychosocial impact on both adult and child patients.[2] It is estimated that 4.5-16.0% of people suffer from keloids or hypertrophic scars, especially individuals of African, Hispanic, or Asian descent. Although keloids can develop at any age, patients between 10 and 30 years old are most often affected.[3] Therefore, children represent a relevant part of this sensitive population. Keloids are usually difficult to eradicate and recurrence is common, even with combination therapy. Treatments include surgery, laser therapies, intralesional or topical therapy: corticosteroids, 5-fluorouracil, bleomycin, interferon, imiquimod, compression, cryotherapy, and radiation.[4] Laser technology has introduced new ways to manage keloids improving aesthetic outcomes and decreasing recurrence.[5] Laser therapy with dye-lasers having wavelengths overlapping the absorption spectrum of oxyhemoglobin, 595 nm, has been proposed for treating keloids. This technique is considered to be the first choice of laser for treating capillary vascular malformations and residual telangiectasias of infantile hemangiomas, using a selective photothermolysis mechanism.[6] Current indications of this technology have been extended to keloids with a vascular involvement due to the thermo-induced lysis of collagen which promotes the remodeling of the tissue, linked to the reduction of Trasforming Growth Factor-B1 (TGF-B1) and Connective Tissue Growth Factor (CTGF).[7]

The aim of the present study was to describe our clinical experience with pediatric patients with keloids, and report the clinical outcomes of the Pulsed Dye Laser (PDL) treatment used as front-line therapy.

Materials and Methods

In this case series, we observed 16 pediatric patients with keloids who underwent PDL over the past 8 years (from January 2012 to December 2019) in the pediatric dermatology Unit of the Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. We did not include in the study patients who had undergone other therapies in the previous six months (*e.g*., topical corticosteroids). A dermatologist (RC) performed all laser procedures in the multiuse outpatient facility in the pediatric clinic. An anesthetic cream (2.5% lidocaine, 2.5% prilocaine; Emla®, AstraZeneca S.p.A., Milan, Italy) was applied one hour before laser therapy, and topical gentamicin was applied afterward. A flash-pumped dye laser was adopted performing a double passage treatment in the same session, 8-9 J/cm2 10 msec followed by 8-9 J/cm2 1.5 msec, with impulse overlapping. Dye laser sessions were performed every three months and up to a maximum of seven sessions on the basis of the clinical evolution of the lesions. The use of topical corticosteroid creams was not allowed during the laser treatment period. Laser treatments were stopped when there was a complete regression of the lesion at the clinical revaluation or when an esthetic functional improvement considered satisfactory by the physician and patient/its relatives was reached. Results evaluation was done 6 months after the last laser session, performed by the same clinician (RC) and by using photographic material, done pre-, post-, and during treatment with a professional camera. Results were obtained by ranking the clinical improvement into four categories, judging scar colour, height, pliability, and texture: 1 no or slow results (0-25% of the lesion area improved), 2 slight improvement (25-50% of the area cleaned), 3 moderate-good improvement (50-75%) and 4 excellent improvement (75-100%). Complete lesion resolution was considered as the absence of clinically detectable lesions/tumefaction and intact skin. Patients and their relatives were also asked for a subjective evaluation declaring if dissatisfied or satisfied with the perceived results at the end of the treatments, as experienced in the study conducted by Cannarozzo *et al*.[8] Furthermore, we registered the color of the keloid before treatments using a spectrum red- scale defined as: red-scale equal to 1 is defined as “not red”, 2 as “slightly red”, 3 as “intensely red”, 4 as “almost purple”. A follow-up call was conducted 5 years after the last visit,

asking the patient and/or family whether the lesion was stable, worsening, or further improving.

Statistical analysis

We performed descriptive analyses by tabulating frequencies and percentages (categorical variables), mean and median values, Standard Deviations (SD), and Interquartile Range (IQR) (continuous variables).

Given the descriptive purpose only of the present case-series study, no formal statistical comparisons between groups were performed.

Results

A series of 16 hypertrophic scars and keloids pediatric patients treated with PDL was described in Table 1: 11 males (69%) and 5 females (31%), with ages ranging between 2 and 14 years (mean age 8.4 years, skin type I-IV). Most of the patients were Causasian (13/16). Lesions have been identified at the abdomen (4/16), lower limbs (5/16), upper limbs (2/16), presternal region (3/16), and head (2/16). Lesions were the result of surgery (3/16), superficial trauma (5/16), chickenpox (2/16), and localized burns (6/16) (Table 2). Multiple lesions were detected in 2/16 cases consequent to chickenpox.

Patients have been classified, at the clinical pre-treatment evaluation, on the basis of the red tone on a rating ranged between 1 to 4. Red-tone 1 (no red-tone) has been reported in 1 patient (6.3%), red-tone 2 (slightly red) in 6 (37.5%), red-tone 3 (intensely red) in 8 (49.9%), almost purple (red-tone 4) in 1 out of 16 children (6.3%). Patients received the laser therapy at least once (ranging between 1 and 7), with a mean number of laser sessions equal to 3.25 (SD=1.8).

Clinical improvements at the end of treatment were reported: an excellent clearance has been achieved in 7 out of 16 (43.8%) treated patients, a good-moderate clearance was noticed in 7 patients (43.8%), and 2 patients (12.4%) obtained slight clearance. No patients detected absent or low results.

The results of self-evaluation on treatment satisfaction were reported: 13 patients (81.2%) were

satisfied and 3 (18.8%) were not satisfied with the final treatment results. Important side effects as scars, crusts, atrophy were not noticed in all treatments. Figure 1 shows the successful treatment of the pubic area.

The correlation between the number of sessions for laser therapy and the clinical level of improvement was considered (Table 2) even if based on a few patients. Globally, a very light correlation was reported: the mean number of laser sessions for patients showing an excellent was 3.7 compared to 3.4 for patients with moderate improvements. The difference in terms of the mean number of laser sessions was higher when patients were compared on the basis of the red-colour during the first visit. Patients with a second grade of red colour during the first visit received an average number of laser sessions equal to 2.3 compared to 3.2 of patients with a third grade of red-colour. Among 8 patients with a third grade of red-colour, 5 patients reported a complete resolution. The mean age of the patients with complete resolution was 10.3 compared to 6.9 years of patients with important improvements. Five years after the last visit, 10/16 (62.5%) patients reported stability of the lesion, 4/16 (25%) reported further improvement, and 2 out of 16 reported worsening.

Discussion

During the past decades, advances in laser technology have made laser therapy one of the reference modalities for the treatment of hypertrophic scars and keloids. Multiple studies using the PDL have demonstrated improvements in scar erythema, pliability, height, and texture, although a specific pediatric case series is lacking.[8-13] Early PDL treatment of scars after skin grafts has shown efficacy in the prevention of keloids at a pediatric burn hospital.[14] Our clinical pediatric experience and other reports allowed us to treat patients with keloids using PDL, largely appreciated in treating vascular malformation and infantile hemangiomas.[6]

Different theories explain the mechanism of action by which PDL irradiation improves the proliferative scars. Laser-induced tissue hypoxia leads to neocollagenesis: the heating of collagen

fibers, the dissociation of collagen bonds, the subsequent realignment of collagen fibers and the release of histamine influence fibroblast activity.[9,10]

Inflammation is the first phase of wound healing. Proliferation and scar maturation are the second and the third overlapping subsequent phases.[15] The initial inflammatory phase has received considerable attention from researchers interested in improving the appearance of healed skin injuries.[16] Early workers noted that scarless healing is correlated inversely with inflammatory response.[17] In fact, inflammatory cells provide or activate signals that promote granulation and fibrosis.[16] Kuo *et al*. performed biochemical studies showing a decrease in the induction of TGF-B1. An upregulation of Matrix Metalloproteinase (MMP) expression has been reported in keloid tissue treated with a 585 nm PDL.[18]

Using the characteristics of PDL in treating keloids we obtained several clinical improvements. We observed that a high number of laser treatments was linked to a better outcome; in fact, the mean number of laser sessions was 3.7 for excellent improvement compared to 3.4 leading to moderate-good improvements. Analysing the grade of red colour we observed a better outcome in treating with laser-active lesions, characterised by a higher red tone. Comparing patients with a second grade of red tone (average number of laser sessions 2.3) with patients with a higher grade (third) of red tone (average sessions 3.2) we observed the possibility of treating with several sessions the keloids characterised by active remodelling phase obtaining a better outcome. The results obtained in this paediatric population could underline the importance of treating the lesions as soon as possible, even at an early age without waiting for adulthood or aesthetic consciousness.

Currently, the mechanism by which the PDL achieves the observed clinical outcome is debated. Inhibition of TGF-B1 and Platelet-Derived Growth Factor (PDGF), stimulation of MMP and IL-6 for matrix degradation, could be PDL-induced effects modifying microvasculature and cellular activity, explaining the results obtained.[19,20]

As reported by Nouri *et al.* there is no difference in short (450 μs) and longpulse (1.5 ms) 585-nm PDL in scar improvement.[20] In all the 16 cases reported it has been performed a double passage in

the same session, 8-9 J/cm2 10 msec followed by 8-9 J/cm2 1.5 msec, with impulse overlapping, in order to obtain a markable purpura effect. The aim of this modality of treatment is to convey an important part of energy through a double passage, using the effect of thermo-induced lysis of collagen, which promotes the switch from collagene 1 to collagene 3 and remodeling of the tissue.[7] The collagen switching is due to the increase of Heat Shock Protein (HSP) 70 and HSP 47 mediated by the laser impulse and promotes tissue repair[21]. In order to increase the lysis we combined a very long pulse (10 ms) with a second passage with a 1,5 ms pulse and used a 10 mm spot size to promote the scattering of the impulse.[8]

Collecting the grade of satisfaction of the little patients' families' we observed 13/16 patients (81.2%) were satisfied with the results and with the treatment modality. This was consistent with other studies conducted[8] and underlines the safety of use in children.

Dissatisfaction was probably due to the laser procedure itself; in fact, it was necessary to keep kids quiet avoiding movements, with eyes closed for few minutes, in order to perform the best treatment.

With this case series, we reported our experience in treating keloids in children using PDL. However, there are some limitations. Firstly, it is a retrospective monocentric report and the clinical revaluation at the end of the treatment wasn't blinded. Secondarily, the small sample of patients who underwent laser treatment cannot lead to statistically relevant conclusions.

Conclusions

Multiple factors are responsible for the appearance of keloids and hypertrophic scars in a pediatric age. PDL has been found to be safe and effective in childhood. We observed that to obtain the best outcome, it is desirable to undergo laser therapy treatment during the active remodeling phase of keloids, even if this therapeutic decision involves treating patients in an early stage of life. To confirm these preliminary data on safety and effectiveness, larger studies have to be carried out.

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Figure 1. A typical keloid caused by an injury at the baseline (A). The first promising result was after two pulse-dye laser sessions (B). The same lesion after the third session and a 3-month follow-up (C).

Table 1. Patients' characteristics and treatment information among 16 pediatric patients (Italy, 2012-2019).

Gender	**N**	**%**
Female	5	31.3%
Male	11	68.7%
Age (Years)	**N**	**%**
2-6	5	31.3%
7-10	6	37.4%
11-14	5	31.3%
Mean (SD)	8.4	4
Median (IQR)	9	7.5
Red-tone	**N**	**%**
1	1	6.3%
2	6	37.5%
3	8	49.9%
4	1	6.3%
Laser sessions	**N**	**%**
1	4	25%
2	2	12.5%
3	3	18.8%
4	2	12.5%
5	4	25%
7	1	6.2%
Mean (SD)	3.25	1.8
Median (IQR)	3	3.3

IQR, Interquartile Range; SD, Standard Deviation

Table 2. Patients' characteristics, treatment information, improvement, and satisfaction obtained from each patient (Italy, 2012-2019).

Patient ID	Gender	Age (years)	Ethnicity	Localization	Trigger	Red tone (1-4)	Laser sessions	Grade of improvement (1-4)	Satisfaction of patients and families (yes/no)
1	M	13	Caucasian	Head	Surgery	2	3	4	Yes
2	M	12	South-American	Presternal region	Chickenpox	2	5	3	Yes
3	M	9	African	abdomen	Chickenpox	1	5	3	Yes
4	M	10	Caucasian	Lower limb	Surgery	4	5	4	Yes
5	F	13	Caucasian	Abdomen	Trauma	2	2	3	Yes
6	F	13	Caucasian	Lower limb	Burn	3	1	4	Yes
7	M	9	Caucasian	Lower limb	Trauma	2	1	2	No
8	F	5	Caucasian	Upper limb	Burn	2	4	3	Yes
9	F	2	Caucasian	Upper limb	Burn	3	2	3	Yes
10	M	4	African	Lower limb	Trauma	2	1	2	No
11	M	7	Caucasian	Head	Surgery	3	5	3	Yes
12	M	10	Caucasian	Abdomen	Trauma	3	3	4	Yes
13	F	14	Caucasian	Presternal region	Trauma	3	3	4	Yes
14	M	3	Caucasian	Upper limb	Burn	3	4	4	Yes
15	M	2	Caucasian	Presternal region	Burn	3	1	3	No

16	M	9	Caucasian	Abdomen	Burn	3	7	4	Yes