NEW DERMATOLOGICAL INDICATIONS FOR PULSED DYE LASERS

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ABSTRACT

Laser therapy has been classically focussed on three different chromophores: haemoglobin, melanin, and water, based on selective photothermolysis theory. Despite the fact that therapy is evolving with the introduction of multiple new wavelengths and the description of more therapeutic targets, some laser devices, such as the pulsed dye laser (PDL), are still relevant in our clinical practice. Based on a redefined concept of selective photothermolysis, PDL seems to be a promising tool for the treatment of skin conditions different to vascular lesions. Its role in viral infections, inflammatory diseases (such as acne or systemic lupus erythematosus), scars, and basal cell carcinoma is reviewed in this paper.

Keywords: Selective photothermolysis, pulsed dye laser (PDL), vascular laser, chromophore.

INTRODUCTION

For years, dermatological laser therapy has targeted three classical chromophores (haemoglobin, melanin, and water) that have allowed the removal of hair follicles as well as the successful treatment of acne scars, some signs of skin ageing, and various vascular and pigmented lesions.[1] Although therapy is evolving with the acquisition of multiple new wavelengths and the description of further therapeutic targets, laser devices such as the pulsed dye laser (PDL) are still present in our clinical practice. Moreover, their role is even more relevant due to the increase in therapeutic indications.

The classical concept of selective photothermolysis[2] establishes the relationship between one tissue target and a fixed wavelength and pulse duration. This theory implies a single correspondence between a laser device and a medical indication. The tissue effect of lasers is well understood. On the one hand, the specific thermal effect on the target chromophore allows for the treatment of vascular lesions with PDL, or achieves hair removal with melanin-absorbed long pulsed lasers. On the other hand, lasers with very short pulses and high energy reach a specific mechanical effect on the target, such as Q-switched lasers for tattoo removal.[3]

Nowadays, the classical theory of selective photothermolysis has been redefined, because one laser target can be applied in multiple indications.[1] Pulse durations are changing, and longer pulses are used in order to target larger structures and to preserve the epidermis. The multi-pass technique (also called 'pulse stacking')[4] enables a greater target destruction, thus preserving laser selectivity. With pulse stacking, two or three pulses are applied to the same cutaneous area immediately after the preceding pulse. Cumulative heating may result in greater overall capillary heating and vessel damage than is achievable from a single high-energy pulse. Epidermis thermal relaxation time is shorter than that of dermal capillaries, and pulse stacking is able to apply cumulative heating to the dermal capillaries, allowing epidermal cooling between pulses.[5]

Larger spot diameters are also available, thus allowing deeper penetration and less scattering. Cooling systems play an important role in our daily practice because they are essential in protecting the epidermis during laser treatment.[6] It is also interesting to highlight the photoinduced modulation of biological functions triggered by lasers: cytokine activation, collagen remodelling, growth factor release, activation of

inflammatory cells, and effects on microvasculature and angiogenesis.[7]

In 1966, Fritz P. Schäfer discovered the dye laser.[3] Since then, PDLs are routinely used in dermatology for the treatment of vascular malformations due to their high haemoglobin absorption.[8] Over time, and according to the redefined concept of selective photothermolysis, the number of PDL indications has grown in a noteworthy manner.[9]

PULSED DYE LASER IN NON-VASCULAR LESIONS

Viral Infections

In the case of viral warts, the PDL mechanism of action is based on laser interaction with wart vasculature and the thermal injury to human papillomavirus.[9-11] It has also been postulated that the resulting tissue damage is followed by a cell-mediated immune response with upregulation of lesional interleukins 2 and 4. It is well known that both play a role in the fight against viral infections.[11]

There are numerous reports in the literature of different treatment protocols and a variable rate of success.[9] In 2008, Park and Choi[10] described a case series of 120 patients with viral warts treated with PDL. Fluences between 9 and 9.5 J/cm^2 and short pulses were used. The treatment was performed every 2 weeks with an overall clearance rate of 49.5% and a better response in flat and periungual warts. Most patients experienced tolerable, minimal-to-mild pain, whereas crusting, scarring, or pigment changes were not significant. A recent article from Sparreboom et al.[11] evaluated the effect of PDL at higher fluences (12.5–15.0 J/cm^2). A retrospective study of 227 patients was performed, which represents the largest report available in the literature with respect to PDL treatment for recalcitrant viral warts. Despite its retrospective nature, the overall efficacy reported in the study was 86%. The authors conclude that PDL therapy is an effective and safe second-line treatment for recalcitrant viral warts.

In our experience, PDL represents an excellent treatment option for recalcitrant warts, and we employ high fluences as has been previously described (Figure 1).

Facial flat warts have also shown a good clinical response to PDL treatment. They are not only a contagious viral disease, but also a cause of distressing cosmetic problems. Their management can represent a therapeutic challenge because no monotherapy has been proven to achieve complete remission in every case. In our experience, treatment with PDL seems to be a promising therapeutic option. We performed a prospective study in 32 patients who were treated with PDL at a wavelength of 595 nm, a laser energy density of 9 or 14 J/cm^2 with a spot size of 7 or 5 mm, respectively, with a pre-cooled airflow skin cooling system at its highest setting and a pulse duration of 0.5 milliseconds. A complete response was noted in 44% of patients and an excellent response was observed in 56% of cases with 1-year follow-up. Only four cases of recurrence were observed. No significant side effects were reported, except intense temporary purpuric response.[12]

In the case of molluscum contagiosum,[9,13,14] this poxvirus infection has also been treated with PDL in a satisfactory way. Although spontaneous regression of this condition has led to proposals to leave lesions to spontaneous resolution, sometimes the infection is recurrent and widespread. The mechanism of action is attributed to vascular damage and a nonspecific thermal effect, with an increase in mast cells and T lymphocytes also involved. Isolated case reports in immunosuppressed patients are described in the literature, and the largest case series to date includes 76 patients.[14] The authors employed 585 nm collagen remodelling, double flashlamp excited pumped dye laser (ED2000®, Deka MELA, Calenzano, Italy) with the following parameters: spot size 5 mm, fluence 2–4 J/cm^2, with a short pulse duration of 250 microseconds in all cases. At higher fluences (3.5–4.0 J/cm^2), the success rate reached 98%. This response was seen with one or two treatments and no relevant adverse events were described (in most cases transient hyperpigmentation was present after treatment). PDL collagen remodelling was used due to better tolerance (due to a shorter pulse duration) and because it uses lower fluences, thus enabling the treatment of paediatric patients with a large number of lesions.

In our practice, conventional PDL treatment is also effective in treating molluscum contagiosum infection. Although it is more expensive than conventional treatments, it is a good alternative for the management of difficult areas, such as the periocular region (Figure 2).

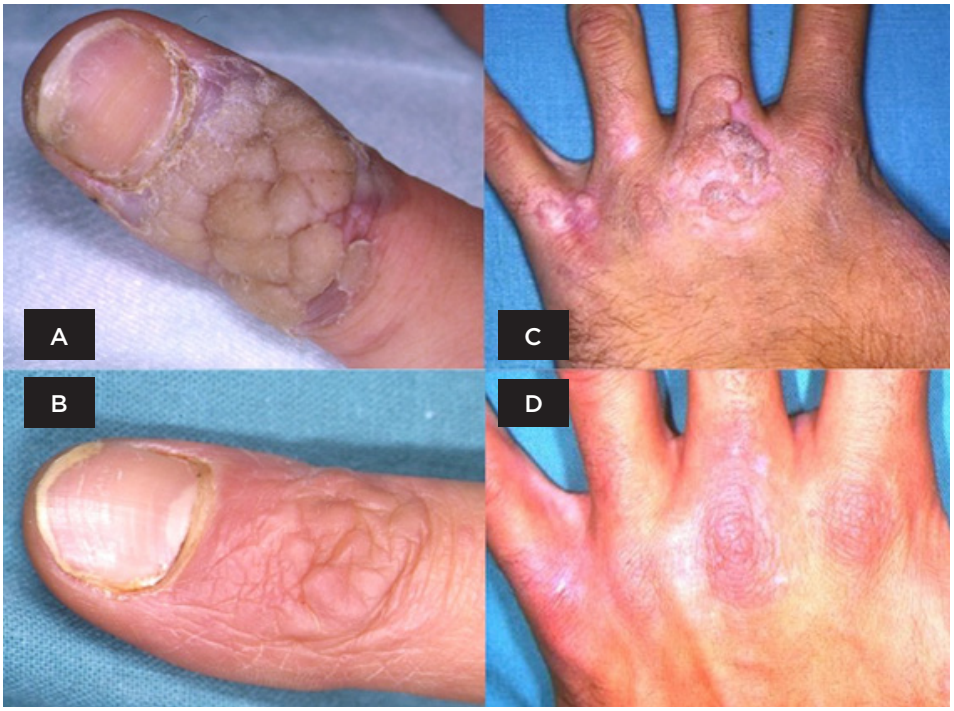

Figure 1: Pulsed dye laser (PDL) treatment for recalcitrant viral warts.
A) Pre-treatment image: a 25-year-old man presented with periungual viral warts resistant to multiple topical treatments. B) Complete resolution after three treatments with PDL (fluence: 12 J/cm^2, pulse duration: 1.5 ms, pulse diameter: 7 mm, pulse stacking: 3). C) Pre-treatment image: a 30-year-old man presented with painful and recalcitrant viral warts on the dorsal aspect of left hand. D) Complete resolution after two treatments with PDL (fluence: 13 J/cm^2, pulse duration: 1.5 ms, pulse diameter: 7 mm, pulse stacking: 5).

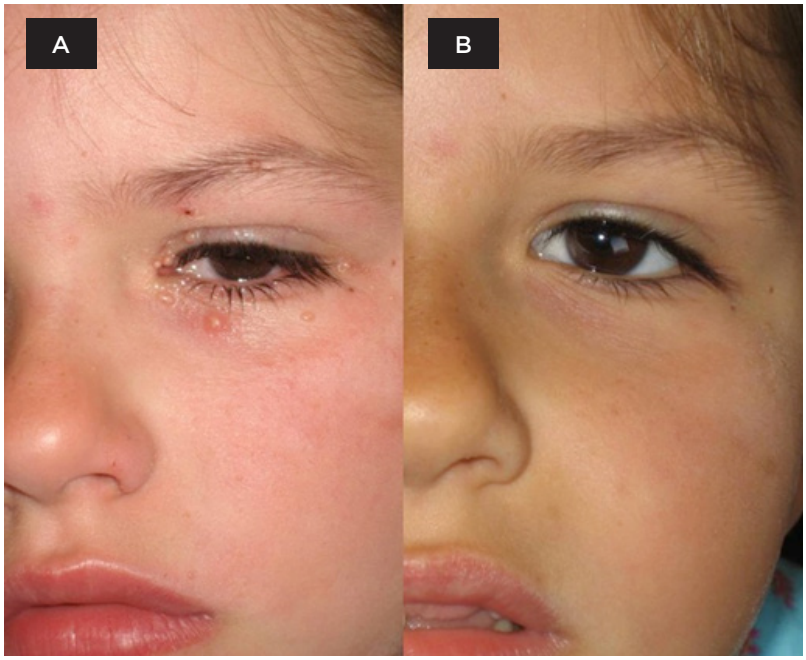

Figure 2: Molluscum contagiosum treated with pulsed dye laser (PDL).
A) Pre-treatment image: a 4-year-old boy presented with multiple palpebral molluscum contagiosum. B) Excellent cosmetic result after one treatment with PDL (fluence: 7 J/cm^2, pulse duration: 0.5 ms, pulse diameter: 7 mm) associated with ocular protection.

Acne Vulgaris

Acne is one of the most prevalent human skin conditions. Conventional topical treatments (retinoids, antimicrobials, and anti-inflammatory agents) are sometimes associated with skin irritation, and conventional oral medications (oral contraceptives, antibiotics, and retinoids) may be associated with adverse effects such as gastrointestinal discomfort, antibiotic resistance, birth defects, and thromboembolic events.[15] Therefore, physical approaches are sometimes applied.[9,15,16] Although recent, prospective randomised trials have shown satisfactory results in acne treatment based on selective photothermolysis of sebaceous follicles and topical gold microparticles,[17] conventional PDL may also be employed with promising results.[9,15,16] Although PDL effectiveness has been associated with *Propionibacterium acnes* selectivity,[15,16] upregulation of transforming growth factor-beta may explain the highly potent immunosuppressive response in acne.[18] As subpurpuric doses are employed, it is well tolerated with mildly adverse effects. Combined physical treatments have demonstrated better results than employing PDL alone.[15,16] Both PDL and 1450 nm diode lasers have shown improvements with no significant adverse events in mild-to-moderate inflammatory acne.[16] Moreover, PDL-assisted photodynamic therapy with methyl aminolevulinic acid is slightly superior to PDL for the treatment of inflammatory acne. Non-inflammatory lesions show a similar reduction with both treatment options.[15]

Systemic Lupus Erythematosus

Although systemic lupus erythematosus (SLE) is associated with cutaneous photosensitivity, the pathogenesis may be linked to ultraviolet-mediated cell apoptosis and chemokine, cytokine, and cellular adhesion molecule-dependent events.[19] There have been no reports to date of the use of lasers in the ultraviolet A or B spectra, due to their recognised photosensitising effect in SLE. However, there are 14 reports of the use of lasers with wavelengths in the visible light spectrum (PDL, argon, and intense pulsed light), with good tolerance. This supports the hypothesis that monochromatic laser light is unlikely to be photosensitising in SLE and may be a safe and effective treatment option in some patients, as suggested by various groups.[19-23]

To date, PDL has been used in eight studies with varying degrees of improvement and no remarkable permanent adverse events.[20] In a retrospective study by our group,[21] 14 patients with different forms of SLE were treated with a dye laser and obtained a clearance rate of >60%. The telangiectasic component related to SLE showed an excellent improvement (Figures 3a and 3b). We also obtained good results with the erythematosus component in discoid SLE (Figures 3c and 3d). Telangiectasias and chronic erythema improvement is based on the selective photothermolytic ablation of the dilated capillaries and venules. Ten lupus tumidus patients were also treated with PDL in a prospective study with excellent response.[22] Post-laser purpura seems to be necessary in order to achieve clinical improvement. However, PDL treatment does not prevent recurrences. The aforementioned improvement is also accompanied by a reduction of the dermal lymphocytic infiltrate and disappearance of mucin deposition. Post-laser immunohistological changes of cutaneous SLE have been described in another prospective study by our group.[23]

Psoriasis

Laser treatment for psoriasis has been studied since the 1980s, with the carbon dioxide ablative laser, the helium–neon laser, and red light photodynamic therapy.[24] Vascular lasers could be effective in psoriasis treatment by targeting the papillary dermal vasculature and allowing a reduction in epidermal thickness.[25] Although the excimer laser seems to be more effective in localised chronic plaque psoriasis treatment,[24] Grade B[26] recommendation has been proposed based on several studies. No solid conclusion could be drawn for the treatment of nail psoriasis with PDL.[27]

Hypertrophic Scars and Keloids

Hypertrophic scars and keloids develop as a result of an exaggerated proliferation of dermal fibroblasts and an excess accumulation of collagen following skin injury. Consensus literature is absent regarding the best treatment approach.[28]

Several studies have demonstrated PDL effectiveness in improving the colour, vascularity, height, texture, and pliability of scars.[29] The mechanism by which PDL improves hypertrophic and keloid scars is not yet known. Selective destruction of small vessels, either directly through heat collagenolysis or indirectly through impaired cellular function, has been proposed.[30] Early treatment, starting at the date of suture

removal, has demonstrated improvement in scar appearance.[29] A recently published prospective study by Gladsjo and Jiang[30] concluded that non-purpuric PDL settings lead to significant improvement in the appearance of fresh surgical scars in terms of vascularity, pliability, and Vancouver Scar Scale total scores. This assessment differs from that of many clinicians, who believe that inducing purpura results in better and quicker scar improvement.

Superficial Pigmented Lesions (Lentigines)

Q-switched Alexandrite is the standard laser treatment for superficial pigmented lesions due to its mechanical effect. Although wavelength of 595 nm has been the standard of treatment for many vascular lesions, it is also well absorbed by melanin.[31-33] This feature can be employed to treat pigmented lesions with PDL when other laser devices are not available. Garden et al.[31] designed a prospective study using a modified PDL device with a compression handpiece and no epidermal cooling. Clearance of up to 79% was observed after four monthly treatments. The meniscus compression element displaces the blood away from the irradiated field, resulting in elimination of postprocedural purpura. It is therefore possible to avoid purpura if PDL is used with compression. Similar results have been described in the literature.[31,32]

Basal Cell Carcinoma

Several reports have shown the effectiveness of PDL for the treatment of basal cell carcinoma.[34-39]

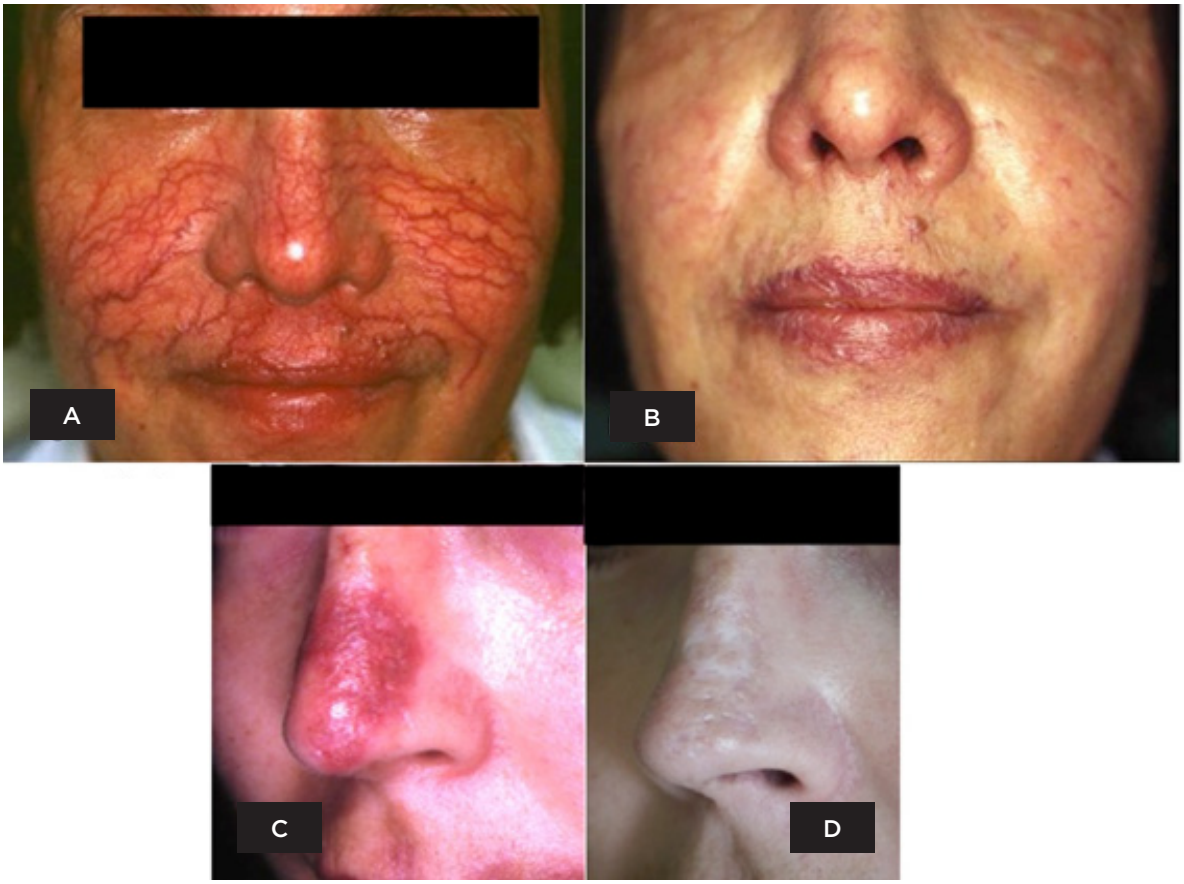

Figure 3: Pulsed dye laser (PDL) treatment for systemic lupus erythematosus.
A) Pre-treatment image: a 62-year-old woman with telangiectatic and erythematous facial lesions due to systemic lupus erythematosus. B) Good response after four treatments with PDL (fluence: 7 J/cm^2, pulse duration: 0.5 ms, pulse diameter: 7 mm). Throughout the treatment, a pre-cooled airflow skin cooling system (Cryo5©, Zimmer Medizinsysteme GmbH, Neu-Ulm, Germany) was used at its highest setting. C) Pre-treatment image: a 36-year-old woman presented with systemic lupus erythematosus nasal plaque resistant to topical steroids. D) Complete response and discrete hypopigmentation after three sessions of PDL (fluence: 8 J/cm^2, pulse duration: 0.5 ms, pulse diameter: 7 mm). The patient reported a high satisfaction.

Most studies have included low-risk basal cell carcinomas (BCCs) and an important limitation has been the lack of histological confirmation of the treatment results.[34,36] Although the exact mechanism of action of using PDL to treat BCC is unclear, the main hypothesis is that PDL has an antiangiogenic effect.[37] BCCs have been shown to utilise a specialised tumour-associated microvasculature for growth.[39] A prospective study developed by our group was performed in order to assess the effectiveness of PDL in high-risk BCCs with complete histological evaluation with Mohs micrographic surgery (MMS).[37] Seven patients with high-risk BCCs located on the face were included. All tumours were treated with three sessions of PDL at 4-week intervals. Apparent complete clinical response was achieved in five of the seven patients. Finally, MMS was performed in six patients, and clear margins were achieved after one stage of MMS. The histological evaluation of the tumour debulking specimens showed complete clearance in four of six cases. One patient who did not undergo MMS showed a recurrence after 14 months. This study demonstrates that PDL can be effective for the treatment of high-risk BCCs. Nevertheless, until further scientific evidence is available, treatment of high-risk BCCs should include histological confirmation of clearance. Although more evidence is needed, PDL treatment of BCC could be an interesting therapeutic option in older patients who are not able to undergo surgery.

Others conditions such as sarcoidosis,[40] dermatomyositis,[41] keratosis pilaris atrophicans,[42] sebaceous hyperplasia,[43] and angiolymphoid hyperplasia with eosinophilia[44] have also been treated with PDL in case reports and small case series, achieving promising results.

CONCLUSION

Scientific and technical advances in laser therapy are gradually making their way into the routine practice of dermatologists. New wavelengths and therapeutic targets are promising tools for the treatment of challenging diseases. Nevertheless, PDL is still present in our clinical practice. Due to the redefined concept of selective photothermolysis, PDL seems to be a promising tool in the treatment of skin conditions different to vascular lesions: viral infections, inflammatory diseases, and tumoural diseases. Prospective studies with a large number of cases are needed in order to establish which are the optimal laser parameters.

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