Case report

Pulsed-Dye Laser Efficacy in the Treatment of Psoriasis in Adult Patients: An Evidence-Based Case Report

Made Ananda Krisna, Hanny Nilasari

Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
*Department of Dermatology and Venereology, Faculty of Medicine, Universitas Indonesia, dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Email: madeananda.krisna@gmail.com

Abstract

Psoriasis is a chronic inflammatory skin disease known to be highly responsive to phototherapy. Narrow-band UVB (NBUVB) phototherapy has been one of the standard treatments for its moderate to severe form. However, its lack of efficacy in treating stable psoriatic plaques on extremities has lead researchers to find alternative treatments, one of which is pulsed-dye laser (PDL). Laser has been known to be effective in treating vascular lesions; in psoriasis, elongation of rete ridge along with tortuous dermal capillaries are one of the first pathologies identified early in the disease progression. Several in vivo and preliminary studies have found the molecular mechanism of action of laser on abnormal vessel growth. In this article, we report a psoriasis vulgaris case in adult whose lesions responded well to NBUVB phototherapy. The psoriatic plaques on her extremities were stable despite NBUVB therapy and some topical treatments afterwards. With knowledge of emerging role of PDL in inflammatory skin disease such as psoriasis, we conducted a literature search and critically appraised the resulting articles. The systematic review article found evaluates PDL efficacy as a treatment for inflammatory skin diseases, including psoriasis, and was appraised using a worksheet from British Medical Journal Evidence-Based Medicine Toolkit. Its validity, importance, and applicability aspects were evaluated, leading to a conclusion that PDL can be used as an alternative treatment for psoriasis plaques in trunks, extremities, hands, or feet (both stable and unstable), with minimal and transient side effects (hyperpigmentation, hypopigmentation, and blistering).

Keywords: psoriasis, treatment, pulsed-dye laser

Abstrak

berbagai penyakit inflamasi kulit, termasuk psoriasis. Telaah kritis dilakukan sesuai dengan sistematika yang dianjurkan oleh British Medical Journal Evidence-Based Medicine Toolkit. Setelah penilaian validitas, importance, dan applicability artikel tersebut, didapatkan kesimpulan bahwa PDL dapat dijadikan sebagai terapi alternatif untuk penanganan lesi psoriasis pada batang tubuh, ekstremitas, telapak tangan, dan telapak kaki (baik yang bersifat stabil ataupun tidak). Efek samping minimal ditemukan, namun bersifat sementara (hiperpigmentasi, hipopigmentasi, dan lepuh).

Kata kunci: psoriasis, terapi, pulsed-dye laser

Introduction

Psoriasis is classified as a chronic inflammatory skin disease characterized by rapid growth and abnormal differentiation of the epidermis, typical vascularization, and dysfunctional immune system. Microscopically, one of the characteristic pathological changes in the skin prior to clinical manifestation of psoriasis skin lesion is dermal capillaries abnormalities. The capillary pathologic reaction start with perivascular mononuclear infiltrate, followed by capillary elongation with prominent rete ridge, and finally end as tortuous capillaries along with elongated rete ridges. These pathologic capillaries are very close to the epidermal-dermal junction.

To date, there are three modalities of treatment for psoriasis: topical therapies, systemic agents, and phototherapy. Phototherapy is chosen as an alternative, especially narrow-band UVB (NBUVB) phototherapy, due to its safer profile and more convenient administration. However, phototherapy may induce non-melanoma skin cancer, especially if the patient receive immunotherapy in the future.

One of the alternative, more often than not neglected, psoriasis treatment modalities is laser modality. Vascular lasers are the most suitable lasers and the target is capillaries located high in the dermal papillae, using hemoglobin in the erythrocytes as a chromophore. Lasing material comes in different forms, such as solid, liquid, gas, electromagnetic, or dye materials. Pulsed-dye lasers (PDL) use ‘dyed’ materials known as chromophores. This “selective photothermolysis”, with the correct laser beam, has been proven to be highly effective for treating skin lesions while the target is heated in reaction to specific absorption of light (e.g. by hemoglobin within the capillaries) while not injurious to the surrounding normal tissue.

A few molecular in vivo studies have revealed that PDLs have additional mechanism of actions in treating vascular excessive growths. One of the study depicting microscopic image of hamster cheek pouch concluded that abnormal vascular growth remediation by laser was caused by physical phenomenon. Meanwhile, a different in vivo study had found that PDL was able to regulate inflammatory processes, leading to apoptosis of endothelial cells of abnormal vessels. Due to the fact that these pathological endothelial cells secrete large amount of VEGF for its sustainability and expansion, its apoptosis causes decreased VEGF level. Without enough concentration of VEGF, involution of abnormal vascular excessive growth will occur. A preliminary in vivo human study proved that a psoriasis plaque treated with PDL showed significant micro-vessel density, length, and width reduction, which are correlated with the plaque severity score as a representative of psoriasis clinical aspects. Furthermore, PDL is precisely targeted to each psoriasis plaque, even preventing potential side effects such as erythema and blistering. This gives rise to a question whether PDL can be used as an alternative treatment for psoriasis in an adult patient, especially for stable psoriasis plaques on the extremities.

Case Illustration

A 31-year old female patient came for her four-weekly follow up on phototherapy response for psoriasis. Psoriasis was diagnosed six years before current admission and has been partially controlled with steroid, retinoic acid, and emollients. One year before current admission, the intensity of psoriasis patches worsened. The patient started NBUVB twice a week, and then reduced weekly after 20 sessions, and further reduced to fortnightly after additional sessions. By February 2015, she had completed a total of 54 NBUVB sessions and her condition had significantly improved, except for some persistent patches that she said to have
minimal improvement, if any. The patient had a history of dyslipidemia, controlled by diet. She was then prescribed two different topical creams (0.05% Betamethasone valerate cream twice daily and 0.005% calcipotriene cream twice daily) for three months for plaques on the extremities, but no significant improvement was seen.

On physical examination, multiple post-inflammatory well circumscribed hyperpigmented macules were found in various sizes (ranging from lenticular to palm-wide); scattered diffusely on the abdomen, upper back, and bilateral limbs. No scales were observed. One well-circumscribed nummular plaque each on the lower legs and bilateral forearms, with minimal erythema and minimal white thin dry scales were also observed. Body surface area (BSA) involved was 2%. She then asked for a treatment other than topical and localized NB UVB treatment that could clear the persistent psoriatic patches on her legs and arms.

Clinical question

In order to investigate this further, we propose a research question:

To what extent is pulsed-dye laser treatment effective for psoriasis in adults?

We broke down the question into four parts, abbreviated as PICO (i.e. Patient/problem, Intervention, Comparison, and Outcome[s] of interest):

- **Patient** : Adult patients with psoriasis vulgaris
- **Intervention** : Pulse-dye laser
- **Comparison** : N/A
- **Outcome** : Psoriasis clinical severity scoring reduction

Method

Type of study

This study is an evidence-based case report (EBCR). An EBCR started from a relevant clinical scenario with corresponding clinical question (PICO) regarding therapeutic options, diagnostic value, prognosis, and etiology of the underlying disease. According to its PICO, several inclusion criteria are set to define what kind of previous original articles are most suitable. The article(s) found were then critically appraised to decide whether their results were valid, important, and applicable for the patients in the predetermined clinical scenario.

Search strategies

We searched through PubMed, Science Direct, and Cochrane Library. The keywords used were ‘pulsed-dye laser’ and ‘psoriasis’ with a Boolean AND. They were already listed in PubMed Medical Subject Headings (MeSH). An article of systematic review and randomized controlled trial type was prioritized.

Selection

Figure 1. Search Strategy Flowchart

Due to the limited amount of systematic reviews found regarding the subject of this study, an expanded search was conducted in order to search for articles with second highest level of evidence, which are randomized-controlled trials with sufficient number of patients. Each article found was critically appraised using three parameters: validity, importance, and applicability. Each aspect of these parameters were assessed using a worksheet from British Medical Journal Evidence-Based Medicine Toolkit.12

Results

There were three RCTs found. Two of which had been included and evaluated in the systematic review, while the other one was more of a pathogenesis study. Thus, the systematic review was the only article appraised for answering the clinical question in this evidence-based case report.

The systematic review appraised aimed to evaluate PDL efficacy as a treatment of inflammatory skin diseases, including psoriasis, acne vulgaris, lupus erythematosus, facial granuloma, sarcoidosis,
chronic eczema, lichen sclerosis, granuloma annulare, Jessner lymphocytic infiltration of the skin, reticular erythematous mucinosis, and papulopustular rosacea. Amongst them, psoriasis was the most studied inflammatory skin disease. These were all clearly stated in the article review, indicating the relevance of its research question to the clinical question of this case report.13

There were a total of 13 clinical studies of psoriasis evaluated in the systematic review.13 Two of these studies strictly examined nail psoriasis, thus the validity of which would not be considered any further. Amongst 11 studies of trunk and/or extremities psoriatic plaques treated with PDL, the highest level of evidence (LOE) was 2B, which consists of individual cohort studies or low-quality RCTs. There were only 2 studies with this LOE, 6 studies were of individual case-control studies (LOE 3B), and 2 were only in the form of case series (LOE 4). The maximum number of subjects included in the study was 41 patients14 and the minimum amount of subjects was eight patients.15, 16

PubMed was the only computerized bibliographic database through which the writer of the systematic review conducted a literature search. The keywords used were a combination of “pulsed dye laser(s)” and a specific term of inflammatory diseases as stated above. Any manual search, citation-indexing, evaluation through research registration to detect possible unpublished studies or ongoing studies, or expert consultation was not stated to have been conducted. The studies included in the systematic review were also limited to those with full-texts available in English, German, or Dutch.13

Inclusion criteria consist of: 1) patients with inflammatory skin disease which is psoriasis; and 2) treated with PDL. The systematic review included a wide range of study types (case reports, case series, retrospective studies, open-label trials, and RCTs) due to the limited available literatures regarding the topic being studied. However, the study did not mention in full details of the patient baseline or demographic criteria nor psoriasis characteristics (location of lesions, severity, previous responsiveness to treatments, etc.). Meanwhile, two exclusion criteria were noted: collateral use of local therapy other than keratolytic pre-treatment and oral treatment started within six weeks prior to PDL therapy and/or during PDL therapy. These inclusion and exclusion criteria were used as guidelines in filtering the studies. Three dermatologists acted as a reviewer in filtering studies. How the three dermatologists coordinate and their agreements in choosing the studies included in the review were not explained further.13

All of the 11 trials included in the systematic review produced significant results. A significant result was defined as clinical improvement of psoriatic lesions treated with PDL compared with either its before-treatment degree of severity or other treatments.13

Table 1. Critical Appraisal of Validity

<table>
<thead>
<tr>
<th>Validity Parameters</th>
<th>Erceg, et al. (2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear relevant research question</td>
<td>Yes</td>
</tr>
<tr>
<td>High-quality studies</td>
<td>No</td>
</tr>
<tr>
<td>Comprehensive search strategies</td>
<td>No</td>
</tr>
<tr>
<td>Assessment of the trials’ individual validity</td>
<td></td>
</tr>
<tr>
<td>Clear inclusion criteria</td>
<td>No</td>
</tr>
<tr>
<td>Clear exclusion criteria</td>
<td>Yes</td>
</tr>
<tr>
<td>More than one investigators with good interpersonal agreement</td>
<td>Yes</td>
</tr>
<tr>
<td>Consistent trial results</td>
<td>No</td>
</tr>
<tr>
<td>Clinically</td>
<td>Cannot be evaluated due to significant clinical heterogeneity</td>
</tr>
<tr>
<td>Statistically</td>
<td></td>
</tr>
</tbody>
</table>
The general patient characteristics are adult patients with psoriasis plaques existing either on the trunk or extremities. There are some patient characteristics that would predictably affect the results and therefore should have been considered as either inclusion or exclusion criteria when recruiting subjects such as demographic profiles (age of onset, sex, comorbidities), genetic predisposition, psoriasis type, psoriasis severity, and previous response to other treatments. Nevertheless, these features were not further mentioned in detail.¹³

Discussion

Regarding psoriasis, some literature categorized it as erythro-papulo-squamous skin disorder, which literally describes its classic lesion as well-demarcated erythematos papule or plaques with white dry scales on the surface. These lesions are usually symmetrical and easily recognized during physical examination (by the presence of Koebner phenomenon, Auspitz sign, and Woronoff ring).¹⁻³ Approximately 90% of psoriasis cases are psoriasis vulgaris.⁴

In treating the disease, topical therapies are indicated for mild localized psoriasis, while systemic agents and phototherapy are the treatment for severe psoriasis. However, there are limitations to systemic agents as they potentially have unfavorable side effects such as hepatotoxicity, bone marrow suppression, hypertension, kidney failure, and teratogenicity.⁵

Other modalities include lasers, which have already been studied in several countries. Based on critical appraisal of the systematic review, pulsed-dye laser does play a role in psoriasis treatment. However, all of the 11 studies included in the systematic review were small-scale studies consisting of less than 50 subjects each: the biggest number of patients enrolled in one study was 41 subjects¹⁴ while the smallest number was eight subjects¹⁶. Furthermore, there were several clinical heterogeneities among them that are further discussed below, including: the wavelength of light emitted by PDL, spot size diameter, pulse duration, PDL fluence, and patients’ baseline and demographic characteristics.¹³

Light wavelength

There were only two wavelength variations, 585 and 595 nm, and three spot size diameters (five, seven, and 10 mm) all of which had been proven to be effective in inducing selective photothermolysis for treating abnormal vascular growth. These small variations would be predicted to minimally impact the result.¹³

Pulse duration

Pulse duration used was quite variable, ranging from 0.2 to 1.5 ms, with 0.45 ms being the most commonly applied.¹³ Decision regarding pulse duration to be applied is crucial in PDL therapy. Also known as pulse width, it influences thermal energy spatial confinement. Each vessel has one unique property known as thermal relaxation time, which is the time needed for the vessel to dissipate ±63% of incident thermal energy.¹⁷ PDL pulse duration should ideally be synchronized to this property of vessel. Pulse duration exceeding vessels’ thermal relaxation time could potentially expose them to greater amount of incidental thermal energy, that rather than being dissipated to surrounding tissue, it would be absorbed, leading to unwanted side effect(s).⁹ In psoriatic plaques, the abnormal capillaries in the dermal papillae are one of the main targets of a PDL therapy. There were no preliminary in vitro or in vivo studies examining those vessels’ thermal relaxation time. However, one of the studies analyzed in the systematic review investigated the effects of different kinds of pulse duration on improvement (0.45 ms vs 1.5 ms) and revealed no significant difference. Difference in side effects was not discussed any further.¹³

PDL fluence

PDL fluence amongst the studies was varied, differing from 2.0 J/cm² to 12.0 J/cm². Fluence is a measurement unit of energy delivered by PDL (in joule) per unit area (in cm²). It is the most common quantitative endpoint previously determined by a pilot study. Different levels of fluence are applied to certain vessels and the level of exposure resulting in permanent vessel damage/disappearance without leading to wall rupture will be considered as the ideal fluence, which is the endpoint of PDL therapy. The previous study in hamster cheek pouches mentioned in the introduction section had revealed that the fluence needed to accomplish vessel disappearance was in accordance with pulse duration, where the longer the pulse duration is, a higher fluence is needed.⁹ This finding is expected and can be explained logically in a sense that longer pulse duration potentially exceeds the vessels’ thermal relaxation time and therefore more thermal energy dissipated into the surrounding...
tissue, rather than absorbed by the hemoglobin inside the vessels, which is a pivotal point leading to its (vessel) disappearance. Consequently, the PDL fluence has to be higher so that the energy lost due to dissipation phenomenon is replaced and effectively absorbed by hemoglobin. In accordance with this deduction, the same study also discovered that increasing fluence is correlated to more abundance of intravascular cavitation, vessel wall rupture, hemorrhage, and shrinkage of perivascular tissue during microscopic observation. One study in the systematic review applying the highest range of fluence, which is 10.0–12.0 J/cm², showed blistering as a side effect of PDL treatment that was not found in other studies without improvement in psoriatic severity exceeding excimer laser.12

Baseline characteristics
Patients’ demographic and their psoriatic patches’ baseline characteristics such as age of onset, sex, comorbidities; genetic predisposition, psoriasis type, psoriasis severity, and previous response to other treatments were possibly varied widely as no strict inclusion criteria were implemented regarding these components.12

Mechanism of Action
Despite the need of careful interpretation of the appraised systematic review, there is some biological plausibility proven by researches which could explain the significant improvement of psoriatic plaques treated with PDL:

- Light energy, in the form of photon emitted by PDL devices, is almost exclusively absorbed by hemoglobin, leading to intravascular coagulation. This coagulum has undergone chemical structure change resulting in splits, being in close proximity to the vessel walls, and retracts them. Observation via real-time microscopy shows vessel disappearance with neither rupture nor haemorrhage.9
- Endothelial cells exposed to PDL therapy showed ultrastructural changes consistent with apoptosis phenomenon followed by a reduced expression of VEGF mRNA, possibly secondary to apoptosis itself. However, what actually induced apoptotic cascade of events at the first time was still speculative: inflammatory process is fairly probable.10
- Reduction in ICAM-1 expression in chronic psoriatic plaques was notable after 3 sessions of PDL treatment performed every 2 weeks.18
- Within 24 hours after PDL therapy in patients with stable psoriatic plaques, VEGFR and E-selectin expression were down-regulated. This is followed by reduced expression of IL-23 and TNF-alpha after second PDL session; normalization of epidermal activation markers and dermal T-cell infiltrates after four times of PDL therapy.19

Decreased epidermal activation markers and dermal T-cell infiltrates were also achieved by NBUVB, but only after 13 weeks of treatment. This means that PDL potentially induce earlier remission onset in psoriasis plaque.19

Conclusion
This appraisal of the only systematic review regarding PDL therapy in psoriasis plaques concludes that PDL can be used as an alternative treatment for psoriasis plaques in trunks, extremities, hands, or feet (both stable and unstable) in addition to NBUVB, an already established treatment of choice for the same indication. Clinically, psoriatic lesions were shown to be significantly improved after PDL therapy and it was also proven to be at least as effective as NBUVB. Considering PDL’s small area coverage, this modality might be more convenient for small psoriatic plaques. This is both an advantage and disadvantage; its smaller area coverage protects the healthy skin surrounding psoriatic lesion from undesirable side effects. However, it requires more time for PDL to cover a larger psoriatic plaque.

There were only three noted side effects of PDL, namely: hyperpigmentation, hypopigmentation, and blistering. Overall, they are transient in nature, compared to more varied potential side effects of NBUVB.

To date, there have not been any reports regarding PDL therapy remission rate when applied as treatment for psoriasis. Prospective studies with high LOE are warranted in the future to firmly establish the utility of PDL therapy in psoriasis treatment.

References


