Pulsed dye laser therapy for infantile hemangiomas: a systemic review and meta-analysis

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Summary

Background: Infantile hemangiomas (IH) are common pediatric tumors. This meta-analysis was performed to review the therapeutic efficacy and safety of pulsed dye laser (PDL) in the treatment of IH.

Methods: Seven databases were searched, including PubMed, OvidSP, Karger, Elsevier, EMBASE, Web of Science and Wiley Online Library. The review collected the characteristics of year of publication, hemangiomas cases, prior treatment, laser parameters, adverse side, pretreatment symptom, and number of response from all articles.

Results: A total of 1580 studies were identified, the first round search retrieved 39 articles met inclusion criteria. Of those, only 13 articles with 1529 hemangiomas were included in the meta-analysis. This meta-analysis demonstrated an overall resolution rate of 89.1% with 6.28% incidence of adverse effect.

Conclusion: PDL may be the effective modality to decrease the proliferative phase and accelerate rates of involution and resolution with few adverse events.

Introduction

Infantile hemangiomas (IH) (Strawberry nevi) are pediatric benign tumors of vascular characterized by an initial phase of rapid proliferation, followed by slow spontaneous involution. They are the most common tumors of infancy, affecting 2–3% of newborns and up to 10% of infants within the first year of life. The head and neck are the most common lesion locations with 60% of hemangiomas. Most hemangioma lesions regress completely over time, but 10–12% of hemangioma lesions will develop complications that can be life threatening or permanent. Complications requiring the intervention appear such as bleeding, obstruction of a vital structure, hemorrhage, and ulceration with secondary infection or pain.

Various treatment options have been used for complications of the hemangioma. These include propranolol, corticosteroids, surgical excision, and laser therapy. The pulsed dye laser (PDL) may be effective in the treatment of IH to reduce the proliferative phase and hasten the process of involution. It has become the treatment for cutaneous vascular anomalies since the late 1980s. A number of studies have assessed the efficacy and safety of the PDL treatment. Many of them report that the hemangiomas of patients were completely clearance or...
excellent improvement in the treatment of the PDL.13–19 However, the conclusions from published studies were inconsistent.20 Therefore, we performed a meta-analysis to systematically review the current published data on the efficacy of PDL in the treatment of IH.

Materials and methods

Literature search

Published literatures assessing the PDL treatment for IH from A to B were searched through seven databases, including PubMed, OvidSP, Karger, Elsevier, EMBASE, Web of Science and Wiley Online Library. The key words used for search were as follows: ‘Hemangioma’, ‘Infantile Hemangiomas’, ‘Childhood Hemangioma’, ‘cutaneous vascular lesions’, ‘cutaneous capillary haemangiomata’, ‘tunable dye laser’ and ‘pulsed dye laser’. Publication language was restricted to English language only. Meanwhile, reference lists were examined manually to further identify potentially relevant studies. Unpublished reports were not considered.

Inclusion and exclusion criteria

Abstracts of all citations and retrieved studies were reviewed. Published reports meeting the following criteria were included: (i) the study has a clear report of effect in the treatment of hemangiomas in pediatric population with the PDL. Studies were excluded if one of the following existed: (i) the study used the PDL for the treatment of non-cutaneous hemangiomas; (ii) there was no clear report of outcomes for extraction of data.

Data extraction

All data were extracted independently by two reviewers (L. Shen and G. Zhou) according to the inclusion criteria listed earlier. The results were compared and disagreements were discussed and resolved with consensus. Evaluation was based on title and abstract whenever available. Full-text articles of potentially relevant studies were obtained and re-evaluated for inclusion. The following characteristics were collected from each study using an Excel data extraction form: first author, year of publication, hemangiomas cases, prior treatment, laser parameters, adverse side, pretreatment symptom, and number of response were collected from all articles (Table 1).

Statistical analysis

The statistical analysis was conducted using R statistical software (Version 3.1.1), package META. Q testing and $I^2$ statistics were used to examine heterogeneity among studies.21 A value of $P < 0.1$ was considered significant for the Q testing and $I^2$ was interpreted as the proportion of total variation contributed by between-study variation. If there was a significant heterogeneity ($P$-value < 0.1), we selected a random effects model to pool the data. Heterogeneity was also quantified using the $I^2$ metric ($I^2 < 25\%,$ no heterogeneity; $I^2 = 25–50\%,$ moderate heterogeneity; $I^2 > 50\%,$ large or extreme heterogeneity).22 We graphed the forest plot that contains individual studies representing the horizontal solid line with their confidence intervals. Publication bias was examined with Egger’s tests.23,24 If the $P$ value of Egger’s tests was <0.05, there is evidence of publication bias.

Results

Study characteristics

One thousand five hundred eighty studies were identified (Figure 1). A total of 39 studies were retrieved after the first search, and 26 of these were excluded from the analysis for reasons detailed in Figure 1. Only 13 studies met the inclusion criteria in this meta-analysis, which included 1529 hemangiomas. Characteristics of studies included in the meta-analysis were presented in Table 1. The flow chart of collection of studies and reasons for exclusion was presented in Figure 1.

Efficacy and complication profile of PDL therapy

One thousand two hundred forty-seven patients were enrolled in this study. The study patient population consisted of 909 girls (73%) and 338 boys (27%). A total of 1529 hemangiomas were treated with PDL. Of these, 764 lesions (50%) were located on head and neck, 413 lesions (27%) on trunk, 298 lesions (19%) on extremity, 40 lesions (3%) on genital area, and 14 lesions (1%) on perineal. Six hundred sixty-seven hemangiomas of pretreatment (44%) were classified as superficial, 371 lesions (24%) as mixed hemangiomas, and 435 lesions (28%) as cutaneous nodular. The wavelength 585 and 595 nm, spot size 5 and 7 mm and pulse duration 0.45 ms were the most commonly used laser parameters. Each hemangioma underwent a mean
<table>
<thead>
<tr>
<th>Study</th>
<th>Prior treatment</th>
<th>No. of hemangiomas with PDL treatment</th>
<th>Pretreatment symptom</th>
<th>Laser/parameters</th>
<th>No. of treatments (mean)</th>
<th>Response of improvement</th>
<th>Evidence level</th>
<th>Adverse effects (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batta et al.²⁰</td>
<td>NR</td>
<td>60</td>
<td>Superficial early hemangiomas</td>
<td>585 nm PDL, 3–5 mm spot size, 0.45–5 mm pulse duration, 6.0–7.5 J/cm² energy fluence</td>
<td>NR</td>
<td>25 patients (complete clearance or minimum residual signs)</td>
<td>IV</td>
<td>Required steroid treatment ($n = 1$, 2%); ulceration ($n = 4$, 7%); painful ulceration ($n = 3$, 5%); bleeding ($n = 2$, 3%); infection ($n = 2$, 3%)</td>
</tr>
<tr>
<td>Hunzeker and Geronemus¹³</td>
<td>NR</td>
<td>22</td>
<td>Superficial IH</td>
<td>595-nm PDL, 0.45–1.5 ms pd, 7 mm spot size, 11.0 to 11.5 J/cm² energy fluence</td>
<td>2–14 treatments (5, 6)</td>
<td>22 patients (76–100% improvement or 51–75% improvement)</td>
<td>III</td>
<td>Hyperpigmentation ($n = 2$, 9.1%)</td>
</tr>
<tr>
<td>Chang et al.²⁵</td>
<td>NR</td>
<td>164</td>
<td>Cutaneous hemangiomas</td>
<td>585 nm PDL 7 mm spot size, 0.45 ms pulse duration, 5.5–8 J/cm² for NC-LT, 9–10 J/cm² for CSC-LT</td>
<td>1–6 treatments (1, 8)</td>
<td>164 hemangiomas (76–100% improvement or 51–75% improvement)</td>
<td>III</td>
<td>NR</td>
</tr>
<tr>
<td>Haywood et al.²⁷</td>
<td>NR</td>
<td>39</td>
<td>Early superficial hemangiomas</td>
<td>585 nm PDL, 7.1 J/cm² energy fluence</td>
<td>Average 2.4</td>
<td>24 patients (complete clearance or minimum residual signs)</td>
<td>II</td>
<td>NR</td>
</tr>
<tr>
<td>Rizzo et al.²⁶</td>
<td>NR</td>
<td>105</td>
<td>Superficial (65) or mixed superficial and deep hemangiomas (40)</td>
<td>595-nm LP-PDL, 7–10 mm spot size, average energy fluence of 11.5 J/cm² (range 7.5–14.0 J/cm²) or 8.6 J/cm² (range 6.2–11.5 J/cm²)</td>
<td>1–17 treatments (6.7)</td>
<td>91 hemangiomas (100% improvement or 76–100% improvement or 51–75% improvement)</td>
<td>III</td>
<td>Hyperpigmentation ($n = 4$, 4%); hypopigmentation ($n = 15$, 14%); ulceration ($n = 1$, 1%)</td>
</tr>
<tr>
<td>Tay and Tan¹⁴</td>
<td>NR</td>
<td>23</td>
<td>Superficial hemangioma (10); mixed hemangioma (13); proliferative phase (21); stable phase superficial</td>
<td>595 nm PDL, 1.5–3 ms or 10 ms Pulse duration, 7 mm spot size, Fluence 10–13.5 J/cm² or 10.5–14.5 J/cm²</td>
<td>Short pulse duration: 3–14 treatments (8); long pulse duration: 4–14 treatments (9)</td>
<td>23 patients (regressed or almost regressed)</td>
<td>IV</td>
<td>Hyperpigmentation ($n = 3$, 13%); hypopigmentation ($n = 4$, 17%); mild textural changes ($n = 3$, 13%)</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Prior treatment</th>
<th>No. of hemangiomas with PDL treatment</th>
<th>Pretreatment symptom</th>
<th>Laser/parameters</th>
<th>No. of treatments (mean)</th>
<th>Response of improvement</th>
<th>Evidence level</th>
<th>Adverse effects (no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admani et al.¹⁵</td>
<td>NR</td>
<td>5</td>
<td>hemangioma (3); mixed hemangioma (2)</td>
<td>585 or 595 nm PDL, 7–12 mm spot size, 5.0–10 J/cm², 0.45–1.5 ms pulse duration</td>
<td>2–8 treatments (5.2)</td>
<td>Five patients</td>
<td>II</td>
<td>NR</td>
</tr>
<tr>
<td>David et al.⁸</td>
<td>NR</td>
<td>147</td>
<td>Ulcerated hemangiomas</td>
<td>585 nm PDL, 5–6.8 J/cm², 5 or 7 mm spot size</td>
<td>Average two treatments</td>
<td>71 patients</td>
<td>II</td>
<td>NR</td>
</tr>
<tr>
<td>Reddy et al.¹⁶</td>
<td>Propranolol (n= 5)</td>
<td>17</td>
<td>Superficial hemangioma</td>
<td>595 nm PDL, 7–10 mm spot size, 8.5–12 J/cm², 0.45–1.5 ms pulse duration</td>
<td>2–8 (4.2)</td>
<td>17 patients</td>
<td>IV</td>
<td>NR</td>
</tr>
<tr>
<td>Alcántara-González et al.²⁷</td>
<td>Propranolol (n=8), systemic corticosteroids (n=3), surgery (n=4)</td>
<td>22</td>
<td>Involuting (20); Proliferative (2)</td>
<td>595 nm PDL, 10 mm spot size, 10 ms pulse, fluence of 6–10 J/cm²</td>
<td>1–5 treatments (2)</td>
<td>16 patients (over five scores)</td>
<td>III</td>
<td>Mild atrophy (n=2, 9.1%); ulceration (n=1, 4.6%); hyperpigmentation (n=1, 4.6%)</td>
</tr>
<tr>
<td>Raulin and Greve¹⁸</td>
<td>NR</td>
<td>29</td>
<td>Superficial hemangioma</td>
<td>585 nm FPDL, 5 mm spot size, 0.3–0.45 ms impulse duration</td>
<td>Average of 3.0 treatments</td>
<td>24 hemangiomas (83%)</td>
<td>II</td>
<td>Hypopigmentation (n=3, 10%); hyperpigmentation (n=6, 20%); atrophic scars (n=1, 3.4%)</td>
</tr>
<tr>
<td>Poetke et al.¹⁹</td>
<td>NR</td>
<td>225</td>
<td>Superficial hemangiomas (153); Mixed hemangioma (54); Small superficial hemangioma (68); Superficial hemangioma (40); cutaneous nodular (435); mixed (128)</td>
<td>585 nm FPDL, 5 mm spot size, 5–7 J/cm², 0.3 ms pulse duration</td>
<td>Average of two treatments</td>
<td>171 hemangiomas (76%)</td>
<td>III</td>
<td>Hyperpigmentation (n=2, 1%); hypopigmentation (n=9, 4%)</td>
</tr>
<tr>
<td>Hohenleutner et al.²⁸</td>
<td>NR</td>
<td>671</td>
<td></td>
<td>585 nm FPDL, 5–7 mm spot size, 0.45 ms pulse duration, 5–10 J/cm²</td>
<td>1–12 treatments (mean, 2)</td>
<td>177 hemangiomas (28.7% total resolution or marked regression)</td>
<td>III</td>
<td>Small atrophic scar (n=27, 4%)</td>
</tr>
</tbody>
</table>

NR = not Report  
NC-LT = non-cooled laser treatment  
CSC-LT = cryogen spray cooling and laser treatment  
LP-PDL = long pulse-pulsed dye laser
of 2.77 laser treatments before remarkable response. The treatments were usually repeated every 2–8 weeks. The mean follow-up period was 6.61 months.

Remarkable lesion improvement was observed in all the 13 studies. Of these, seven studies (54%) reported that all of their patients have remarkable response, three studies (23%) reported 60–90% of their patients responded, and the remaining three studies (23%) reported 25–50% of their patients responded. Meta-analysis demonstrated an overall response rate of 89.1% of patients regressed their lesions markedly following treatment with PDL ($I^2 = 99\%$, $P < 0.0001$) (Figure 2).

There were 96 out of 1529 hemangiomas (6.28%) occurred adverse effects in the review of 13 studies. The complications identified in their study included steroid (1, 1.04%), atrophic scarring (30, 31.25%), ulceration (9, 9.38%), bleeding (2, 2.08%), infection (2, 2.08%), mild textural changes (3, 3.13%), hyperpigmentation (18, 18.75%), and hypopigmentation (31, 32.29%).

Sensitivity analysis and publication bias

The influence of a single study on the overall meta-analysis was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable. Publication bias of the literature was assessed using Egger’s test. P-value of Egger’s test is 0.09575, so no publication bias was observed in this meta-analysis.

Discussion

IH, especially facial hemangiomas with slow regression, have the negative effect on a child’s confidence and create considerable emotional stress in parents. In addition, hemangiomas may also develop painful ulcerations, respiratory compromise, impaired vision, or inability to feed. Accelerated regression of hemangiomas have both psychological and physiological benefits. Laser therapy is one of the effective modalities of treatment for IH.
Some studies reported that the PDL has the low rate of complications in treatment of IH.\textsuperscript{19,31–32} The PDL has also been advocated to intervene hemangiomas early in other studies.\textsuperscript{19,28} Our meta-analysis demonstrated an overall resolution rate of 89.1% with 6.28% incidence of adverse effect. This treatment modality seems to show the effect and safety in the treatment of IH.

The PDL uses the mechanism of selective photothermolysis. Specifically, it affects blood vessels by heat transfer.\textsuperscript{46} The clinical objective of laser therapy of hemangiomas is to maximize thermal damage to vascular while minimizing injury to the surrounding epidermis and dermal tissue.\textsuperscript{14} To decrease this risk of damage to the epidermis and papillary dermis, clinicians have used the flash lamp-pumped PDL (LP-PDL) (575–600 nm wavelength), which emits light absorbed preferentially by hemoglobin in the cutaneous vessels.\textsuperscript{32–34} In our systematic review, 585 and 595 nm are two commonly used wavelengths. Previous studies have shown unfavorable outcomes when the 585-nm PDL with a pulse width of \(\leq 0.45\) ms was used in the treatment of hemangiomas with a subcutaneous component.\textsuperscript{19,28,34,35} Recently, the 595-nm LP-PDL with dynamic cooling and pulse widths of up to 1.5 ms have enabled the better targeting of the deeper component of hemangiomas.\textsuperscript{26} Because the suitable laser energy from PDL is selectively absorbed by oxyhemoglobin, the target chromophore,\textsuperscript{8,46,47} there is minimal heat radiation to the surrounding epidermis and dermal tissue.

A variety of treatment modalities have been used in the treatment of IH, including propranolol hydrochloride, systemic corticosteroids, PDL or other vascular-selective lasers, imiquimod, and topical timolol.\textsuperscript{16} PDL generally effectively affects the most superficial aspect of hemangiomas.\textsuperscript{2} Because the efficacy of the PDL is limited by its depth of vascular injury (1–2 mm) and the mixed hemangiomas might be far beyond this depth, subcutaneous or mixed hemangiomas do not benefit from PDL treatment.\textsuperscript{19} In our study, 1123 cases (73.45\%) of hemangiomas are in initial, small, superficial hemangiomas, where 79\% of the lesions showed a complete or marked clearance after mean follow up of 6.61 months. The success of laser treatment in subcutaneous or mixed hemangiomas is observed in 35.77\% lesions. Because PDL treatment may be inadequate for some lesions consisting of large or deep vessels, the propranolol are often used in the treatment of deep or large facial hemangiomas.\textsuperscript{37–40} Some studies proved propranolol to be a consistent and rapid therapeutic effect for IH with fewer side effects and good clinical tolerance.\textsuperscript{41–44} However, the experience of propranolol for treatment of IH is limited and the mechanism of action is currently unknown.\textsuperscript{39,44} In addition, propranolol has some potentially side effects, including hypoglycemia, bronchospasm, and hypotension, so hemangiomas are preferably treated in a multidisciplinary setting by physicians knowledgeable about the effects and side effects of propranolol.\textsuperscript{45}

There are some limitations in this study. Most of individual studies included in this review are non-randomized trials and lack of the control group. Some of them have the relatively small number of patients. The other limitation is that the criteria of marked regression among all included studies are inconsistent. Randomized trials with adequate patients and similar criterion should be included to determine the effectiveness and safety of the PDL treatment.

In conclusion, PDL is an effectiveness and safety therapy in the treatment of hemangiomas, especially for superficial hemangiomas. Our study suggests that this treatment modality to be considered as one option to intervene IH. However, further randomized controlled studies are suggested to evaluate PDL therapy for IH.

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\textbf{References}


