Comparison of Two Generation Photosensitizers of PsD-007 and Hematoporphyrin Monomethyl Ether Photodynamic Therapy for Treatment of Port-Wine Stain: A Retrospective Study

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Abstract

Objective: To compare the efficacy and safety of the two generation photosensitizers, PsD-007 and hematoporphyrin monomethyl ether (HMME), for photodynamic therapy (PDT) of port-wine stain (PWS).

Background: Vascular-targeted PDT has shown potentially beneficial results in treating PWS; however, the efficacy and safety of various photosensitizers have not been fully investigated.

Materials and methods: We retrospectively analyzed 38 patients with PWS, who were treated with one session of PsD-007-mediated (n = 21) or HMME-mediated (n = 17) PDT. Clinical efficacy was assessed by a chromameter and visual assessment of color blanching of the PWS lesion. Adverse events were evaluated.

Results: Neither visual nor chromameter optical evaluations showed significant differences between the PsD-007 and HMME groups (p = 0.337 and p = 0.191, respectively). The total response rate was 76.2% (n = 16) in the PsD-007 group and 88.2% (n = 15) in the HMME group. Good or excellent clearance was achieved in 42.9% patients in the PsD-007 group and 29.4% patients in the HMME group. The average ΔE (color expressed change or improvement) and mean blanching rate measured optically were higher in the PsD-007 group than in the HMME group without statistical differences (8.51 vs. 7.39, p = 0.649; 0.37 vs. 0.29, p = 0.191). Incidences of swelling, pruritus, scab formation, and other adverse reactions were similar for the two groups. There were no blisters, scarring, or hypopigmentation in either group.

Conclusions: Both PsD-007- and HMME-mediated PDTs are effective and safe for treatment of PWS. However, HMME has a shorter photosensitivity period than does PsD-007, which might be more recommended.

Keywords: port-wine stain, photodynamic therapy, PsD-007, HMME, photosensitizer

Introduction

Port-wine stain (PWS) is the most common congenital, progressive capillary malformation of human skin, reported in 0.3% to 0.5% of newborns worldwide.1 PWS has been characterized by ectatic capillaries that are 10–150 nm in diameter, located predominantly in the papillary and mid- reticular layers of the dermis at depths of 300–600 μm.2 The visible manifestations of PWS may significantly impede the patient’s psychosocial well-being and overall health, and many patients seek advice for treatment because 70% to 80% of these lesions occur in the head and neck regions.3,4 The pulsed dye laser (PDL, 585–595 nm) is the mainstream treatment for PWS worldwide, although complete lesion removal is infrequently achieved in most patients with PWS.5–7 Therefore, the need for alternative effective treatment protocols remains unfulfilled.

One promising treatment modality for PWS is photodynamic therapy (PDT), which is based on interactions between light, photosensitizers, and oxygen to induce the formation of cytotoxic singlet oxygen. This approach causes cell death via apoptosis, necrosis, or autophagy and potentially enables photocoagulation of vessels of all sizes and at greater depths than does PDL therapy, with less risk of
epidermal necrosis. PDT as a vascular-targeted approach to treat PWS has been used most commonly in China since the 1990s and has achieved substantial beneficial results.8–14 PsD-007 (photocarcinorin), a mixed porphyrin preparation containing almost all the components of hematoporphyrin derivatives, including 3-(or 8-)-(1-hydroxyethyl)-8-(or 3-)-(1-methoxyethyl)-deuteroporphyrin (MHD), 3-(or 8-)-(1-methoxyethyl)-8-(or 3-)-(vinyl)deuteroporphyrin (MVD), 3-(or 8-)-(hydroxyethyl)-8-(or 3-)-(vinyl)deuteroporphyrin (HVD), di(1-methoxyethyl) deuteroporphyrin (DMD), hematoporphyrin (Hp), protoporphyrin (Pp), and other active substances, is a first-generation photosensitizer.15 PsD-007-mediated PDT, combined with application of alternative light sources [including copper vapor laser or the potassium-titanyl phosphate (KTP) laser], appears to be a safe and effective approach for treating PWS; however, it is associated with prolonged systemic photosensitivity for at least 1 month and presents a significant scarring risk.16

The porphyrin-related photosensitizer hematoporphyrin ether 3- or 8-monomethyl ether (HMME) is a new monomer of porphyrin and is a second-generation photosensitizer. It was approved by the China Food and Drug Administration (CFDA) for the treatment of PWS with an acceptable photosensitivity period of 2 weeks and good safety data.17,18

After reviewing past clinical treatments, we found that the efficacy and safety of various photosensitizers have not been fully compared. Hence, the purpose of this study was to evaluate outcomes of a single session of PsD-007- or HMME-mediated PDT for patients with PWS lesions occurring in the head or neck regions.

Materials and Methods

Study design and data collection

In this retrospective study, medical records dated between November 2008 and July 2011 were reviewed. In total, 38 adolescent and adult untreated PWS patients were treated with PsD-007 or HMME photosensitizer PDT. They all returned after 4 days (HMME group) or 1 week (PsD-007 group) and both groups returned at 2 months after one treatment and had complete medical records. Information regarding the patients and the locations and types of lesions was recorded.

Treatment procedures

A less than 11-cm-diameter lesion was covered by one PDT treatment during each session. Medical adhesive plasters and double-layered black cloths were applied to cover surrounding normal skin outside and untreated areas. Twenty-one patients were treated with one session of PsD-007-mediated PDT (at the Second Military Medical University, Shanghai) according to the following protocol: 5 mg/kg, injected at a constant speed within 5 min, and 532-nm laser continuous irradiation applied immediately as soon as the injection started for 25–30 min, 80–90 mW/cm². Seventeen patients were treated with one session of HMME-mediated PDT (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd., China) according to the following protocol: 5 mg/kg, 532-nm laser continuous irradiation applied 10 min after the transfusion of HMME initiated for a total of 20 min, 80–90 mW/cm². Pethidine hydrochloride injection was used 15 min before treatment to control pain. Post-treatment skin cooling was carried out by applying an ice pack to minimize pain. To prevent effects of photosensitivity, patients were required to avoid strong light exposure for 30–60 days after PsD-007 injection and 14–30 days after using HMME.

Evaluations

All patients were followed up for 2 months. Both objective chromameter assessments and visual assessments of color blanching were used to evaluate efficacy.

The blanching of the PWS lesions was evaluated using a chromameter (CR-400; Minolta, Tokyo, Japan) to measure the skin color of the treated sites and normal skin nearby before and 2 months after treatment objectively. The L*, a*, and b* color system was used to measure color change: the values of ΔE (color expressed change or improvement), Δa* (vascular erythema expressed change), and blanching rate were calculated by comparing pre- and post-treatment values. Chromameter optical equations have been used in many previous studies.19–22

Digital photographs were taken with the same camera settings and lighting conditions (D80, Nikon, Japan) before treatment, immediately after treatment, within 1 week, and 2 months or longer postoperatively. Improvements of the lesions were evaluated. Photographs were evaluated by four independent blinded observers grading the extent of PWS fading (improvement) according to color blanching, using the following five-level scale: excellent color blanching >75% (five points), good color blanching 51–75% (four points), fair color blanching 25–50% (three points), poor color blanching <25% (two points), and no blanching (one point). Patients judged to have excellent, good, and fair responses were defined as total "response rate," which indicated that >25% color blanching was achieved.

All local or systemic events and adverse events, including edema, pruritus, scabs, blisters, scars, hyperpigmentation, or hypopigmentation, reported by the patients were recorded in detail.

Statistical analyses

The results of the chromameter evaluations (Δa*, ΔE, and blanching rate) and photographic evaluations were compared using Wilcoxon rank two-independent sample non-parametric tests. The average visual efficacy measured by four blinded evaluators was compared using the Mann–Whitney U test (two independent samples). The results of the colorimetric and photographic evaluations of the PsD-007 and HMME groups were compared using Pearson correlation coefficients. Data were analyzed using software SPSS 22.0 (IBM Corp., Armonk, NY). A p value <0.05 was considered statistically significant.

Results

Demographic data

Individuals in the PsD-007 group included 12 females and 9 males with the mean age of 24.33 ± 4.374 years (range, 16–32 years). The majority of lesions (n = 15) were located on the facial trigeminal dermatome V2 region. The HMME group included 14 females and 3 males with a mean age of 24.06 ± 7.044 years (range, 14–44 years). All 38 patients included in the study had skin type III–IV on the Fitzpatrick phototype scale. The details are provided in Table 1.
Treatment outcomes

Chromameter evaluations (Δa*, ΔE, and blanching rate). The average Δa* after PDT was 3.51 (95% confidence interval (CI) 1.58–5.44) for PsD-007 group and 3.25 (95% CI 1.62–4.87) for HMME group, respectively (p = 0.490). The average ΔE for the PsD-007 was 8.51 (95% CI 6.45–10.58) and for the HMME group was 7.39 (95% CI 5.82–8.96), respectively (p = 0.649). The mean blanching rate measured optically was 0.37 (95% CI 0.276–0.457) for PsD-007 group and 0.29 (95% CI 0.198–0.377) for HMME group, respectively (p = 0.191). Δa*, ΔE, and blanching rate were all higher in the PsD-007 group than in the HMME group, but showed no significant differences between the two groups (Table 2).

Photographic evaluations

In the PsD-007-mediated PDT group, excellent response was seen in three patients (14.3%), good in six patients (28.6%), fair in seven patients (33.3%), poor in three patients (14.3%), and no response in two patients (9.5%). In the HMME-mediated PDT group (n = 17), excellent response was seen in 1 patient (5.9%), good in 4 patients (23.5%), fair in 10 patients (58.8%), poor in 1 patient (5.9%), and no response in 1 patient (5.9%). The total response rate was 76.2% (n = 16) in the PsD-007 group and 88.2% (n = 15) in the HMME group. A total of 42.9% patients were assessed as achieving excellent and good clearance for the PsD-007 group and 29.4% for the HMME group. There was no significant difference between the PsD-007 and HMME groups (p = 0.330). The average score on the improvement scale was 3.27 (95% CI 2.746–3.801) and 3.04 (95% CI 2.653–3.436) after one session treatment for the PsD-007 and HMME groups, respectively (p = 0.337) (Table 2).

Side effects

All patients experienced treatment reactions, including pain, burning sensation, edema, and purpura in both groups. Crusting began 5–7 days after PDT and scabs fell off 2–7 days later. Mild and moderate temporary hyperpigmentation was observed after scabs fell off and did not fade totally 2 months later. Drug extravasation occurred at elbow intravenous injection point in one patient in each group; after 2 months of avoiding strong light exposure locally, there were no drug residues or hyperpigmentation. No patients developed blisters, hypopigmentation, atrophy, scarring, keloids, or systemic side effects in either group.

Discussion

In the 1990s, Chinese clinicians began to explore the feasibility of vascular-targeted PDT for the treatment of PWS because of ambitions to develop alternate or adjuvant treatment protocols.8,23 There have been few studies comparing PDT and PDL treatment of PWS; it was believed that PDT was safe and at least as effective as PDL and, in some cases, was superior.24–26 Several photosensitizers have been used for treatment of PWS in China and have now been investigated, including

Table 1. Patient Demographic Data

<table>
<thead>
<tr>
<th>Feature</th>
<th>PsD-007-PDT (N=21)</th>
<th>HMME-PDT (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)± SD</td>
<td>24.33±4.374</td>
<td>24.06±7.004</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>12 (57.1)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>9 (42.9)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Side of PWS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left, n (%)</td>
<td>8 (38.1)</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Right, n (%)</td>
<td>13 (61.9)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Region of PWS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V1, n (%)</td>
<td>3 (14.3)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>V2, n (%)</td>
<td>15 (71.4)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>V3, n (%)</td>
<td>2 (9.5)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Neck, n (%)</td>
<td>1 (4.8)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Type of PWS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pink or bright red</td>
<td>11 (52.4)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Purple</td>
<td>4 (19.0)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>6 (28.6)</td>
<td></td>
</tr>
</tbody>
</table>

HMME, hematoporphyrin monomethyl ether; PDT, photodynamic therapy; PWS, port-wine stain.

Table 2. Efficacy Assessment (Photographic and Chromameter Evaluations)

<table>
<thead>
<tr>
<th>Efficacy assessment</th>
<th>PsD-007-PDT (N=21)</th>
<th>HMME-PDT (N=17)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photographic evaluations, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent (&gt;75%)</td>
<td>3 (14.3)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Good (51–75%)</td>
<td>6 (28.6)</td>
<td>4 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Fair (25–50%)</td>
<td>7 (33.3)</td>
<td>10 (58.8)</td>
<td></td>
</tr>
<tr>
<td>Poor (&lt;25%)</td>
<td>3 (14.3)</td>
<td>1 (5.9)</td>
<td>0.330</td>
</tr>
<tr>
<td>No blanching</td>
<td>2 (9.5)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Total response (&gt;25%)</td>
<td>16 (76.2)</td>
<td>15 (88.2)</td>
<td></td>
</tr>
<tr>
<td>At least good (&gt;50%)</td>
<td>9 (42.9)</td>
<td>5 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Average score</td>
<td>3.27 (95% CI 2.746–3.801)</td>
<td>3.04 (95% CI 2.653–3.436)</td>
<td>0.337</td>
</tr>
<tr>
<td>Chromameter evaluations, score (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δa*</td>
<td>3.51 (1.58–5.44)</td>
<td>3.25 (1.62–4.87)</td>
<td>0.490</td>
</tr>
<tr>
<td>ΔE</td>
<td>8.51 (6.45–10.58)</td>
<td>7.39 (5.82–8.96)</td>
<td>0.649</td>
</tr>
<tr>
<td>Blanching rate</td>
<td>0.37 (0.276–0.457)</td>
<td>0.29 (0.198–0.377)</td>
<td>0.191</td>
</tr>
</tbody>
</table>

CI, confidence interval; HMME, hematoporphyrin monomethyl ether; PDT, photodynamic therapy.
hiporfin, photocarcinorin (PsD-007), hemoporfin (HMME), and talaporfin sodium.7,9,16,27

PsD-007 (photocarcinorin) contains almost all the components of hematoporphyrin derivatives, and each component has a different half-life, thereby generating a long period of sunlight avoidance, more than 1 month.16 In the photosensitization process, it can maintain effective blood drug concentrations in the vascular network for longer periods than those of the hematoporphyrin derivative monomer HMME, producing more persistent reactive oxygen species and continuous damage to vascular endothelial cells. Early Chinese trials primarily studied photocarcinorin.8,16 More recently, it has been gradually replaced by HMME that requires a shorter period of sunlight avoidance (2 weeks).9,18

Unlike first-generation PDT drugs, such as Photofrin and HpD, hemoporfin is characterized by known structure, higher photoactivity, stronger photodynamic efficiency, lower toxicity, and faster clearance rate.17 Hemoporfin is capable of producing higher $^1$O$_2$ quantum yield and faster self-sensitized photo-oxidization. This photo-oxidization might contribute to improved tissue selectivity of HMME-PDT. The epidermis, located above the dermis, receives a low amount of the photosensitizer; therefore, PDT reduces the damage of the epidermis.28

In 1997, we showed that, after one session of PsD-007-mediated PDT, 91.5% excellent or good lightening was seen.8 Lu et al. reported that the complete clinical remission rate was 57.33% and the effective rate was up to 94.67% for no more than four courses of treatment.16 A recent randomized controlled phase III trial in adolescent and adult patients showed that after one session of HMME-mediated PDT, 89.7% patients achieved at least some improvement.9 Other studies reported safe use of HMME-mediated PDT in pediatric patients with PWS.13,14 Therefore, we believe that, for treatment of PWS, both photosensitizers promise good efficacy and safety. However, these trials used different design methods, treatment histories, treatment sessions, evaluation methods, follow-up times, and assessment scales to analyze only one of the two generation photosensitizers separately. We cannot determine which design method was better based on previous trials. It was thought by many clinicians that PsD-007 had better clinical therapeutic effectiveness for PDT than did HMME, but with more local reactions, slower healing procedures, longer period of skin photosensitivity, and the resulting prolonged repeated treatment interval.17 Therefore, a direct comparison of all untreated patients receiving PDT performed by the same senior doctor, and assessed by an identical evaluation index, is needed to show whether there is difference between treatments.

In this study, we compared outcomes for the two common photosensitizers. There was no significant difference in median age, gender, or location of PWS in the two groups. Our results evaluated by visual and chromameter assessment showed that there were no significant differences in effects and side effects between PsD-007 and HMME groups, providing objective evidence and results for the comparison of PsD-007- and HMME-mediated PDT for PWS. Figure 1 shows representative photos of excellent responses after PsD-007-mediated and HMME-mediated PDT treatments.

Further, the changes in optical values of $\Delta a^*$, $\Delta E$, and blanching rates were significantly correlated at the 0.05 level. Nevertheless, only changes in $\Delta E$ values and blanching rates were in good agreement with those of photographic evaluations. We have no valid explanation for this; nevertheless, it might be explained by the PDT-associated pigmentation changes not fading 2 months after treatment, thereby affecting the chromameter evaluations.22 With normative operation as well as good nursing after treatment, the side effects and complications were very rare in both groups.

The lack of long-term follow-up period and the small number of cases included were all limitations of this study. Therefore, it would be beneficial to assess the efficacy after hyperpigmentation fades. In addition, group analysis cannot be performed as a result of the small number of cases, which constituted a limitation of the study.

Conclusion and Summary

This study demonstrated that using two generation photosensitizers, PsD-007- and HMME-mediated PDT, was both effective and safe for treatment of PWS. However, in terms of photosensitivity period, HMME was the superior photosensitizer, which might be more recommended. Future studies are needed to demonstrate the safety and efficacy of different photosensitizers and light sources used in PDT for the treatment of PWS.

Author Disclosure Statement

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References


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