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REVIEW ARTICLE

Current clinical evidence is insufficient to support HMME–PDT as the first choice of treatment for young children with port wine birthmarks

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Abstract

Background: Port wine birthmark (PWB) is a congenital vascular malformation of the skin. Pulsed dye laser (PDL) is the "gold standard" for the treatment of PWB globally. Hematoporphyrin monomethyl ether (HMME or hemoporfin)-mediated photodynamic therapy (HMME–PDT) has emerged as the first choice for PWB treatment, particularly for young children, in many major hospitals in China during the past several decades.

Aim: To evaluate whether HMME–PDT is superior to PDL by comparing the clinical efficacies of both modalities.

Method: PubMed records were searched for all relevant studies of PWB treatment using PDL (1988−2023) or HMME–PDT (2007−2023). Patient characteristics and clinical efficacies were extracted. Studies with a quartile percentage clearance or similar scale were included. A mean color clearance index (CI) per study was calculated and compared among groups. An overall CI (C_0), with data weighted by cohort size, was used to evaluate the final efficacy for each modality.

Result: A total of 18 HMME–PDT studies with 3910 patients in China were eligible for inclusion in this analysis. Similarly, 40 PDL studies with 5094 patients from nine different countries were eligible for inclusion in this analysis. Over 58% of patients in the HMME-PDT studies were minors (<18 years old). A significant portion (21.3%) were young children (<3 years old). Similarly, 33.2% of patients in the PDL studies were minors. A small proportion (9.3%) was young children. The overall clearance rates for PDL were slightly, but not significantly, higher than those for HMME–PDT in cohorts with patients of all ages (C_0, 0.54 vs. 0.48, $p = 0.733$), subpopulations with only minors (C_0, 0.54 vs. 0.46, $p = 0.714$), and young children (C_0, 0.67 vs. 0.50, $p = 0.081$). Regrettably, there was a lack of long-term data on follow-up evaluations for efficacy and impact of HMME-PDT on young children in general, and central nervous system development in particular, because their blood-brain barriers have a greater permeability as compared to adults.

Conclusion: PDL shows overall albeit insignificantly higher clearance rates than HMME-PDT in patients of all ages; particularly statistical significance is nearly achieved in young children. Collectively, current evidence is insufficient to support HMME–PDT as the first choice of treatment of PWBs in young children given: (1) overall inferior efficacy as compared to PDL; (2) risk of off-target

exposure to meningeal vasculature during the procedure; (3) administration of steriods for mitigation of side effects; -and (4) lack of long-term data on the potential impact of HMME on central nervous system development in young children.

KEYWORDS

efficacy, hematoporphyrin monomethyl ether, photodynamic therapy, port wine birthmark, pulsed dye laser

BACKGROUND

Congenital capillary vascular malformations, also known as port-wine birthmarks or stains (PWB or PWS), have an estimated prevalence of 0.3%−0.5% per live births.[1] PWBs appear as flat red macules in childhood and tend to progressively darken to a purple color in adults. By middle age, PWBs often develop vascular nodules.[1] Moreover, devastating lifelong psychological and social impacts can greatly impair the quality of life of affected children during their development and growth.[1] The vascular phenotypes of PWB lesions typically show the proliferation of endothelial cells (ECs) and smooth muscle cells, replication of basement membranes, disruption of vascular barriers, progressive dilatation of vasculature, and increased vascular exocytosis.[2–9] Pathologically, our group and others have found that PWB ECs exhibit stem-cell-like phenotypes, which are considered aberrant endothelial progenitor cells,[2,10] leading to differentiation-defective ECs.[2] Our group recently generated PWB patient-derived induced pluripotent stem cells (iPSCs) and differentiated them into clinically relevant ECs. Those iPSC-derived ECs recapitulated many vascular phenotypes of PWB and were able to assemble PWB-like vasculatures in vitro and in vivo.[11–13]

The pulsed dye laser (PDL) is generally considered the "gold standard" treatment for PWB. Unfortunately, complete removal of PWB occurs in less than 10% of patients due to the recurrence of lesions.[14–17] Approximately 20% of PWBs respond poorly to PDL treatment.[18] Between 16% and 50% of patients experience redarkening of their PWB as early as 5 years after multiple PDL treatments.[18] One recent meta-analysis study suggested limited improvements in clinical outcomes using laser- and other light-based modalities for PWB treatment over the past three decades.[19–21] Differentiation-defective PWB ECs likely survive after PDL treatments, resulting in the revascularization of lesional blood vessels after laser exposure.[2,6] More recently, hematoporphyrin monomethyl ether (HMME or hemoporfin)-mediated photodynamic therapy (HMME-PDT) has emerged as a major modality for PWB treatment in China. Several clinical studies have demonstrated the efficacy of HMME–PDT for the treatment of PWB in adult and pediatric patients.[22–27] However, HMME–PDT has only been tested and approved for the treatment of PWB in China. Unfortunately, there has been little investigation of HMME-PDT in any other countries. Therefore, there are many questions regarding the clinical efficacy of HMME–PDT as compared to PDL. In this meta-analysis study, we aimed to perform an up-to-date systemic comparison of both modalities based on available studies. The overall conclusion has shown that HMME–PDT shows similar efficacy as compared to PDL in patients of all ages, providing a reasonable alternative for adult patients. However, other factors, such as the risk of off-target exposure to meningeal vasculature during the procedure and the lack of long-term data on the potential impact of HMME on central nervous system (CNS) development in young children do not support the use of HMME–PDT as the first choice of treatment of PWBs in young children.

METHODS

We used similar selection criteria as described in a previous report[19] for retrieval of PDL-related studies from 1988 to 2023 using the terms "Port Wine Stains" and "pulsed dye laser" or "PDL." For the HMME–PDT studies, PubMed was searched using the terms "HMME," "Hemoporfin," "PDT," and "Port Wine Stains" from 2007 (a year before the first clinical study of HMME–PDT for PWB was reported in English)[27] to 2023. For a valid comparison of outcomes, the following inclusive criteria were used: (1) studies implemented quartiles of percentage clearance scales (i.e., 0%−24%, 25%−49%, 50%−74%, and 75%−100%); and (2) studies with other outcome classification systems that could be converted into a quartile percentage clearance scale. Exclusion criteria included other vascular malformations, studies with less than five subjects, other modalities except for PDL and HMME–PDT, other types of articles such as review papers, and outcome scoring not being sufficiently defined. In the one study where HMME-PDT and PDL were compared, data for the efficacies of both treatment modalities were extracted.[28] There were 12 HMME–PDT studies and one PDL study from China where clearance categories were defined as 0%−20%, 20%−59%, 60%−89%, and 90%−100%.[22,26,29–39] We used the equations to convert that data into a quartile scale as follows: $N_{converted\_0-24} = A + (B/39) \times 4$, $N_{converted\_25-49} = (B/39) \times 25$, $N_{converted\_50-74} = C \times 0.85 + (B/39) \times 10$, and

$N_{converted\_75-100} = C \times 0.15 + D$. While $N_{converted\_0-24}$, $N_{converted\_25-49}$, $N_{converted\_50-74}$, and $N_{converted\_75-100}$ represented the converted number into a quartile category of 0%−24%, 25%−49%, 50%−74%, and 75%−100%, respectively. A, B, C, and D represented the original numbers used in the scale of 0%−20%, 20%−59%, 60%−89%, and 90%−100%, respectively.

Inasmuch as most patients underwent multiple treatment sessions (≥2) as the endpoint of clinical evaluation, data from the last treatment session were included for simplification of the analysis. All eligible studies were pooled to generate the overall efficacy of PDL as compared to HMME–PDT. The extracted data from each study were also categorized for the subgroup of minors (<18 years old). There were 12 studies with the following patient age categories: <0.5, 10, 14, or 16, then 10−20, 14−20, or 16−20 years.[24,25,28–30,34,39–44] For those studies, the only data extracted were for patient categories <0.5, 10, 14, or 16 years. The data extraction summary was based on the availability of age information. In the PDL study group, there were 17 studies extracted including seven studies with patients <18 years old,[45–51] one study with patients <16 years old,[43] two studies with patients <14 years old,[52,53] four studies with patients <10 years old,[28,39,42,54] two studies with patients <1 years old,[55,56] and one study with patients <0.5 years old.[57] In the HMME–PDT study group, data from eight studies were extracted including two studies with patients <18 years old,[38,58] five studies with patients <14 years old,[22,24,29,30,34] and one study with patients <10 years old.[28] In the PDL study group, there were seven studies on young children (<3 years old).[42,43,46,54–57] In the HMME–PDT study group, there were five studies all comprised of infants.[22,24,29,30,34]

We used the same equations from a previous report[19] to calculate a mean clearance index (CI) for each study, the overall clearance percentage per category of the entire population (H), and overall CI (C_0). CI (%) = $(12.5d + 37.5e + 62.5f + 87.5g)/100$, where *d, e, f*, and *g* represent the percentage of patients with 0%−24%, 25%−49%, 50%−74%, and 75%−100% clearance, respectively.[19] H = number of subjects in the selected category/total subjects in all studies. The C_0 was calculated using the same equation as CI but using the overall clearance percentage per category of the entire population (H), which weighed data based on cohort size. The data were presented as means with standard deviations ("mean ± SD") or medians with interquartile ranges (IQR). A Mann–Whitney *U* test was used for nonparametric data and $p < 0.05$ was considered significant.

RESULTS

Our search related to "Port wine stain" resulted in 1653 PubMed records, including 140 publications related to PDL since 1988 and 51 publications related to HMME–PDT since 2007, respectively (Figure 1). For the PDL-related studies, 88 publications were excluded, including 78 other types of studies such as review papers, 3 where the full text was not available, 3 without quartile data available, 1 in non-English, and 3 with more than one treatment modality under study. After screening, a total of 40 studies were eligible comprising 5094 patients.[28,39,42–57,59–80] The HMME–PDT studies were all performed in China where HMME was approved as a photosensitizer for PWB treatment by the appropriate governmental authorities. For the HMME–PDT study group, 33 studies were excluded due to the following reasons: noncompliant outcome scoring systems ($N = 4$), other types of articles (23), studies with insufficient data reporting ($N = 4$), and studies in animal models ($N = 2$). A total of 18 studies were eligible for analysis comprising 3910 patients.[22,24,26,28–38,40,58,81,82] A flow chart of the literature search is shown in Figure 1. The clinical characteristics of patients in both treatment categories, including study types, laser treatment parameters, population demographics, and PWB lesion types are summarized in Table 1.

For the PDL study group, studies were performed in various countries and regions, including USA ($N = 10$), China ($N = 8$), UK ($N = 7$), Germany ($N = 4$), Japan ($N = 2$), Taiwan ($N = 2$), Vietnam ($N = 2$), Iran ($N = 1$), Korea ($N = 1$), India ($N = 1$), Singapore ($N = 1$), and Hong Kong ($N = 1$). The interquartile percentage PWB clearance by PDL showed large variations between studies due to different patient skin types, lesional types, population ages, laser treatment parameters, and so forth. For example, several studies showed the least clearance outcomes (0%−24%) for PDL treatment on resistant lesions or PWB located on the extremities.[47,51,70] There was no significant difference between the mean CI from studies in each group. The C_0 (overall clearance rate which weighed data based on cohort size) from all PDL studies was 0.54, which was slightly, but not significantly higher ($p = 0.823$) than the 0.48 of HMME–PDT studies (Figure 2).

To address the potential impacts of skin phototypes or geographical regions on efficacies between studies, we extracted the PDL studies performed in Southeast Asia ($N = 19$)[28,39,42,44,45,53,54,57,59,60,62,63,66,67,73,75,76,78,80] where the populations have darker skin phototypes (Fitzpatrick II−IV). There was no significant difference between the mean CI from studies in each subgroup. The C_0 from all PDL studies in Asia was 0.41, which was not significantly lower ($p = 0.338$) than that of PDL studies in non-Asia countries (0.64), but very similar to the C_0 (0.48) ($p = 0.921$) from HMME–PDT studies in patients with similar skin phototypes in the same regions (Figure 2).

Over 58% of patients in HMME–PDT studies were minors (<18 years old); while about 33.2% of patients in PDL studies were minors. To address whether age could be a potential efficacy factor between the two

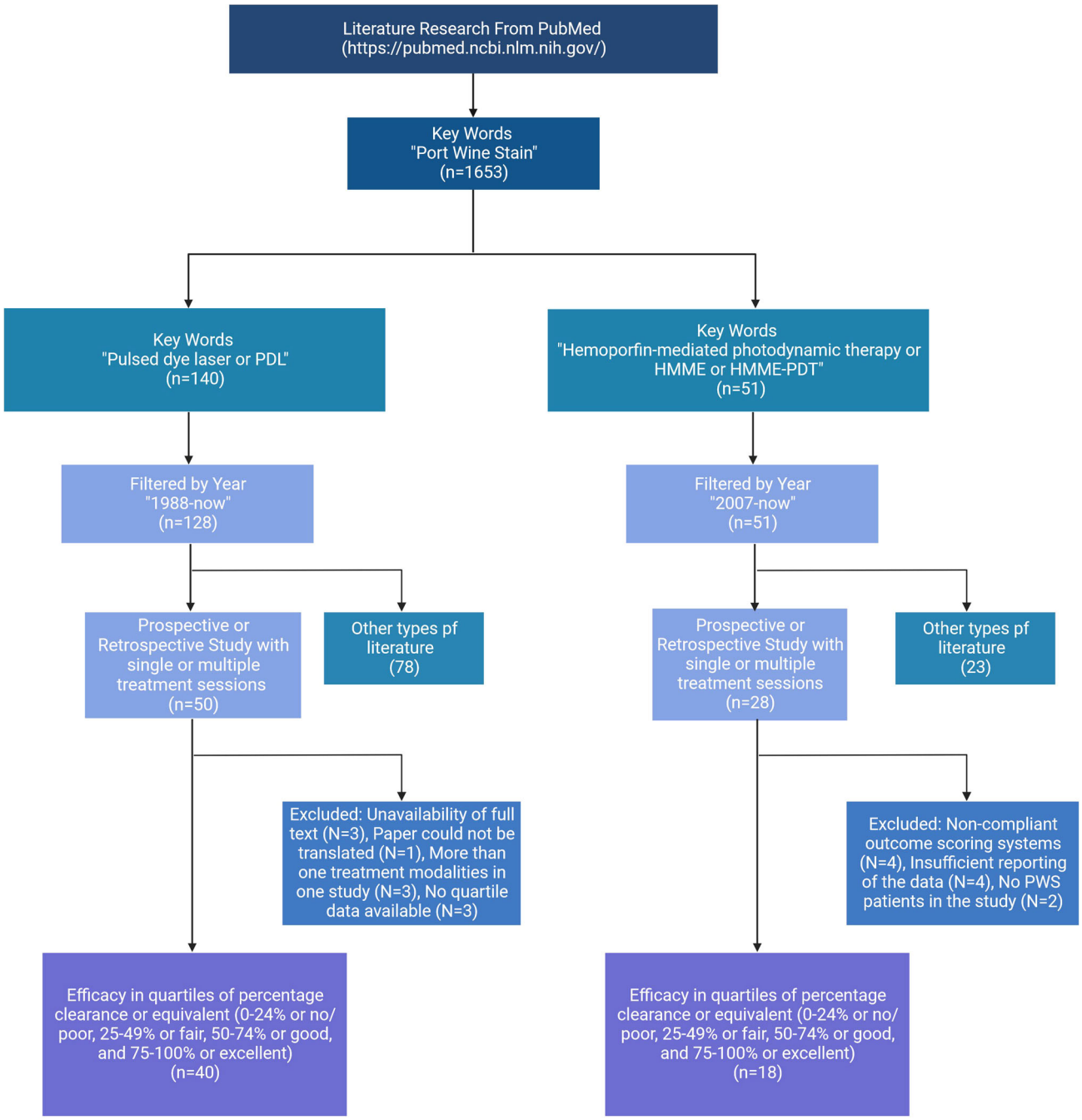

FIGURE 1 Flowchart for study inclusion and exclusion.

modalities, we extracted the available data from patients (<18 years old in both groups. In the PDL study group, the data were extracted from 17 studies comprising 1692 patients.[28,39,42,43,45–57] In the HMME–PDT study group, the data were extracted from eight studies comprising 2281 patients.[22,24,28–30,34,38,58] There was no significant difference between the mean CI between the PDL and HMME-PDT study groups ($p = 0.662$). The C_0 from PDL studied (<18 years old was slightly but insignificantly higher than that of HMME–PDT studies (0.49 vs. 0.46) (Figure 3).

In the third analysis on young children (<3 years old), the PDL group comprised 475 patients from seven studies,[42,43,46,54–57] accounting for 9.3% of the total patients. The HMME–PDT group comprised 833 patients from five studies,[22,24,29,30,34] accounting for 21.3% of the total patients. The C_0 from PDL studies was higher but not significant ($p = 0.081$) as compared to that of HMME–PDT studies (0.67 vs. 0.50) (Figure 4).

TABLE 1 Study characteristics for the PDL and HMME–PDT studies.

	PDL	All studies ($N = 40$)	HHME–PDT	All studies ($N = 18$)
Country/region	USA	10	China	18
	China	8		
	UK	7		
	Germany	4		
	Japan	2		
	India	1		
	Iran	1		
	Korea	1		
	Singapore	1		
	Hong Kong SAR, China	1		
	Taiwan, China	2		
	Vietnam	2		
Therapy	577 nm	1	HMME 5−7.5 mg/kg, 532 nm LED	14
	585 nm	14	HMME 2.5 or 5 mg/kg & 532 nm Nd-YAG	3
	595 nm	20		
	577 or 585 nm	1	HMME 3.5 or 4−5 mg/kg & 510.6 nm + 578.2 nm	1
	585 and/or 595 nm	4		
Age category	<1 year only	5	>2, 3, or 4 only	5
	>2, 3, or 4 years only	7	>6 only	1
	>10 years only	2	<14 only	4
	<14 years only	2	>14 or 16 only	4
	>14 years only	1	All ages	4
	>18 years only	5		
	All ages	18		
Previous treatment	Yes	3	Yes	2
	No	15	No	5
	Mixture	7	Mixture	8
	Not listed	15	Not listed	3
PWS localization	Face only	5	Face only	4
	Neck only	0	Neck only	0
	Face/neck	12	Face/neck	8
	Trunk/extremities	2	Trunk/extremities	0
	Various	19	Various	6
	Not listed	2	Not listed	0
PWS types	Flat lesions only	2	Flat lesions only	1
	Therapy-resistant only	2	Therapy-resistant only	2
	Hypertrophic only	0	Hypertrophic only	0
	Various	22	Various	14
	Not listed	14	Not listed	1

(Continues)

TABLE 1 (Continued)

	PDL	All studies ($N = 40$)	HHME–PDT	All studies ($N = 18$)
Cooling	Air cooling	4	Air cooling	1
	Cryogen spray cooling	22	Cryogen spray cooling	0
	No cooling/not listed	14	No cooling/not listed	17
Study design	Prospective	17	Prospective	5
	Retrospective	23	Retrospective	13
Treatment sessions	Multiple treatment sessions	35	Multiple treatment sessions	13
	Single treatment session	5	Single treatment session	5

Abbreviations: HMME, hematoporphyrin monomethyl ether; PDL, pulsed dye laser; PDT, photodynamic therapy.

DISCUSSION

Our data show that the overall efficacy of PDL is albeit insignificantly higher than that of HMME–PDT in cohorts of patients of all ages, subpopulations with only minors, and young children. This data suggests that HMME–PDT is a reasonable alternative for the clinical management of PWB. However, current evidence is insufficient to support that HMME−PDT should replace PDL as the first choice for young children, due to the lack of long-term data on follow-up evaluation on the impact of HMME-PDT on CNS development. There are many factors of concern regarding HMME–PDT which are discussed as follows.

(1) Efficacy comparison among young patients

There were several early studies comparing HMME–PDT to PDL.[27,28,83] Two studies were excluded from the analysis because quartile percentage clearance scales were not reported.[27,83] One study with compatible percentage clearance scales showed that HMME–PDT had a higher efficacy as compared to PDL in purple PWB lesions in children who had not received previous treatment.[28] The data from the HMME–PDT group (cohort size = 132) showed that only 10% of children (<10 years old) had a poor response rate (<25% clearance percentage) as compared to 70% of children with clearance rates greater than 50%. However, two newer studies with large cohorts ($n = 1080$ [multicenter] and 402 patients, respectively; <14 years old previously treated and untreated) showed that 37%−65% of children had a poor response (<25% clearance percentage) while only 28%−36% had clearance rates greater than 50% after HMME–PDT.[22,24] One potential contributing factor to the discrepancy among these studies was whether children were treated previously or not. Nevertheless, the latest study may help control for confounding factors with its larger sample size.[24] The common treatment session for HMME–PDT is 1−4 sessions with an interval of 8 weeks between two consecutive sessions. Therefore, one potential advantage of HMME–PDT is that it may achieve similar results in fewer treatment sessions than PDL.

Reports have shown that younger children treated by PDL had much better outcomes,[43,46] which is supported by the overall data in this study ($C_0 = 0.67$ [<3 years old] vs. 0.54 [all ages]). In contrast, the overall C_0 in the HMME–PDT has no changes between the two age groups ($C_0 = 0.50$ [<3 years old] vs. 0.48 [all ages]). One potential factor was that over 58% of patients were children in those studies. Furthermore, data shows that PDL shows a higher efficacy as compared to HMME–PDT in young children. Therefore, evidence supports that PDL treatment of PWB is superior to HMME–PDT and should remain the clinical "gold standard."

(2) Potential impact on CNS development in HMME-PDT-treated children

In general, drug approval should have public information available specific to a defined pediatric age group if the compound is to be administered to children. Unfortunately, we have been unable to find any available documentation regarding safety profiles of HMME-PDT for young children related to the initial approval by governmental health agencies.

HMME-PDT has been used to treat PWB in China for more than 30 years.[84] Therefore, the authors are expecting to find comprehensive long-term (i.e., 30 years old) follow-up evaluations of the efficacy on PWB in children treated by HMME–PDT. In addition to long-term efficacy, the other critical question is whether HMME could impact CNS development in young children. Young children have immature glial cells, resulting in greater permeability of the blood-brain barrier (BBB) (birth through 6 years but largest differences in the first 2 years), allowing rapid access of drugs to the CNS, particularly for water-soluble chemicals, and imposing greater potential toxicity.[85–87] There is no animal model data available to show whether HMME can penetrate the neonatal or infantile BBB and whether and how it might impact CNS

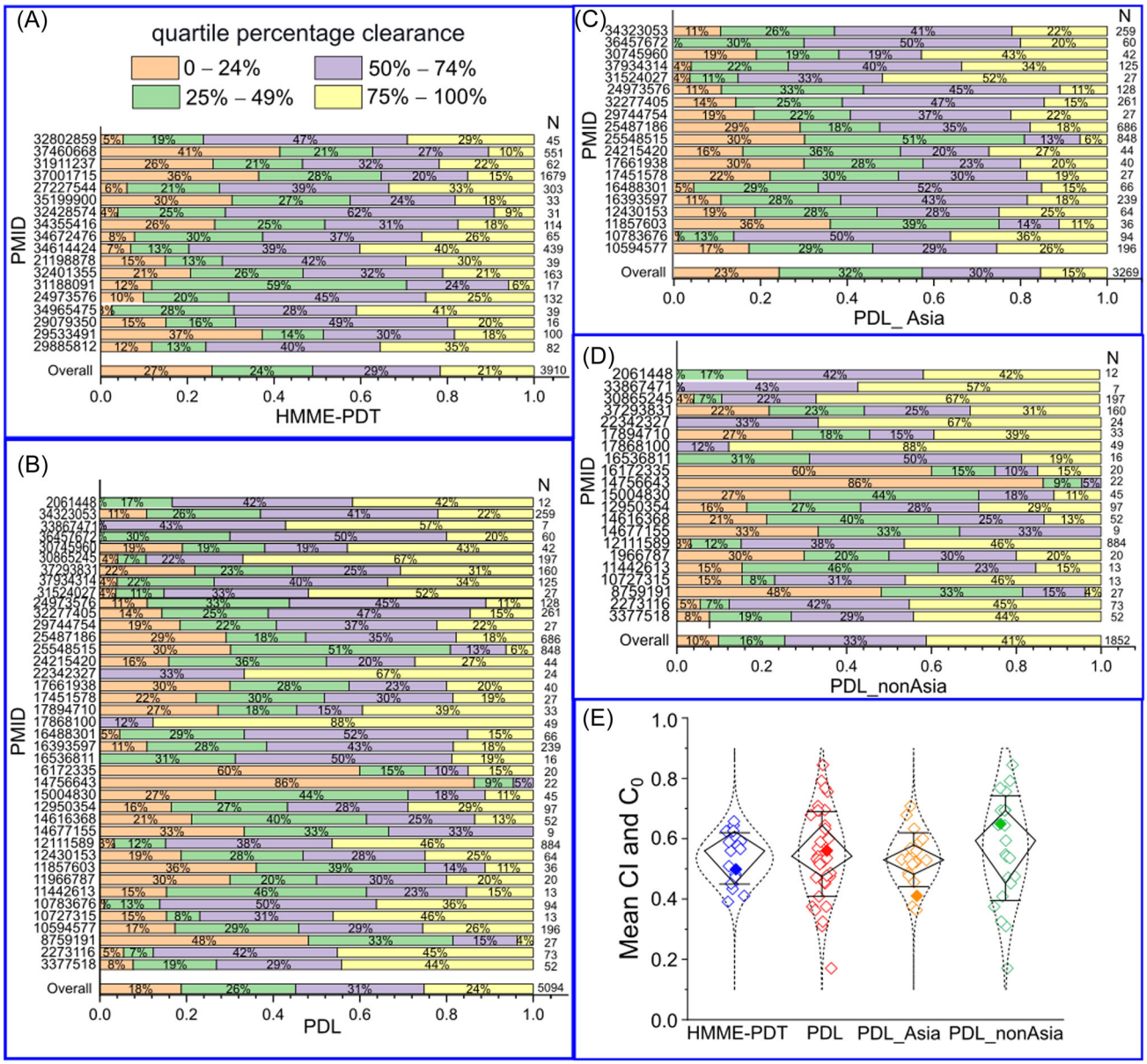

FIGURE 2 Clearance rates reported in PWB using HMME–PDT or PDL. (A) Clearance rates in all HMME–PDT studies. (B) Clearance rates in all PDL studies. (C) PDL studies performed in Asian countries. (D) PDL studies performed in non-Asian countries. The clearance rates are stratified in quartiles in four colors. Each bar represents one study and the PMID for each publication is listed on the left side of the bar. The clearance rate in each category is labeled within the corresponding section of the bar. Overall clearance rates from all studies are shown at the bottom of the *y*-axis. The cohort size of each study is listed on the right side of each bar. (E) Scattered plots show the mean CI of each study and overall cohort-size-weighted C_0 for each group in the panels (A), (B), (C), and (D), respectively. Each empty symbol represents the mean CI for one study. The filled color symbol represents the C_0 for each group. Whiskers: SD; diamond box: interquartile range (IQR); dotted curve: data distribution. A Mann−Whitney *U* test was used. HMME, hematoporphyrin monomethyl ether; PDL, pulsed dye laser; PDT, photodynamic therapy; PWB, port wine birthmark.

development and function. Furthermore, hematoporphyrin derivatives have been used as antidepressants,[88] indicating potential effects on brain function by this category of compounds. Therefore, the risk of HMME exposure to CNS in neonates, infants, and young children cannot be ignored. The potential toxicity of HMME on CNS development should have been addressed before intravenous administration of this drug to pediatric patients.

(3) Pharmacokinetics of HMME

The available pharmacokinetic data of HMME was obtained from adult subjects after a single-dose intravenous injection. Mild and transient adverse events such as nausea, stomach upset, abdominal pain, and vomiting were reported. The half-life of HMME for a dose of 5 mg/kg was approximately 1.31 h and urinary execration after 12 h was less than 0.2%.[89] After decades of HMME–PDT treatment for

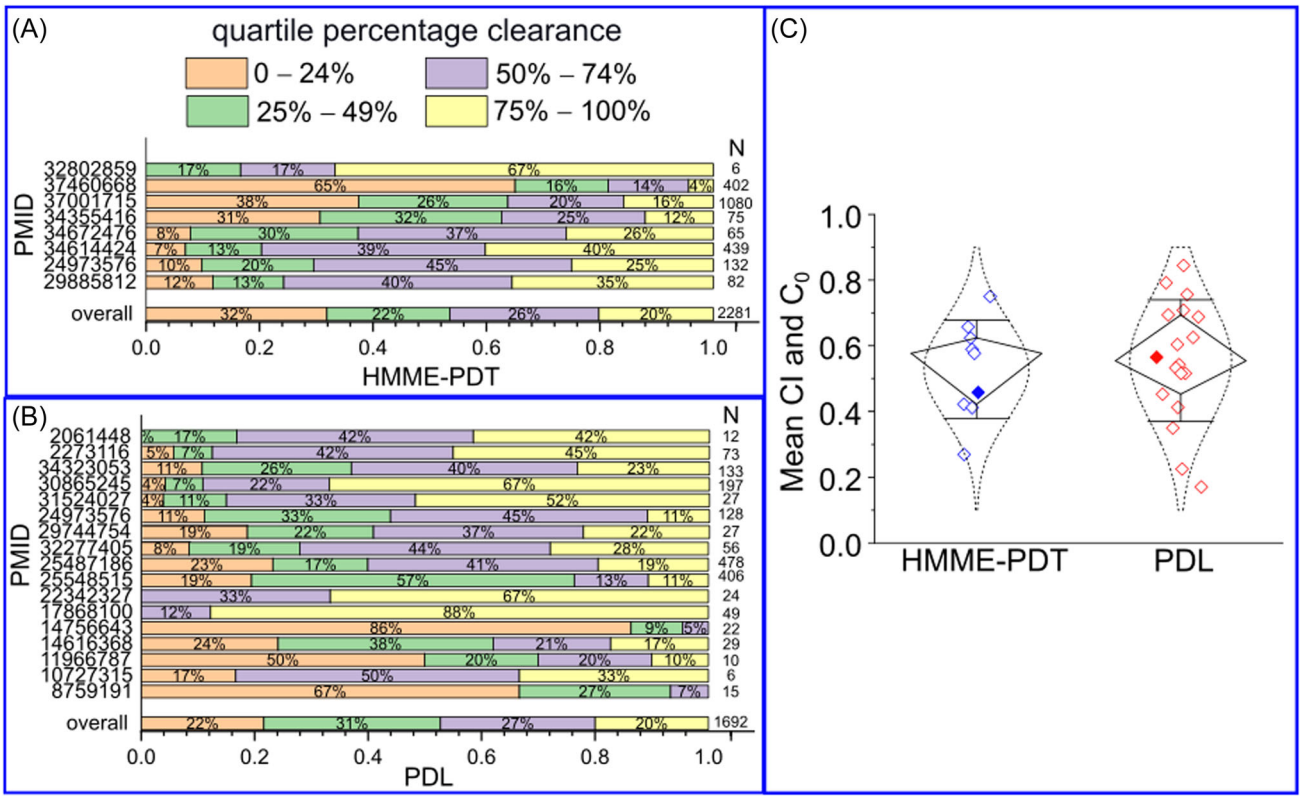

FIGURE 3 Clearance rates reported in PWB studies with patients <18 years old. (A) The data of subjects <18 years old was extracted from HMME–PDT studies. (B) The data of subjects <18 years old was extracted from PDL studies. Every bar represents one study and the PMID for each publication is listed on the left side of the bar. The clearance rate in each category is labeled within the corresponding section of the bar. Overall clearance rates from all studies are shown at the bottom of the *y*-axis in each panel. The cohort size of each study is listed on the right side of each bar. (C) Scattered plots show the mean CI of each study and overall cohort-size-weighted C_0 for each group in (A) and (B), respectively. Each empty symbol represents the mean CI for one study. The filled color symbol represents the C_0 for each group. Whiskers: SD; diamond box: interquartile range (IQR); dotted curve: data distribution. A Mann−Whitney *U* test was used. HMME, hematoporphyrin monomethyl ether; PDL, pulsed dye laser; PDT, photodynamic therapy; PWB, port wine birthmark.

PWB in children in China, the first piece of pharmacokinetic data in children was published in April 2023.[90] Various tests for liver and kidney function, blood, urine, and electrocardiogram remained within normal ranges after HMME administration in children. However, detailed values of these tests were not provided.[90] In addition, many essential parameters were not evaluated such as clearance, the volume of distribution, elimination half-life, area under the curve, mean residence time, the elimination rate constant, and the fraction of the drug excreted in urine, and so forth. The pharmacokinetics of HMME differs between children and adults due to physiological differences. The rates of drug metabolism and excretion are generally lower in children as compared to adults due to immature liver enzymes and kidney function.[85,87] These may affect the treatment dosage and potential side effects of HMME in young children as compared to adults. Collectively, pharmacokinetic and pharmacodynamic data on HMME remains incomplete, even though more than 3000 pediatric patients have been reported to be treated by HMME–PDT over decades in China.

(4) Cost of HMME

The cost of either PDL or HMME–PDT for PWB treatment is not covered by the state Medicare system in China. Patients usually pay out of pocket for the HMME. For a pediatric patient (≤25 kg weight), one session of HMME–PDT treatment can cost approximately $1200, including the $800 cost of HMME per vial (100 mg) and the $400 laser treatment fee. The cost will double for those patients weighing between 26 and 50 kg. The cost of the HMME remains a major economic burden for patients.

(5) Optical properties of HMME and 532 nm as a suboptimal light source

HMME was synthesized by Xu in the 1980s as a new photosensitizer to replace hematoporphyrin derivatives.[91,92] In water and saline-based solvents, HMME shows multiple absorption peaks at 393, 503, 539, 565, and 617 nm, with a gradual decrease in molar extinction coefficients.[93] The LED 532 nm light source is close but not optimal for generating the

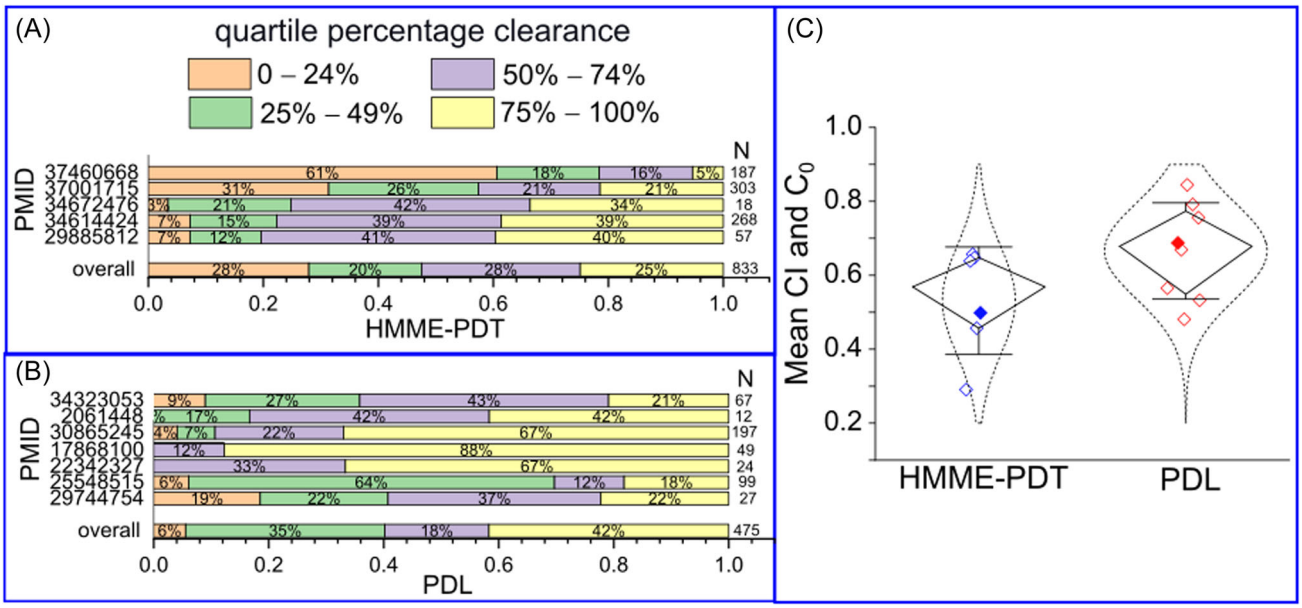

FIGURE 4 Clearance rates reported in PWB studies with patients <3 years old. (A) The data of subjects <3 years old was extracted from HMME–PDT studies. (B) The data of subjects <3 years old was extracted from PDL studies. Every bar represents one study and the PMID for each publication is listed on the left side of the bar. The clearance rate in each category is labeled within the corresponding section of the bar. Overall clearance rates from all studies are shown at the bottom of the *y*-axis in each panel. The cohort size of each study is listed on the right side of each bar. (C) Scattered plots show the mean CI of each study and overall cohort-size-weighted C_0 for each group in (A) and (B), respectively. Each empty symbol represents the mean CI for one study. The filled color symbol represents the C_0 for each group. Whiskers: SD; diamond box: interquartile range (IQR); dotted curve: data distribution. A Mann−Whitney *U* test was used. HMME, hematoporphyrin monomethyl ether; PDL, pulsed dye laser; PDT, photodynamic therapy; PWB, port wine birthmark.

maximal therapeutic result. However, light sources with longer wavelengths (>570 nm), which can penetrate deeper into the skin, show substantially lower molar extinction coefficients than those at the 539 or 565 nm peaks.[93] The light sources ranging from 538 to 541 nm are much more expensive to manufacture than the 532 nm LED. Therefore, the 532 nm LED remains the most cost-effective choice of light source. A major disadvantage of the 532 nm wavelength is that the depth of light penetration into the skin is much less than that of the 577−595 nm PDL for targeting PWB vascular lesions.

(6) Sole study locality

HMME was approved by the Chinese National Medical Products Administration in October 2016. All HMME–PDT studies to date have been performed in China. There were five reports included in this analysis published or had patient enrollment before 2016.[26–28,36,37] However, there was no conflict-of-interest statement available or claimed in three of the studies.[27,28,36] It was unclear how physicians/patients received the HMME before the official approval date without a manufacturer's sponsorship. The concern remains whether there were any ethical incompliance in those three reports. Furthermore, the data has not been verified in neighboring regions or countries where patient populations have similar skin phototypes nor in other countries where patients have different skin phototypes. Therefore, the actual efficacy of HMME–PDT in PWB patients beyond China is yet to be determined.

(7) Side effect management related to HMME–PDT during and after operation

During treatment of HMME–PDT, HMME (5 mg/kg dose in 50 mL saline solution) is slowly intravenously injected (2.5 mL per min). To prevent the drug allergic reactions related to photosensitizer (such as pain, skin rashes, and itching, nausea, abdominal cramps) and decrease short and long-term adverse effects associated with treatment (such as swelling, blisters, crusting, edema, hyperpigmentation, hypopigmentation, and scarring formation), dexamethasone (2−3 mg for children or 5−10 mg for adults) is usually coadministered with HMME intravenously.[38] After injection, patients will usually wait for 5−10 min and be given a light irradiation (such as 532 nm LED green light, 96−115 J/cm^2, 80−95 mW/cm^2). The treatment time is usually about 20−25 min. About 5%−15% and 45%−60% of adult patients could experience mild and moderate pain which occurs in about 5−10 min of onset of the light, respectively.[37] Light pause and cold wind blowing can be used to relieve side effects during treatment. The procedure is well-tolerated by most teens and adults in general. However, for children younger than 5 years old, parents need to be accompanied, and wrist restraints are

often used in clinical practice due to the constant pain and discomfort caused by the procedure. In some cases, general anesthesia has been used in these young patients.[94] In contrast, numerous studies have shown that PDL is safe and well-tolerated even by infants, without anesthesia, which can avoid the risks associated with anesthesia.[56]

The overall side effect profiles of PDL and HMME–PDT are very similar including local red swelling, blisters, crusting at the treated site, edema, and purpura. However, patients experience more pain during HMME–PDT treatment because the procedure takes much longer to perform, that is, 20−30 min per location. In addition, patients need to avoid light exposure for 2 weeks after HMME administration. Other considerations include potential off-target exposure to the meningeal and eye vasculature in young children during the HMME–PDT procedure. All studies of HMME–PDT were performed in the Chinese population (Fitzpatrick skin type III–IV). Therefore, it remains to be determined whether HMME–PDT is safe in skin types darker than Fitzpatrick type IV.

Hyperpigmentation in the HMME–PDT treated areas can be observed in 22%−31.6% of patients and usually fades in 3−6 months. However, long-term cosmetic changes such as hyperpigmentation, hypopigmentation, and scar formation have been reported in 5%, 1%, and 1%−3% of patients treated with HMME–PDT, respectively.[94] The incident rate of hyperpigmentation and scar formation can be reduced in patients when coadministration of dexamethasone with HMME and the use of cold wind blowing during the entire procedure (L. G., personal communication).

CONCLUSION

PDL shows overall albeit insignificantly higher efficacies than HMME–PDT in PWB patients of all ages. On the one hand, it is exciting to observe the promising efficacy of HMME–PDT, providing an additional option to some adult PWB patients. On the other hand, PDL has a proven safety record in the treatment of PWB in young children whereas HMME-PDT remains inadequate. The uncertainty of the long-term potential impact of HMME on CNS development in young children needs to be addressed in future studies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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