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REVIEW

Hematoporphyrin Monomethyl Ether Photodynamic Therapy of Port Wine Stain: Narrative Review

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Abstract: Port wine stain (PWS) is a congenital and progressive capillary malformation characterized by structural abnormalities of intradermal capillaries and postcapillary venules. The visible manifestation is often considered a disfigurement and the accompanying social stigma often causes serious emotional and physical impact. Hematoporphyrin monomethyl ether (HMME) is a newly authorized photosensitizer for treating PWS in China. Hematoporphyrin monomethyl ether photodynamic therapy (HMME-PDT) has successfully treated thousands of Chinese patients with PWS since 2017, and HMME-PDT may be one of the most promising strategies for the treatment of PWS. However, there are few reviews published about the clinical use of HMME-PDT. So in this article, we want to briefly review the mechanism, efficacy evaluation, effectiveness and influencing factors, and the common postoperative reactions and treatment suggestions of HMME-PDT in the treatment of PWS.

Keywords: port wine stain, photodynamic therapy, photosensitizer, HMME, PDT

Background

PWS is characterized by well-defined red, purple patches or plaque, usually unilateral or segmental distribution, and can occur anywhere on the body. PWS generally will not fade naturally, and the lesions will be deepened in color, thickened, and even nodules. A large cross-sectional study in China suggests that the incidence of neonates with PWS is about 0.8%, intrauterine hypoxia and hypertension during pregnancy may be two significant risk factors for the development of PWS,[1] but more evidence is needed to support these studies. PWS can be accompanied by the hypertrophy of skin, soft tissue and bone, combined with structural and functional disorders, such as choroidal hemangioma, glaucoma, epilepsy,[2] and severe psychosocial diseases.[3]

PWS is usually sporadic, but familial cases have been reported, which may be related to the inheritance of RAS p21 protein activator 1 (RASA1).[4] Most of PWS are congenital, and few of them are acquired, which may be related to trauma, drugs and other reasons.[5] Although the exact cause of PWS is unknown, it has been reported that the development of PWS may involve a variety of mechanisms, including vasodilation, loss of neuronal control of blood flow, overexpression of vascular endothelial growth factor (EGF) and its receptors (EGFR), and compensatory collateral pathway formation of venous return.[6] In addition, genetic mutations, especially in the somatic mosaic gene of G protein subunit alpha q (GNAQ), which plays an important role in the pathogenesis of PWS. The mutations of GNAQ gene may be associated with the clinical phenotype, with simple PWS suggesting a delayed mutation of GNAQ gene, while in Sturge-Weber syndrome, mutations may appear earlier, occurring in progenitor cells at the embryogenesis stage, resulting in a syndromic phenotype.[7] Generally, these findings suggest that PWS may be a malformation caused by a genetically controlled disorder of endothelial cell differentiation, accompanied by progressive dilation of immature venulous-like vessels.[8]

It is reported that 70–85% of PWS occur in exposed parts such as the face and neck, which have obvious disfigurement, which has a significant impact on patients' mental health and social activities, and reduces the overall quality of life.[3] For these reasons, most patients are eager to seek effective treatment. There are various treatments for

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PWS, including freezing, surgery, x-rays, isotopes, etc., but these treatments either leave obvious scars or cannot completely eliminate the color of the lesion or have a potential risk of skin cancer, none of these has been recommended as treatment options nowadays. Pulsed dye laser (PDL) is usually recommended as the gold standard for treatment, but according to clinical application, PDL has limited efficacy and high recurrence rate.[9–11] Therefore, an effective and safe treatment modality is still needed for PWS.

Photodynamic therapy (PDT) induces photochemical reactions through photosensitizers, light, and oxygen to produce highly reactive singlet oxygen molecules that can cause cell death through apoptosis, necrosis, or autophagy,[12] it had been proposed as an alternative treatment for angioproliferative skin lesions in the early 90s of the 20th century. Many clinical data show that PDT has a good effect on PWS.[12,13] Hemoporfin, also called hematoporphyrin monomethyl ether (HMME), is a second-generation porphyrin photosensitizer. Due to its more stable structure, higher photoactivity, and lower phototoxicity, HMME is widely used in PDT of PWS in China. The previous national multi-center study in China showed that the effective rate of HMME-PDT was 97.4%, the significant improvement was 64.0%, and the clinical basis was 28.1%.[12]

As a new porphyrin photosensitizer developed in China, HMME mediated PDT has successfully treated thousands of Chinese patients with PWS, and HMME-PDT may be one of the most promising strategies for the treatment of PWS. In recent years, many clinical studies of HMME-PDT had been published, but few reviews. This article briefly reviews the mechanism, efficacy evaluation, effectiveness and influencing factors, and the common postoperative reactions and treatment suggestions of HMME-PDT in the treatment of PWS. This review can provide a systematic understanding of HMME-PDT for clinicians.

Mechanism

HMME-PDT is a pharmaco-mechanical combination therapy, which requires three basic conditions: photosensitizer, light and oxygen. After intravenous injection into the body, HMME can form a concentration in the blood, and rapidly spread to tissues and specifically distribute in vascular endothelial cells. Under the excitation of 532nm green light, it can produce reactive oxygen species (ROS), such as singlet oxygen and oxygen-free radicals by photochemical reactions, which can selectively destroy vascular endothelial cells rich in photosensitizer. Due to the selective distribution of HMME, the normal epidermis will not be damaged by the PDT.

PDT can lead to cell death by apoptosis, autophagy, necrosis and paraptosis through oxidative stress, inducing immune responses meanwhile, and all these mechanisms can act simultaneously.[14,15] The cell death pathway activated by PDT varies not only by cell type, but may also vary with light duration, energy, different types and concentrations of photosensitizers and their intracellular location.[16] Apoptosis is the main mode of cell death mediated by HMME-PDT, but the role of autophagy in HMME-PDT remains unclear.[17,18] Studies have shown that there is interference between autophagy and apoptosis in the process of vascular endothelial cell death induced by HMME-PDT. HMME-PDT induces apoptosis of vascular endothelial cells and inhibits autophagy. Autophagy protects vascular endothelial cells from cell death caused by apoptosis.[19] Both apoptosis and autophagy are involved in the complex process of cell death and survival. Inhibition of autophagy may be a way to enhance the efficacy of HMME-PDT. However, many crux remain to be elucidated.

It has been observed in clinical practice that the less redness of PWS after HMME-PDT treatment, which may due to HMME-PDT inhibition of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) expression,[6,8,20] affecting vascular regeneration.

Effect Evaluation

Effect Prediction

It is well known that the depth, diameter and thickness of vessels are the most critical factors affecting the treatment effect of PWS.[21] Histological examination is the most intuitive and standard method to know the diameter, depth and thickness of malformation vessels of PWS, but it is an invasive examination with limited practice. Dermoscopy is a simple, noninvasive examination, and vascular pattern of PWS under the dermoscopy has been found to be associated with histopathology, so dermoscopy can be used as an alternative option.

In a prospective study, the vessels of PWS were divided into the following eight vascular pattern:[22,23] ① dotted and globular vessels; ② short clubbed vessels; ③ curved vessels; ④ pale halos surrounding brown dots; ⑤ arborizing vessels; ⑥ Mixed vessels; ⑦ a grey-whitish veil; ⑧ reticular vessels. There is a certain correlation between the vascular pattern and treatment response of HMME-PDT.

Dotted and globular vessels, short clubbed vessels, and curved vessels, are characterized by a clean background and well-defined reddish vascular morphology.[24] These vessels may be located in the upper third of the dermis, are superficial and perpendicular to the skin with no dense proliferation of collagen fibers, and have relatively thin-vessel walls.[22,23] HMME-PDT can more easily destroy or remove deformed vessels that are superficial to the location.[22,23] The presentation of these three patterns may thus be predictive of curative or at least good effect outcomes of HMME-PDT in PWS.

Arborizing vessels and a pale halo surrounding brown dots are PWS vascular patterns associated with moderate impacts of HMME-PDT and may therefore be predictive of such outcomes.[22] Arborizing vessels may be horizontal and are likely to be located at varying and inconsistent depths in the dermis, and suggest that many malformed vessels will be without the scope of the penetration depth of the light.[23] A pale halo surrounding brown dots in the sebaceous gland-rich site suggested a thicker of the lesion, which might block PDT light penetration.[22] This phenomenon also reflects the fact that the accessory of hair follicle, such as sebaceous glands, can reduce and hinder the energy of light. However, some scholars believe that these two vascular models can achieve better outcomes by increasing the amount of drug and energy or multiple treatment.[12,21]

Dermoscopy patterns were mixed vessels and a grey-whitish veil, characterized in a hazy red background with badly defined vessels, which not only are associated with a larger diameter and thicker blood vessel wall, but also with dense collagen fibers in the deeper dermis, the thicker vessel walls and the dense collagen fibers can block the energy of the light source.[21–24] The reticular vascular patterns under dermoscopy may represent a large number of parallel or cross-arranged vessels in the deeper dermis, and these malformed vascular structures are not easily penetrated by HMME-PDT light source.[22,23] Therefore, the presentation of these three vascular patterns suggests the lower effect of HMME-PDT.

Another study found that the immediately dermoscopy performance after HMME-PDT, which showed vascular rupture, punctate or globular hemorrhage shadow, indicating a better later efficacy.[25,26] That may be a predictive marker of efficacy.

Efficacy Evaluation Tool

The evaluation of the treatment effect of PWS has always relied on the subjective evaluation of physicians. At present, the most commonly used and convenient way is camera photography, which has low cost but many interference factors. Therefore, clinical photos need to be taken under standardized conditions, such as the same camera and settings, light, background, angle, etc. With the development of non-invasive diagnostic techniques, many non-invasive tests have been widely used in the field of skin diseases. Because of its many advantages such as visualization, real-time, dynamic, quantitative, multi-modal and efficacy monitoring, in recent years, non-invasive tests have also been gradually applied to evaluate the efficacy of PWS treatment.

Visia-Cr™

Standard images acquired with the VISIA-CR™ system at 6500-K white light can visually show lesion discoloration before and after treatment, which are comparable. Canfield's patented RBX™ (Red/Brown/X) technology provides a semiquantitative assessment of specific chromophores in the skin.[26] RBX red image shows highly aggregated and densely distributed blood vessels in PWS patients. In addition, inconspicuous lesions can be observed in the RBX red images, which is important for the determination of lesion boundaries and precise treatment.[26] However, VISIA-CR™ images cannot effectively show the thickened lesions, and some other diseases, such as acne post-inflammatory erythema, which may affect the judgment of the lesions in red images. Therefore, the red images of VISIA-CR™ need to be combined with the standard images from multiple angles. In addition, VISIA-CR™ is only suitable for the detection of facial lesions due to the particularity of the device structure.

Skin High Frequency Ultrasound (HFUS)

The most commonly used ultrasound to study skin diseases has a frequency with 15–20 MHz, a penetration depth of 10mm, and a resolution of more than 0.1mm. It can clearly show the structure of skin epidermis and dermis. As a non-invasive and repeatable examination method, HFUS can measure the changes of skin thickness and density, which can theoretically meet the requirements for the measurement and evaluation of skin lesions in patients with PWS. A study has found that the thickness and density changes of the contralateral normal skin of patients with PWS and the affected side of the skin before and after treatment were measured by 15MHz HFUS. It was found that after HMME-PDT treatment, the skin thickness of the affected side of patients with PWS became thinner and dense, indicating that the therapeutic effect of HMME-PDT is closely related to the thickness and density of skin lesions.[27]

In another study, 20–50MHz HFUS was used to detect PWS lesions. They found that PWS lesions were significantly thicker than normal skin, and the dermis was loosely arranged, showing linear hypoechoic signals, which could be considered as vascular malformation. After HMME-PDT, it was observed that the thickness of skin lesions under ultrasound decreased significantly, the linear hypoechoic signal decreased, and the tissue tended to be dense.[26] Therefore, linear hypoechoic signal can be used as an indicator of prognosis. However, not all skin lesions have this ultrasound signature, which may be due to the fact that most PWS blood vessels are shallow and small in diameter, and the resolution of the existing HFUS does not respond to their blood vessels. Thus, the prospects of HFUS in HME-PDT depend on the increase in the frequency of high-frequency ultrasound.

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a noninvasive tool for imaging skin tissue. Based on the principles of light reflection delay and interference imaging, OCT can effectively image the internal structure of tissues. Scanning optical scattering media, OCT can provide histomorphological images with micron resolution. OCT can be used to quantitatively measure the diameter and depth of PWS's malformed blood vessels before and after HMME-PDT treatment, which can provide objective data for observing the difference of treatment effect and avoid the subjectivity of human eye visual judgment.[28] Precisely because OCT can observe the diameter and depth of malformed blood vessels, it may provide the basis for individualized and precise treatment in the future.

Laser Speckle Contrast Imaging (LSCI)

Laser speckle contrast imaging (LSCI) is a non-contact and near-infrared imaging system with high temporal and spatial resolution, which is used to detect blood flow on the skin surface.[29] LSCI can form full-field blood perfusion map of the detected area through real-time blood flow detection based on speckle comparative analysis. After HMME-PDT, most effective lesions showed decreased blood perfusion, some effective lesions and the ineffective lesions did not reduce blood perfusion. However, skin blood perfusion may be affected by many factors, such as ambient temperature and physical activity.[30] Therefore, LSCI need to be measured in a temperature-controlled room, and patients need to remain an adjustment period before measurement. That requires more patients' compliance and it has more limitations.

At present, the methods used to analyze therapeutic efficacy in PWS-related studies are highly heterogeneous, thus making study structures non-comparable and hindering evidence-based clinical decision-making.[31] Therefore, an objective and effective standardized efficacy measurement tool is needed in the future, which depends on the development of non-invasive detection techniques and the establishment of expert consensus or guidelines.

The Effect and Safety

The therapeutic effect of HMME-PDT on PWS is affected by various factors, which are described in detail in The Influencing Factors of Effect. In professor Gan Liqiang's team in Chongqing Children's Hospital in China,[32] they observed a trial of the effectiveness and safety of HMME-PDT in treating Chinese pediatric patients with PWS (ages between 1 and 14 years old). The patients received an intravenous injection of 5 mg/kg HMME and the irradiation power density between 80 and 85 mW/cm^2. After two treatments, 24 of the 82 cases were cured (29.27%), 34 cases indicate a good efficacy (41.46%), 16 cases showed alleviation (19.51%), while 8 cases displayed no efficacy (9.76%). No other obvious systematic adverse reactions were reported.

In Li et al's study,[33] 62 patients aged 2–55 with PWS were enrolled, among which, 20 cases were pink type, 32 cases were purple type and the remaining 11 cases were nodular thickening type. All patients received an intravenous injection of 5 mg/kg HMME, and the irradiation power density ranged between 80 and 100 mW/ cm^2. After 2 times treatments, 11 of the 62 cases were cured (17.74%), 17 cases showed a good efficacy (27.42%), 20 cases indicated alleviation (32.26%), while 14 cases displayed no efficacy (22.58%). The side effects after treatment mainly displayed with edema, crust, hyperpigmentation. No recurrence within 2 years.

In a retrospective study by Yang Jun which included 212 patients with PWS, that the mean age of these patients was 13.01 ± 12.67 years, here were 143 patients with red, 56 patients with purple, and 13 patients with hypertrophic PWS. The excellent response rate after 1–4 PDT sessions was 9.4%, 17.6%, 32.7%, and 42.9%, respectively.[21]

In the past, there is no more effective way to treat pulsed dye laser-resistant port wine stains. In recent years, more and more clinicians found that HMME-PDT could be a good choice. A retrospective study had evaluated the efficacy and safety of HMME-PDT for 67 patients with pulsed dye laser-resistant cervicofacial port wine stains, which showed that, based on the overall visual assessment, 46.2% patients showed excellent or good levels of improvement (>50% color blanching).[34] Another study also showed that HMME-PDT had good treatment response to PWS resistant to pulsed dye laser therapy.[11] Adverse events were minimal, transient and self-limiting. In a conclusion, HMME-PDT is effective and safe, which can serve as an alternative treatment of PWS resistant to pulsed dye laser therapy.

The Influencing Factors of Effect

Malformed Vascular

It is well known that the depth and diameter of blood vessels and the thickness of vessel walls are the most direct factors affecting the therapeutic effect of PWS. The presence of malformed vessels in the superficial dermis, perpendicular to the skin surface, and thin-vessel walls usually suggests that HMME-PDT works well; the vascular diameter is large, the vascular is located in the deep dermis, and the vascular arrangement is staggered, which usually indicates the poor effect of HMME-PDT.[22,23] Histological examination is the most intuitive and standard method to understand the vessel diameter and depth of PWS, but its practical application is limited due to the invasive examination. Dermoscopy is currently recognized as a simple and noninvasive method to evaluate vascular morphology before treatment of PWS, other noninvasive tests, such as optical coherence tomography (OCT) and reflection confocal microscopy (RCT), can also be used to observe the diameter and depth of malformed blood vessels, but their clinical application of PWS is limited and needs more supporting evidence.[26]

Non-Vascular Factors

The factors of malformed blood vessels are the most direct factors affecting the effect of HMME-PDT, but the characteristics of the skin, such as skin appendages (sebaceous glands, etc.) and dense collagen fibers in the dermis, will also affect the penetration of light, resulting in the attenuation of the energy, which will also affect the therapeutic effect.[22,23] But in another study, this non-vascular morphology may have some effect on light penetration, but it can be improved by adjusting the treatment parameters.[21] In another study, it suggested that the skin color is also a factor affecting the therapeutic effect. Melanin in the epidermis will absorb the energy from the light, resulting in the attenuation of the energy reaching the malformed blood vessels, which affects the therapeutic effect.

Treatment Parameters

The dose of HMME and the energy parameters of PDT are also important factors affecting the therapeutic effect. In earlier trials of intravenous hemoporfin about pharmacokinetics and tolerance in healthy volunteers, they found that compared to the 7.5 and 10 mg/kg dose groups, fewer adverse events were found in the two lower-dose groups (2.5 and 5mg/kg), as expected. Based on the above results, they chose the dosage range from 2.5 to 5 mg/kg for Phase II clinical trials.[35] In phase IIb clinical trials, they found that compared to the patients in the low-dose hemoporfin group (2.5 mg/kg) and the control group, patients in the high-dose hemoporfin group (5 mg/kg) had a statistically significant higher proportion to achieve "at least some improvement" and "at least great improvement".[36] As for the energy parameters of

the treatment, theoretically, the higher the energy, the heavier the response and the better the effect. But unfortunately, there has been no relevant article on the systematic explanation of the choice of energy parameters.

Others

Some clinicians have observed that a better response to HMME-PDT in the lateral than in the central area, that maybe vessels in the lateral regions were primarily located in the papillary dermis, whereas in the central regions they were extensively distributed from the dermis into the subcutaneous tissue,[37] but not every clinician is convinced.[21] Some scholars suggest that the number of treatments was a favorable factor for HMME-PDT, smaller lesion sizes showed a better effect than the larger one, and the location of extremity and trunk was a negative factor.[32,38] Of course, there still are some different research results from different medical center, such as types of the lesion, some clinicians think pink lesion showed a better effect than purple lesion,[32,33,39] but our team had contrary opinion (unpublished). There is no consensus on these factors, which need more study to prove.

Treatment Response and Management

Pain

The main manifestation of HMME-PDT is pain. As a subjective feeling of patients, there is no objective medical instrument for the evaluation of pain intensity, which mainly depends on the subjective description of patients. At present, the commonly used pain assessment methods in clinical practice are verbal description scales (VDS), face pain scale-revised (FPS-R), verbal rating scale (VRS), visual anoalogue scale (VAS), numerical rating scale (NRS), etc.[40]

Pain is a complex process affected by many factors, and its mechanism is not fully understood. The same pain stimulus can produce different pain sensations and responses in different individuals, and a recent study involving identical twins found a genetic link between pain and pain sensitivity.[41]

In HMME-PDT, the mechanism of pain is not clear, which may be related to the production of a large number of reactive oxygen species (ROS) during light irradiation. Increasing the use of photosensitizers and the energy of light irradiation both accelerate the production of ROS and nerve stimulation. However, when the dose of photosensitizers and the energy of light irradiation reach the threshold level, they either saturate the capacity of cells to produce ROS or it desensitizes pain receptors and ion channels, leading to a plateau of pain sensation.[42] In clinic, pain is also found to be related to skin site, skin area, skin temperature and other factors.

Local Cold Therapy

Local cold therapy is one of the common and proven effective pain management methods in PDT. Kroon et al found a statistical difference in pain scores among patients treated with ALA-PDT for actinic keratosis with or without cold air.[43] There are several possible reasons of alleviating pain with local cold therapy:①it relieving pain caused by tissue swelling and compression of nerve endings by constricting blood vessels and reducing vascular permeability; ②it can inhibit cell activity and slow down the transmission of nerve impulses; ③it can reduce the sensitivity of nerve endings to reduce pain; ④transient receptor potentials (HAET-TRP) can sense hypothermia and decrease the firing of nociceptive neurons;[42] ⑤it can reduce the activation of TRPV1 and simultaneously activates TRPM8, thereby inhibiting pain transmission in A-δ and C-type fibers.[42,44] During the treatment process, cold air can be used to reduce the skin temperature without affecting the treatment process. After treatment, cold spray or compress can be used to reduce skin temperature.

Topical Anaesthesia

Before treatment, topical anesthetics such as lidocaine cream and tetracaine glue have been used in clinical practice, but no positive effect on pain has been found.[45]

Oral Analgesic

Patients can reach the peak pain during the HMME-PDT, and the pain degree decreases after the treatment, but the pain will still last for 24 to 48 hours or even longer due to the inflammation response in the treatment area. Common oral analgesics include NSAIDS and central analgesics. Naiyan Huang et al used an analgesic strategy of oxycodone 5mg/paracetamol

325mg for the treatment of pain in HMME-PDT, their results showed that the VAS score between the treatment and placebo groups was not significantly different, but interestingly, in follow-up, this analgesic strategy was shown to relieve pain after HMME-PDT.[46] One of the reasons may be that the dose of 5 mg of oxycodone/325 mg of acetaminophen was insufficient to relieve the serious pain during PDT. And acetaminophen relieves this pain after HMME-PDT by reducing the oxidized form of the COX enzyme and preventing it from forming pro-inflammatory chemicals. However, most recent evidence suggests that oxidative stress and inflammatory responses are key to HMME-PDT efficacy,[42] so whether blocking the inflammatory response decreases HMME-PDT efficacy requires further investigation.

Nerve Block

Nerve block is clearly effective in relieve pain in PDT. Paoli et al conducted a half-face control on 16 patients who received ALA-PDT for actinic keratosis mainly in the forehead, and they found that the pain on the side receiving nerve block was significantly reduced compared with that on the side without nerve block.[47] By comparing the efficacy of local nerve block with cold air analgesia in reducing pain in PDT, Serra-Guillen et al found that nerve block was superior to local cold therapy.[48] The application of nerve block in HMME-PDT is relatively rare. We have recently tried local nerve block in our center, and the clinical effect of analgesia is satisfactory. However, some anesthetics may cause vasoconstriction, enlarge its local concentration, or may reduce ROS production by blocking oxygen transport, thus affecting the efficacy of PDT.[42] However, a nerve block does not represent the perfect management of limited anesthesia areas, with painful pricking and the risk of nerve and blood vessel damage. In addition, nerve block is costly in time and can only be performed by adequately trained and experienced clinicians, which further limits its use.

General Anesthesia

General anesthesia is the only way to completely relieve the pain during HMME-PDT, but it does not solve the pain after treatment. The FDA recommends that anesthesia duration less than 3 hours is safe for infants and young children, but the benefits and disadvantages of general anesthesia and sedatives should be carefully considered if the duration of anesthesia is longer than 3 hours and children under 3 years of age are repeatedly used.[49]

Edema

Local edema is one of the most common reactions of HMME-PDT. Facial lesions, if large, or near the midline of the face, edema may involve the contralateral normal skin. Skin lesions near the lower jaw, edema may involve the neck. The edema generally increases gradually in 72h, and most of the edema is completely reduced in a week.

Cold compress is an important method to reduce edema and inflammation. Some scholars believe that many treatment-related adverse reactions are related to inadequate cold compress.[50] Cold compress can be applied immediately after treatment and should be strictly applied within 72 hours, each time for 20 to 30 minutes, once every half hour. When applying cold compress, in order to prevent skin frostbite, you can use a soft thin-cotton towel to cover the wrapped ice pack. Infants, with high skin fat content, should pay more attention to fat necrosis caused by improper cold compress.

Purpura

Purpura is a common and normal reaction after HMME-PDT and indicates that the malformed blood vessels are destroyed.[51] The purpura reaction of the skin does not require special treatment. But, if there is a gray-white reaction on the skin surface, it may reflect a more severe vasospasm, suggesting that skin may occur necrosis, thick crust, or infection and other adverse reactions. Early administration of corticosteroids can prevent such adverse effects. If a gray-white skin reaction is found, prednisolone is taken orally immediately at dose of 1–2 mg/kg and stopped when the skin returns to purpura color.[50]

Pruritus

Most people will feel pruritus at the beginning of treatment, especially in children.[50,52] At the beginning of treatment, cold air are used to relieve discomfort. After treatment, the duration of itching varies from individuals. Pruritus can be relieved by cold and wet compress and cold air.[50] For severe pruritus, antihistamines or corticosteroids can be prescribed.

Crust, Scar and Post-Inflammatory Erythema

Dry, thin crusts floating on the skin surface usually indicate that HMME-PDT is effective and generally does not leave scar.[52] Care should be taken to prevent scratching and to apply a topically moisturizer.

It should be noted that some scab surfaces are dry, however the basal site is depressed and there may be exudation and infection under the crust.[32] If not accompanied by exudation and infection of the sag dry scab, it can be natural removal, but prone to leave depressed scar and post-inflammatory erythema. For the thick scabs that are not infected and accompanied by exudation, local wet compress can be used. The solution of wet compress can be boric acid solution, or povidone iodine and normal saline mixed at a ratio of 1:20. Of course, you can also choose some new dressings, such as hydrocolloidal dressings, silver ion dressings and so on. In cases of co-infection or suspected infection, oral antibiotics should also be used.

Photosensitivity

The metabolic time of HMME in the blood vessel is short. According to the previous pharmacokinetic data, about 6 hours, the blood concentration is less than 0.1mg/L.[35] At 52h after administration, no phototoxic reaction was caused by the daylight simulator, 532nm therapeutic laser and outdoor sunlight.[53] However, in clinical practice, after treatment, the time of avoiding light is extended, usually 1–2 weeks, avoid direct sunlight and indoor strong light exposure. Except that, patient should avoid eating large amounts of photosensitive food. If patient have to go out, they should do the whole body physical cover. After 1–2 weeks, solar radiation is generally acceptable except in the treated area. Patients and parents should pay attention to the typical signs of local and systemic photosensitivity and consult a doctor if skin photosensitivity is found. Strict avoidance of light after treatment is the key to prevent photosensitive reaction.

Post-Inflammatory Hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) is caused by increased melanin and abnormal distribution of melanin, usually secondary to inflammatory skin reactions.[54] There are individual differences in the severe and duration of pigmentation after skin inflammation. Skin color may be one of the factors affecting the occurrence of pigmentation. People with dark skin color are more prone to pigmentation, but there is no significant relationship between the severity of pigmentation and the severity of inflammation.[45] Post-inflammatory pigmentation can fade over time, but it can also be improved by reducing melanin production and speeding up melanin metabolism.

Eczema

Due to individual differences and the influence of HMME-PDT on the skin barrier, some patients, especially infants, are prone to dry on treatment sites and secondary eczema.[32,33,50] Eczema, before or after treatment, increases the risk of scabs and infection after treatment. Therefore, moisturizer can be used after HMME-PDT to reduce the incidence of eczema.

Conclusion

Photodynamic therapy is an important and promising modality for the treatment of PWS. This treatment has demonstrated high therapeutic potential, with the improvement of people's awareness and living standard, and the significantly increased demand for diagnosis and treatment of PWS. Since the clinical application of HMME-PDT in China, good results have been achieved. Because of the clear efficacy and high safety, HMME-PDT has a good prospect for development, perhaps not only in China.

Disclosure

The authors report no conflicts of interest in this work.

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