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PHOTODYNAMIC THERAPY IN TREATMENT OF LICHEN PLANUS – A LITERATURE REVIEW

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ABSTRACT

Introduction: Photodynamic therapy (PDT) is a recognized method in treating various conditions in dermatology, oncology, and gynecology. PDT involves introducing a substance called a photosensitizer into the patient's body, which accumulates in specific, targeted tissues. These tissues are then exposed to a light of a wavelength absorbed by the photosensitizer, leading to the release of cell-damaging factors from the photosensitizer within the targeted cells. Due to its effectiveness and good tolerance, PDT is used in treating both benign and malignant neoplasms, inflammatory diseases and autoimmune skin disorders.

Objective: This study aims to analyze the literature on the application of PDT on treating lesions in oral lichen planus (OLP).

Materials and Methods: A literature review was conducted using the PubMed database with the following keywords: 'lichen planus', 'oral lichen planus', 'photodynamic therapy', 'LP', 'OLP', 'PDT', applying filters 'clinical trial' and 'randomized clinical trial'.

Conclusions: Photodynamic therapy is a promising method for treating oral mucosal lesions in LP. Clinical studies show comparable efficacy to topically applied steroids, with minimal reported adverse effects.

Keywords: lichen planus, oral lichen planus, photodynamic therapy, LP, OLP, PDT.

INTRODUCTION

Photodynamic therapy (PDT) is a recognized treatment modality for both neoplastic and non-neoplastic conditions. PTD was first applied in the late 19th century in treatment of lupus vulgaris [1]. Early in the 20th century, the first reports of PDT use in treating patients with solid tumors appeared [2]. Since then, PDT has been widely used in treating neoplasms - from benign precancerous conditions like actinic keratosis to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, and is used in neoplasms of the esophagus, stomach, lung, and bladder [3].

Regarding non-neoplastic skin diseases, PDT is used to treat acne, viral warts, psoriasis, and infections, including those of mucosal membranes [4,5]. A novel application of PDT is the treatment of lesions in lichen planus, particularly in its oral manifestation (OLP – oral lichen planus).

MAIN BODY OF THE REVIEW

PDT is a modality based in three components – a photosensitizer, a light source, and oxygen present in the tissues. None of these elements independently exhibit toxicity to the surrounding area. PDT involves introducing a photosensitizer (PS) – a light-sensitive substance – into the patient's body, which can be administered systemically or topically [6]. The targeted area is then illuminated using light of a specific wavelength absorbed by the PS. Illumination causes the release of free radicals from the PS, generating reactive oxygen species (ROS) through the oxidation of O2 in the patient's tissues, leading to the destruction of surrounding cells via oxidative stress. Upon exposure to light of a suitable wavelength, the PS reaches an excited singlet state, and subsequently a triplet state, from which electrons can be transferred directly or indirectly to oxygen molecules in the cytoplasm and cell organelle. This process produces ROS, causing damage to cell membranes and extensive intracellular organelle destruction, resulting in apoptosis of affected cells [7]. PDT is however characterized by low carcinogenic and mutagenic potential, as PS typically do not accumulate in the cell nucleus and do not significantly damage the DNA [8]. Tissue damage is confined to the illumination site, as ROS, being highly unstable substances, decompose immediately at their site of formation, minimizing damage to surrounding tissue [9]. The therapeutic effects are restricted to the pathologically altered tissue, as non-irradiated PSd accumulated in healthy tissues are harmless, thereby minimizing toxic effects on distant tissues [10].

PHOTOSENSITIZERS

Photosensitizers (PS) are substances used in PDT that exhibit oxidative potential responsible for the therapeutic effect. An ideal PS is characterized by several properties – it should be stable in the absence of light, toxic to tissues under specific light wavelengths, selectively accumulate in pathological tissues at significantly higher concentrations than in healthy tissues, and should not negatively impact healthy cells [7]. PSs can be administered orally, intravenously, or topically. Currently, the most used PS are porphyrins, particularly protoporphyrin IX and its derivatives [11]. A breakthrough in PS use was the introduction of 5-aminolevulinic acid (5-ALA) in 1987, now widely used as a precursor to protoporphyrin IX in PDT [9]. ALA is endogenously produced in most cells, being part of the heme synthesis pathway. Under physiological conditions, endogenous ALA production is tightly regulated by negative feedback mechanisms [12]. However, exogenous administration leads to significant accumulation in cells and conversion to protoporphyrins [13]. Porphyrins appear in cells usually within 30 minutes of ALA administration, at which point illumination can begin. Due to their relatively short half-life (approximately 24 hours), their photosensitizing potential does not last excessively long, which is another advantage of using these compounds in PDT. Methyl aminolevulinate (MAL), a derivative of ALA with a similar mechanism of action and conversion to protoporphyrins, has higher lipophilicity and penetration into the skin upon topical application [14]. These PS selectively accumulate in tissues with increased metabolism, such as rapidly dividing cells. Although several theories exist, the mechanism of this phenomenon is not yet fully understood [15]. In oral cavity disorders, phenothiazine derivatives like methylene blue and toluidine blue are widely used due to their suitability for topical application [16,17].

LIGHT SOURCE

The purpose of tissue illumination is to transfer energy to the PS and subsequently activate it. Any light source can be used for PDT (both halogen lamps and specialized lasers). The type of light source used is determined by the PS properties, location of the lesion, its depth, and size. The maximum absorption range for most PS is within the wavelength range of 600-700 nm [18]. Due to light reflection, scattering, and absorption by skin components, the penetration depth of the light beam is limited and closely related to the wavelength – the longer the wavelength, the deeper the penetration. For light with a wavelength of 630 nm, the optimal penetration depth is approximately 2-3 mm [18]. In PDT pulsed dye lasers (PDL), intense pulsed light sources (IPLs), potassium-titanyl-phosphate (KTP) lasers, neodymium-YAG lasers, and gallium-aluminum-arsenide (GaALAs) lasers can be used. Using lasers in PDT allows for the use of monochromatic light with the most suitable wavelength for the selected PS. The use of optical fibers enables the delivery of the beam to hard-to-reach areas, also with implementation of endoscopic techniques [20]. LEDs are also used, although they tend to heat the illuminated tissues more. Old generation broad-spectrum lamps with optical filters are also widely applied due to their low cost of use. [18,21]

COMPLICATIONS

PDT complications can be divided based on the time of occurrence into immediate, short-term, and long-term. During the procedure, patients may experience pain, discomfort, burning, or itching [22]. Immediately after the procedure, erythema may occur, followed by occasional swelling. Urticaria or contact dermatitis may occur in reaction to topical PS administration [23,24]. Long-term complications may include scarring or pigmentation changes of the illuminated skin [4].

LICHEN PLANUS

Lichen planus (LP) is a chronic inflammatory disease presenting with lesions of the skin, scalp, hair follicles, genital area, mucous membranes, and nails. LP manifests as polygonal, bluish papules, often arranged linearly, typically affecting the extremities and back. Lesions on the scalp can cause scarring alopecia, also nail involvement can occur. The lesions typically resolve without scarring but may leave some hyperpigmentation. In the oral mucosa, whitish, reticulated patches of an irregular shape typically appear on the buccal mucosa, less frequently on the tongue's lateral surfaces or lips. Oral lesions are often asymptomatic although more advanced, erosive lesions can be painful and cause intense itching [25,26,27]. The disease prevalence is 0.5-2% of the general population, with a slight female predominance [27,28,29]. There is an association between LP and the development of graft vs host disease (GVHD) and liver conditions, especially hepatitis C infection [30,31]. A higher incidence of LP is observed in patients with autoimmune diseases, particularly autoimmune thyroid disease and type I diabetes [32]. Typical treatments include topical steroids, systemic steroids, calcineurin inhibitors, and retinoids. As mentioned, oral lichen planus (OLP) lesions are often asymptomatic or mildly symptomatic, but symptomatic cases respond poorly to pharmacological treatment. OLP lesions carry a risk of malignant transformation, especially in the erosive form and in conjunction with other risk factors for oral cancer, such as alcohol consumption and smoking [33].

Scales used to assess the severity of OLP lesions:

Thongprasom score [27] – a scale used to assess the severity of OLP lesions:

5 - Reticulation with an erosive area larger than 1 cm^2.

4 - Reticulation with an erosive area smaller than 1 cm^2.

3 - Reticulation with an atrophic area larger than 1 cm^2.

2 - Reticulation with an atrophic area smaller than 1 cm^2.

1 – Reticulation only.

0 – No lesions.

Another scale for assessing the severity of changes in OLP is the REU scale, which evaluates the presence of:

R (reticulation) - reticulated whitening (0-1 points),

E (erythema) - redness and its extent (0-3 points),

U (ulceration) - presence of ulcers and their size (0-3 points).

The score is obtained by multiplying the components by the multipliers appropriate for the given components; in cases where more than one lesion is present, the scores for the lesions are added up. [34] The scale shows a strong correlation with the assessment of pain on the NRS scale for lesions. [35]

RESULTS (TRIALS SUMMARY)

A study conducted in Saudi Arabia by Mostafa et al. included 20 patients with histopathologically confirmed erosive OLP and divided patients into groups - receiving either topical triamcinolone therapy or PDT with methylene blue and diode laser irradiation at a wavelength of 660 nm once weekly. Both groups showed a statistically significant reduction in pain on the VAS scale and improvement of the lesion size and the Thongprasom scale after 2 months compared to baseline, with more lesion size reduction in PDT arm. On top of that, the PDT arm showed to have statistically significant higher improvement of VAS score both immediately after treatment and in the 2 month follow up. [36]

The randomized double-blind study by Fatemeh et al in Iran enrolled 11 patients with symptomatic bilateral OLP. A study used a split-mouth designs – sites of patient’s mouth were randomly assigned to a control group receiving topical triamcinolone therapy for 3 weeks and interventional grop receiving PDT with toluidine blue and diode laser irradiation at a wavelength of 660 nm once a week for 3 weeks. The steroid group also undergone sham laser irradiation. After this period, all lesion areas received topical triamcinolone treatment for another 4 weeks. Pain on the VAS scale, Thongprasom score (TH) and Severity Index (SI) were assessed on each treatment session and then 7 weeks after randomization. VAS, TH and SI showed significant improvement in the PDT group between sessions 0 and 3 but not between sessions 0 and 4. There were no significant differences between groups regarding any of the end points between sessions 0 and 4. No adverse events were reported. [37]

In randomized study by Bakhtiari et al., 30 patients with histopathologically confirmed OLP were assigned to

a test group receiving PDT mediated by methylene blue and LED irradiation at a wavelength of 630 nm four times on days 1, 4, 7, and 14, and a control group treated with topical dexamethasone four times a day for two weeks. Pain on the VAS scale, lesion severity on the Thongprasom scale, and REU score were assessed on days 0, 15, 30, 60, and 90. Both groups showed statistically significant improvement in all evaluated parameters, with no statistically significant differences between the groups in any of the assessed parameters. [38]

In a Norwegian study, 40 female patients with erosive LP of the genital area were randomized to a test group receiving a single PDT session with topical hexyl aminolevulinate in an occlusive dressing for 3 hours and irradiation with light at a wavelength of 633 nm. The control group received topical treatment with clobetasol for 6 weeks. Efficacy was assessed at weeks 6 and 24 post-randomization using the VAS pain scale and the clinical severity scale GELP (genital erosive LP). Both groups achieved statistically significant improvement in both assessed parameters at 6 and 24 weeks post-randomization, with no statistically significant differences between the groups. [39]

A RCT by Mirza et al. included 45 patients with biopsy-proven erosive-atrophic OLP who were randomized into three groups: PDT with toluidine blue and GaAlAs laser illumination with a wavelength of 630 nm twice a week for a month, a second group receiving Low Level Laser Therapy (LLLT), and a control group receiving topical dexamethasone treatment four times daily for a month. Pain on the VAS scale and lesion severity on the Thongprasom scale were assessed. A statistically significant improvement in the measured parameters was achieved for all groups, but the improvement in VAS pain scores was significantly greater for the control group. The efficiency index (an intermediate parameter for severity improvement) showed a statistically significant improvement for the PDT group compared with the control group. No side effects were reported during the follow up period. [40]

A study by Jajarm et el. in which 25 patients with histopathologically confirmed OLP were randomized into a test group receiving PDT with methylene blue and GaAlAs laser irradiation with a wavelength of 630 nm twice a week for a month, or a control group receiving topical dexamethasone therapy four times daily for a month. Patients were observed for 4 weeks after treatment completion. Both groups showed a statistically significant reduction in sign score change but only in Mann-Whitney test and not the Wilcoxon test. Pain reduction was significant in both groups, with a statistically significant difference favoring the control group in this regard. No adverse events were reported. [41]

A study by Zborowski et al. conducted in Poland included 28 patients with bilateral HP confirmed OLP each patient received PDT – toluidine blue solution, diode laser irradiatation 650 nm waveneght on days 0, 3, 6, 9 on one side of the mouth and topical triamcinolone for 9 days on the other side. Lesion size, VAS score, Thongsprasom scale, ABSIS I/II and quality of life (OHIP-14) were calculated on days of treatment and 12 weeks after treatment completion. Both groups reached significant improvement of lesion size, Thongprasom score reduction and VAS reduction. Both groups failed significantly improve in OHIP-14 parameter after 12 weeks. 4 subjects in the PDT side reported regional side effects after first or second PDT session (erythema, itching) resulting in withdrawal from the study. No systemic side effects were reported. [42]

Case control study by Cosgarea et al. included 20 patients with HP confirmed OLP with lesin size > 10 mm diameter undergone PDT with methylene blue and laser diode with 660 nm wavelength irradiation in 4 sessions on days 1, 4, 7, 14. Study assessed lesion size, Thongspransom score, ABSIS, VAS score and quality of life. Treatment lead to significant reduction in size of the lesions and reduction in Thonsgspransom scale, as well as improvement in mean VAS score. Regarding QOL parameters only burning sensation and self-performed oral hygiene showed significant improvement. [43]

The study from by Salinas-Gialbert et al. 60 patients were randomized to 3 groups – PDT using methylene blue and laser irradiation, laser irradiation without the use of PS, topical steroid therapy and sham irradiation. Phototherapy was implemented in a once w week for 4 weeks regimen, and patients were followed up for 3 months after randomization. Pain, Thonsgsprasom scale, Oral Health Impact Profile-14 and Hamilton depression scale were accessed. PDT group achieved significantly higher improvement of pain intensity, Thongsprasom scale results, and quality of life in OHIP-14 questionnaire in comparison with the steroid therapy group. No adverse events were reported. [44]

DISCUSSION

Mentioned studies suggest a positive response of OLP lesions to PDT therapy compared to standard steroid treatment. However, it is important to note significant methodological differences between cited studies. A wide range of treatment protocols were used ranging from just a single treatment session to numerous sessions over the course of a month. Different PS were used – ALA, toluidine blue and methylene blue, on top of that one study used occlusive dressing for the drug delivery. Different light sources were used LED and GaAlAs laser being two of the most common. Drug exposure times, illumination times, and wavelengths used varied between studies.

All of the studies used some form of pain assessment – VAS or alternative, all studies implanted Thongsprasom scale, but some studies used also lesion size, REU score, ABSIS score, EI, and Carozzo Gandolfo score. Implementation of different end points makes it impossible to directly compare the results. Small sample sizes and lack of statistical significance in some results, or statistical significance only in indirectly measured indicators, do not allow for a clear assessment of PDT therapy efficacy. Some results suggest better pain control with steroid therapy, which may be related to the adverse effect of PDT, which is irritation and pain of the illuminated site.

One study however shows significantly greater pain reduction in PDT arm even after the first treatment session. Studies available in the field don't present a placebo control group, all randomized studies are controlled with steroid therapy. Some studies however involve a sham procedure – illumination without a PS applied beforehand - which is an interesting direction of trial design regarding treatment modality such as PDT - easily recognized by enrolled subjects. Despite all the above, results obtained across all studies are consistent and suggest that PDT efficacy is comparable to that of steroid therapy.

CONCLUSION

There are no available studies showing lack of symptom improvement in PDT arm. Combined with the minimal number of reported adverse effects, PDT represents a promising direction for OLP therapy, though further research is needed in this field. Only limited data is present regarding the use of PDT in clinical presentations of LP other than OLP. One RCT assessing the use of PDT in genital LP was available witch is insufficient to draw conclusions in this matter.

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