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Therapeutic Use of Photodynamic Therapy in Leukoplakia

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Abstract

Potentially Malignant oral disorders, formerly referred to as potentially malignant lesions or conditions or oral dysplasia, are identified by ruling out other possible causes of white and red lesions in the oral cavity. Leukoplakia and erythroplakia are the most common Oral Potentially Malignant Disorders (OPMDs) that occur in oral cavity. Photodynamic therapy (PDT) is one of the pharmacological therapies that was very effective in treating in oral leukoplakia. PDT is also referred to as photoradiation therapy, phototherapy, or photochemotherapy. This review will give a wide idea about the use of PDT in treating leukoplakia.

Keywords: Photodynamic Therapy, Oral Leukoplakia, 5-Aminolevulinic Acid, Diode Laser

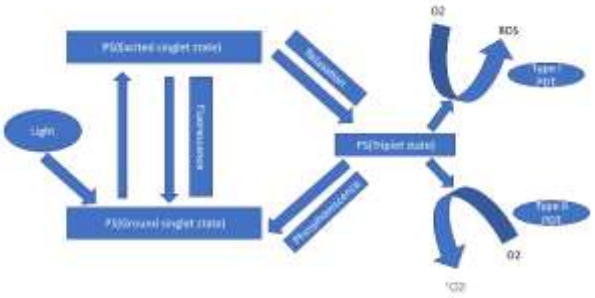
Introduction

The term oral leukoplakia (OLK) refers to a primarily white patch or plaque on the oral mucosa that is not easily removed and is not associated with any particular disorder.[1] The range of malignant change from leukoplakia to squamous cell carcinoma is 0.13% to 34%[2] Smoking, chewing areca nuts, and prolonged irritation are some of the things that are thought to contribute to its development, while the actual cause is yet unknown[3] OLK is often classified as either homogeneous or nonhomogeneous[3,4] .OLK treatment modalities encompass both non-surgical and surgical techniques[5,6]Alternative treatments such as photodynamic therapy (PDT) may be required in vast or functionally vital areas[4] where surgical procedures such as excision, laser ablation, and cryosurgery may not be effective because of postoperative discomfort.

Concept of PDT

Oscar Raab introduced the concept of PDT[7]. The three core components of PDT are oxygen, a light activated compound, and a particular wavelength of visible light[8]. PDT is a treatment that involves the use of a photosensitizing agent, which is activated by a specific wavelength of light. This activation leads to a chemical reaction that produces reactive oxygen species (ROS), Which can selectively damage or destroy cancer cells or other targeted tissue. One of the significant advantages of PDT is its ability to selectively target and damage diseased or cancerous tissue while sparing adjacent healthy tissue.[9] PDT preserves vital structures and minimizes collateral damage, making it an attractive treatment option for various conditions.[8] This targeted approach reduces the risk of complications and improves patient outcomes.

Mechanism of Photodynamic Therapy



Fig, 1: PS: Photosensitiser, O2: Oxygen, 1 O2: Singlet oxygen, ROS: Reactive oxygen species[24]

Photosensitizer

- A Singlet and a triplet are the minimum number of excited states of photosensitive species [29]
- After the proper absorption of light, typical electronic transition in photosensitive species occur between the ground and singlet excited state. [29]
- This singlet excited state PS is highly unstable and releases its extra energy as either internal conversion or light emission (fluorescence)
- To create a more stable excited triplet state with parallel spins, the excited singlet PS may go through a procedure called "Intersystem crossing" [30]
- Further transition to the triplet excited state, which is theoretically forbidden.

The triplet PS can react chemically in two different ways when ambient oxygen is present [31]

Successful PS agents in the clinic typically possess the majority of the following traits:

- Hydrophilic for easy systemic application.
- Harmless until activated, activated by a light wavelength.
- Consistently generate the Photodynamic reaction.[28]

5-Aminolevulinic acid (5-ALA)

- Second generation photosensitizer
- ALA stimulates the body to produce protoporphyrin IX, an endogenous photosensitizer that can be used in photodynamic therapy.
- It is the only photosensitizer that has the ability to be applied topically or taken orally [14]
- Low molecular weight
- Brief phototoxicity period (24-48 hours)
- Excellent tissue penetration
- High singlet oxygen yield
- Water – soluble administered via intravenous, oral and local applications [16,17]

Oxygen

- Sufficient levels of dissolved molecular oxygen in the tissues during irradiation are a prerequisite for PDT therapy.[10]
- Oxygen allows an excited molecule to react with the substrate directly by transferring a proton or

electron, resulting in the formation of radicals or radical ions. These combine with oxygen to generate oxidized products, which is a type I reaction.[11]

- Singlet oxygen is created when photosensitizer energy is directly transferred to oxygen, a type II reaction.[12,13]
- These reactive oxygen species (ROS) molecules exhibit high toxicity, a brief half-life (less than 0.04 microseconds), a narrow therapeutic window (less than 0.02 micrometres), and a role in the breakdown of injured tissue, resulting in oedema and cellular demise.[9]
- After the injured tissue is eventually removed, the area goes through the usual processes of healing and regrowth.

Light Source

- In Photodynamic therapy, light is used to stimulate a photosensitizer which produces ROS in presence of oxygen.
- Due to its high potential for DNA mutagenesis leading to oncogenesis and formation of hazardous products, UV light (< 400 nm) should be avoided during PDT treatment. [32]
- The therapeutic window of 600 – 800 nm is the most suitable wavelength for PDT[24]
- PDT light source falls into three main categories
  - Lamps
  - LEDs
  - Lasers
- Laser sources and LEDs show comparable efficacy in PDT for OLK
- Lesion features (such as tissue type, size, and accessibility), the photosensitizer's absorption spectrum, and pragmatic concerns (including cost and availability) are all taken into account when selecting light sources [18]

Lamps

- Currently tungsten filament, Xenon arc, Metal halide, Sodium and fluorescent lamps are used for PDT[34]
- For large area therapy, sodium and fluorescent lights can be utilized without connecting to fibers[35]

Advantage of lamps

- Less expensive
- Easier to handle than lasers

Disadvantage of lamps

- Production of heat by infrared light
- Tissue damage by UV light[36]
- Needs optical filtering

Light-emitting diodes (LEDs)

- LEDs are semiconductor devices that produce light through the recombination of electrons and holes
- LEDs output light is huge beam divergent, broad spectral width, incoherent

Advantage of LEDs

- Portable
- Reasonably priced
- Used in areas without access to electricity [37]

Disadvantage of LEDs

- Thermal effect
- High beam divergence
- Wide spectral width
- Low power

Laser

- High irradiance monochromatic, coherent, collimated light is produced by lasers
- For PDT – Argon Ion lasers, Metal vapour – pumped lasers, Nd-YAG lasers, diode lasers are a few common options [32]
- The most used light source for PDT is diode lasers

Diode Laser

- Diode lasers are semiconductors devices that produces light by electron hole recombination [33]
- Diode lasers are less expensive, lighter, more portable, more compact, more stable.
- PDT usually uses diode lasers with output wavelength in the range of 415 – 690 nm

Advantage of laser

- monochromatic light
- Accurate calculation of light dosage
- Optimal wavelength matching with specific photosensitizers.

Disadvantage of laser

- Quite expensive
- High maintenance requires
- Possible issues with eye safety

Indication of PDT

- Recur oral leukoplakia after cryotherapy, laser therapy, or scalpel excision
- Erythroleukoplakia
- Oral verrucous hyperplasia

Contraindication of PDT

- Porphyria
- Coagulopathy
- Pregnancy
- Serious uncontrolled systemic illnesses
- Allergy to light, porphyrin, or anaesthetic drugs

Advantage of PDT

- Minimal adverse effects
- Less invasive than surgical procedures
- Short treatment time
- Several applications at one site
- Excellent cosmetic result
- Less expensive [27]
- Scarring is typically minimal or non-existent

Disadvantage of PDT

- Photosensitivity following treatment
- Treatment efficacy relies on accuracy of tumour light irradiation
- Tissue oxygenation is necessary for the photodynamic effect
- Very difficult to treat metastatic malignancies with existing technology[27]
- PDT is not recommended for those with specific blood disorders

Clinical Procedures

Points that require extra care to ensure a secure PDT process

1. A thorough medical history is necessary
2. Pre-treatment assessment
3. Documentation of all patient characteristics
4. Capture and store photographs of the lesions
5. Doctors explain available treatment choices, including PDT advantages, dangers, possible results, adverse reactions, mitigating measures.
6. Control of the therapy area before the ALA-PDT
7. Equipment inspection before the ALA-PDT process
8. Lesion preparation before the ALA-PDT technique
9. Preparation and administration of ALA
10. Safety measures for the ALA-PDT procedure
11. Following the ALA-PDT process
12. Informed Consent [26]

Preoperative Care

Duties of the nursing staff

- Preparing PDT materials
- Confirming patient information
- Providing assistance during the operation

Comprehensive pre-procedural examinations

Liver and kidney function tests

Glucose levels [19]

Complete blood cell counts

Blood coagulation markers.

- **PDT requires**

Darkened area

Double-layered blackout curtains block out outside light interference.

- **Thorough inspections**

➢ Photosensitizer (e.g., ALA)

➢ Optical fibers (e.g., microlens optical fibers)

➢ PDT device parameters (e.g., wavelength 630 nm ± 5 nm, adjustable semiconductor output power 0.1–2 W).

➢ General supplies like goggles, sterile isolation films, 0.1% chlorhexidine gargling solution, syringes, disposable oral examination trays, mouthwash cups, sterile cotton rolls and balls, local anesthetics, medical swabs.[20]

Operative Care

Patients should sit quietly for five to ten minutes after entering the treatment room

Patients should sit quietly for five to ten minutes after entering the treatment room

⇩

Heart rate and blood pressure checked.

⇩

Eligible for treatment

Heart rate of at least 100 beats per minute

Diastolic pressure of 90 mmHg

Systolic pressure of at least 140 mmHg

⇩

Patients should clean their mouths for one minute with a 0.1% chlorhexidine solution

Just before use, nurses combine

⇩

Sterile water + ALA → 20% solution for the photosensitizer

⇩

Soaked cotton swab placed over lesion

⇩

Starch film is placed over the swab to aid the photosensitizer's adhesion to the mouth lining

⇩

Gauze and cling film are placed over the treated area

⇩

For optimal penetration, the swab should extend 3-5 mm past the lesion margin.

⇩

Needles made from plum blossoms can be useful if movement of the tongue or saliva impacts absorption. In certain situations, injections might be employed.[21]

⇩

Remove the swab after two to three hours, then use UV light (370–470 nm) to monitor the reaction.

⇩

After cleaning the region and rinsing off any remaining photosensitizer with water, provide local anesthetics.

For laser treatment, use a semiconductor laser at 630 nm ± 5 nm with 100 mW•cm^−2 power [22]

Each 3-minute session is followed by a 3-minute break to maintain effective oxygen levels until reaching a total light dose of 100 J•cm^−2.

Protect everyone's eyes with goggles during the procedure.

Keep the patient's eyes closed to minimize discomfort.

To ensure even treatment, position the laser beam perpendicular to the lesion surface.

Adjust the distance between the fiber and lesion for best results. Monitor treatment details closely and adjust as needed.

Treat the lesion every 2–3 weeks based on healing progress.

Post-operation

Patients should keep their mouth clean and avoid irritating foods and drinks.

Shield the treated area from light for 48 hours, longer if on exposed areas like the lips.

Promptly report any issues to medical staff, and use a visual scale to measure pain.

Treatment Follow-Up and Response

- After treatment, patients are often prescribed 0.01% dexamethasone paste and 0.1% chlorhexidine gargling solution to reduce inflammation.
- Four weeks following the final treatment, the treatment response was usually documented. For the first year, the follow-up was done every three months, and then every six months for a maximum of two years.
- The classification of treatment response is: no response (NR, lesion reduction of less than 20% or worsening), partial response (PR, lesion reduction of more than 20%), and complete response (CR, lesion removal).

Adverse Reactions

In and around the treated area

- Photosensitivity reaction
- Burning or tingling feelings
- Mild to moderate pain
- Redness
- Swelling
- Erosio
- Ulcers
- Bleeding[24]
- Immune system changes

Management of adverse reaction of PDT

- Mild cases - heal on their own
- More severe - 0.1% chlorhexidine gargling solution
- Topical glucocorticoids like prednisolone, or benzocaine gel
- Extensive erosion or ulcers, short-term - low-dose oral prednisone acetate tablets

Skin reactions

- wear protective clothing
- sunscreen
- Avoid direct, strong light.
- Try to spend as much time indoors
- Wide-brimmed hats
- Avoid places where there is a lot of light reflection, such as snow, bright-coloured pavement, beaches, and other surfaces.

- Lesions on exposed areas to reduce pigmentation risk - 48 hours light avoidance
- Symptoms due to sunlight exposure - move to shade
  - Antihistamines like cetirizine
  - Anti-inflammatory gargles
  - Apply topical steroids
  - Consult a dermatologist [24]

Conclusion

The effectiveness and advantages of Photodynamic Therapy (PDT) in treating oral leukoplakia. PDT is a minimally invasive treatment option that selectively targets diseased tissue while preserving healthy structures, thus reducing the risk of complications and improving patient outcomes. The therapy's ability to provide excellent cosmetic results, along with its relatively short treatment time and minimal adverse effects, makes it a valuable option in managing oral leukoplakia, especially in cases where traditional surgical methods may not be suitable.

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