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REVIEW ARTICLE

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Low level laser therapy: An effective tool to enhance quality of life in head and neck cancer survivors

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ABSTRACT

Patients treated for head and neck cancer commonly suffer from oral mucositis, ulceration, bacterial infection causing pain, discomfort, impairment of speech and deglutition, leading to dehydration, poor nutrition, and mortality. Low level laser therapy (LLLT) is a promising state-of-the-art method which can be used effectively to reduce these side effects. It works on the principle of photo-bio stimulation. LLLT induces a biological response through energy transfer within the cells. It has anti-inflammatory effects, stimulates the immune system, increases of blood flow, upsurges cellular metabolism, and boosts rapid wound healing. Cells play a crucial role in oral healing. However, little is known about the molecular basis of LLLT to modulate cell mechanisms. Hence for better understanding, this review article aims to discuss the mechanism of action, recommended parameters of LLLT, biological effects on various oral cells, and potential application to revive the adverse effects of onco-therapy on head and neck cancer patients.

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Introduction

Patients with head and neck malignancies undergo radiotherapy and chemotherapy as the treatment of choice. Various complications include oral mucositis, pain, dysphagia, infections, dysgeusia, mucosal atrophy, muscular fibrosis, neuropathies, and salivary changes like xerostomia that leads to tooth demineralization and rampant caries, progression of periodontitis, and bone necrosis. Chemotherapeutic agents target rapidly dividing healthy tissues causing cell damage [1]. Oral cell damage results from the loss of secretion of growth factors, early release of inflammatory cytokines, and reactive oxygen species inducing the over-regulation of specific genes, triggering apoptosis that prevents the deregulation of normal mucosal epithelial growth patterns. The cascade of events leads to complications that are associated with morbidity and mortality and increased use of health care resources and costs [2]. Among the few supportive care measures available, low level laser therapy (LLLT) has shown significant promise and has been considered as effective tool for the management adverse effects of oncotherapy [3]. LLLT uses light in the red and near-infrared electromagnetic spectrum. It is applied topathology to promote tissue regeneration, reduce inflammation, and relieve pain. LLLT is typically not ablative, but rather refers to a photochemical effect where light is absorbed exerting a chemical change. This change generates a series of modifications in tissue metabolism termed as "Laser bio-stimulation" [4]. Laser bio-stimulation enhances wound healing. Therefore, this paper discusses the mechanism of action, recommended parameters, and biological effects on various oral cells and proposes its potential application to resuscitate the adverse effects of onco-therapy on head and neck cancer patients.

Mechanism of Action of LLLT

LLLT is a noninvasive, simple method where high density monochromatic light is applied. The local

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atraumatic application of a narrow-band of light to the tissues brings about a healing effect by the principle of tissue bio modulation. The therapeutic mechanism of action at the molecular and enzymatic level consists mainly of tissues photobiology [5]. The law of photobiology states that for low power visible light to have an effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to a molecular chromophore or photoacceptor. When a photon of light is absorbed by a chromophore in the treated cells, an electron in the chromophore can become excited and jump from a low-energy orbit to a higher-energy orbit. The absorption of photons by molecules leads to an electronically excited state which consequently causes acceleration of electron transfer reactions [6]. More electron transport necessarily leads to increased mitochondrial activity, consequently an increased production of adenosine triphosphate. This stored energy can then be used by the system to perform various cellular tasks. The cellular activity includes stimulation of collagen production, enzyme activity, cellular mitosis, migration, and proliferation. LLLT improves vasodilation, neoangiogenesis, and protein synthesis while it decreases local hypoxia, inflammation, prostaglandin levels thus reducing pain [7]. However, its effect is determined by the magnitude of the absorbed light, exposure time, depth of penetration, wavelength, scattering coefficient, wave shape and optical characteristics of tissue. Its ease of use, high patient acceptance, and positive results make this therapy a feasible treatment approach [8].

Recommended Parameters of LLLT

LLLT is also known as "cold laser" therapy as the power densities used are lower compared to other forms of laser therapy which are used for ablation, cutting, and thermally coagulating tissues. LLLT refers to the application of light that falls into an optical window of wavelength of 600–1,000 nm [9]. Effective tissue penetration is maximized in this range, as the principal tissue chromophores have high absorption bands at shorter wavelengths. Shorter wavelengths are more effective since they affect the superficial layer of the epithelium while longer wave lengths penetrate deeper and adversely affect the sub-epithelial tissues. It is seen that longer wavelength has limited biochemical activity [10].

The effectiveness of LLLT depends on both the dose and power density used. The power density typically ranges between 1 and 1,000 mW with doses of 1–6 J. A dose of 2–4 J/cm^2 is used for prophylactic use and above 4 J/cm^2 is used for therapeutic reasons. Dosage depends widely on the type of treatment. The other parameters are the light source and mode of application [11]. Initially, LLLT used HeNe laser, which emits light of wavelength 632.8 nm. The other sources include ruby (694 nm), argon (488 and 514 nm), krypton (521, 530, 568, and 647 nm), gallium–aluminum–arsenide (805 and 650 nm), and gallium arsenide (904 nm), while nowadays semi-conductor diode lasers are also used. Apart from lasers, light emitting diodes have also increased in popularity. The emission can be pulsed or continuous-wave producing photobiostimulation effect [12].

Effect of LLLT on Various Oral Cells

Oral cells play an important role in wound healing and maintenance. Oncotherapy may hamper differentiation, proliferation, migration, tissue formation, and remodeling of cells. LLLT is considered as an effective method to rejuvenate this complex biological process. Here, below is a summary of the effect of LLLT on various cells and how it could possibly improve the prognosis and survival of cancer patients.

Fibroblasts

Oral tissue healing involves diverse cell types among which fibroblasts that play a key role. Fibroblasts secrete multiple growth factors and participate actively in the formation of granulation tissue [13]. Treatment of head and neck malignancy affects the proliferation and migration capacity of these cells. It was suggested that on application of LLLT, there is a significant increase in fibroblast proliferation, maturation, and locomotion through the matrix. The enhanced tissue repair process by LLLT is due to stimulation of basic fibroblast growth factor which supports fibroblast proliferation and differentiation [14]. LLLT also induces transformation of fibroblasts into myofibloblasts, a cell type that expresses smooth muscle α-actin, and desmin that hastens wound contraction and in turn may contribute to the higher tensile wound strength [15]. A cDNA microarray examination of human fibroblasts revealed gene expression profiles upon irradiation. Most of the genes related to cell proliferation were upregulated. This suggests that LLLT stimulates cell growth directly as well as indirectly. LLLT regulates the expression of specific genes and the genes

related to DNA synthesis, repair, and cell metabolism [16].

Osteoblast

LLLT has been suggested to improve bone tissue healing. An *in vitro* study using LLLT at 632 nm with power output of 10 mW concluded an increased proliferation and differentiation of human osteoblast cells. It is possible that the observed results in irradiated specimens are due to an increased release of growth factors such transforming growth factor b1. These growth factors have a direct stimulatory effect on the replication of precursor cells of the osteoblast lineage and on bone healing [17]. It is reported that LLLT increases bone nodule formation and alkaline phosphatase (ALP) activity. There is also up regulation of ALP gene expression thereby enhancing the quality of bone formation. LLLT modulates the healing process by bone cell proliferation, osteoblastic and osteoclastic differentiation thus encouraging bone remodeling and regeneration [18].

Immune cells

LLLT may affect immune cells which secrete cytokines and other growth regulatory factors. Immune cell facilitate debridement of the wound and improves the conditions necessary for the proliferative phase of healing. Another prominent effect of LLLT is stimulation of microcirculation and increased neoangiogenesis. This contributes to increased vasodilatation which in turn brings in oxygen and also allow for greater traffic of immune cells. There is also enhancement of the phagocytic activity [19]. Mast cells play a fundamental role in the immune response and tissue repair. They release chemical mediators which influence the development, extension and duration of inflammatory reactions. In a study, the use of red laser (λ685 nm) and infrared light (λ830 nm) in rats significantly decreased the density of mast cells [20]. Mast cells contain a broad spectrum pro-inflammatory mediators, immunoregulatory and angiogenic molecules that participate in inflammatory reactions as well as tissue protection and repair [21].

Muscle cells

LLLT has shown beneficial effect on muscle cells by modulation of matrix metalloproteinase activity and gene expression. A study concluded that LLLT activates skeletal muscle satellite cells by enhancing their proliferation, inhibiting differentiation and regulating protein synthesis [22].

Vascular endothelial cells

Vascular endothelial cells play a vital role in the maintenance of vessel homeostasis. Disturbance in the endothelial integrity affects vasomotor properties, hemostasis, inflammation, and angiogenesis. The application of LLLT increases the proliferation of the cells and induces angiogenesis. These effects are associated with absorption of the radiation by cytochrome C oxidase. This enzyme is responsible for activating multiple biochemical reactions which affect cellular functions [23].

Healthcare Guidelines for Oral Rehabilitation in Head and Neck Cancer Survivors

Post oncology treatment health care requires a multidisciplinary team-based approach. The healthcare team includes primary care clinicians, oncologists, dentists, and other allied professionals. This professional team should coordinate a prompt evaluation, cater to treating the principal lesion, and be prepared to manage adverse effects of treatment [24]. Dentists serve as integral component and play a pivotal role. Apart from using LLLT as a palliative measure, the patient should be motivated to follow certain healthcare guidelines. The healthcare guideline can be divided into three segments which include pre onco-treatment care, during oncotherapy, and post oncology care [25].

Pre onco-treatment care

It comprises of comprehensive evaluation of head and neck and dental hard and soft tissues 2–3 weeks prior to cancer therapy. The use of radiographs and cone beam computed tomography to evaluate temporomandibular joint, teeth, and periodontal status. Assessment of salivary gland functions. Provide definitive treatment for caries, periodontal debridement, and oral hygiene maintenance [26].

During oncotherapy

Symptomatic management of pain using topical analgesic, anesthetic agents, and systemic analgesics if required. Symptoms of dry mouth can be treated by hydration, oral rinses, and coating agents. Reinforcement of oral hygiene by using fluoride applications and pit and fissure sealants is recommended. Personal hygiene maintenance can be encouraged by using soft tooth brushes with fluoridated toothpaste and regular flossing. Patient should be educated on the ill effects of tobacco and

alcohol consumption. Suitable dietary and nutritional guidance should be provided [27].

Post oncology care

Monitoring and prevention of cancer recurrence. Management of oral complications such as mucositis, dry mouth, mucosal pain, taste change, and infection. Dental demineralization and radiation caries can be treated using remineralizing agents and restorative therapy. Encourage non-cariogenic diet, cessation of tobacco and alcohol. Motivate patient oral hygiene using soft toothbrushes or ultrasonic brushes with fluoridated toothpaste [28].

Conclusion

Patients receiving cancer therapy for head and neck malignancy have significant side effects which can negatively affect their quality of life. Adequate palliative and supportive care needs appropriate treatment planning and involvement of a multidisciplinary team. The benefits of LLLT are multi-fold. LLLT reduces inflammation, relieves pain, increases proliferation and differentiation of cells by photobiomodulation. Considering the advantages of LLLT to enhance healing it can be employed as an effective therapeutic tool. As the population of head and neck cancer survivors is increasing, it has become increasingly important for health care providers to understand and manage its complications. The growing application of LLLT encourages healthcare professionals to follow apt prophylactic strategies and maintain appropriate healthcare guidelines. Further research in this field is imperative.

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