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Laser Therapy for Wound Healing: A Review of Current Techniques and Mechanisms of Action

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Along with conventional medications, different techniques have been used for wound healing such as ultrasound, electric field, magnetic field, pressure relieving beds, cushions, etc. These methods are usually utilized for prevention and healing of pressure wounds. One of these methods with great potential is LASER (Light Amplification by Stimulated Emission of Radiation) therapy. Different parameters can affect the efficiency of laser therapy. Several studies have attempted to develop this technique in different medical applications. This paper aims to provide a review of the LASER techniques for wound healing, sketch their background, determine the biological effects that support the use of LASER sources in the treatment of wounds and as well as the optimal light parameters such as wavelength and dose for wound healing.

Key words: Laser, Wound Healing, Mechanism of Action.

Wound is a physical injury specified by disruption of the normal structures of body. Wound can injure some superficial cutaneous and basic structures of skin[1]. To manage wounds preventive measures such as health professional continuous education, family counseling and guidelines should be provided to the people. Different therapeutic approaches such as conventional medications, pressure relieving beds, cushions, medicinal plants have been developed for wounds treatment. Physical treatments such as therapeutic ultrasound and electromagnetic therapies have been introduced as alternative or adjunctive treatment in wound healing[2, 3]. Although these techniques have some advantages, their results are not always promising.

Recently, applications of laser as a non-surgical technique have gained great attention for accelerating the wound healing procedure. Nevertheless, the effects of laser in decreasing pain and repairing tissue have not been completely understood[4]. It was reported that applying laser could facilitate repairing the injured biological tissue[5]. One of the great approaches for treating lesions of wounds is applying low-power light therapy which promoted by light devices such as LASER (Light Amplification by Stimulated Emission of Radiation)

The history of using LASER in the healing of wounds have drawn back to 1960[6,7]. Nevertheless, the results are very contradictory due to lack of standardization in the experiments. The effectiveness of LASER therapy is widely depends on the Selection of the appropriate parameter.

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Since the introduction of photobiomodulation in healthcare, different studies have investigated the feasibility and efficacy of light resources for the skin wounds treatment. However, the exact biological mechanisms of low intensity light in tissues are still not explained. In this regard, some researches demonstrated that applying light can enhance cellular proliferation of several cell types such as fibroblasts, endothelial cells and keratinocytes, conflicting.

There are different parameters which affect the interaction of light and the biological tissues such as the wavelength and dose as well as the optical properties of the tissue. With respect to the features of light devices, LASER consists of a resonant optical cavity and various types of active media including liquid, solid, or gaseous materials. The light is produced through the passage of an electric current from these materials[8].

There are various laser systems such as He-Ne, AlGaAs, InGaAlP, etc[9-12], different laser parameters (wavelength, power, energy, pulse frequency, pulse duration)[13, 14] and irradiation conditions (exposure time, frequency and duration of treatment)[15, 16] which produce wide range of therapeutic protocols[17].

The common parameters of LASER light include power in the range of 10^{-3} to 10^{-1} W, wavelength from 300 to 10,600 nm, as well as in the continuous mode at 5,000 Hz frequency, pulse duration of 1 to 500 milliseconds, total radiation of 10-3000 seconds, intensity between 10^{-2} and 10^{0} Wcm^{-1} and dose from 10^{-2} to 10^{2} Jcm^{-2} [18]. It was reported that laser therapy can affect wounded cells or cells with suboptimal growth, while with no effects on normal cells[19].

This paper aims to comprehensively review LASER techniques for wound healing and their underpinning principles. In addition, laser-tissue interactions and optimal light parameters such as wavelength and dose in wound healing are discussed.

Effects of Photon on Cell Level

The light of laser has some unique characteristics such as monochromaticity (has a single wavelength), coherent and collimation (travels in a single direction without divergence)[20] which cause to penetration this light into the skin surface non-invasively[18,20]. The most considerable biological effects were revealed at dose of greater than 5 J/cm^2 [21]. Sommer *et al* (2001) reported biological effects are not observed at very low doses, whereas at higher doses cellular function was inhibited[22].

Some studies have demonstrated that cytochrome c oxidase can absorb wavelengths in the range of red to near infrared[23, 24]. Lasers which are used for therapeutic applications have a thermic procedure with a negligible heat transfer. Thus, the photonic energy is directly delivered to the target cells without producing thermal damage[20, 25]. Monochromatic light with the range of wavelength of 630 to 905 nm is utilized in therapeutic lasers[26]. In order to survey the biological effects of light, it can be divided into 3 categories including: (1): primary (induced by light), (2): secondary (is occurred in response to the primary effects) and (3): tertiary effects known as systemic effects[18, 26, 27].

Primary reactions are only associated with the absorption of photons in the other means, they are considered as the interactions between photons and the photoreceptor, and also they are appeared in a few seconds or minutes after the light exposing[23, 28]. These primary reactions of light are not still clearly established, however there are hypotheses. Indeed, the primary mechanism of action of laser which leads to production biological effects in tissue is Energy absorption. Absorption of laser is widely depending on the range of wavelength play an important role in the absorption of laser light. In addition to wavelength, tissue chromophores (hemoglobin and melanin) can affect energy absorption. Due to the highly absorption of light with wavelength of shorter than 600 nm by chromophores, a therapeutic window is introduced in the optical spectral range of red and infrared, wherein the light penetration in the tissue is maximum[29].

After the absorption of light in the irradiated wavelength, cytochrome c oxidase displays an electronically excited status, from which it alters its redox status and causes the acceleration of electron transfer in the respiratory chain[30]. Another hypothesis is that a part of the electronically excited status energy is converted into heat, causing a localized and transient heating in photoreceptors[31].

Secondary reactions can reinforce the

primary effect of photon. Secondary effects are not only depends on the adsorption of photon but also associated with the cell sensitivity. For this reason, secondary effects are less predictable as compared with primary effects[27]. They are observed in several hours or even days after exposing.

In this stage, various metabolic effects are occurred which lead to production of different physiological changes at the cellular level i.e. changes in the permeability of cell membrane[19, 27, 32]. Releasing calcium from mitochondria into the cytoplasm is occurred. This induces with changes in intracellular calcium levels [5, 19] which leads to stimulation the metabolism of cell and also adjusting the signaling pathways responsible for significant events required for wound repair such as cell migration, RNA and DNA synthesis, cell mitosis, protein secretion and cell proliferation[25, 33].

Tertiary effects are influenced by the internal and external environment and as well as intracellular interactions. So, these effects are the least predictable than other effects. The tertiary effect expresses that why healing of one part of wounds leads to develop the treating to the both directly stimulated area of wound and other lesions[27].

As mentioned above, during primary responses, the photon energy is transferred to the mitochondria[25] and cell membranes of low lying cells (fibroblasts, keratinocytes or endothelial). Afterward chromophores adsorb this photonic energy and as well as convert it to the chemical kinetic energy within the cell[20, 32]. This event leads to changing the permeability of cell membrane, improved the signaling between mitochondria, nucleus and cytosol, shaping nitric oxide and also enhances the oxidative metabolism in order to create more ATP[34-36] which causes to healing wounds and also pain relief[20, 27, 32].

Other mechanisms may be induced in laser therapy. After photon absorption, some molecules such as porphyrins can convert into a long-lived triplet state. This triplet state can interact with ground-state oxygen with energy transfer leading to the production of a reactive singlet oxygen species[37].

Another possible mechanism is that the change in the metabolism of mitochondrial and also activation of the respiratory chain by photon. This leads to enhancing superoxide anions O_2 production. It was reported that laser irradiation reversed the cytochrome c oxidase inhibition which increased the rate of respiration with consequently more ATP synthesis[37].

Effective parameters

As mentioned, several parameters can affect the efficiency of phototherapy. These parameters can determine an effective therapeutic modality for the treatment of superficial wounds or musculoskeletal injuries:

Lasers

Different studies investigated the therapeutic effect of each lasers. It was reported that coherent length of light which is exposed from He-Ne laser are longer as compared with diode laser. Furthermore, the biological effects of light which emitted from diode laser at 663 nm are less obvious as compared with the light from a HeNe laser. Also it was reported that when a diode laser act at a higher power (25- 50 mW) and higher dose, its effect is similar with He-Ne laser[5, 32].

Wavelength

It was demonstrated that the wavelength range can widely affected the efficiency of phototherapy. For example applying laser at wavelength of 630 produces bacterial inhibition[38]. In this regard, it was proved that the most effective wavelength of light was 660nm[39].

Energy density

It was reported that effective doses of near-IR light may be much higher than 10 J/cm2 in particular for deep injuries. Too low doses produce negligible effect. On the other hands, prescribing a dose above the highest one suitable leads to production negative effect[40]. Also even greater dose can induce a biosuppressive or inhibitory effect[41].

Power

The power density is considered as an intensity of the light on the tissue surface, and also is expressed in mW/cm^2. Indeed, it expresses the dividing power by the target tissue area[18]. Applying stronger power of LASER leads to reducing the treatment time.

Continuous and pulsed wave

Continuous wave is considered as a light source which has constant intensity while pulsed light is a light source that emits light at various intensity[32]. If a pulsed laser is used, the power of laser light is not constant. So, in order to determine the dose, the average power is considered whereas continuous wave lasers utilize the output power.

Contact and non-contact

A laser can be employed in two different ways including Contact and non-contact[32, 42]. In order for providing great penetration into the skin, the laser probe must be used be in the direct contact with the skin and also at an incident angle of 90 degrees. This leads to minimization of any reflection from the surface of skin and great penetration into the tissue is occurred[13, 32].

Therapeutic applications of laser

Some investigators reported both inhibitory and excitatory effect of LASER on the wound healing process[40]. Nevertheless, it was revealed that applying LASER can produce beneficial effect on wound treatment. Due to the lack of knowledge about optimal therapeutic parameters, dosimetry and action mechanism of LASER, the exact mechanism is not thoroughly understood[19, 41, 43]. In this regard, some studies demonstrated Contradictory results which may due to lack of quality control[5]. It was reported that using LASER can reduce the duration of wound healing process as compared with other techniques although it was reported that applying LASER reduces pain and decreases the healing time[44], some scientists demonstrated that HeNe laser could not produce significant effect on wound healing[45, 46]. It was demonstrated that LASER can produce some effects such as: biostimulatory, analgesic, anti-exudative, antihaemorrhagic, anti-inflammatory, anti-neuralgic, anti-oedematous, anti-spasmotic and vasodilatory[47]. Similarly, Medrado *et al*, (2003) found LASER therapy decreased the inflammatory reaction and also enhanced the collagen deposition with a greater proliferation of myofibroblasts in experimental cutaneous wounds[48]. In addition, LASER has other clinical efficacies including: (1) Decreases swelling and inflammation related to the acute wounds in superficial muscles, tendons, and sheaths[19, 49, 50], (2) Reduces the pain of some acute and chronic wounds particularly related to abnormalities in nerves, muscles, soft tissue, tendons and bone, (3) Increases tissue oxygenation which leads to facilitation healing wounds which are nonhealing or have a slow healing rate particularly in soft tissues, tendons and bone[4, 25, 49, 51], (4) Increases the interstitial fluid absorption and also improve s tissue regeneration by enhancing the lymphatic circulation and drainage[25], (5) Improves blood circulation which is beneficial in blood-related conditions such as Buerger's and Raynaud's injuries, (6) enhance autoimmune response in immune-deficient conditions such as psoriasis, rheumatoid arthritis and atopic dermatitis[49], (7) and can restore the normal pigment in anti-natural colored cutaneous lesions.

Laser therapy for superficial wound healing

In surveying the therapeutic applications of LASER, healing of various wounds such as pressure sores and ulcers, burns, skin donor areas and postoperative wounds are considered[32, 42, 52]. It was found that applying LASER following the initial treatment with necrotic clearance lead to reducing infection signs, decreasing the amount and smell of fluid in exuding wounds, decreasing the pain and as well as resuming the immune response which is initiated by the inflammatory phase. In this regard, it was revealed that LASER therapy produced beneficial effects on the cutaneous wound healing. Also it was suggested that applying LASER at dose of 8 J/cm^2 were more effective than those at 4 J/cm^2 [48]. In another study, it was found that applying HeNe laser at dose of 5 J/cm2 accelerate the wound closure by normalization the cell function and stimulation the cell proliferation and migration of wounded fibroblasts which were induced by exhibiting the activity of mitochondria whereas they reported molecular damage using LASER at dose of 10 J/cm^2 [53, 54]. As well as it was demonstrated that GaAs LASER at 3 J/cm2 can stimulate the proliferation of fibroblast[55]. Another study reported that optimal effect of Er:YAG laser were achieved at dose of 3.37 J/cm^2 [56].

It has been reported that a visible light at wavelength of 630-780 nm can penetrate to a depth of 0.5-50 mm. this light has shown great potential for wound healing and superficial skin conditions[32, 57]. In this regard, Karu *et al* (1993) reported that the most effective wavelength of light was 660nm[39]. Various studies revealed that applying light at 660 nm improves superficial wounds and skin conditions [40], acne, scar tissue and small lesions. In order to treating large wounds or burns which the treatment area need a deeper effect, using large cluster probes have gained better efficiency. For healing wounds which are placed at a medium depth, the probe should be pressed against the skin. In order to heal open wounds, the laser probe is held 1-2cm from the wound, whereas in order to expose the periphery of the wound, the probe must be contacted directly. In addition, the skin periphery of the wound should gained more dose than its open area[5]. Usually the functional probes of LASER are existed in the form of single or cluster. A single laser probe (660 nm) is utilized around the margin of superficial wounds whereas a cluster probe (visible red and infra-red laser light) is utilized for the treatment of inflammation of soft tissue.

To heal wound, the periphery of the wound requires higher dose (3-4 J/cm2) while the open wound requires a lower dose (0.5 J/cm2)[5, 32]. It was demonstrated that for open wound, a lower dosage are used as compared with the skin-covered periphery because the laser light is more absorbed in the unprotected wound.

It was revealed that applying LASER at wavelength of 630 nm caused to bacterial inhibition which may be an important consideration when selecting the correct wavelength for infected wounds[38]. An infected ulcer can be treated twice weekly until the infection clears.

It was found that LASER should expose acute wounds daily whereas chronic wounds should be healed 1-2 times a week[32]. In order to healing chronic wound, it requires more treatment intervals, as two or three times during a week are considered as the maximum[32].

Tunér *et al*(2002) reported that it is more beneficial to apply 3-4 treatments a week with moderate doses as compared with utilizing higher doses and fewer treatments time[5].

CONCLUSION

This paper shows that laser is an effective therapeutic modality to promote healing of some wounds. The main biological effects of this therapeutic technique are related to the decrease in inflammatory cells, increased fibroblast proliferation, angiogenesis stimulation, formation of granulation tissue and also increased collagen synthesis. Also biological effects of laser will be affected by some parameters such as energy density, wavelength and amount of dose. With respect to the type of applied laser (visible or infra-red, continuous or pulsed), the treatment parameters can be changed. In order to achieve full acceptance as a authentic medical technique, high quality studies are required.

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