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ORIGINAL ARTICLE

Innovative Laser Therapy in Chronic Wound Healing Disorders; Multi Wavelengths Transdermal and Interstitial Laser Therapy

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ABSTRACT

One of the most important diabetic complications is diabetic neuropathy, which results in impaired wound healing, leading to numerous difficulties and morbidity and mortality, and is the ultimate consequence of micro- and macrovascular disease. It seems. There are several advanced techniques that reverse many degenerative processes and help heal chronic wounds in diabetics. Laser therapy has shown in many studies to improve wound healing in all phases: inflammatory, (2) proliferative, and (3) tissue remodeling. All of the sixteenth subjects were diagnosed with amputation. They all suffer from chronic severe wounds, and they are all diagnosed with diabetic neuropathy. This study used an advanced laser therapy called multi-wavelength interstitial laser therapy. We used 400nm, 450nm, 530nm, 630nm and 808nm. We applied transdermal laser irradiation on a wound area, and beside the wound, we applied interstitial laser irradiation. In interstitial irradiation, the output power at the end of the fiber is 50 mW. In transdermal irradiation the output power was 100mw. The laser was applied continuously with a total energy density of 1 J/cm² at the wound surface and 2 J/cm² in the area adjacent to the wound. All of the laser wavelengths were applied on each point, in both transdermal and interstitial laser irradiation. Patients are treated twice weekly for 6 weeks. Results show a rapid and conclusive effect on wound healing. All of them begin to feel and feel pain. The inflamed sore area is much better. More investigations can be done by regenerative methods combination.

***Keywords**: Wound healing, diabetes, LLLT, PBM, mitochondria, ATP, interstitial laser*

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INTRODUCTION

Wounds are termed skin deformities caused by electrical, thermal, chemical and mechanical injuries that open or damage the skin or create underlying therapeutic or physical problems. Organization[1, 2]. Innate to all species, wound healing is the biological process by which the body repairs itself after traumatic, complicated, infectious and/or surgical injury. A physical or physical injury that results in the disruption of the skin's natural anatomy and physiological function[2].

The wound healing process is governed by a series of events including coagulation, inflammation, granulation tissue formation, epithelialization, and tissue regeneration[3, 4]. The investigation of various pharmacological and non-pharmacological modalities to promote wound healing is a developing field of biomedicine. Currently, new strategies include PRP[5, 6], exosome- and stem-cell-based therapies[7-9], and light-based therapies (photobiomodulation: PBM) [10-14], or to promote healing and thereby regenerate the body tissues. These methods can save patients from amputation and other serious complications [15-24]. Laser therapy hassled to improved wound care management and overall body metabolism and has increased our understanding of the processes involved in tissue repair, tissue regeneration, and improved cell metabolism. Many studies have used transcutaneous laser irradiation at red and infrared wavelengths. However, there are more beneficial wavelengths that enhance the effects on mitochondrial regeneration and adenosine-3-phosphate (ATP) release. Because these wavelengths cannot penetrate deeply percutaneously, they are delivered targeted via laser fibers as interstitial laser therapy[19, 25, 26].

This article specifically discusses recent advances in photobiomodulation therapy, also known as interstitial PBM, which is an interstitial Laser therapy, and its applications are used to promote cutaneous and subcutaneous wound healing and subsequent prospects[27-34].

Wound healing depends on several factors, including blood supply, wound size, wound edge pressure and motion, individual susceptibility to infection, underlying tissue type and condition, as well as age, malnutrition and disease[35, 36]. Depending on the type of injury and tissue blood flow, the wound healing process can be compromised. In diabetics, there is a fundamental problem with metabolic function, impairing blood flow, oxygenation, and nutrition to the wound area[37].

Photobiomodulation regulates micro and macro blood circulation, cellular supply of oxygen, ATP release, increased lymphatic drainage, increased over 100 repair genes, increased and supplied ATP for circulating stem cells and growth factors, and others. It can increase the effects equivalent to many beneficial therapeutic agents, beneficial and therapeutic drug equivalent effects, capable of healing and regeneration. All of these metabolisms can reverse the side effects of diabetic ulcer damage[25, 26].

Wound healing is an active process consisting of four sequential stages including hemostasis, inflammation, proliferation, and remodeling. The initial stage of the wound healing process is the inflammatory phase, which is considered to be a fundamental step in the wound healing process, essential for disease prevention and involved in tissue regeneration. PBM has anti-inflammatory effects, as evidenced by many studies. Once the wound begins to heal, the procedure usually dictates a complete cessation of injury.PBM also affects cell function, proliferation and migration, and plays an important role in tissue regeneration [10, 14, 19, 20, 28].

Except for a few studies, photobiomodulation therapy with red and near-infrared light is the most commonly used and reported method for healing both acute and chronic wounds, appears promising as a drug-free approach to Inflammatory, pain, and restorative functions combined with the ability to positively modulate biochemical and molecular responses[30, 32]. However, other wavelengths of light such as blue, green, yellow, or far infrared may have many positive effects at the cellular level[38-45]. The data suggest that simultaneous illumination of multiple wavelengths is more effective than single wavelengths, but optimal single and multiple wavelengths should be better defined to be more reliable across wound types. Comprehensive healing must be induced. These limitations are due to the ability of red and infrared wavelengths to penetrate deep from the skin into subcutaneous areas to help normal and healthy cells rebuild damaged skin and blood vessels and promote angiogenic mechanisms. The fact about the superficial penetration of different Near-infrared (800–830 nm) and red (630–680 nm) into the tissue is reported in many other indications of laser therapy in medicine. The reason in all these studies goes to the same fact[46-48].

There is an advanced technology, 904 nm superpulsed light that the most important approach is transdermal irradiation, that can penetrate more deeply transdermal that the other wavelengths. But this is just one wavelength, and then we are neglecting the patient fro the other wavelengths[48-50].

The fact that various near-infrared (800-830 nm) and red (630-680 nm) penetrate superficially into tissue has been reported in many other indications of laser therapy in medicine. The reason for all these studies lies in the same fact that these wavelengths can penetrate in comparison to the other wavelengths. There is an advanced technology, 904nm Superpulse Light, whose main approach is transcutaneous irradiation, which can penetrate deeper into the skin than other wavelengths [48-50].But that's just one wavelength for the patients, and just by using these wavelengths, we ignore the other beneficial colors (wavelengths) for the patients.

Transdermal PBM therapy has been practiced for over 60 years, with exponentially positive clinical and experimental studies reported. Despite its impressive therapeutic benefits, PBM has yet to reach the stage of mainstream medical acceptance. The main limitation is that other wavelengths have limitations in delivering photons deep into tissue. These limitations lead to different dosimetry parameters. Therefore, there is not a conclusion of a therapeutic dosage of laser therapy protocol in different diseases [10, 51, 52].

This is due to the different mechanism of photon reaction with the skin until the photons reach the target area include reflection, refraction, transmission, absorption, differences in oily or dry skin, differences in skin color, and differences in target tissue distance, andtarget tissue, pathway tissue, contact or non-contact irradiation, and all of these do not trigger inference information for a conclusive PBM in medicine [10, 51, 52].

We resolved these limitations using interstitial laser irradiation. This makes it easy to calculate the actual photon dose reaching the target area. There is no limit to photon transmission and different wavelengths.

MATERIAL AND METHODS

Volunteers

Sixteenth male and female patients with chronic wounds and repeated unsuccessful and recurrent wound recurrences for more than two years participated in the study. All of them were the case for amputation by a surgery medical committee. Eight of them underwent at least three small surgeries with wounds that did not heal properly.

Procedure

All interstitial laser irradiations were performed using five different wavelengths: blue (400nm, and 450nm), green (530nm), red (630nm) and infrared (808nm) wavelengths (colors). After the surgeon had cleaned the wound, we applied five-point interstitial laser irradiation adjacent to the wound, targeting healthy cells. A disposable fiber optic for interstitial laser irradiation was inserted into the healthy area at least 2 cm deep to the nearest point around the wound by an intervention radiologist under ultrasound guide. Each point was passed through an optical fiber and the output power for all wavelengths was fixed at 50mW. 400 nm, 20 joules, 450 nm, 20 joules, 530 nm, 20 joules, 630 nm, 20 joules, 808 nm and 20 Joules were applied. Then, after receiving the energy of 20 joules, the needle was taken out 0.5mm and again 20 joules were irradiated. Figure, and Figure 2 presents the conceptual schematic of the treatment method.

Also, on the wound area, all wavelengths were used in the order 400nm, 450nm, 530nm, 630nm, 808nm, and for each color (wavelength), 1 j/cm2 was applied for each laser wavelength. The patient was treated twice a week for 6 weeks. Figure 3 presents the conceptual picture of the wound area.

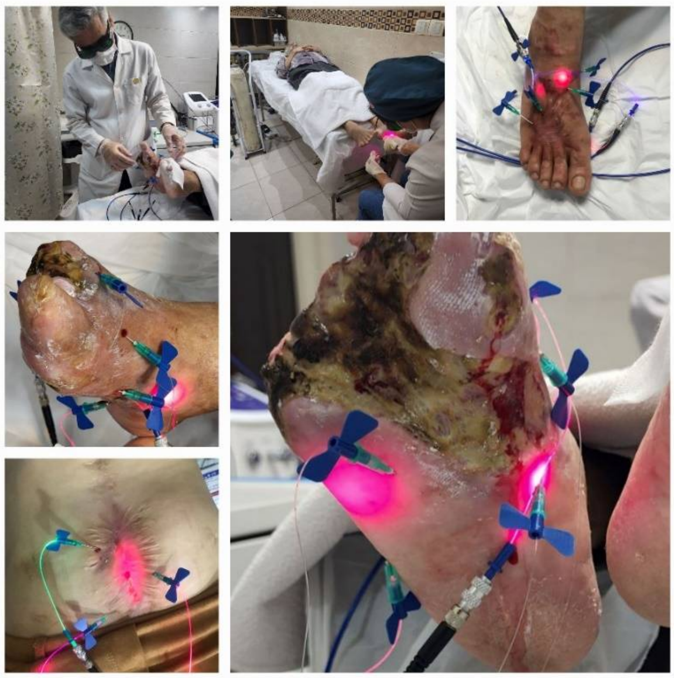

Figure 1. The interstitial multi color laser therapy can be applied to penetrate the other laser therapy wavelength targeted to a desired area.

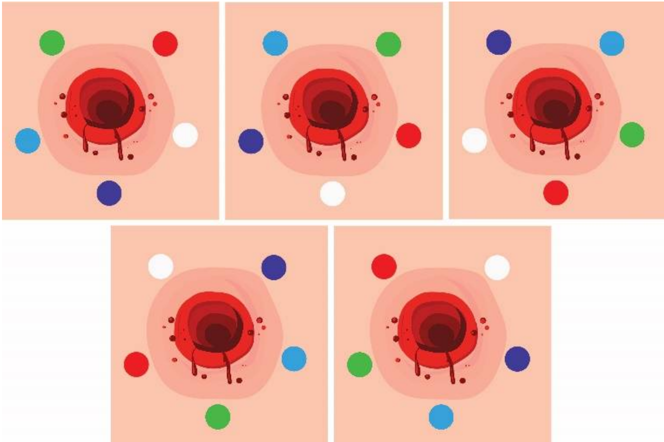

Figure 2. A disposable fiber optic for interstitial laser irradiation was inserted into the healthy area at least 2 cm deep to the nearest point around the wound. Each point was passed through an optical fiber and the output power for all wavelengths was fixed at 50mW. 400 nm, 20 Joules, 450 nm, 20 Joules, 530 nm, 20 Joules, 630 nm, 20 Joules, 808 nm and 20 Joules were applied.

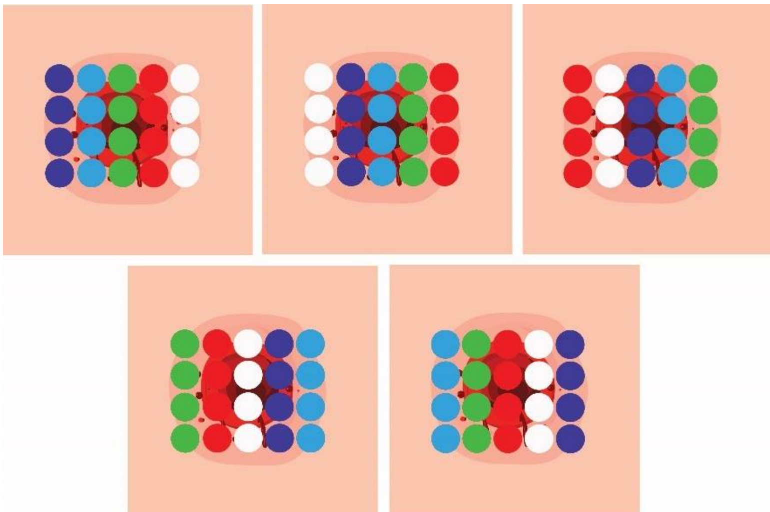

Figure 3. On the wound area, all wavelengths were used in the order 400nm, 450nm, 530nm, 630nm, 808nm, and for each color (wavelength), 1 j/cm2 was applied for each laser wavelength.

RESULTS

In Figure 4,in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the sixth week. In the bottom left, the results are after the second week, and in the bottom right, the results are after four weeks. The patient is female, and she is 49 years old.

Figure 5, in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the fourth week. In the bottom left, the results are after the sixth week.The patient is male, and he is 63 years old.

Figure 6, at the top, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the fourth week. At the bottom, the results are after the sixth week. The patient is male, and he is 60 years old.

Figure 7, in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month. The patient is male, and he is 65 years old.

Figure 8, in the top left, the wound is before starting the interstitial laser therapy. In the top right, and the bottom left, the results are after the second week, and in the bottom right, the results are after the sixth month. The patient is male, and he is 19 years old.

Figure 9, in the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is male, and he is 63 years old.

Figure 10, at the top, the wound is before starting the interstitial laser therapy. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month. The patient is female, and she is 23 years old.
Figure 11,in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month. The patient is female, and she is 53 years old.
Figure 12, on the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is female, and she is 43 years old.
Figure 13, on the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the second week. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is female, and she is 55 years old.
Figure 14, on the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is male, and he is 23 years old.
Figure 15, in the middle center, the wound is before starting the interstitial laser therapy. In the top left, the results are after the first week. In the bottom left, the results are after the second week, and in the bottom right, the results are after the fourth week, and in the right bottom, the results are after the sixth week. The patient is male, and he is 38 years old.
Figure 16,on the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the second week. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is male, and he is 42 years old.
Figure 17,in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom right, the results are after the fourth week, and in the bottom left, the results are after the sixth month. The patient is male, and he is 37 years old.
Figure 18, on the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the fourth week. On the right, the results are after the sixth week of interstitial laser irradiation. The patient is male, and he is 49 years old. Figure 19,in the top left and right, is a picture of the procedure starting. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month. These figures are for the same patient.
Figure 20, in the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom right, the results are after the fourth week, and in the bottom left, the results are after the sixth month. The patient is female, and he is 51 years old.

Figure 4. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the sixth weeks. In the bottom left, the results are after the second week, and in the bottom right, the results are after four weeks.

Figure 5. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the fourthweek. In the bottom left, the results are after the sixth week.

Figure 6. At the top, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the fourth week. At the bottom, the results are after the sixth week.

Figure 7. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month.

Figure 8. In the top left, the wound is before starting the interstitial laser therapy. In the top right, and the bottom left, the results are after the second week, and in the bottom right, the results are after the sixth month.

Figure 9. On the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 10. At the top, the wound is before starting the interstitial laser therapy. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month.

Figure 11. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month.

Figure 12. On the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 13. On the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the second week. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 14. On the left, the wound is before starting the interstitial laser therapy. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 15.In the middle center, the wound is before starting the interstitial laser therapy. In the top left, the results are after the first week. In the bottom left, the results are after the second week, and in the bottom right, the results are after the fourth week, and in the right bottom, the results are after the sixth week.

Figure 16. On the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the second week. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 17. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom right, the results are after the fourth week, and in the bottom left, the results are after the sixth month.

Figure 18. On the left, the wound is before starting the interstitial laser therapy. In the middle center, the results are after the fourth week. On the right, the results are after the sixth week of interstitial laser irradiation.

Figure 19. In the top left and right, is a picture before starting the procedure. In the bottom left, the results are after the fourth week, and in the bottom right, the results are after the sixth month.

Figure 20. In the top left, the wound is before starting the interstitial laser therapy. In the top right, the results are after the second week. In the bottom right, the results are after the fourth week, and in the bottom left, the results are after the sixth month.

DISCUSSION AND CONCLUSION

Wound healing is a complex therapy method. Once the wound begins to heal, it usually closes completely and heals. However, acute and chronic wound healing can be compromised by patient factors (i.e.,

comorbidities) and/or wound factors (i.e., infections). Wounds with compromised healing are difficult to reopen because good standard wound care does not always lead to better healing outcomes and more advanced treatments are often used. We face a failure in the healing system in diabetic patients. They have metabolic problems, and their regenerative capacities are severely impaired[3, 35, 36].
The targeted multi-wavelength use of laser-based therapies in the treatment of various pathophysiological conditions has received significant attention from researchers worldwide after their introduction as therapeutic modalities over the past decades[10, 28]. Since then, the field of PBM has developed rapidly and is widely used to treat a variety of conditions, including healing wounds, muscle and nerve damage, reducing inflammation and pain, restoring function, and rejuvenating, and is known as a part of regenerative medicine [3, 10, 14]. Several studies have shown that low level lasers can induce protein tyrosine kinase receptors (TPKR) and activate mitogen-activated protein kinases (MAPK) to induce cell proliferation. PBM can activate proliferation and cell migration through ELF4E phosphorylation. Application of PBM can increase calcium levels and thereby promote cell proliferation. Application of PBM (632.5 nm) can enhance the expression of endothelial nitric oxide synthase in endothelial cells, thereby promoting proliferation and migration of endothelial cells, which is important in angiogenesis. PBM can lead to increased cyclic adenosine monophosphate (cAMP), resulting in increased expression of genes involved in proliferation, survival, and angiogenesis[10, 14].
Different wavelengths have different mechanisms at the cellular level that can trigger and promote self-repair, regeneration and healing processes. Green laser light increases ATP production in irradiated mitochondria by more than 30%. Red lasers stimulate the immune system, activate macrophages, and release cytokines and interferons. Green laser can increase oxygen supply. Blue lasers can enhance the antibacterial effects by nitric oxide signaling. Irradiation with wavelength of 532 nm can promote the wound-healing ability of hADSCs, suggesting that green has potential for preclinical applications. Targeted PBM can increase microcirculation, angiogenesis, vascular endothelial growth factor (VEGF), microcirculation, lymphatic drainage, antibacterial/antiviral/antifungal effect, relief of itching, increased local nutrition and ATP release at mitochondrial level, stimulation of regeneration (transformation of growth factor TGFβ), increased RNA/DNA synthesis and many other pluses effect of[10, 48, 53].
Laser therapy can be directed towards wound healing by using alternative methods of applying the laser. Laser therapy can be used in two completely different but complementary therapeutic applications: PBM therapy as a regenerative medicine, and photodynamic therapy (PDT). PDT relies on the action of laser or light to excite endogenous chromophores or exogenously supplied nontoxic photosensitizers to react with ambient oxygen to generate reactive oxygen species (ROS).Reactive oxygen species (ROS) kill infectious microorganisms and destroy unwanted tissue. PBM plus photosensitizers plus oxygen (intravenous or tube) can be used after PDT and disinfection. If it is an internal wound, it is possible to perform laser treatment using ultrasound-guided interventional methods. In interstitial laser therapy, there are few restrictions on the application and delivery of the laser wavelength to the target area or tissue. If the problem is systemic, intravenous laser irradiation or intravenous PDT can be used. So, with sterile disposable fiber optics, we can target the tissues with more precision[28, 33, 48].
In general, PBM with red and near-infrared light can be viewed as a promising biophysical healing and regenerative modality due to its numerous applications. However, targeted laser therapy with interstitial lasers should be used as an interventional method if a more advanced, targeted and more effective method is desired. Red and infrared light therapy are gaining attention as potential therapeutic strategies for both acute and chronic wound healing and regeneration. However, this article highlighted further research into the biological role of other wavelengths of light in regeneration and repair. We will continue to provide painless, potentially non-invasive and drug-equivalent biophysical therapeutic interventions for chronic, non-healing skin wounds in the presence of unacceptable side effects[20, 25, 26, 39, 53].
The development of such non-invasive light-based curative therapies is urgent to avoid the treat of antibiotic resistance and possible unwanted drug side effects due to different photosensitizers with absorption peaks at different wavelengths.
Interstitial laser irradiation can be used to solve one of the main challenges in many studies, namely the standardization of optical parameters that vary from disease to disease. The real reason lies in the different phenomena of transdermal laser treatment and the different reactions of different tissues and transmission of light to the target area. Therefore, intra-tissue, interstitial laser treatment avoids these complex physical calculations and considerations. Our method removes all of these limitations, allowing all desired wavelengths to be delivered to target tissue at targeted doses as part of an interventional procedure. Therefore, we can use different benefits of different light colors, just as we simply did many positive effects in our study.

The cell and molecular mechanisms of effect of PBM have ended up fairly nicely understood in recent years. Briefly, the stimulatory impact of PBM is primarily based totally on the absorption of blue, green, yellow, red and NIR photons by means of intracellular chromophores placed within the mitochondria, which includes complicated one to complicated five complexes of mitochondria respiration chain, and possibly additionally via way of means of hemoglobin, chromophores with inside the plasma membrane of cells, changing endogenous enzymes and electron transport, thereby growing mitochondrial respiratory and ATP production[54-56].
There is a lot of scientific evidence that inspects alternation of many metabolic phenomena, cell, and subcellular, and mitochondrial alternations. The organic effectiveness of wavelengths has an effect on PBM on ion channels. Light can affect ion channels may be activated, permitting Ca+2 to go into the mobile and ultimately by various intracellular signaling pathway activation mediated via means of ROS, nitric oxide (NO), cyclic AMP (cAMP) and Ca+2 led to the activation of transcription elements worried with protein synthesis, extracellular matrix (ECM) deposition, mobile migration, proliferation, anti-inflammatory, mobile survival and inhibition of apoptosis[26, 55, 57].
On the other hand, since our goal is to investigate a faster and easier regeneration process, other possibilities of regeneration methods should be explored. Future hypotheses may be the application of exosome therapy, PRP therapy, stem cell therapy with PBM, especially multi-wavelength interstitial laser therapy.
Exosomes, growth factors, stem cells and progenitor cells seem to be particularly susceptible to PBM therapy. CCO has distinct absorption bands in the red (around 665 nm) and in the NIR (around 810 nm) regions. In future investigations, we recommend using stemcell and exosome injections into or beside the wound regions. The reason for the necessity of targeted multi-wavelength laser therapy is that besides CCO, a number of other molecules have been proposed to act as photo-receptors, and have other wavelengths of excitation. Ubiquinol, flavins and flavoproteins, free porphyrins, hemoglobin, and myoglobin, have all been proposed to be able to absorb photons and mediate photochemical and photobiological reactions to other wavelengths like blue, green, and yellow[10, 28, 33, 38, 53, 57, 58].
Exosomes, growth factors, stem cells, and progenitor cells appear to be particularly susceptible to PBM therapy. CCO has distinct absorption bands in the red (~665 nm) and NIR (~810 nm) ranges. In future studies, we recommend that stem cells and exosomes be injected into or adjacent to the wound area. The reason for the need for multi-wavelength targeted laser therapy is that, besides CCO, many molecules have been proposed to act as photoreceptors and have other excitation wavelengths. Ubiquinol, flavins and flavoproteins, free porphyrins, hemoglobin, and myoglobin have all been proposed to absorb photons and mediate photochemical and photobiological reactions at other wavelengths such as blue, green, and yellow[32-34, 53].
As explained previously, the reason they are so rarely used and understudied in medical PBM indications is the neglect of the technology that has passed through semi-invasive laser applications. Many studies show that superpulse played an important role in his PBM, as previously described. This is especially important in clinical applications where deep tissue penetration (up to 10 cm in bone, tendon, ligament and cartilage) is required. However, using this wavelength ignores the beneficial effects of other wavelengths on the patient [48-50].
In the end, besides all we discussed in this study, there are many crucial effects of PBM on stem-cells, and growth factors survival rate, that can lead to a new promising combinational regenerative method[45, 53, 59]. We emphasized that it is technically easy to inject mesenchymal stem cell, PRP, exosomes, and do the multi wavelength interstitial laser therapy for different medical indications and let the mitochondria shine. Combining the power of advanced interstitial laser therapy with other regenerative modalities such as exosomes, stemcell therapy, platelet-rich plasma (PRP), intravenous micronutrient therapy and oxygen therapy may lead to achieve better clinical outcomes and improve patient life.

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