Review Article

Use alone or in Combination of Red and Infrared Laser in Skin Wounds

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Abstract:

A systematic review was conducted covering the action of red laser, infrared and combination of both, with emphasis on cutaneous wound therapy, showing the different settings on parameters such as fluency, power, energy density, time of application, frequency mode and even the type of low-power lasers and their wavelengths. It was observed that in general, the lasers brings good clinical and histological results mainly, but there is not a protocol that defines a dosage of use that has predictability of therapeutic success in repairing these wounds.
Keywords: wound healing; infrared; laser.

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Introduction

The theoretical basis for the laser were postulated by Einstein in 1917, but only became real in 1960 with the ruby laser[3], since the low power laser is used as an aid in the treatment of skin wounds[26], seeking its closure and reestablishment of morphological structures and functions compromised by inflammatory processes[12,23,32,33], associated or not with infections[29,36] and comorbidities like diabetes that retard the reparative process[10,11,13,28].

The low power laser, biostimulation generator, emits no ionizing energy. Even despite being widely cited by the scientific community, it is shown with the wide field of research that it has not yet fully been explored because of its many variables: different types of lasers available, variations in their tuning parameters and form of use. Even with good results in the literature for the use of low power laser in skin wounds[5,10,11,13,18,19,28,29], it does not seem to exist a defined protocol for each of the variables to the use of laser, and this a challenge for future studies.

The present study aims to conduct a systematic review of the literature addressing the use of red laser, infrared and their combinations, mechanisms of action, indications and results in wounds. This research was performed using scientific articles filtered on site: www.pubmed.com

Literature review

Low power red laser

Passarela et al. in mitochondria isolated from Wistar rats and applied helium–neon (HeNe) laser, with fluency of 15J/cm^2 and power density of 15mW to cause an increase in mitochondrial ATP production [29].

Master et al. reported that studies from 1966 to 1984 showed that the use of HeNe and Ruby lasers accelerated cell division, have increased leukocytes, their phagocytosis, collagen synthesis, regeneration of lymph vessels and the development of granulation tissue[25]. And found that small doses of laser at a time are more effective for tissue repair that higher doses at once by maintaining mitochondrial activity.

Karu, showed that the lasers of Helium-Cadmus (HeCd) and diode, induced wound repair with photons

stimulating mitochondrial DNA, increasing the production of energy (ATP) and subsequent mitosis as well as protein synthesis[20]. Karu et al. applying HeNe laser with fluency of 56J/cm^2 demonstrated that lymphocytes had early response, where after the first six minutes the cell undergoes calcium influx and that for 12 hours RNA synthesis increases, and also between 2 and 8 hours increment of DNA, proteins synthesis and mitosis followed[19].

Searching doses of low-level laser to stimulate and inhibit the repair of skin wounds, Al-Watban and Zhang used Argon laser and found that the maximum restorative stimulation occurred with 19J/cm^2, but doses higher than 130J/cm^2 caused inhibition of repair and found that daily frequency during the week of treatment reduces the expectation of better results[5].

Almeida-Lopes using diode laser in cultured fibroblasts varying fluencies, power and the continuous or intermittent modes of use, observed that the proliferation of these cells occurred at lower fluencies (2J/cm^2), higher power (56mW) and continuous mode of use[3].

Nascimento et al. used diode laser (670nm and 685nm) in skin wounds in rats, varied power density at 2, 15 or 25mW for seven days, observed that material was then removed for histological analysis and concluded that there was better repair when combined high power intensity with shorter wavelength or vice versa[26].

Using the laser with 650nm/80s and varying fluencies (1 to 2.5 J/cm^2), Albertini et al. found a reduction of edema by 27% and 45.4% similar to anti-inflammatory effect of sodium diclofenac with the laser using 2.5J/cm^2, adrenalectomized animals also observed that the laser had no success in reducing edema[2].

Applying HeNe laser in normal and diabetic rats with wound, Carvalho et al. have used 48 Wistar rats, and laser with fluency 4J/cm^2/60s. Histological analysis showed diabetic and non-diabetic rats with an increase of collagen fibers in the wounds[9].

Mast cells received HeNe laser (405 and 532nm / 10mW 0.96 to / 60s, 28μm^2) to study the effect of laser in intracellular calcium concentration and histamine synthesis, Yang, Chen, Yu and Zhou observed an increase of mast cells without increasing intracellular calcium, which occurred after laser application, when there was histamine release by calcium influx into the cell[41]. Bayat et al. found mast cells response to burns with HeNe laser on a sample of 60 rats by using 38.2 or 76.4 J/cm^2 and 0.2% nitrofuzarone, observed that the laser and the nitrofuzarone promoted growth of mast cells, reducing inflammation and remodeling of the wound[7].

Applying daily 635nm-5J/cm^2 varying irradiance of 1, 5 and 15mW/cm^2 in rats with and without prednisone, Gál et al. treated wounds and observed histologically that the laser provided compensation only when not associated with corticosteroids[16].

The influence of laser indium-gallium-aluminum phosphide (InGaAIP) on the percentage of collagen and macrophages in skin wounds in diabetic rats, Carvalho et al. selected 30 male Wistar rats with and without diabetes (100mW, 10J/cm^2, 24s and continuous mode), after 3, 7 and 14 days they were examined histologically and immunohistochemically[10]. The control group showed more macrophages and the laser influenced the increase of collagen in diabetics.

Cultured fibroblasts by Frigo et al. using biostimulation daily with laser InGaAIP (50mW, 1050J/cm^2, 3 or 21J and 2mm2) had dose-dependent response to energy applied, where 3J reduced cell death and increased their proliferation[15].

Mitochondrial mechanisms for histamine release by mast cells irradiated with low laser power was used by Wu et al. applied in cell cultures 405 or 532 or 633nm, 3mm, 0.1 mW. The bands laser irradiation were consistent with the absorption bands of cytochrome c oxidase in the mitochondrial membrane, suggesting that this enzyme to be a photoreceptor, to increase the permeability of Mitochondrial calcium and release of histamine[40].

Tacon et al. assessed the AlGaInP laser therapy on wound healing, observing angiogenesis and growth of collagen in 54 Wistar rats treated with laser on alternate days with 3 or 6J/cm^2, and noted on the 5th day reduction of the inflammatory infiltrate in both fluencies, and from 10th to 15th day increased fibroplasia[38].

Esmaeelinejad et al. using fibroblasts irradiated with He-Ne laser with 0.5, 1 and 2J/cm^2 and irradiance of 0.66mW/cm^2 for three days, they proved that the laser stimulated fibroblast activity, even in environments with high presence of glucose[14].

Corticosteroids and inflammatory cytokines were measured in tissues removed from wounds of 36 Wistar rats treated with diode laser (670nm 9mW, 0.031W/cm^2 0.28cm^2 diameter) by Lima et al. and after six hours there was an increase of corticosteroids and reduction of cytokines[21].

Low power infrared laser

A study on the laser Gallium Arsenide (GaAs) with (904nm 27MW and, at 3min per day) was conducted by Bae et al. with 60 rats subjected to trauma with pressure[6].

Electromyography done in life and after euthanasia histopathology found laser to improve of movements of the treated limb speeding up the recovery of nerves.

The Gallium Aluminum Arsenide (GaAlAs) laser with 4J/cm^2 and 9mW was used in wounds of rats which were treated during 3 to 60 days by Medrado et al. Assessed histologically, deposits of collagen revealed to be packed more neatly with treatment[23].

Gonçalves et al. compared GaAlAs laser (830nm and 9mW) with healing oil in 24 rats with skin wounds. The animals were treated with 30 or 60J/cm^2 or healing oil over 20 days with collections every four days. The oil was effective in the growth of fibroblasts and the laser with 60J/cm^2 presented angiogenic potential[17].

Investigating the decreased expression of mRNA for inflammatory cytokines and cyclooxygenase 2, Pires et al. used 42 Wistar rats with tendonitis. The laser with 780nm, 22MW, 7.7 J/cm^2, and 75s 2cm^2 in therapy performed on alternate days using parameters like IL_6 and 1β, and TNFβ Cyclo-oxygenase 2 were compared in the acute and chronic phases, confirming the decreased expression of mRNA for proinflammatory mediators[31].

Diabetic rats with two wounds, one treated with diode laser with 890nm, 1.08mW, pulsing at 80Hz in 180μs and the other treated as placebo for 15 days. Dadpay et al. varied fluencies into distinct groups using 0.03J/cm^2 (1:30s) and 0.2J/cm^2 (200s). The laser repair increased in the groups receiving 0.2J/cm^2. [12]

Red lasers, infrared and combinations

Using various lasers (HeCd=442nm, Argon=488 and 514nm, HeNe=632.8nm, GaAlAs=780 and 830nm) with fluencies of 20J/cm^2 and frequency of three times weekly, AL-Watban and Zhang achieved the best results in wound repair with HeNe laser. Also found that the absorption of the laser and its effects were not associated to the penetration of irradiation and that low power lasers do not promote significant temperature changes in the tissues[5].

Comparing the HeNe laser with 2.4mW/cm^2 using continuous mode and GaAs with 904nm, 10mW pulsed mode to study the activity of ATP and ATPase (*in vitro*), Bulognani et al. used ATP synthesis inhibitors and the laser in an attempt to stimulate. The inhibition and specially the stimulation were confirmed[8].

Sroka et al. used normal urothelial cells with spinocellular carcinoma, glioblastoma and breast adenocarcinoma, to understand the behavior of different cells before different wavelengths with a spectrum of color until the infrared[37]. The laser used was Nd: YAG with 410, 488, 630, 635, 640, 805 and 1064nm, with fluencies between 0 to 20J/cm^2 and irradiance 10mW/cm^2, there was increased mitosis in all cells, especially with fluencies between 4 and 8J/cm^2, but independently of wavelength, with higher fluencies mitosis were reduced.

Wounds treated with the combination of lasers (HeNe with 3J/cm^2 or Neodymium-Doped Yttrium Aluminium Garnet (Nd: YAG) 30J/cm^2) and photosensitizers were tested by Jayasree et al[18]. They found that closed for 13 days with the laser associated with aminolevulinic acid, and 14 days when lasers were associated with derivatives hematoporphyrins in the control group reached 18 days to repair.

Using GaAlAs lasers (830nm 35mW and Ø2mm^2) and InGaAIP (685nm 35mW and Ø2mm^2) in an isolated manner and combined only changing fluencies Mendez et al. with 60 Wistar rats divided into groups using 20J/cm^2 and 50J/cm^2 obtained better recovery of wounds in the association of lasers with fluency 20J/cm^2. [24]

Enwemeka et al. and Woodruff et al. with meta-analyzes have shown that red and infrared laser can collaborate in wound repair, they stimulate collagen formation, pain control, mast cell degranulation and angiogenesis within an interval greater than 8.25J/cm^2 and less than 130J/cm^2, being better in the range between 19 and 24J/cm^2.[13,39]

Pinheiro et al. compared laser therapy (685nm) and polarized light (400 - 2000nm) in Wistar rats, radiating intercalary days for 7 days with fluency ranging from 20 or 40J/cm^2 and 40mW[30]. Histological analysis demonstrated that the laser and polarized light with 20J/cm^2 induced increase in collagen fibers, but the myofibroblasts were increased only with polarized light.

The systemic effect in repairing skin wounds has been reported with red laser (685nm AlGaInP with, 30mW, 20J to 667s), infrared laser (GaAlAs with 830nm, 50mW, 20J and 401s) and the association of both. Rodrigo et al. used 36 Wistar rats, with three dorsal wounds, where only the center wound was treated every other day[32]. Histological analysis showed superiority of the combination of lasers, where also the best repair of wounds occurred far of focus of treatment, indicating systemic reparative effect of the laser.

Jahangiri Noudeh et al. combined GaAlInP laser with 670nm and GaAlAs with 810nm in diabetic Wistar rats[27]. They used 500mW, 10J and 48s for GaAlInP laser, plus 250mW, 12J and 50s of GaAlAs laser applied in the same session and irradiated on the margins of the wound, with intervals of 3 days for 24 days. There were no differences in wound healing of diabetic and non diabetic.

Ablon compared the combination of red laser (633nm

and 126J/cm^2) plus infrared (830nm and 60J/cm^2) with the use of photodynamic therapy Light Emitting Diode (LED) in nine patients with chronic psoriasis for 4 or 5 weeks, every other day, 20 minutes per session[1]. Patients were followed for 3-8 months. Both therapies had removal rates between 60 and 100% free of inflammation, pain and side effects.

Studying laser in contaminated wounds, Nussbaum et al. with 70 rats infected with *Staphylococcus aureus* have been treated for 19 days using diode laser with 635nm or 808nm, fluencies of 1 and 20J/cm^2 with time 36 and 710s[28]. Histological and immunohistochemical analysis as well as Gram staining swabs semi-quantitative technique showed that the 808 nm did not produce good results because it reduced the normal microbiota and allowed the growth of *Staphylococcus aureus*.

Evaluating necrosis of surgical flaps sutured margins, Cury et al. irradiated 48 rats, two lasers groups with 660nm and 30 or 40J/cm^2 and two other lasers groups with 780nm and 30 or 40J/cm^2, microscopic analysis of the points treated showed 62.83% area of necrosis, and no satisfactory results with the isolated use of these lasers[11].

Investigating infected wounds with *Staphylococcus aureus* and *Staphylococcus pyogenes*, Santos et al. used 24 Wistar rats with dorsal wounds inoculated with bacteria, then treated with diode laser (680nm, 5J/cm^2, 30mW continuous mode, Ø3mm, 424mW/cm^2, 11.8s, 0.35J, daily for 7 days) and (790nm, 5J/cm^2, 40mW, continuous mode, Ø3mm, 566mW/cm^2, 8.8s, 0.35J, daily for 7 days) and when used in combination with each laser the fluency was 2.5J/cm^2, cumulatively the irradiated points received 20J/cm^2 per session[35]. Histological analysis showed the combined therapy to be better, with less inflammation, increased production of collagen and overcoming the infectious process.

Silveira et al. used HeNe laser with 1 or 3J/cm^2 and GaAs diode laser with 1 or 3J/cm^2.[36] The therapy was applied in post-surgical wounds using intervals of 2, 12, 24, 48, 72, 96 and 120 hours. The analysis was performed by photometry, observing hydroxyproline, the activity of superoxidase, dismutase, catalase, lipid and protein oxidation. Wounds treated with laser had reduced their measures and increased collagen synthesis, as well as the reduction of enzymes and lipids, mainly using the HeNe laser with 1 and 3J/cm^2 and GaAs with 3J/cm^2.

Santos Jde et al. 114 pregnant women were selected for the evaluation of pain in region of episiotomy, in the control group the usual procedures were performed, a group received diode laser with 660nm and another group using diode laser with 780nm, both with 8.8J/cm^2, 35mW and 0.35J per point, adding 1.05J on three points, after an interval of 6 to 56 hours, no significant differences were observed between the groups regarding pain[34].

The laser alone or combined with different wavelengths in the laryngeal reflux induced by nasogastric intubation was used by Marinho et al. The diode laser GaAlAs (780nm, 70mW, Ø=0.04cm^2, 1.75W/cm^2, 17.5J/cm^2, 10s per point, 2.1J, and application in continuous mode every other day) and the other group with diode laser associated (GaAlAs=780nm) to (InGaAIP=660nm), for this association the radiated energy was 2.1J of InGaAlP with 1.2J of GaAlAs[22]. The production of myeloperoxidase had reduced, there was lower inflammatory response in histological analysis with greater production of collagen synthesis in combination of lasers.

Discussion

In this systematic review the term "wound healing" joined with other keywords: "red laser", "infrared laser" and "combination of red and infrared lasers" was searched in Pubmed website, in this way we obtained a total of 321 articles suggested but considering our aims, we selected 41 to perform this study.

The low power laser releases energy in the form of photons, which are absorbed by photoreceptors called chromophores, especially when cells are under stress. These photons have their light energy converted into chemical energy by increasing the ion exchange[19,20,29,40]. In wavelengths of red this reaction occurs in mitochondria and lysosomes, and in infrared wavelengths it starts in the cytoplasmic membrane, but both occur to increase production of ATP in the intracellular environment, enabling opening of calcium channels in the cytoplasmic membrane and mitochondrial with energy stimulus generated by the cytochrome C oxidase, enabling an increase in the production of RNA by DNA who also suffers increase, all these events are essential for tissue repair, such as collagen synthesis, release of histamine by mast and cell mitosis[7.20, 29,37,40,41]. It is cited in the literature that it is possible to reduce the inflammatory infiltrates in histological analyzes of injuries treated with low intensity laser with different wavelengths [22,23,25,32,33,37,38]. This happens through the additional stimulus of corticosteroids released by the adrenal glands during laser therapy, helping to reduce pro-inflammatory cytokines[2,16,21], contributing to the reduction of phagocytic activity of macrophages[10]. These phenomena have as principle the reduced expression of the mRNA that knocks down the levels of these cytokines and their

effects[31]. The low level laser also helps in reducing the enzymatic effect generated by oxidative stress that exacerbates fibrogenesis[36], reinforced by the systemic effect of laser[32]. This shows that laser therapy promotes tissue repair, because it is able to induce an increase of fibroblast[3,15], protein and collagen synthesis[9,13,14,15,23,36,39], angiogenesis[13,17,38,39], edema reduction[2] and repair of nerve fibers[6] as it inhibits proteolytic enzymes[36] and pro-inflammatory cytokines[21] that are fundamental in the process of cleaning the wound contaminated [28], even if it's not clear how the laser stimulates and inhibit protein synthesis selectively.

The cutaneous wound compromise the blood vessels and nerves, the low power laser may contribute to induce the repair of these wounds acting in more superficial layers with red laser and deepest with infrared laser[13,18,39]. However this ability to penetrate is challenged, which makes it more relevant to know what absorbs the laser[5]. Red wavelengths show efficacy in fibroblast proliferation[3] and infrared wavelengths show better results for angiogenesis[17], however when separately comparing these wavelengths, variable results were found. Diode laser with fluencies of 1 and 20J/cm^2 and 808nm have not been successful with bacteria in contaminated wounds[28]. In another study, which confronted laser 685nm and 20J/cm^2 with polarized light (400 to 2000nm), an increase of collagen fibers for both[30] was showed, which occurred also when compared to GaAs and HeNe 3J/cm^2 with 1 or 3J/cm^2 in wounds subjected to histological and biochemical analyzes[36]. In therapy under sutured flaps, this association did not contribute satisfactorily to the tissue vitality[11] and also did not show good clinical results in controlling postoperative pain in episiotomies[34]. However the treatment of psoriasis with phototherapy using 633 and 830nm combined reduced 60-100% of the affected area[1]. And when the red and infrared lasers are used on alternate days, even compared with the same laser used alone, there was histological advantage of better modulation of the inflammatory response and induction of collagen synthesis [22]. Also when assessed with 20J/cm^2 fluency, the results of the combination are greater[24]. In addition this combination brought improvements to distant wounds not directly irradiated, indicating systemic effects[32].

The lasers were also administered in association with non-photodynamic therapy. While the laser with 635nm used along corticosteroids proved useless, however it was inducer of wound repair, when used alone[16]. Diode laser with 830nm was compared to healing oil and both were repairers in the angiogenesis as the oil in fibrogenesis[17]. Using photosensitizing substances lasers can accelerate the wound closure[18]. The association improved burns wounds using laser and nitrofuzarone[7].

The laser is adjusted in a continuous or pulsatile mode with adjustment of hertz (Hz) and pulse time. Adjusting the diode infrared in pulsed mode (80Hz and 180μs) it achieved good results, including with diabetic wounds[12]. On the other hand continuous mode can promote mitosis of fibroblasts more than pulsatile mode[3], as there are many researches successful with continuous mode[27,32,35].

Induction of cell mitosis is a relevant characteristic to the use of low power laser, but this occurs in normal cells and malignant cells, this desired capacity in non-cancerous wounds, occurs more significantly through the calibration of fluency than by the wavelength[37]. It was also found that wound repair were higher when laser therapy was adjusted with higher power intensity and shorter wavelengths[26]. The same authors demonstrated in different years, that the increase in application frequency from three to five weekly sessions did not result in changes in wound repair, but higher frequencies can inhibit the repair of these lesions[4,5], which corroborates with this thesis articles with good results using therapy sessions on alternate days[1,22,24,31]. However intervals of 72 hour were not effective[27]. Also performing laser therapy for a certain period of time brings better results than shortening the amount of sessions[25], but there are also good results with daily use of laser[35,41].

A range that induces collagen formation, pain control and angiogenesis, may occur at doses of 8.25J/cm^2 and 130J/cm^2 [13], this minimum limit was increased to 19J/cm^2 [5], 60 to 126J/cm^2 was the lower interval clinically tested on a combined basis[1], however the best results were obtained between 19 and 24J/cm^2 [39]. But independently of wavelength, 20J/cm^2 did not influence mitosis[37], these results show us differences and the absence of fluency value to serve as therapeutic protocol.

Conclusion

The low-power lasers in general are efficient collaborators in the repair of skin wounds, inducing growth of fibroblasts, collagen synthesis, angiogenesis and subsequent re-epithelialization to wound closure. A promising alternative for the use of lasers to achieve these results is the combination of red and infrared wavelengths, applications on alternate days during a range of approximately two weeks time. However there is still no defined protocol with dose of fluency to apply to these skin wounds.

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