REVIEW ARTICLE

Application of laser for treatment of cutaneous leishmaniasis: a review of literature

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Abstract
Cutaneous leishmaniasis (CL) is a major health problem in developing countries with high economic and health impact. Despite suggested treatment for CL, there is still no definite therapy for this infection, and many of these treatments are associated with serious local and systemic side effects. In the current paper, use of different laser types including continuous and fractional CO_2, argon, PDL, erbium glass, and Nd:YAG have been reviewed. Based on our review, given the high reported efficacy and low side-effect profile, use of laser can be considered as a good alternative to standard treatment of cutaneous leishmaniasis (CL). Performing more studies using different types of lasers is recommended to evaluate the efficacy of this method for treatment of CL.

Keywords Cutaneous leishmaniasis · Laser · Treatment

Background

Leishmaniasis is a major health problem in developing world with the annual incidence of 900,000 to 1,300,000 cases. It is endemic in 90 tropical and subtropical countries, and about 350 million people are at the risk of acquiring it [1]. Leishmaniasis has three clinical subtypes including cutaneous leishmaniasis (CL), mucoCL, and visceral leishmaniasis [2].

CL is the most common type of leishmaniasis caused by unicellular parasite and transmitted by sandfly [3, 4]. The most common causes of CL are *L. major*, *L. tropica*, *L. aethiopica*, *L. mexicana*, *L. braziliensis*, and *L. amazonensis* [5].CL classically presents with single or multiple papule or ulcerated nodules that typically have the appearance of volcano having raised edge with central crater. They are usually painless but may become painful especially in the case of superinfection [6].

Common differential diagnosis of CL includes ecthyma, malignancy, sarcoidosis, tularemia, yaws, myiasis, cutaneous anthrax, deep mycosis, atypical mycobacterial infection, cutaneous TB, tertiary syphilis, and insect bite reaction [6].Most of the Old World CL are caused by *L. tropica* and *L. major* causing urban (dry ulcer) and rural (wet ulcer) disease, respectively [7].

Definite diagnosis of CL depends on confirmation of leishmania parasite in lesion's aspiration, and scraping or biopsy with PCR is the method of choice for species determination and is considered gold standard for CL diagnosis [6, 8]. PCR is therefore helpful for determining type of treatment and monitoring of the patients. Culture in the NNN or Schneider's Drosophila medium is the other method of diagnosis that usually takes [1–]3 weeks and may be unreliable [6].

The Leishmanin skin test (Montenegro skin test) is performed by intradermal injection of dead promastigotes and turns positive 3 months after CL lesions appearance. However, this test is not specific, and 70% population in the endemic areas have positive test. Other serologic tests including K39 ELIZA, DAT, and IFA have been used for diagnosis of the visceral but not CL [6].

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Many treatment have been suggested for this infection including systemic and intralesional antimony [9–11], amphotericin B [12], dapsone, photodynamic therapy [13], cryotherapy [14], heat therapy [15, 16], miltefosine, topical paromomycin [17], nitric oxide [18], topical and systemic imidazoles [19] with antimony compounds regarded as first line treatment [20]. In addition, many experimental studies are underway to find new treatment methods for leishmaniasis [12, 21, 22]. Despite suggested treatment for leishmaniasis, there is still no definite therapy for this infection, and many of these treatments are associated with serious local and systemic side effects [12].

Lasers have been used for a long time to treat various dermatologic conditions and for esthetic purposes. Common esthetic applications of laser include hair removal [23], rejuvenation [24], vascular treatment [25], dyspigmentation [26], etc. Some of its applications for dermatologic disorders include treatment of the acne [27], vitiligo [28], and rosacea [29].

One of the suggested applications of the laser is treatment of CL [30]. In the current paper, we review the efficacy of lasers including continuous and fractional CO_2, argon, PDL, erbium glass, and Nd:YAG in the treatment of CL (Table 1).

Use of CO2 laser for treatment of CL

The first of use of laser for treatment of the CL goes back to 1981. Babajev KB et al. used CO_2 laser for 6 patients affected by CL in 1981 and achieved encouraging results [30] (Table 1). They subsequently treated 108 patients with CL; 97(90%) of them were resistance to the local or systemic treatment [30]. Continuous CO_2 laser was emitted to the tissue (power density 203–3 kw/cm^2) until the wound base become even pink, and then, defocused laser beam (200–400 W/cm^2) was emitted to provide a thin brown layers as a barrier to wound for prevention of secondary bacterial infection. The resulting wound completely healed by day [10–]30 [30]. The results of bacterial culture showed that the resulting wounds were sterile in 96% of cases and no leishman body was found in the wound as the end of laser therapy [30].

The mean of recovery time was 21 ± 2.2 days with some correlation between primary ulcer size and the recovery time [30]. Authors suggested that laser can improve healing speed by 1.5 times as compared with the other methods [30] with good cosmetic results. No recurrence was observed at [7-]year follow-up in 82 patients [30]. Babaev OG and Babaeva OB also described use of laser in Russia in1985 [40].

Rodríguez ME et al. described use of single irradiation of CO_2 laser for therapy of CL lesions in 10 patients in 1990 [41]. The lesions had different clinical forms, and all of them cured without any relapse at [2-]year follow-up. No side effect was reported, and the authors recommended this method of treatment of the choice for CL [41].

Asilian et al. evaluated continuous CO2 laser (Sonic 500), with power of 30 W in 123 patients with 183 lesions versus systemic glucantime (50 mg/kg/day for 15 days, repeated if needed) in 110 patients with 250 lesions in 2004. Only 83 patients with 111 lesions cutaneous leishmaniasis in the CO2 laser group completed the follow-up. Laser was directed to the lesion and its surrounding of [2–]3 mm. After each laser irradiation, the ulcer was cleaned using soaked gauze, and this procedure was repeated until the ulcer bed become brown, and then, irradiation was performed from further distance to provide hemostasis. The ulcer was then covered with erythromycin ointment [35].The ulcer healing was complete by day [14–]30. Seven out of 111 lesions showed recurrence after 1 month of follow-up. Side effects of treatment were observed in only 4.5% of cases and included persistent erythema, hyperpigmentation, and hypertrophic scarring [35]. CO2 laser showed more efficacy than systemic glucantime ($p = 0.0007$) and with less side effects [35].

The efficacy of CO2 laser for lupoid leishmaniasis has also been shown [36]. Lupoid leishmaniasis is a chronic form of leishmaniasis that typically follows acute leishmaniasis and presents with new papules and nodules at the borders of previous leishmaniasis scar and in the majority of cases are associated with *L. tropica* infection [36]. No standard treatment has been proven for this type of leishmaniasis [36].In this study, 24 patients with confirmed lupoid leishmaniasis were treated by the continuous CO2 laser with the same protocol described by Asilian A et al. in 2004. Twenty-one patients completed the study, and only 2 patients had recurrence at 1-year follow-up (90.47% efficacy) (34).Post-inflammatory hyperpigmentation and hypertrophic scar were observed in 14.28% and 9.5% of cases, respectively, that responded successfully to treatment. The authors recommended use of CO2 laser for therapy of lupoid CL [36].

In a prospective study, Shamsi Meymandi et al. used CW CO2 laser versus intralesional glucantime plus cryotherapy for dry-type leishmaniasis in Kerman, Iran [37].In this study, 96 patients were treated with single session of CO2 laser (COSMOPULSE-25 CO2, 6–8 W, continuous wave) to the lesion and area [2–]3 mm around it using the same protocol described by Asilian et al. [37]. Ninety-five patients were treated with biweekly cryotherapy plus weekly meglumine antimoniate. This combination method was continued for 12 weeks or complete cure of the lesions, which ever was earlier [37].

Complete cure was observed in 93.7% in CO2 laser group and 78% of patients in glucantime + cryotherapy group at week 16 of follow-up. Side effects including dyspigmentation, atrophic and hypertrophic scar, sporotrichoid, raised papular lesions, and persistent erythema were observed in 46.5% of cases and 45% of glucantime + cryotherapy groups, respectively, with the most common adverse effect was dyspigmentation in both groups [37].

Table 1 Summary of studies used laser for treatment of the cutaneous leishmaniasis

Laser type	Authors and references	Year	Number of patients	Number of laser treatment	Results
Fractional CO2 laser + paromomycin	Basnett A et al. [31]	2015	1	2 session at 1 month interval	Largest lesion was treated with good result. Healing in 1 month was observed
Fractional CO2 laser	Jaffary F et al. [10]	2016	90 patients: 30 glucantime alone, 30 TCA + fractional CO2 laser, 30 intralesional glucantime + fractional CO2 laser	Patients in the laser treatment group were treated with 2 sessions of laser at 2 weeks intervals with intranasal injection of glucantime twice weekly for 8 weeks	Complete healing observed: 38.5% in glucantime alone, 90% glucantime + TCA, 87% glucantime + fractional CO2 laser (No serious side effects or complications)
Pulsed dye laser (PDL)	Radmanesh M and Omidian E [32]	2017	81 lesions: 49 lesions PDL group, 39 lesions glucantime group	[1–]4 sessions [1–]2 pass	100 cure [1–]4 session laser. The mean number of the sessions required for the patients to be treated with MA is 4.6
	L. Elasaie et al. [33]	2018	12 patients, 25 lesions	Single pass	Excellent response was observed in 13 of the 25 lesions after 3 sessions, and 12 remaining lesions required 4 sessions No side effect reported
	Slaoui W et al. [34]	2014	3	3 sessions	Just erythematous papule and nodule were treated; all responded successfully No side effect reported
Continuous CO2 laser	Babajev K.B. et al. [30]	1991	108	1	100% parasitological cure (108/108), no recurrence at [7-]year follow-up in 82/108
	Asilian A et al. [35]	2004	123 patients with 183 lesions in CO2 laser group versus 110 patients with 250 lesions in systemic glucantime group	1	93.7% effectiveness in CO2 laser group. 83.3% effectiveness in glucantime group (Side effects included hyperpigmentation, persistent erythema, hypertrophic scar)
	Asilian A et al. [36]	2006	24 patients, 21 patients completed study	1	19/20 patients cured = 90,47% efficacy 2 case recurrence Side effect: PIP (14.28%), hypertrophic scar (9.5%)
	Shamsi Meymandi S et al. [37]	2011	80 patients with 95 lesions in laser group, 80 patients with 95 lesions in glucantime + cryotherapy group	1	Complete group = 93.7% (89/95) in laser group, 78% (74 / 95) in glucantime + cryotherapy group Side effect: 30% dyspigmentation change, 10% hypertrophic scar, 1.25% sporotrichoid, 1.25% raised papular lesions, 3.75% erythema
Erbium glass laser	Mashayekhi Goyonlo V et al. [38]	2019	14 patients 20 lesions	Four consecutive sessions	Six (50%) improved at 6 weeks and eleven lesions (91.7%) at 12 weeks No adverse effect except erythema, edema, pain
Nd:YAG laser	Omidian M et al. [39]	2019	16 patients: one lesion treated with glucantime and another with ND:YAG laser	2 weeks intervals until complete recovery of the lesion	Mean number of glucantime injections: 7.31 ± 4.01 Mean number of laser therapy sessions: 2.56 ± 0.89 The mean number of laser was significantly less than that of injections of the MA group ($p < 0.001$) Scars were larger and observed more frequently in the MA group PIH was observed in the 2 groups.

In the other study in Iran, the efficacy of fractional CO_2 laser plus glucantime was compared with glucantime alone and glucantime plus 50% trichloroacetic acid [10]. Ninety patients with confirmed diagnosis of CL were recruited. The fractional CO_2 laser parameters were as follows: 1 pass; energy, 25 J; dot cycle, 5; and pixel pitch ,1 mm at every 2 weeks for 2 times. These patients also received intralesional glucantime two times a week for up to 8 weeks. The mean duration of treatment was 6.3 ± 3 weeks in the glucantime plus laser group. Complete healing of the lesions was observed in 38.5%, 90%, and 87% in glucantime alone, intralesional glucantime + TCA, and fractional CO_2 laser plus intralesional glucantime, respectively. The authors concluded the addition of fractional CO_2 laser or topical TCA would significantly enhance the efficacy of treatment as compared will intralesional glucantime alone ($p = 0.011$). No significant difference regarding side effects were observed in the treatment groups [10]. This finding may be explained by destructive effect of CO_2 laser and TCA on leishman bodies.

Fractional CO_2 plus paromomycin has also been used for treatment of a non-healing CL wound on the distal lower extremity of [16-]year-old female [31].In this study, the patient had 5 other lesions on the other parts of the body that respond successfully to [6-]week course of 400 fluconazole plus once daily application of paromomycin. However, the larger lesion on the distal lower extremity did not respond to this treatment, and therefore, patients was treated with 2 sessions of fractional CO_2 laser at monthly interval with subsequence application of paromomycin on daily basis. At the end of intervention, the wound was completely healed with minimal scoring [31]. The authors concluded that use of ablative fractional laser resurfacing (AFR) plus topical paromomycin might be useful for resistant cases of CL [31] and this technique provides early remodeling of wounds and scar mitigation, and in addition, no leishmania species subtyping is required [31].The other possible mechanism is possibly through penetrance enhancement of paromomycin by fractional CO_2 laser.

Use of PDL laser for treatment of CL

PDL laser (pulsed dye laser) has been used for treatment of the erythematous papules and nodules of leishmaniasis in 3 patients [34]. All of these patients were resistant to conventional therapy. Three sessions of PDL irradiation were used with the following settings: 595 nm, spot size [7–]10mm, and energy 8 J/cm^2 [34]. It was proposed that erythematous papules and nodules of CL have vascular pattern that possibly response best to PDL based on selective photothermolysis theory [34]. According to the authors, PDL improved erythematous, texture, pliability, and scar size of the lesions [34].

Radmanesh et al. compared 1 to 2 passes of PDL every 2 weeks for [1–]4 sessions versus intralesional glucantime

on weekly basis. Forty-nine lesions were treated with PDL laser, and 39 lesions received intralesional glucantime. Almost 66.7% of lesions responded to first session of PDL, and 23.3% responded to second and the remaining responded to the 3rd or 4th session with mean of 1.85 sessions. In the glucantime group, all of the lesions were cured with [3–]8 injection of intralesional glucantime (mean of 4.6 sessions). The scar of PDL was slightly less in the laser group. According to the authors, more superficial lesions responded better to the PDL therapy [32]. This finding might be due to the limited depth of PDL penetration.

Elsaie ML et al. also evaluated efficacy of 595 nm PDL in CL and its impact on quality of life. In this study, 25 CL lesions in 12 patients were treated with single pass of PDL with the following parameter: fluence of 7 J/cm^2, 10 mm spot size, and pulse duration of 0.45 msec. Fifty-two percent of the lesions cured after 3 sessions. And the remaining 48% cured after 4 sessions at intervals of 3 weeks. The dermatology life quality index in all of the patients also improved significantly. The larger, deeper, and more indurated lesions needed more treatment [33].

Use of argon laser for treatment of CL

The only reported use of argon laser for leishmaniasis was described by Rakaheev AP. One patient with treatment resistant, *L. tropica* lesion was cured with 6 session of argon laser at intervals of [4–]5 days [42]. Based on our literature review, we did not find any other reported use of argon laser for CL, and therefore, performing a RCT for better evaluation of this method is recommended.

Use of erbium glass laser for treatment of CL

The use of erbium glass for treatment of CL has been suggested by Mashayekhi Goyonlo et al. This is the only reported use of erbium glass laser for CL. In this study, 20 lesions of CL in 14 patients were treated with weekly therapy of fractional erbium glass with the following parameters: spot size 10 mm, 4 passes, fluence 50 mJ/cm^2, and 10 ms pulse duration including a margin of 1 cm for maximum of 4 sessions [38].

Fifty percent of lesions healed at 6 weeks and 91.7% at 12 weeks. No recurrence was reported at 6 and 12 months follow-up. The authors suggested use of 1540 erbium glass for treatment of old world CL as a promising method [38]. However, given the self-healing nature of CL, performing a randomized clinical trial that include a control group was recommended.

Use of neodymium-doped yttrium aluminum garnet laser for treatment of CL

The efficacy of Nd:YAG laser versus intralesional meglumine antimoniate has been evaluated by Omidian et al. Sixteen patients with confirmed diagnostic of CL were selected. In each patient, one lesion was treated with intralesional meglumine antimoniate, and the other received Nd:YAG laser treatment with the following parameter: fluence 200 mJ/cm^2, pulse duration 20 m sec, and spot size 3 mm. Laser was applied at 2 week intervals until complete recovery of the lesions. The mean number of laser therapy sessions was 2.56 ± 0.89 and for meglumine antimoniate injection was 7.31 ± 4.01 ($p < 0.001$). Leishmaniasis scar was observed only 62.5% in the MA group and 18.7% in Nd:YAG group [39]. Scar was significantly smaller in the laser group, and only PIP was higher in laser group [39]. The author suggested that Nd:YAG laser might be more effective than CO2 laser for treatment of leishmaniasis [39]. However, it seems necessary to perform an RCT to compare these 2 methods of treatment.

Proposed mechanisms and benefits of laser in cutaneous leishmaniasis

Although M.A is still regarded as treatment of choice for leishmaniasis, its use is associated with many side effects that ranges from mild local reaction to nephrotoxicity, hepatotoxicity, and even shock [32, 43]. M.A is usually painful and time-consuming, it is an expensive medication, and its correct injection especially for intralesional one needs training, and it is not universally effective for CL [32]. These limitations of MA make use of alternative methods such as laser application as an option.

Difference mechanisms can be proposed for the efficacy of laser in the therapy of CL lesions. Laser especially CO2 laser has been used for debridement of the tissue necrosis [44–46]. The limitation of destructive methods including bleeding and secondary bacterial infections is minimized using continuous CO2 laser [30].

Regarding the fact that necrosis tissue requires less energy to vaporize than living tissue, laser beam can give almost optimum precision to destroy necrotic tissue [30, 35] by inducing selective photothermolysis [36]. As compared with the cryotherapy or electrosurgery, the risk of lateral thermal damage is [2–]4 times laser when using CO2 laser [30].

In addition to its direct therapeutic effect for CL, CO2 laser may be helpful for their effects regarding improved wound healing, delivery of topical medications, and mitigation of scar [34].

The mechanism of PDL on treatment of CL is unknown [32]. It may be partly due to heat generation following laser [32]. As in has been previously mentioned, leishman bodies are sensitive to heat and therefore can only grow on body surfaces [32]. Stimulation of immune system and inflammatory reaction along with cytokine change is the other passive mechanisms [32, 47]. Regarding presence of vascular pattern in leishmaniasis, another mechanism explaining the mechanism of PDL might be through vascular efficacy injury [33].

The fractional erbium glass laser has wavelength of 1540 that can induce microcolumns of thermal injury in the dermis with epidermal sparing. As a result, risk of secondary bacterial infection and post inflammatory dyspigmentation would be low in the treated patients. The possible role of Er glass may be done to heat therapy [38].

It has been shown that He:Ne and ND-YAG lasers have impact on viability of *L. donovani* and *L. major* promastigotes in culture media [38, 48, 49]. However, it seems that mechanism of Nd:YAG may also through vascular injury or heat production. It has the highest penetration between the other lasers [39], and the authors suggested that it was more effective than CO2 laser. To prove this claim, performing a RCT comparing these 2 laser type is recommended.

Conclusion

Despite performing numerous studies and development of many therapies for cutaneous leishmaniasis that includes both local and systemic methods, treatment of CL is still a challenge for medical practitioner. Many of these treatments have high failure rate and are associated with minor or life-threatening side effects. To our best knowledge, it is the first study that reviews use of laser for CL. Our review showed that different types of laser with different wavelengths may be regarded as a valuable resource for treatment of the CL. Use of these lasers may have limitations for some type of leishmaniasis, e.g., sporotrichoid type. Comparing different laser systems to find the best laser method for treatment of CL might be an ideal research subject for the future studies.

Compliance with ethical standards

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