Review Article

Heat therapy for cutaneous leishmaniasis: A literature Review

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Cutaneous leishmaniasis (CL) is endemic in many parts of the world with a high economic and health impact. Despite many treatments that have been suggested for this zoonotic infection, there is still no definite therapy for CL. Meglumine antimony compounds are considered as a standard treatment for leishmaniasis, however, these medications have a relatively high side effect profile and not always effective. Physical modalities including cryotherapy, laser, and heat therapy have also been used for this purpose. As a source of heat therapy, different methods have been used including radiofrequency, ultrasound, infrared, exothermic crystallization thermotherapy, and microwave. We reviewed all of the articles in PubMed regarding the use of heat therapy for the treatment of CL up to January 2020. According to our literature review, heat therapy using different sources showed promising results for the treatment of CL that were comparable to meglumine antimony. In addition, heat therapy has very low side effect profiles that are localized to the treatment area suggesting this method as a safe procedure for CL therapy. This study is a brief review of the literature about the effect of heat therapy on the treatment of CL. Performing randomized clinical trials to compare different methods of heat therapy and to compare it with meglumine antimony compounds is recommended.

Key words: Cutaneous, leishmaniasis, thermotherapy

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INTRODUCTION

Cutaneous leishmaniasis (CL) is an endemic disease of the tropical and subtropical areas of the world that is transmitted by the bite of the infected sand fly. It has an estimated incidence of 1.5 million cases.[1]

CL of the old world is caused by *Leishmania major* (*L. major*), *Leishmania tropica* (*L. tropica*), *Leishmania aethiopica,* and *Leishmania donovani* (*L. donovani*) and *Leishmania infantum*. After obtaining the blood meal from the superficial vascular network in the human skin, these promastigotes are transferred from the sand fly to the human skin. These promastigotes are engulfed by histiocytes and immigrated monocytes. A few numbers of these engulfed parasites will result a localized or disseminated CL.[2,3]

The usual incubation period for CL is a few months but may range from a few days to more than 1 year. The most common areas for the infection are exposed areas of the body including face, neck, arms, hands, and legs. CL lesions usually start from a papule, progress to nodule and then become ulcerated and crusted and eventually heals with scar.[2]

As CL could become chronic and also it will resolve by a remaining disfiguring scar, the selection of a more effective and less disturbing treatment modality is so important. Different treatment approaches have been suggested for leishmaniasis including both medical and physical methods. Antimony compounds (meglumine antimoniate [MA] and sodium stibogluconate [SSG], amphotericin, dapsone, ketoconazole, mefloquine, allopurinol, miltefosine, fluconazole, terbinafine, and

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azithromycin) have been used as a medical treatment for CL. Antimony compounds have been regarded as a treatment of choice for CL since 1940.[4] Many experimental studies are being performed to provide a new therapy for leishmaniasis.[5-7]

In spite of the efforts to find definite therapy for CL, none of the suggested treatments are universally effective and many of them are associated with serious local and systemic side effects.[7]

The use of physical methods for the treatment of CL, besides their efficacy, has the possible advantage of not having systemic side effects. Both cold and heat have been used for this purpose. Cryotherapy, heat therapy, photodynamic therapy, laser, and radiofrequency are among the physical methods that have shown promising results for the treatment of leishmaniasis.[4,8-10] Ultrasound,[12] infrared light,[13] hot water baths,[14] radiofrequency,[15] and exothermic crystallization thermotherapy[16] have also been used to deliver heat to leishmaniasis lesions.

For many years, heat has been suggested for the treatment of leishmaniasis with different studies have shown different results.[13,14] In the current paper, we review the use of heat therapy in the treatment of human CL.

STUDY METHOD

We reviewed all of the articles in PubMed regarding the use of heat therapy for the treatment of CL from 1951 up to January 2020.

Definition of heat therapy

Heat therapy, also known as thermotherapy, is defined as the use of heat for the treatment of various conditions and as a method for pain relief.[11] Different methods for heat therapy have been suggested and used including hot cloth, hot water bottle, ultrasound, heating pad, whirlpools baths, and others.[11] It seems that *Leishmania* parasite sensitivity to heat and increased blood flow following heat therapy along with other mechanisms are responsible for the efficacy of heat therapy in CL.[11,12]

Techniques of heat therapy used for leishmaniasis

Different methods are utilized to generate and deliver heat to CL lesions including ultrasound,[12] infrared light,[13] hot water baths,[14] radiofrequency,[15] and exothermic crystallization thermotherapy.[16]

Hot water baths

Device specifications

In this technique, heat was delivered to CL lesions through the hot water pads encasing lesions to provide a temperature of 39°C–41°C for at least 20 h of treatment over several days.[14]

Clinical application

This technique has been used successfully only in patients with diffuse CL (DCL). Neva *et al*. used this technique for 3 patients with DCL. The diagnosis of DCL and its cure had been confirmed by culture and biopsy, and all of the patients achieved a complete response following at least cumulative duration of 20 h of treatment. The authors concluded that this method was effective for certain types of leishmaniasis and that this method should be further evaluated.[14]

Ultrasound

Device specifications

The equipment that was used for the treatment of leishmaniasis ultrasound machine with a handheld applicator (2 cm), intensities range of 0.5–3 W/cm^2, and temperature was monitored using ThermoProbe.[12]

Clinical application

The only use of ultrasound to treat CL has been described in 1987 [Table 1]. In this study, 28 lesions in 13 patients were treated with ultrasound, 2–3 sessions per week, with total number of 10–15 sessions. The ultrasound intensity was 1.5–3 W/cm^2, and ThermoProbe was used to confirm reaching the target temperature of 42°C. The cure of lesions was confirmed using direct smear, photography, and clinical examination. Overall, 18.5% (22/28) of lesions showed complete resolution within 5–10 weeks.[12] Patients tolerated ultrasound very well, and no side effect was reported. The authors concluded that heat therapy using ultrasound was safe and effective for CL. Regarding the lack of enough data about the use of ultrasound for the treatment of CL, performing more researches is recommended.

Infrared and microwave

Device specifications

The wave of infrared is between 4000 and 7700 nm. The equipment that was used for the treatment of leishmaniasis had a coil of wire wound on a cylinder of fire clay that was connected from one side of electrical current of 110 v and from the other side to the focal point of gently curved spherical reflector. The resulting infrared radiation is delivered at the right angle to the center of CL, and to protect the normal surrounding skin, a pad of 0.5–1 cm asbestos plate was used.[13]

Clinical application

Junaid used infrared heat for the treatment of CL for 178 patients in 1986. The target temperature was 55°C with a duration of 5 min. The results were satisfactory, and 162 patients were treated in 1 session: 15 patients with 2 sessions and the remaining patients with 3 sessions. The authors concluded that the mechanism of infrared therapy

Table 1: Summary of the studies used radiofrequency as a source of heat therapy for treatment of cutaneous leishmaniasis

Reference	Year	Country	Type of leishmaniasis	Groups and number of patients	Protocol of RF	Results (cure rate)
[15]	1990	Guatemala	*L. braziliensis* *L. mexicana*	22 patients in systemic glucantime group 22 patients in RF group 22 patients in placebo group	50°C for 30 s 3 treatment 7-day intervals Devise used: RF generator	Systemic glucantime: 16 (73%) RF: 16 (73%) Placebo: 6 (27%)
[47]	1997	Mexico	*L. mexicana*	201 patients in RF	Single application 50°C for 30 s (LCF-RF)	RF: 90% cure rate
[23]	2005	Afghanistan	*L. tropica*	148 patients in IL-SSG group 144 patients in IM-SSG group 139 patients in RF group	Application at 50°C for 30 s RF generator (ThermoMed 1.8; Thermosurgery Technologies)	1 IL-SSG: 70/93 (75.3%) ≥1 IM-SSG: 26/58 (44.8%) RF: 75/108 (69.4%)
[4]	2007	Iran	Anthroponotic	57 patients with 83 lesions in RF group 60 patients with 94 lesions in IL glucantime	50° for 30 s once weekly for 4 weeks RF heat generator (4 MHz, maximum Output 90 W; Ellman International Inc., NY, USA)	RF group: 80.7% IL glucantime group: 55.3%
[24]	2013	India	*L. tropica*	50 patients in RF 50 patients in IL-SSG (7 session)	30-60 s RF ThermoMed 1.8 LCF-RF generator (Thermosurgery Technologies, Arizona, USA)	RF group: 98% IL-SSG: 94% (side effect: none was reported)
[2]	2013	Colombia	*L. panamensis* *L. braziliensis*	149 patients in RF group 145 patients in miltefosine group	RF: 50°C for 30 s (ThermoMed®, Thermosurgery Inc., Phoenix, USA)	RF group: 59% Miltefosine group: 59% (side effect: none)
[25]	2009	Colombia	*Not identified*	47 patients in thermotherapy group 59 patients in MA group	One time 50°C for 30 s ThermoMed 1.8 LCF-RF generator (Thermosurgery Technologies, Arizona, USA)	RF protocol cure rate: 100% MA protocol cure rate: 19%
[26]	2010	Iraq Afghanistan	*L. major*	27 patients in systemic SSG group 27 patients in RF group	One time: 50°C for 3 s ThermoMed (TM)	Per lesion efficacy SSG: 59% TM: 73% (side effect: blistering, oozing, erythema)
[30]	2012	Afghanistan	*L. tropica*	390 patients in 2 groups 195 patients in RF group 195 patients in IL glucantime group	One-time thermotherapy 50°C for 30 s (ThermoMed 1.8; Thermosurgery Technologies, Phoenix, Arizona)	RF: 82.5% cure rate IL glucantime: 74% cure rate
[27]	2018	Brazil	Not identified	15 patients in RF group	50°C for 30 s (ThermoMed) Model 1.8 (1 session) ThermoMed Model 1.8 (Thermosurgery Technologies, Inc., Phoenix, AZ, USA)	RF Group: 85.7% (side effect: pain, itch, burning sensation, blister)
[21]	1992	Sudan	*L. tropica*	1 patient with 10 red nodules and plaques	50°C surface temperature for 30 s A handheld RF heat generator (RDM Engineering Inc., Phoenix, Arizona)	Six weeks after initial treatment: all lesions were almost completely granulated At 6 months after treatment, the lesions showed complete healing
[29]	2012	Colombia	*L. panamensis* *L. braziliensis* *L. amazonensis* *L. mexicana* *L. infantum*	149 patients in RF group 143 patients in systemic MA group	One-time 50°C thermotherapy for 30 s (ThermoMed®, Thermosurgery Inc., Phoenix, USA)	RF: 64% full cure MA: 85% full cure (side effect: Local pain, especially 4 days after initiation of therapy)
[28]	2017	Sri Lanka	*L. donovani*	93 patients in RF group 115 patients in IL-SSG group	ThermoMed Model 1·8	RF: 65.9% IL-SSG: 59.4% (no side effect)

L. braziliensis=Leishmania braziliensis; L. mexicana=Leishmania mexicana; L. tropica=Leishmania tropica; L. panamensis=Leishmania panamensis; L. major=Leishmania major; L. amazonensis=Leishmania amazonensis; L. infantum=Leishmania infantum; L. donovani=Leishmania donovani; RF=Radiofrequency; IL=Intralesional; SSG=Sodium stibogluconate; MA=Meglumine antimoniate; LCF: Localized current field; IM=Intramuscularly

might be through the distraction of the parasite or immune response provoking.[13]

As an experimental study, Eskandari *et al*. evaluated the effect of microwave and infrared radiation and its combination on skin lesions of *L. major* in 20 BALB/C mice. The infrared device was used with a power of 150 W and a wavelength of 890 nm. The power and frequency of microwave were 600 W and 2.450 GHz, respectively.

These results showed that infrared radiation had more efficacy than microwave for inhibition of ulcer growth.[17]

Infrared beam with a wavelength of 890 nm enhances nitrous oxide production which, in turn, accelerates recovery of skin lesions.[17] In addition, it has been shown that continuous microwave accelerates healing of both aseptic and septic ulcers and triggers the immune system.[17,18]

The efficacy of microwave for treatment was also shown by Sharquie *et al*. in a case-controlled clinical trial. Thirty-five patients with one or multiple CL lesions were either treated every 2 weeks with microwave radiation for maximum of 8 weeks or left untreated as a control and were followed for 2–6 months after intervention. With 1–4 sessions of microwave therapy, 85.33% of lesions were clinically cured; only 20.83% of lesions in the control group showed slight healing. The authors reported no side effect and suggested microwave heat therapy as a new, highly effective therapy for CL.[19]

Handheld exothermic crystallization thermotherapy

Device specifications

It is claimed that this device is a nonexpensive, safe, and reliable technology for the treatment of CL. This device is composed of supersaturated sodium acetate solution and flexible metal disc within a sealed plastic pouch. With flexing of the disc, an exothermic liquid-to-solid phase change reaction will happen that releases heat with a maximum temperature of 52°C ± 2°C.[16]

Clinical application

Three studies have evaluated the efficacy of this method for the treatment of CL.

Valencia *et al*. first described the use of this method for the treatment of CL in Peru. Twenty-five patients with confirmed CL were treated with this method for 7 days and followed for 6 months. 68.4% of patients showed complete cure with 2 cases of second-degree burn. The authors suggested further study to evaluate this technique as adjuvant or monotherapy.[16]

The second study was performed in Pakistan. The patients were treated for 7 days, with an initial temperature of 51.6°C for 3 min. At 6 months of follow-up, out of 23 patients who completed the study, 19 (83%) patients were completely cured. The treatment was well tolerated and showed no side effect.[20]

On the contrary to the two aforementioned studies, a recent prospective study, also in Pakistan, showed a high failure rate of 3 min, 7 continuous days of handheld exothermic crystallization thermotherapy heat pack therapy for CL due to *L. tropica* in 56 patients. They reported a 91% failure rate and suggested that this finding might be due to low heat sensitivity and slower spontaneous healing of *L. tropica*.[21]

Radiofrequency

At least three devices have been used for the purpose of heat therapy using radiofrequency technique that include RDM handheld radiofrequency heat generator, ThermoMed device, and Ellman radiofrequency (RF) heat generator [Table 1].

Handheld radiofrequency heat generator

Device specifications

This is a battery-operated bipolar RF device (RDM Engineering Inc., Phoenix, Arizona, USA), with a maximum power of 10 W and a frequency of 6.78 mHz. The probes are 4 mm apart with resulting in a 4 mm × 4 mm heating area.[22]

Clinical application

In only one case report, a man from Sudanese origin with 10 resistant lesions of CL was heated up to 50°C surface temperature for 30 s and then dressed with hydrocolloid dressing. Nine lesions responded completely to one session of treatment and the one remaining responded to the second treatment.[22]

ThermoMed 1.8 device

Device specifications

This device has a weight of 5.5 lbs or 2.6 kg with output power: 7 W (±1) into a 50 Ω load and operating frequency: 6.78 MHZ ± 15 KHZ. ThermoMed has shown excellent results in the treatment of various common skin lesions, both benign and malignant, and has the Food and Drug Administration market approval, which has been approved for the treatment of CL.[23]

Clinical application

This device has been used as a source of radiofrequency in many studies [Table 1], and it was effective both new and old world CLs and effective for different leishmanial species. The treatment was performed to achieve the temperature of 50°C in target issue from 30 to 60 s.[24-31]

Ellman radiofrequency heat generator

Device specifications

The patented Surgitron® Dual RF™ generator is the high-frequency, 4.0 MHz device that minimizes heat dissipation and thus cellular alteration. The system generates 120 W of power and operates at 4.0 MHz in a monopolar mode and 1.7 MHz in bipolar mode for the treatment of leishmaniasis. The probe was placed in contact with the skin. The target area was heated to 50°C surface temperature for 30 s (controlled with a digital thermometer) every week for four times temperature was assessed using digital thermometer.[32]

Clinical application

Sadeghian *et al*. used RF heat therapy method in 83 CL lesions and compared it with intralesional MA in 94 lesions. Complete response was seen in 80.7% of lesions in the RF treated group while only 55.3% of lesions in the RF-treated group with only 55.3% of lesions in the intralesional MA showed complete response ($P < 0.005$). The authors concluded that RF heat therapy was superior to MA for the treatment of CL [Table 1].[4]

DISCUSSION

Topical therapy has an important role in the treatment of CL with thermotherapy (heat therapy), cryotherapy, paromomycin, CO_2 laser, and 5-aminolevulinic acid hydrochloride plus visible red light, which are the main topical interventions used for this purpose.[33] A systematic review performed by Wolf Nassif *et al*. in 2017 showed safety, high cure rate, and effectiveness of these methods with the exception of cryotherapy that showed a moderate cure rate.[33]

The use of heat therapy alone for the treatment of leishmaniasis goes back to 1950. The authors reported complete healing of skin lesions and marked improvement of mucosal lesions.[12,34]

According to our literature review, almost the results of all studies, except one study,[21] showed comparable efficacy of heat therapy and pentavalent antimony and SSG.

Different mechanisms have been attributed to this efficacy. Heat therapy has been used for rehabilitation purposes through an increase of collagen tissue extensibility, decrease of joint stiffness, pain reduction, and decrease of muscle spasm. It also reduces inflammation and oedema and increases the blood flow with resulting post-acute phase of healing. This increased blood flow results in a better supply of the tissue with proteins, nutrients, and oxygen for better healing.[11]

In addition, the mechanism of heat therapy can be partly explained by the fact that *Leishmania* parasites are sensitive to different temperatures. The rate of multiplication for *L. tropica in vitro* in macrophage is maximum at a temperature of 35°C, and they are completely destroyed at 39°C. On the other hand, for *L. donovani*, there is no difference in multiplication at temperatures of 35°C and 37°C and only 40% of them are eliminated at 39°C.[35]

Synthesis of DNA, RNA, and protein and also glycolysis and cell respiration are blocked by temperature over 42°C. It has been proposed that ultrasound can improve T-cell function and block the growth of leishmanial organism.[36,37]

Damage to plasma membrane with resulting injury nucleus and cell death along with reduced tissue circulation, enhanced lysosomal activity, PH reduction, and prostaglandin release are other suggested mechanisms of heat therapy.[12]

The benefit of heat therapy has also been shown in mice. Aragort de Rossell *et al*. evaluated and compared the long-term effects of thermotherapy versus MA in BALB/C mice and showed that thermotherapy was better than MA regarding faster healing of the lesions and prevention of relapse without no difference regarding clinical cure. None of those treatments cleared all of the parasites.[38]

It has been shown that heat therapy may have the same cytokine response, as seen in systemic glucantime therapy.[39] Lakhal-Naouar *et al*. evaluated an immunity response before, during, and after heat therapy in *L. major* treated by heat therapy using ThermoMed™ device and compared it with a group treated with intravenous SSG.[40] These researches evaluated peripheral blood immune cells of these patients using multiparameter flow cytometry and lymphoproliferative assays. They observed a significant decrease of T-cells along with an increase of NK-cells in both groups without significant difference between them, highlighting the importance of innate immunity for leishmaniasis control. The NKT-like cells showed a modest reduction with no significant change in proportion of B-cells.[40] These changes did not show any correlation with severity of the lesions.[40] Furthermore, a significant decrease of interferon-gamma (INF-ɣ) was observed or posttreatment in both groups. Overall, the authors showed posttreatment downregulation of Th1 proliferation probably through Th2 mechanism along with areduction of leishmaniasis-specific Th1. It seems that CD4+/CD8+ proportion balance has an important role in leishmanial healing.[40-42] The results of this study showed that heat therapy of CL could induce both cytokine response and cellular response that is identified to the use of systemic pentavalent antimony.[40] A reduction of INF-ɣ, interleukin-5 (IL-5), and tumor necrosis factor-α was observed at day 28 of treatment using both systemic glucantime therapy and heat therapy as compared with day 0.[39]

Heat therapy using different devices, especially nonexpensive ones, can be considered as a valuable resource for the treatment of CL, particularly in the endemic areas. Heat therapy looks to be a cost-benefit method for the treatment of CL and has the advantage of limited side effects, especially systemic ones. This treatment has a faster response with a shorter treatment

schedule.[24] The average cost-effectiveness of glucantime for CL was 721–1275 and 187–390 $ for thermotherapy in 2017.[43] In Columbia, a recent study by Cardona-Arias and López-Carvajal showed also the superiority of heat therapy upon glucantime in terms of safety, cost, patient compliance, and application simplicity.[44] However, the same authors showed similar efficacy of heat therapy versus systemic treatment (73.2% vs. 70.6%, respectively) for the treatment of CL in a meta-analysis of eight studies in 2015.[45] According to their results, the authors recommended the use of heat therapy as the first-line therapy against CL in patients from areas with low incidence of mucocutaneous leishmaniasis, contraindication of systemic therapy, infants, pregnant women, and immunodeficient patients.[45]

It has also been shown that RF heat therapy will result in less scar size as compared with lesions treated with IL MA.[3] The possible explanation for this finding is hypothesized to be collagen contraction, synthesis, and remodeling that occur following RF therapy.[4,46]

However, the limitation of heat therapy should not be overlooked. Size, location, number, and the patient's characteristics should be considered when selecting patients for heat therapy. Sporotrichoid lesions and lesions close to eyes and lips are not good candidates for heat therapy, and *L. tropica* lesions are more resistant to heat therapy than *L. major* lesions.[24,14]

CONCLUSION

Based on our literature review, it seems that heat therapy can provide therapeutic results comparable to the pentavalent antimony and SSG. We believe that with good patient selection, heat therapy is an effective, safe, and nonexpensive treatment for CL.

Heat therapy can be specially regarded as the first-line therapy in patients with systemic treatment contraindications, pregnant women, and infants living in areas with rare occurrence of mucocutaneous leishmaniasis. Sporotrichoid lesions and lesions close to eyes and lips are better not to be considered for heat therapy.

We suggest that the efficacy and safety of different methods of heat therapy are compared in a randomized, controlled clinical trial.

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Conflicts of interest
There are no conflicts of interest.

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