

Efficacy of infrared thermotherapy for treatment of cutaneous leishmaniasis: a descriptive study of 39 cases in Mashhad, Iran

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Background: The treatment of cutaneous leishmaniasis has long been a challenge. The application of heat to the lesions has been described in some studies, with no consensus regarding the types of thermotherapy and their practical implications. We sought to evaluate the efficacy of infrared thermotherapy in the treatment of cutaneous leishmaniasis.

Methods: We evaluated the results of infrared thermotherapy in 35 cutaneous leishmaniasis patients (53 lesions) who attended the leishmaniasis clinic of Imam Reza Hospital, Mashhad, Iran. Three times a week, the lesions were warmed to 45 degrees centigrade for two cycles of 10 minutes. Treatment outcomes were classified as complete (90-100%), good (50-89%), and poor responses (less than 50% size reduction).

Results: Thirteen (24.5%) lesions were cured after three months; 31 (58.5%) and 9 (17%) lesions showed good and poor responses, respectively. Treatment outcomes were significantly related to the number of treatment sessions ($P \leq 0.05$). No significant side effects were seen.

Conclusion: Infrared thermotherapy is a relatively effective and well-tolerated treatment for cutaneous leishmaniasis.

Keywords: leishmaniasis, treatment, thermotherapy

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INTRODUCTION

Cutaneous leishmaniasis (CL) is the clinical consequence of infection with the dermatropic species of the *Leishmania* parasite, which is transmitted by sandflies between the affected

hosts. The worldwide incidence is estimated at 1.5 million cases per year ^{1,2}. *Leishmania tropica* and *Leishmania major* are the two prevalent species in Iran, where Mashhad, the capital city of the Khorasan Razavi province in the northeast of Iran, is an endemic focus ^{3,4}.

Pentavalent antimony derivatives have long been known as the standard treatment, although a maximum efficacy of 70% has been reported in most trials⁵. Furthermore, these compounds have a relatively considerable side effect profile during systemic administration⁶. Pain due to repeated injections (either intralesional or intramuscular) is also agonizing for many patients, especially children. The physical modalities of therapy (cryotherapy and thermotherapy) are reasonable alternatives for many clinical settings because of the relatively low cost of treatment, lack of systemic side effects, and less distress for the patient^{7,8}.

To date, different sources of heat have been applied in trials for the treatment of leishmaniasis including hot water soaks, circulating hot water in heating pads, infrared (IR) heat, and ultrasonically induced hyperthermia of the skin⁹. Of note, a recent trial for CL in Afghanistan compared the efficacy of one session of thermotherapy by radiofrequency with five sessions of intralesional Glucantime injection and found that the former was more effective, shorter in duration, had fewer side effects, and had better patient compliance¹⁰.

Due to the diversity of the studies in the literature in terms of heat sources, treatment protocols, inclusion and exclusion criteria, follow-up, outcome definitions, and parasite species, further research in this field is necessary for yielding valuable, practical results. Thermotherapy using IR radiation has been used as an alternative treatment for CL in our department for a few years, and we evaluated its outcome in a two-year, prospective, descriptive study.

PARTICIPANTS AND METHODS

In this prospective-descriptive study conducted between 2011 and 2012, we evaluated new cases of CL who received IR thermotherapy for skin lesions in the leishmaniasis clinic of Imam Reza Hospital, Mashhad, Iran.

The diagnosis of leishmaniasis was based on clinical features and parasitological confirmation (direct smear or histopathology specimen). We could not detect the species of leishmaniasis due to financial limitations, though clinically the lesions were of the dry type and the most common species in the area is *Leishmanial tropica*.

The exclusion criteria were a lesion duration

of > 6 months (to decrease the impact of the self-healing process) and the simultaneous use of other treatments for CL.

Besides demographic data, the number, location, shape, size (surface diameter obtained by multiplying the longest and shortest diameters by one another), and duration of skin lesions were recorded.

Thermotherapy was offered as an alternative treatment to patients with a limited number of lesions (less than 4) who were resistant or hypersensitive to antimonial compounds or were reluctant to receive injections. After fully discussing the treatment protocol and other alternatives, in the case of obtaining informed consent, the patients were enrolled in this study. Treatment sessions were scheduled three times a week. In each session, the lesions were warmed to 45°C using a 250 W IR lamp (Ofog Tavanbakhshi Co., Iran) for two cycles of 10 minutes (Figure 1). This lamp emits rays with a wavelength of 69 cm, frequency of 444.92 MHz, and penetration depth of 3 cm. The distance between the device and the skin lesion was 10 cm. The full duration of the treatment was considered as 20 sessions, but if complete remission was achieved earlier, or when there was no more improvement after 5 consecutive sessions, the treatment was discontinued.

Patients were followed up by weekly physical examinations to evaluate the clinical response and any possible local or systemic adverse effects during the treatment course and at the third month after treatment.

Clinical response was assessed according to the

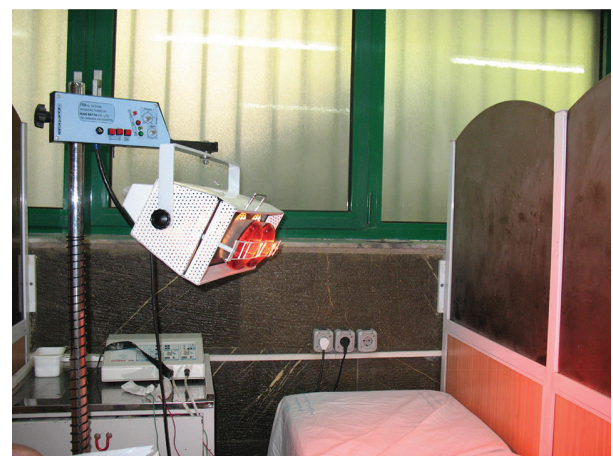


Figure 1. Infrared thermotherapy for the treatment of cutaneous leishmaniasis lesions.

reduction in size and induration of the lesions and classified as:

1. Complete response: 90-100% reduction.
2. Good response: 50-89% reduction.
4. Poor or no response: < 50% reduction.

Statistical analysis

SPSS version 11.5 was used for statistical analysis. Normally distributed quantitative variables were demonstrated as mean ± standard deviation (SD). The normality condition of the quantitative variables was investigated using the Shapiro-Wilk test. The Mann-Whitney and Kruskal-Wallis tests were used to compare the means of age, lesion size, and the number of thermotherapy sessions according to the response. Fishers’ exact test and the Chi-squared tests were used to assess the relation between sex and response to treatment. A p-value of less than 0.05 was considered significant.

RESULTS

The participants included 10 males and 25 females. The mean age of the 35 participants was 19.68 ± 1.78 years (range: 1.5-66 years). The characteristics of the participants and their lesions are demonstrated in Table 1.

Thermotherapy was done across 6-10 sessions for 7 patients, 11-15 sessions for 9 patients, and 16-20 sessions for 18 patients.

Since the response rate of different lesions was variable even in one patient, we evaluated and analyzed the treatment results of each lesion separately.

Altogether, from the 53 lesions treated by thermotherapy, a complete response was achieved in 13 lesions (24.5%). Thirty-one lesions (58.5%) showed a good response and 9 lesions (17%) showed mild or no improvement.

Table 2 shows the relation between the number of thermotherapy sessions and the clinical response rate. The Kruskal-Wallis test showed a significant relationship between these two parameters (test

Table 2. Relationship between clinical response and number of treatment sessions*

Clinical response	Treatment sessions		
	Min	Max	Median
Complete	15	20	20
Good	10	20	17
Poor	5	10	7

Abbreviations: Min, minimum; Max, maximum. *The Kruskal-Wallis test showed a significant relationship between clinical response and the number of treatment sessions (test statistic = 26. 977; P ≤ 0.001)

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In terms of side effects, only mild and transient erythema was seen in four lesions. The remaining 49 lesions (92.45%) did not show any side effects in response to the treatment.

The treatment response was not statistically related to sex, age, lesion size, or duration of lesions (P > 0.05).

Although chronic and non-healing forms of Old World CL (OWCL) are most commonly seen in sun-exposed sites of the body and it was expected to find more resistant lesions in these areas, we detected complete/good responses in 46.50% (20 out of 43 lesions) of sun-exposed lesions compared with 30% of lesions (3 out of 10) in sun-protected areas, with Fisher’s exact test revealing that this difference was not statistically significant (P = 0.45). In other words, CL lesions in areas of sun-exposure were more responsive to thermotherapy, although the difference was not statistically significant.

DISCUSSION

This study indicated a relatively good efficacy of IR thermotherapy in the treatment of OWCL.

Aragort *et al.* compared thermotherapy and meglumine antimonials in the evolution of *Leishmania mexicana* infections in BALB/C mice and concluded that although both treatments appeared equally effective in terms of clinical cure, thermotherapy was better in that it healed the lesions quicker and prevented relapse ¹¹. Berman *et al.* showed that *Leishmania tropica* multiplied more rapidly within human macrophages in vitro at 35°C

Table 1. Characteristics of the patients and their lesions

Gender		Location of lesions n (%)			Number of lesions n (%)			Size of lesions n		
Male	Female	Head & neck	Upper arm	Lower arm	Single	Two	Three	<5 cm ²	5-10 cm ²	>10 cm ²
10	25	27 (50.94)	18 (33. 96)	8 (15.09)	23 (65.71)	6 (17.14)	6 (17.14)	38	11	4

than at 37°C, whereas it was almost completely eliminated at 39°C¹².

Jabbar *et al.* treated 178 CL cases by exposing the largest lesion once to a source of IR heat and followed them for 5-6 weeks. They concluded that the provocation of the immune response leads to improvements in the lesions¹³. Aram *et al.* used ultrasound-induced hyperthermia in the treatment of 28 lesions of acute CL and reported a complete improvement rate of 78.5% within 5 to 10 weeks of therapy¹⁴.

Velasco-Castrejon *et al.* used a localized current field radiofrequency device to generate precisely controlled heat (50°C) for a single 30-seconds session, which led to 95% total improvement within 4 weeks¹⁵. Also, Meawad *et al.* used flash lamp pulsed dye laser (585 nm) in patients with CL due to *L. tropica* for two sessions two weeks apart, to achieve a selective high temperature with minimal injury. Complete improvement with no scarring was achieved in six weeks¹⁶.

Lobo *et al.* showed that heat therapy elicited a cytokine response similar to that of antimonials¹⁷. In a randomized controlled trial, Reithinger *et al.* showed that thermotherapy by radiofrequency waves (one session at 50°C for 30 seconds) was as effective as Glucantime injection in terms of cure rate, while time to cure was significantly shorter in the former group¹⁸.

In a randomized controlled trial by Aronson *et al.*, skin lesions due to *L. major* were treated by either radiofrequency-induced heat or antimonials. They showed that both groups healed at the same rate, but with far less adverse effects in the prior group¹⁹. Two consecutive studies in Peru and Pakistan evaluated the efficacy of a novel and low-cost thermotherapy method (handheld exothermic crystallization therapy) in the treatment of CL. Heat was generated by an exothermic process involving a change from the liquid to the solid crystallization phase, achieving an initial temperature of 52°C. It was shown to be effective in both studies^{20,21}.

In Iran, Sadeghian *et al.* repeated the same comparison but applied heat to the lesion once weekly for four consecutive weeks, and came to the conclusion that thermotherapy was significantly more effective²². Eskandari *et al.* confirmed the efficacy of microwave and IR radiation in the treatment of animal models of *L. major* infection²³.

To our knowledge, this is the first study evaluating

the effects of IR-induced heat in the treatment of OWCL. IR lamps, also called heat lamps, are used for generating heat in different industrial, scientific, and personal instruments. These lamps are also widely available in physiotherapy units.

Complete and good remission (more than 70% improvement) were observed in only 43.4% of lesions treated by thermotherapy in our study. This result is lower than cure rates with most other heat modalities. One prominent influencing factor may be the different and rather conservative treatment protocol in our study, where the temperature was raised to 45°C for 10 minutes in 2 cycles instead of 50°C for 30 seconds in just one cycle, which was the goal temperature in most other studies. This was done to reduce discomfort and the risk of long-term erythema or burns. In other words, higher temperatures across fewer treatment sessions (a single session in many studies) seem to be more effective. The role of other parameters like *Leishmania* species (in our region, most commonly *L. tropica* and then *L. major*) should be considered.

Initially, the temperature in our study was set lower to decrease the discomfort for the patient, considering that 45°C is still higher than the temperature needed to eliminate *L. tropica* amastigote¹¹. It should be noted that 44°C is the temperature at which proteins start becoming denatured²⁴. It might be presumed that the effects of heat in the treatment of CL are due to nonspecific tissue injury rather than specific leishmanicidal effects.

Although thermotherapy by IR seems less effective than by radiofrequency, it might still be of use when other devices are not available. Moreover, IR thermotherapy is an accessible, low-cost, and pain-free treatment method whereas radiofrequency is painful, necessitating local anesthesia and causing wound formation and discharge. At last, controlled trials with higher numbers of enrollees are needed to elucidate the disposition of this treatment method among anti-*Leishmania* armamentaria.

Conflict of interest: None declared.

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