

Effectiveness of Thermotherapy in Cutaneous Leishmaniasis: Systematic Review

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ABSTRACT

Background: Thermotherapy (TT) is an alternative treatment option for cutaneous leishmaniasis (CL), which is a neglected skin disease. This study aimed to determine the effectiveness of TT in treating CL compared to conventional treatment methods. **Methods:** This review followed the PRISMA guidelines, analyzing randomized and clinical trials on thermotherapy for CL, sourced from MEDLINE and the Cochrane Library. Excluding reviews and non-journal documents, ten out of 41 studies met the criteria. All selected studies, assessed for quality using the Jadad score, were of high quality. **Results:** Out of ten studies, radio frequency-induced heat therapy (RFHT) was more effective and cost-efficient than intralesional sodium stibogluconate (IL-SSG) (2 studies) ($p < 0.05$), intramuscular sodium stibogluconate (IM-SSG) (1 study), and intralesional (IL) meglumine antimoniate (1 study). Combining single-session TT with a short course of miltefosine (MLT) led to higher cure rates (80.3%) compared to TT alone (57.8%) ($p = 0.0055$). Regarding the mode of TT, RFHT was more effective than handheld exothermic crystallization thermotherapy (HECT-CL) ($p > 0.05$). One study showed that the efficacy of intramuscular meglumine antimoniate was higher compared to TT, while oral miltefosine and intravenous sodium stibogluconate (IV-SSG) did not show a significant difference in efficacy compared to TT ($p < 0.05$). **Conclusion:** The analysis indicates that RFHT is a superior, cost-efficient treatment for CL compared to IL-SSG, IM-SSG, and IL-meglumine antimoniate. Combining TT with MLT improves cure rates significantly. Further research is warranted to refine these treatment protocols and confirm their long-term benefits.

Keywords: Leishmaniasis, Cutaneous Leishmaniasis, Thermotherapy, Alternative Treatment Options

ABBREVIATIONS

CL: Cutaneous Leishmaniasis

TT: Thermo-therapy

RFHT: Radio Frequency-Induced Heat Therapy

IM-SSG: Intramuscular Sodium Stibogluconate

IL: Intralesional

MLT: Miltefosine

IV-SSG: Intravenous Stibogluconate

HECT-CL: Handheld Exothermic Crystallization Thermo-therapy

INTRODUCTION

Leishmaniasis is a tropical parasitic disease caused by intracellular flagellated protozoa of the genus *Leishmania*. The global prevalence of cutaneous leishmaniasis (CL) is estimated to be approximately 12 million cases across 97 countries [1]. An estimated 600,000–1 million new cases occur annually, while 211,000 cases were reported to the World Health Organization in 2024, with children accounting for more than half of those affected [2]. The disease is transmitted by the bite of infected female sandflies. Humans serve as intermediate hosts, while rodents and canines act as reservoirs. The incubation period ranges from two to eight months [2].

Leishmaniasis presents in three major clinical forms: cutaneous, mucocutaneous, and visceral. CL typically begins as a papule that may progress to a nodule or ulcerative lesion. Disease progression depends on the infecting *Leishmania* species, parasite virulence, and the host immune response [2]. Lesions caused by *L. major* generally heal spontaneously within three to six months but often leave depressed scars [2,3]. In contrast, *L. tropica* infections may persist for more than a year and can evolve into chronic, non-healing forms if untreated. Although CL is rarely fatal, untreated CL lesions may act as reservoirs for continued transmission and can lead to disfigurement, psychological stress, and social stigma, and it places a burden on healthcare systems, especially in areas with poor living conditions and limited access to medical care [3,4].

Chemotherapy remains the mainstay of treatment [5]. However, limited drug availability, treatment failures, adverse effects, and emerging drug resistance are major challenges [6,7].

Pentavalent antimonials, including sodium stibogluconate (SSG) and meglumine antimoniate, are widely used but they are associated with serious systemic adverse effects such as pancreatitis, hepatotoxicity, and cardiotoxicity. Treatment also requires series of prolonged painful injections, resulting in poor adherence. This lack of adherence significantly contributes to the emergence of drug-resistant strains of the parasite, especially in regions affected by anthroponotic leishmaniasis, including India, Sudan, and Nepal [8]. As a result, research is going on to find alternative treatment options that explore different types of dosage schedules, new medications or novel drug delivery methods.

Consequently, alternative treatment modalities are being explored, including thermo-therapy (TT). TT is based on the thermosensitivity of *Leishmania* amastigotes. Localized heat induces tissue destruction and enhances the Th1 immune response, promoting lesion healing [9,10]. Common delivery methods of TT include radiofrequency-induced heat therapy (RFHT) and handheld exothermic crystallization thermo-therapy (HECT-CL) [11].

Although several clinical trials have evaluated TT, findings remain inconsistent. Therefore, this systematic review was conducted to assess the safety and effectiveness of thermo-therapy in the treatment of cutaneous leishmaniasis.

MATERIALS AND METHODS

Search Strategy

The review was conducted in coherent to the extended guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in identifying the effectiveness of Thermo-therapy as a treatment option for CL. A search for bibliographic references was executed through MEDLINE (via PubMed) and Cochrane Library using the keywords ["Leishmaniasis" OR "Cutaneous Leishmaniasis"] AND ["Thermo-therapy"].

The search included only studies involving humans that were published in English, without any restrictions on the publication date or article type. The clinical trials and randomized clinical trials (RCT) were considered eligible.

Study Selection

All retrieved citations were independently screened by two authors (NVNNV and GDH) according to the inclusion

and exclusion criteria to assess the eligibility of the studies. Disagreements between two reviewing authors were resolved by discussion and consensus.

The PRISMA flow chart of the selected articles is shown in Figure 1.

Data Extraction

Data extraction included first author, publication year, sample size, characteristics of study participants, type of intervention in treatment and control groups and results obtained including the follow up details.

Inclusion and Exclusion Criteria

Inclusion criteria: RCT and clinical trials

1. Population: Patients who were diagnosed with cutaneous leishmaniasis
2. Intervention: Thermotherapy delivered in any modality
3. Comparison: Other standard treatments for leishmaniasis
4. Outcomes: Effectiveness of TT compared to other treatment modalities

Exclusion criteria:

1. Study types other than clinical trials; cohort and case control studies
2. Secondary analyses; Meta Analyses and systematic analyses
3. Reviews, books and documents

Quality Assessment

The quality of each study was evaluated using the Jadad score, which focuses on essential aspects such as randomization, blinding, and appropriate long-term follow-up of patients. This scoring system has a maximum of 5 points, with scores above 3 indicating good quality. Two authors (NVNNV and GDH) conducted the quality assessment, resolving any discrepancies through discussion.

RESULTS

Overview of Identified Research Protocols

The initial search of the literature found 40 records. After removing duplicates, 26 records remained. Among these, 11 were excluded based on their titles and abstracts. Consequently, 15 articles were evaluated for eligibility, and ten articles that met the selection criteria were included in this systematic review (Table 1-4).

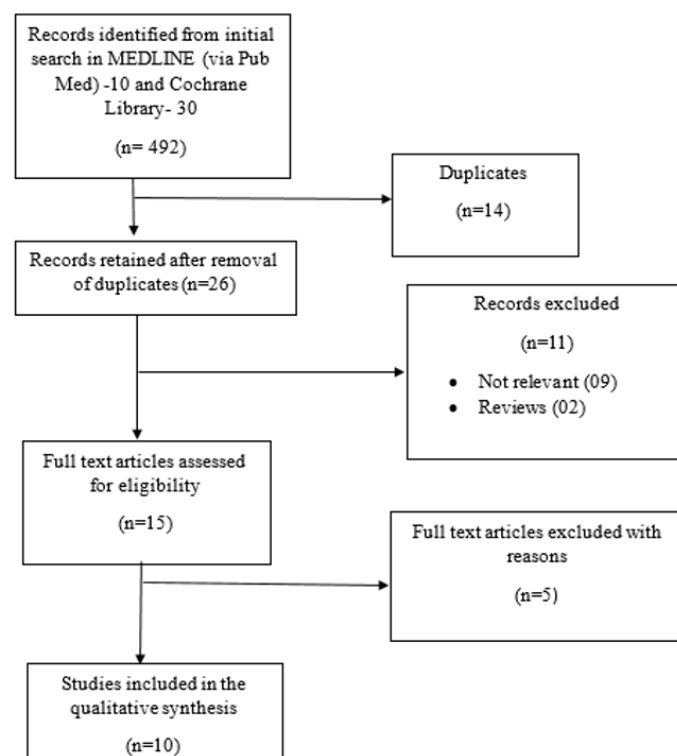


Figure 1: Identified Research Protocols

Table 1: Studies selected for the systematic review

Treatment Group	Control Group	Number of studies
RFHT	HECT-CL	1 study
RFHT	Oral Miltefosine	1 study
RFHT	IL SSG	2 studies
RFHT	IV SSG	1 study
RFHT	IM SSG	1 study
RFHT	Meglumine Antimoniate	3 studies
RFHT	RFHT+Miltefosine	1 study

Table 2: Summary of the studies

Author and year	Study population (T/C)	Age	Treatment (T)	Treatment (C)	Mean Follow-up
Liliana López March 7, 2022 Colombia [12]	64/66	T: 32.3 years C:34.3 years	Thermotherapy	Thermotherapy + Miltefosin	6 months
Hermali Silva 2021 Sri Lanka [11]	20/20	T: 42.6 ± 12.3 C:39.0 ± 10.8	Thermotherapy (RFHT)	Thermotherapy by an HECT-CL device	6 months
Wardha F. Refai 2017 Srilanka [13]	115/98	T: - C: -	Thermotherapy (RFHT)	Intralesional sodium stibogluconate	12 weeks
Liliana LÓPEZ 2013 Colombia [14]	145/149	T: 23 (19 - 39) C: 23 (19 - 37)	Thermotherapy	Oral Miltefosin	6 months
Liliana López 2012 Colombia [15]	149/143	T: - C: -	Thermotherapy	Intramuscularly Meglumine antimoniate	6 months
Najibullah Safi 2012, Afghanistan [16]	195/195	T:14 C:13	Thermotherapy (RFHT)	Intralesional Glucantime	4 weeks
Naomi E. Aronson 2010 USA [17]	28/28	T: 25 (20–53) C:24 (18–57)	Thermotherapy	Intravenous sodium stibogluconate	12 month
R. Reithinger 2005 Afghanistan [18]	139/292	T:14 C:13	Thermotherapy (RFHT)	Intralesionally or Intramuscular Sodium stibogluconate (SSG),	100 days
R.A. Bumb [9]	50/50	T:20 (4-70) C:20.5(4-85)	Thermotherapy (RFHT)	Intralesional sodium stibogluconate (SSG) injections	18 months
G. Sadeghian [19]	57/60	25.12 ± 13 22.6 ± 12	Thermotherapy (RFHT)	intralesional injection of meglumine antimoniate	6 months

Table 3: Treatment vs Control interventions in selected studies

Author and year	Treatment(T)	
Liliana Lo'pez March 7, 2022 Colombia [12]	RFHT (one session, 50°C for 30") plus MLT 2.5 mg/kg/day for 21 days	RFHT (one session, 50°C for 30")
Hermali Silva 2021 Sri Lanka [11]	RFHT by a ThermoMed device (one session at 5°C for a duration of 30s)	Thermotherapy by an HECT-CL device (one session at 52 ± 2 C for 3 minutes for seven consecutive days)
Wardha F. Refai 2017 Srilanka [13]	RFHT (one session of 5°C for 30 second)	IL-SSG (Pentostam, GlaxoSmithKline) 1–3 mL administered weekly inoculations until cure or up to 10 doses
Liliana LÓPEZ 2013 Colombia [14]	RFHT (one session of 50°C over the lesion for 30 seconds)	Miltefosine 50 mg capsule was administered orally three times per day for 28 days
Liliana López 2012 Colombia [15]	RFHT (one session of 50°C)	Meglumine antimoniate was administered intramuscularly at a dose of 20 mg Sb5/kg weight/day for 20 days
Najibullah Safi 2012, Afghanistan [16]	RFHT (one session of 50°C (122°F) for 30 seconds)	Intralesional injections of Glucantime 2–7 mL weekly for 5 weeks.
Naomi E. Aronson 2010 USA [17]	RFHT (one session of 50°C)	Intravenous sodium stibogluconate 20 mg/kg/day for 10 days
R. Reithinger 2005 Afghanistan [18]	RFHT (one session of 5°C for 30 second)	Sodium Stibogluconate administered either intralesionally 5 injections of 2–5 mL every 5–7 days or intramuscularly 20 mg/kg daily for 21 days
R.A. Bumb 2012 India [9]	RFHT (one session for 30–60 s)	Intralesional SSG (50 mg cm) twice a week for seven injections.
G. Sadeghian 2007 Iran [19]	RFHT (one session of 5°C for 30 second)	0.1–4 mL of Intralesional injection of meglumine antimoniate once weekly for four consecutive weeks.

Table 4: Summary of the different treatment options

Interventions	Study Number	Intervention	Duration of treatment	Number of Patients	Final cure rates	Side Effects
RFHT Vs HECT-CL	1	RFHT	Single session	20	95%	Second degree burns (65%)
		HECT-CL	Seven days	20	80%	Second degree burns (15%)
RFHT Vs Miltefosine	2	RFHT	Single session	149	58%	Pain the lesions
		Miltefosine	28 days	145	59%	GI side effects
RFHT Vs IL-SSG	3	RFHT	Single session	98	65.90%	No major side effects
		IL-SSG	10 days	115	59.40%	No major side effects
	4	RFHT	Single session	50	94%	Not mentioned
		IL-SSG	Seven	50	92%	Not mentioned
RFHT Vs IL and IM SSG	5	RFHT	Single session	139	69.40%	Second degree burns
		IL-SSG	5 injections of 2-5 mL every 5-7 days	148	75.30%	Bradycardia undefined local reaction
		IM-SSG	20 mg/kg daily for 21 days	144	44.80%	Bradycardia, tachycardia, palpitation
	6	RFHT	Single session	27	54%	Abdominal pain pancreatitis, arthralgias, myalgias, headache, fatigue, mild cytopenias
		IV SSG	10 doses	27	48%	elevated transaminase
RFHT Vs IV SSG	7	RFHT	Single session	134	64%	Blistering, oozing, erythema
		IM SSG	20 days	121	85%	Pain the lesions
	8	IM SSG	five doses seven days apart	193	74%	Myalgia, Arthralgia, Headache, Fever
		RFHT	once weekly for four weeks	57	80.70%	No
RFHT Vs Meglumine antimoniate	9	IL SSG	once weekly for four weeks	60	55.30%	Anorexia, vomiting, nausea, abdominal pain, malaise, myalgia, arthralgia, headache
		RFHT	once weekly for four weeks	60	55.30%	No
						Allergic reactions such as erythema, oedema and pruritus around the lesions

		RFHT	Single session	64	57.80%	Presence of vesicles at the site of heat application
RFHT Vs RFHT and Miltefosine combination	10	RFHT + Miltefosine	21 days	66	78.80%	Vomiting (31.8%) Elevation of liver enzymes (28.8%)

RFHT vs. HECT-CL

The findings of this study indicate a higher efficacy of RFHT compared to HECT-CL as a treatment option for cutaneous leishmaniasis (CL). At day 90, the initial cure rate was 100% (20/20) in the RFHT group and 80% (16/20) in the HECT-CL group. By day 180, one patient in the RFHT group experienced a relapse, resulting in a final cure rate of 95% (19/20). In contrast, no relapses were observed in the HECT-CL group, and the final cure rate remained 80% (16/20). Cure rates between two groups were comparable ($p > 0.05$).

Both groups experienced second-degree burns, with a higher prevalence in the RFHT group. However, all second-degree burns in both groups healed completely without complications [11].

RFHT vs. Miltefosine

The findings of this study indicate that the efficacy of single-dose thermotherapy (TT) is comparable to that of oral miltefosine administered over a 28-day treatment period for cutaneous leishmaniasis (CL) ($p = 0.9$), with a more favorable side-effect profile. Recurrence rates were 2.1% among patients treated with miltefosine and 4.1% among those who received TT.

Additionally, no significant differences in treatment efficacy were observed based on the infecting *Leishmania* species (miltefosine, $p = 0.3$; thermotherapy, $p = 0.6$) [12].

RFHT vs. IL-SSG

The findings of both studies demonstrated that IL-SSG was significantly effective in treating cutaneous leishmaniasis (CL) ($p < 0.05$). In one of the studies, no major adverse events were reported in either treatment group. However, transient flare-ups were observed in 31 of 50 nodular ulcers (62%) and in 3 of 5 ulcers (60%), with an increase in lesion size noted for up to two weeks following thermotherapy (TT). These ulcers subsequently healed rapidly [9,13].

RFHT vs. IL-SSG and IM-SSG

A single localized heat treatment was found to be as effective as IL-SSG and more effective than IM-SSG in treating CL ($p < 0.05$). The time to achieve cure was significantly shorter with TT compared to SSG regimens ($p < 0.001$). Additionally, none of the patients who achieved complete healing experienced relapse during the 100-day follow-up period [13].

RFHT vs. IV-SSG

This study demonstrated that a single heat treatment of lesions was as effective as IV-SSG administered at a dosage of 20 mg/kg/day for 10 days. After treatment initiation, five wound infections related to lesions (19%) were reported in the TT group, compared to one infection (4%) in the IV-SSG group ($p = 0.19$). However, systemic antimonial therapy with IV-SSG was associated with several serious systemic adverse effects, whereas TT resulted only in localized reactions such as blistering, oozing, and skin erythema [14].

RFHT vs. Meglumine Antimoniate

One study found that the final cure rate with IM Meglumine antimoniate was higher than that with TT for treating CL ($p < 0.05$); however, it was also associated with a higher incidence of side effects. Considering treatment adherence issues, adverse effects, and progressive lack of therapeutic response, TT was deemed more favorable than IM Meglumine antimoniate. Recurrences were observed in six patients (4.1%) in the TT group and four patients (3%) in the with IM Meglumine antimoniate group. *Leishmania* species were identified in 167 patients, and no significant association was found between treatment type (IM Meglumine antimoniate, $p = 0.5$; TT, $p = 0.6$) and the infecting *Leishmania* species (15). In two additional studies comparing RFHT with IM Meglumine antimoniate, TT demonstrated higher final cure rates and fewer side effects [16].

RFHT vs RFHT and Miltefosine combination

The combination of TT and a short course of miltefosine was found to be significantly more effective than TT alone for treating uncomplicated CL ($p < 0.01$). Subjects with lesions caused by *L. braziliensis* and *L. peruviana* showed a better response to the TT + MLT combination (20 out of 27 patients, or 74.1%) compared to those receiving TT alone (9 out of 21 patients, or 42.8%). According to the above ten studies RFHT was found to be more effective and cost-efficient than IL-SSG (2 studies), IM-SSG (1 study), and IL and IM meglumine antimoniate (1 study). Combining single-session TT with a short course of miltefosine led to higher cure rates (80.3%) compared to TT alone (57.8%) ($p = 0.0055$). Regarding the mode of TT, RFHT and HECT-CL was comparable while oral miltefosine and intravenous IV-SSG did not show a significant difference in efficacy compared to TT [17].

DISCUSSION

The findings of this systematic review demonstrate that TT is an effective treatment option for CL, particularly when compared to conventional therapies. Among the various TT modalities, RFHT appears to be more promising than other options due to its higher efficacy and greater cost-effectiveness. Higher cure rates were observed when TT was combined with M iltefosine, suggesting a synergistic effect between treatment modalities and warranting further investigation to optimize treatment regimens. The variability in efficacy among different TT techniques, particularly the advantage of RFHT over HECT-CL, emphasizes the importance of selecting the appropriate modality to optimize patient outcomes.

TT is a local treatment modality that involves the application of controlled heat directly to the lesion using portable, battery-operated devices such as RFHT and HECT-CL. This approach is effective because *Leishmania* amastigotes are sensitive to elevated temperatures. TT promotes healing through heat-induced tissue destruction and upregulation of the Th1 immune response, thereby facilitating ulcer resolution [11]. Indications for TT include papules, nodules, or ulcers measuring less than 4 cm in diameter, with a maximum of four lesions per patient. Lesions located near the eyes, nose, or lips are generally excluded. Despite certain limitations, TT remains a cost-effective and relatively safe treatment option for CL.

The ThermoMed device used for RFHT involves a relatively high initial cost and is typically restricted to facilities with

adequate healthcare infrastructure. In contrast, the HECT-CL device is more affordable and can be operated by minimally trained personnel in community settings. A topical anesthetic cream is usually sufficient to provide analgesia prior to treatment [11].

Cost estimates suggest that a single application of TT using the ThermoMed device costs approximately USD 1.54 per patient, whereas the HECT-CL device costs around USD 2. The HECT-CL device can be reused for seven consecutive days, bringing the total cost of one treatment course to approximately USD 3.20. Furthermore, a single HECT-CL pack may be used for multiple patients, thereby reducing overall treatment expenses. Because the HECT-CL device generates heat through a chemical reaction, it is suitable for patients in whom RFHT is contraindicated, such as individuals with pacemakers [11,13].

Systemic antimonials, including SSG and meglumine antimoniate, are commonly used treatments for CL [18]. A recent meta-analysis indicated that pentavalent antimonials administered at a dosage of 20 mg/kg/day for 20 days remain among the most effective treatments for CL [14]. No significant differences in final cure rates have been observed between meglumine antimoniate and sodium stibogluconate [18]. However, antimonials are associated with several adverse effects, including arthralgia, myalgia, pancreatitis, transaminitis, headache, bone marrow suppression, and skin rashes. Additional side effects include nausea, vomiting, abdominal pain, and reactivation of herpes zoster [13,18]. Although most adverse effects are reversible and resolve within three to twelve days after initiation of therapy without requiring discontinuation, some patients experience prolonged myalgia and arthralgia that resolve only after treatment cessation [15].

SSG can be administered intravenously, intramuscularly, or intralesionally. Intralesional SSG treatment typically requires two to ten hospital visits, which may be inconvenient and negatively affect patient compliance [14,15,19]. Reduced adherence raises concerns regarding the potential development of resistance to SSG, which has already been reported [13]. The total cost of standard SSG therapy exceeds USD 11.09, making it more expensive than TT [18, 19]. Considering cost, adverse effects, and patient compliance, TT represents a viable alternative treatment for CL.

Miltefosine primarily affects the gastrointestinal system, with common adverse effects including anorexia, nausea,

vomiting, and diarrhea [12]. Although these symptoms are usually mild, more severe gastrointestinal complications have been reported in some cases. A fatal case of acute pancreatitis associated with miltefosine has also been documented. Elevations in serum aminotransferase and creatinine levels have been observed; however, these changes are generally mild, reversible, and dose-dependent [14,12]. Animal studies have demonstrated embryotoxic, fetotoxic, and teratogenic effects of miltefosine [12]. Due to these risks and the lack of controlled studies in pregnant women, miltefosine is contraindicated during pregnancy [14]. Additionally, insufficient data exist regarding its safety during breastfeeding; therefore, its use is not recommended in lactating women.

The combination of a single application of local TT with a short course of miltefosine was significantly more effective than TT alone in treating uncomplicated CL. Lesions treated with combination therapy healed more rapidly than those treated with TT alone. The additive effect likely results from the systemic therapy targeting circulating or residual parasites at the lesion periphery that may not be eliminated by local heat treatment alone. Furthermore, when used in combination therapy, the duration of miltefosine treatment is shorter than when used as monotherapy, potentially reducing both costs and adverse effects [17]. Although miltefosine offers the convenience of oral administration, its disadvantages include high cost, potential fetotoxicity, and increasing reports of treatment failure. Moreover, miltefosine monotherapy has not consistently demonstrated superior efficacy, highlighting the need for further pharmacokinetic, pharmacodynamic, and clinical studies, particularly evaluating combination regimens.

Overall, TT has been shown to be more favorable than several systemic and oral treatments for CL. It is generally safer, requires fewer treatment sessions, does not require laboratory monitoring, improves patient adherence, and is less costly [16]. Consequently, TT may be considered a first-line treatment option for patients in whom systemic therapies are contraindicated, including those with renal, hepatic, or cardiac disease, as well as pregnant women and infants. TT has also been shown to stimulate a protective immune response and may be effective in immunocompromised patients, including individuals with HIV who do not respond to intralesional SSG therapy [11].

The existing evidence supporting the efficacy, safety, and cost-effectiveness of TT suggests that it can be utilized as an

effective alternative therapy for CL. This review highlights the potential value of TT as a practical and accessible treatment option in endemic settings.

CONCLUSION

The analysis indicates that RFHT is a superior, cost-efficient treatment for CL compared to other treatment options. Combining TT with MLT improves cure rates significantly. A quantum of benefits can be derived from TT as an alternative treatment method hence it is cost effective, well tolerated and has less side effects. Further research is warranted to refine these treatment protocols and confirm their long-term benefits.

REFERENCES

1. Karimkhani C, Wanga V, Coffeng LE, Naghavi P, Dellavalle RP, Naghavi M. (2016). Global burden of cutaneous leishmaniasis: a cross-sectional analysis from the Global Burden of Disease Study 2013. *The Lancet Infectious Diseases*. 16(5):584-591.
2. Organization WH. (2010). Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22-26 March 2010: World Health Organization.
3. Akilov OE, Khachemoune A, Hasan T. (2007). Clinical manifestations and classification of Old World cutaneous leishmaniasis. *International Journal of Dermatology*. 46(2):132-142.
4. Bailey F, Mondragon-Shem K, Hotez P, Ruiz-Postigo JA, Al-Salem W, Acosta-Serrano A, et al. (2017). A new perspective on cutaneous leishmaniasis—Implications for global prevalence and burden of disease estimates. *PLoS Neglected Tropical Diseases*. 11(8):e0005739.
5. Handman E. (2001). Leishmaniasis: current status of vaccine development. *Clinical microbiology reviews*. 14(2):229-243.
6. Refai FW, Madarasingha NP, Fernandopulle R, Karunaweera N. (2016). Nonresponsiveness to standard treatment in cutaneous leishmaniasis: a case series from Sri Lanka. *Tropical parasitology*. 6(2):155-158.

7. Croft SL, Coombs GH. (2003). Leishmaniasis—current chemotherapy and recent advances in the search for novel drugs. *Trends in Parasitology*. 19(11):502-508.
8. Chakravarty J, Sundar S. (2010). Drug resistance in leishmaniasis. *Journal of Global Infectious Diseases*. 2(2):167-176.
9. Bumb R, Prasad N, Khandelwal K, Aara N, Mehta R, Ghiya B, et al. (2013). Long-term efficacy of single-dose radiofrequency-induced heat therapy vs. intralesional antimonials for cutaneous leishmaniasis in India. *British Journal of Dermatology*. 168(5):1114-1119.
10. Lobo IM, Soares MB, Correia TM, de Freitas LA, Oliveira MI, Nakatani M, et al. (2006). Heat therapy for cutaneous leishmaniasis elicits a systemic cytokine response similar to that of antimonial (Glucantime) therapy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 100(7):642-649.
11. Silva H, Liyanage A, Deerasinghe T, Sumanasena B, Munidasa D, de Silva H, et al. (2021). Therapeutic response to thermotherapy in cutaneous leishmaniasis treatment failures for sodium stibogluconate: a randomized controlled proof of principle clinical trial. *The American Journal of Tropical Medicine and Hygiene*. 104(3):945-950.
12. López L, Cruz C, Godoy G, M. Robledo S, D. Vélez I. (2013). Thermotherapy effective and safer than miltefosine in the treatment of cutaneous leishmaniasis in Colombia. *Revista do Instituto de Medicina Tropical de São Paulo*. 55(3):197-204.
13. Reithinger R, Mohsen M, Wahid M, Bismullah M, Quinnell R, Davies C, et al. (2005). Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clinical infectious diseases*. 40(8):1148-1155.
14. Aronson NE, Wortmann GW, Byrne WR, Howard RS, Bernstein WB, Marovich MA, et al. (2010). A randomized controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous *Leishmania major* infection. *PLoS Neglected Tropical Diseases*. 4(3):e628.
15. López L, Robayo M, Vargas M, Vélez ID. (2012). Thermotherapy. An alternative for the treatment of American cutaneous leishmaniasis. *Trials*. 13:58.
16. Sadeghian G, Nilfroushzadeh M, Iraj F. (2007). Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. *Clinical and Experimental Dermatology*. 32(4):371-374.
17. López L, Valencia B, Alvarez F, Ramos AP, Llanos-Cuentas A, Echevarria J, et al. (2022). A phase II multicenter randomized study to evaluate the safety and efficacy of combining thermotherapy and a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World. *PLoS Neglected Tropical Diseases*. 16(3):e0010238.
18. Refai WF, Madarasingha NP, Sumanasena B, Weerasingha S, De Silva A, Fernandopulle R, et al. (2017). Efficacy, safety and cost-effectiveness of thermotherapy in the treatment of *Leishmania donovani*-induced cutaneous Leishmaniasis: a randomized controlled clinical trial. *The American Journal of Tropical Medicine and Hygiene*. 97(4):1120-1126.
19. Safi N, Davis GD, Nadir M, Hamid H, Robert Jr LL, Case AJ. (2012). Evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Kabul, Afghanistan: a randomized controlled trial. *Military medicine*. 177(3):345-351.