CUTANEOUS LEISHMANIASIS: THE SUCCESSFUL USE OF RADIOFREQUENCY-INDUCED HEAT THERAPY.

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1. ABSTRACT

The present gold standard for the treatment of cutaneous leishmaniasis is pentavalentantimonials either sodium stibogluconate (Pentostam) or meglumine antimoniate (Glucantime). These drugs are quite toxic. They are given by injection and usually administered IM, IV for three weeks or intralesionally for seven or more weeks. That is why the successful introduction of radiofrequency-induced heat therapy (RFHT) using a Thermomed™1.8 instrument administered in a single application, with minimal toxic effects, is cost effective and so important for the treatment of cutaneous leishmaniasis. A review of the studies on heat therapy for cutaneous leishmaniasisis the subject of this article.

KEYWORDS: Cutaneous LeishmaniasisRadiofrequency Heat Therapy

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2.1 INTRODUCTION.

Leishmaniasis is caused by *Leishmania,* a protozoan parasite(Figure 1). and is one of the most important vector-borne diseases. *Leishmania* is second only to malaria of parasitic diseases causing morbidity and mortality. An estimated 350 million people live at risk of contracting leishmaniasis with a prevalence of 12 million cases and an annual case incidence of 2 million[1].Leishmaniasis is found in Central and South America, Asia, Africa and in Southern Europe. It is transmitted by sand flies (Figure 2). Many *Leishmania* species cause several different disease manifestations.

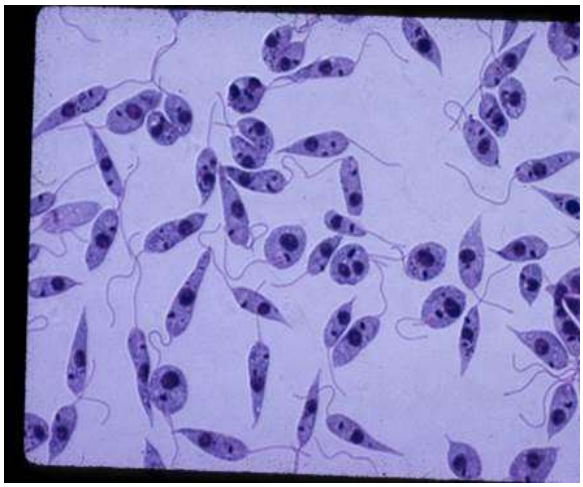

Figure 1. Leishmaniapromastigotes.

Figure 2. Sand fly from David JR

2.2 VisceralLeishmaniasis

Visceral leishmaniasis (VL), also known as Kala azar, is a systemic disease. There are approximately 50,000 deaths each year. VL is manifested by hepato-splenomegaly, fever, malaise weight loss, gastrointestinal symptoms, and when untreated is usually fatal. Death comes from many factors including pneumonia and tuberculosis. However, only 10% of the people infected by the parasite get the disease itself. VL caused by *Leishmania infantum* is a zoonotic disease with children being especially involved (Fig 3), and the dog being the usual reservoir host. VL in the Western Hemisphere is caused by *L. chagasi*, now known to be identical to *L. infantum*. *L. donovani* is another species causing VL, mainly in India and Africa; it is transmitted from person to person by sand flies, not needing a reservoir host.

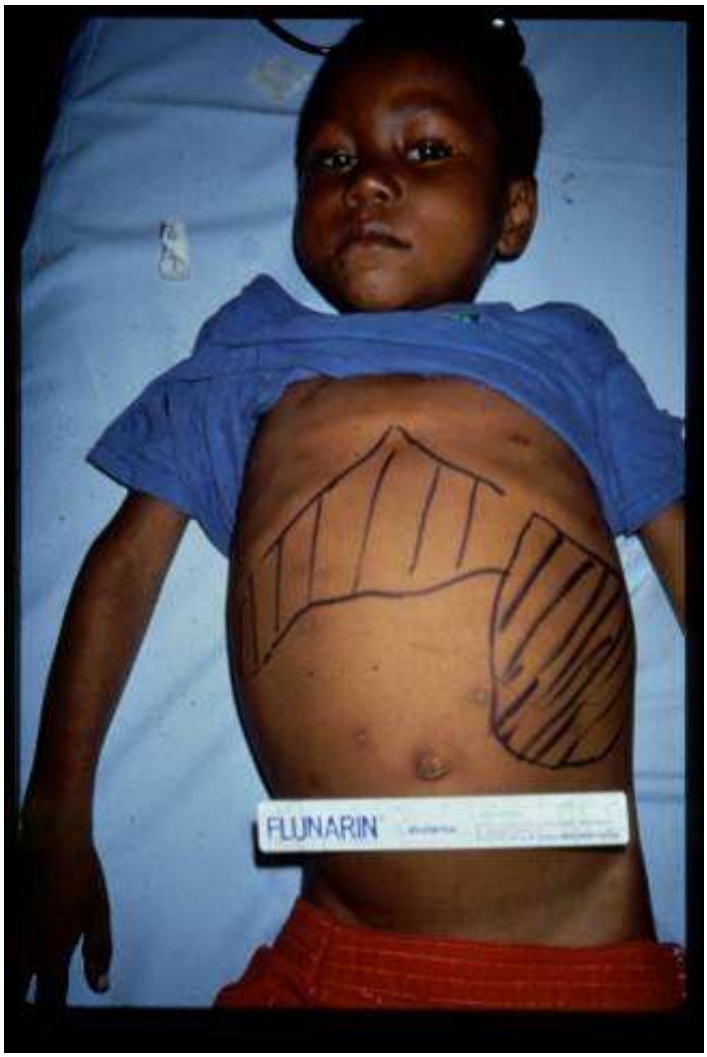

Figure 3. Child with visceral leishmaniasis and enlarged liver and spleen.from David JR

2.3 Cutaneous Leishmaniasis

Cutaneous leishmaniaisis (CL) is caused by *L. major*, *L. tropica* and *L. aethiopica* in the Old World and by *L. mexicana*and *L. amazonensis* in the New World, two species thought to have been brought over from the Old World and similar to *L. major*. CL is also caused by a group of *Viannia* species: *L. (V) braziliensis, L. (V) guyanesis, L. (V) panamensis* and *L.(V) peruviana*, that originated in the New World. The global incidence of CL is thought to be 1.5 million [1].CL is manifested by ulcers that can last for many months when untreated and leave disfiguring scars. *L.aethiopica* in Africa and the *Viannia Leishmania* species in the New World in addition to causing ulcers in the skin, can produce a systemic disease called mucocutaneous leishmaniasis (MCL). In MCL, the parasite leads to the destruction of mucous membranes especially around the mouth, nose and palate, causing incredible disfigurement (Figure 4). It can lead to anorexia, loss of weight and in some cases can be fatal.

Figure 4. Patient in Bahia, Brazil with mucocutaneosleishmaniasiscaused by L. (V) braziliensis on left and after treatment on right. from collection of Dr. Philip Marsden.

2.4 Treatment

The present gold standard for the treatment of cutaneous leishmaniasis (CL) is Pentavalent antimonials either sodium stibogluconate (Pentostam) manufactured by GlaxoSmithKline, or meglumine antimoniate (Glucantime) manufactured by Aventis. These drugs are quite toxic, though a little less so than the first antimonial introduced in the 1930's as urea stilbamine. They are given by injection and usually administered either intramuscularly, intravenously for three weeks or intralesionally for seven or more weeks. Liposomal amphotericin is the drug of choice for VL. Other drugs have been used for CL including oral rifampicin, dapsone, miltefosine, fluconazole, itraconazole and paromomycin ointment with various successes. But none have the advantage of obtaining a successful cure with a single application such as RFHT with minimal toxic effects.

3.1 REVIEW OF STUDIES

3.2 de Silviera and Brenner in 1950 [2] first used heat treatment based on reports that CL patients treated with trivalent arsenic and other toxic products improved when they became febrile. They injected one patient with CL and one with mucocutaneos leismaniasis (MCL) with the bacteria *H.ducrey*. Twenty days later both MCL and CL lesions had closed.

3.3 Berman and Neva in1981 [3]studied the effect of heat on *Leishmania* in human macrophages and found that *L.tropica* multiplies faster at 35^{o}C than at 37^{o}C and were completely eliminatedat 39^{o}C whereas *L.donovani* grew equally well at 35 and 37^{o}C and only 40% were eliminated at 39^{o}C.

3.4 Sacks *et al*. in 1983[4] compared the thermosensitivity of New and Old World *Leishmania*. All 8 CL strains grew optimally at 35^{o}C. Three of the 4 New World strains were completely destroyed at 39^{o}C, whereas all *L. tropica* strains survived and grew well at 39^{o}C, concluding that *L. tropica* may be less responsive to heat therapy than New World strains. They were not considering the use in the future of the ThermoMed instrument, which uses 50^{o}C.

3.5 Neva *et al*. in 1984 [5] treated three patients with diffuse cutaneous leishmaniasis with heated water 39^{o}C to 41^{o}C circulating through a pad around the lesions for cumulative total of 20 hours over several days. They improved as documented by biopsy and culture. Ordinary cutaneous leishmaniasis was not affected by this treatment.

3.6 Junaid in 1986 [6] carried out the treatment of CL in Baghdad, Iraq, using an apparatus that produced infrared rays that raised the temperature over the lesion to 55^{o}C for about 5 minutes. Of 178 patients, only 16 needed re-treatment after 3 weeks. He further noted that treatment of only one lesion "provokes an immune response in patients" that causes all the other lesions to disappear in 5-6 weeks. This systemic responsewas also observed in a subsequent study by Lobo *et al*.(2006) described below.

3.7 Aram and Leibovici in 1987 [7] used ultrasound-induced hyperthermia at 42^{o}C for treatment of CL, delivered 2-3X a week for 10-15 treatments to 28 lesions in 18 patients aged 4-57 years. Twenty-two of the 28 lesions (78.5%) showed compete resolution in 5-10 weeks. One patient with 2 lesions failed to respond. Others only responded partially or treatment had to be stopped because of headache as the lesions were on the face.

3.8 Navin*et al*. in 1990 [8] using an early model of ThermoMed carried out a placebo controlled clinical trial of meglumine antimonate (Glugantime) vs. localized radiofrequency-induced heat therapy (RFHT) of CL in Guatemala. Sixty-six Guatemalans with parasitology proven CL were divided into 3 equal groups, 1st. Glucantime, 859mg antimony a day given IM for 15 days, 2nd. localized RFHT at 50^{o}C for 30 seconds, 3 treatments at 7 day intervals, and 3rd. a placebo. Of the 53 isolates identified, 40 were *L. (V) braziliensis* and 13 were *L.mexicana.* Thirteen weeks after treatment patients with completely healed lesions and negative parasitology were with Glucantime 73% (16), Heat Rx 73% (16) and Placebo 27% (9). Cure rate of patients with *L. (V) braziliensis* was: Glucantime 79% (11 of 14), Heat 64% (9 of 14) and Placebo 0% (0 of 11).

3.9 Levin in 1992 [9] reported a case of a Sudanese patient with multiple lesions caused by *L.tropica* who was cured 6 months after receiving RFHT, a single treatment at 50^{o}C for 30 seconds.

3.10 Velasco-Castrejon *et al*. in1997, [10] carried out a feasibility trial for an endemic area (not a control trial), where

the organism was *L. Mexicana*. 201 patients with ages ranging from 2-75 years, 63% males, 37% female were treated with a single application on an anesthetized lesion at 50°C for 30 seconds using a ThermoMed instrument. At 4 weeks, 95% of 122 patients available for evaluation were totally healed and at 8 weeks 90% of 191 were totally healed.

3.11 Lobo *et al*. in 2006 [11] carried out a random study on 37 patients with CL that showed that RHFT elicited a systemic cytokine response similar to that of Glucantime. The RFHT group had 17 patients, the Glucantime 20, with no significant difference in the gender of patients or ulcer size. RFHT was applied at 50°C for 30 seconds to anesthetized lesions using a ThermoMed Model 1.8. (Fig 5), which had received 510 (K) clearance from the Food and Drug Administration for treatment of CL. Glucantime was given 20mg/Kg for 20 days.

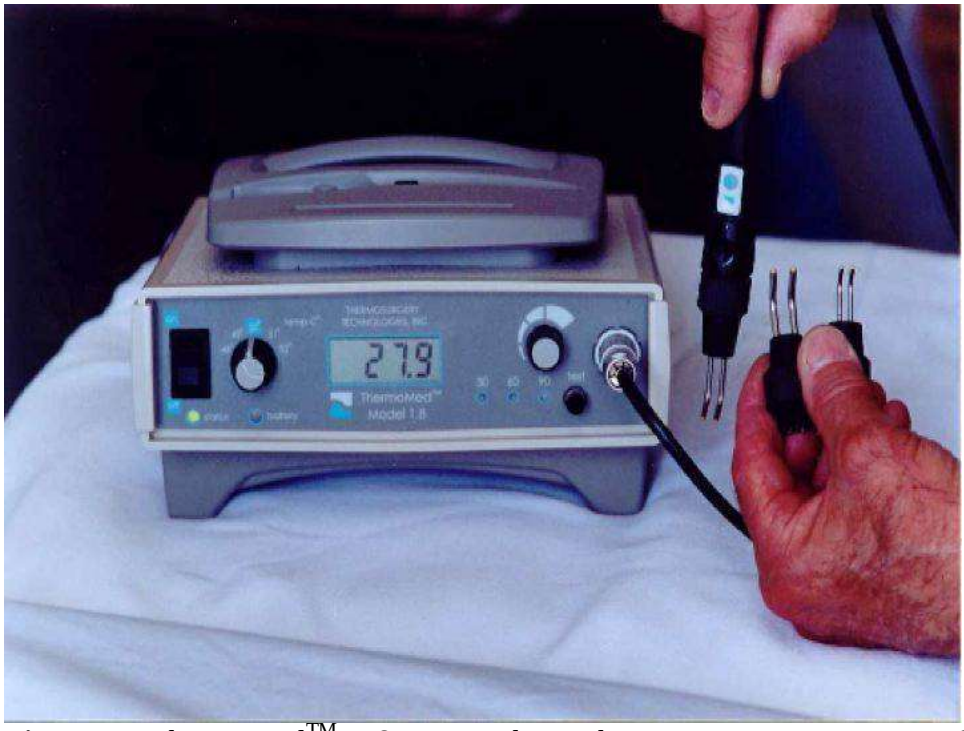

Figure 5. Thermomed™ 1.8. It is shown heating up on it way to 50°C. The three different sized applicators are shown, the thinner one for thin skin, such as on the face, the largest when deeper penetration is needed on the extremities. from David JR

At 28 days, the RHFT group received Glucantime for 20 days since the organism was *L.(V). braziliensis*, which cause MCL, and we did not know whether there would be a systemic effect of the heat therapy. Biopsies were taken at 0, 14, and 28 days, and lymphocyte proliferation, CD4/CD8 characterization and cytokine assayed at those times. There was a significant drop in the levels of INF-γ, IL-5 and TNF-α at 28 days compared to day zero $p<0.01$(Fig 6).

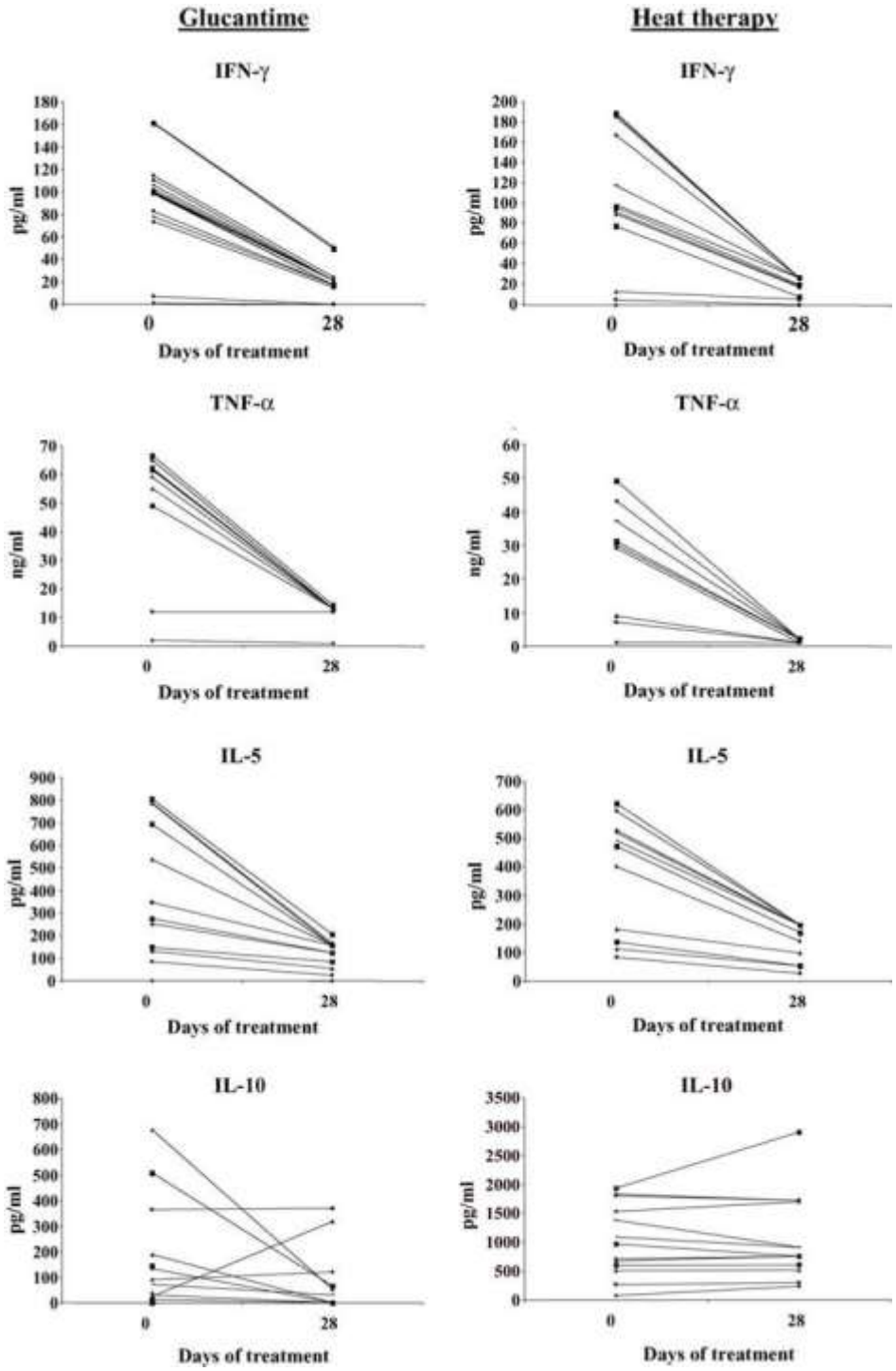

Figure 6. The cytokine response of peripheral blood mononuclear cells (PMBC) of patients with Glucantime or heat therapy. Levels of IFN-*g*, TNF-*a*, IL-5, and IL-10 in the supernatants of PMBC stimulated with leishmanial antigen before day O and 28 days after heat therapy or Glucantime treatment. From Lobo et al. Trans. Roy Soc Trop Med Hyg.(2006) 100, 642-649.

There was no statistical difference, however, between the two therapy groups. Further, there was no significant difference in the healing of the lesions by 28 days: 71% in the RHFT group and 89% in the Glucantime group. In two patients with lesions on each extremity, the lesion not treated by RHFT also healed, further indicating a systemic effect (Fig 7). A possible mechanism for this systemic effect is that the RHFT causes a secondary burn killing and disrupting most of the parasites, and this is followed by an influx of inflammatory cells including lymphocytes and macrophages, which could lead to an immune response similar to introducing a vaccine. During this study, about a dozen patients resistant to Glucantime, having received 60-100 days of this therapy without healing, also responded well to RFHT.

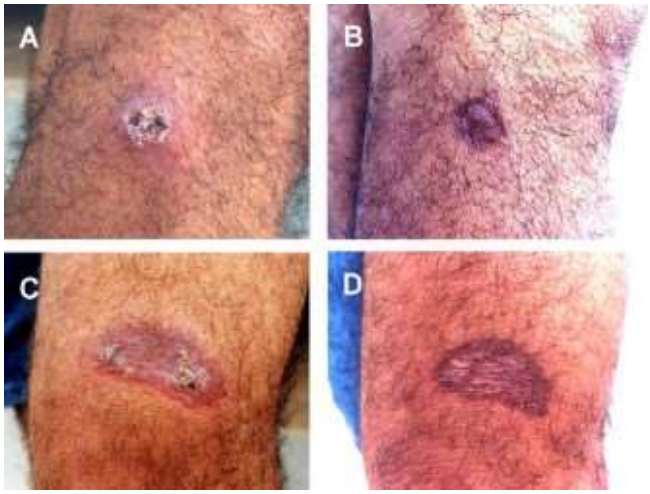

Figure 7. Systemic effect of heat treatment on cutaneous leishmaniasis (CL) lesions.Two CL lesions of a patient included in the heat treatment therapy group. Heat treated CL lesion after day 0 (A) and 28 days (B). Contralateral untreated lesion at day 0 (C) and 28 (D). From Lobo et al as Figure 2.

3.12 Reithinger *et al*. in 2005 [12] determined the efficacy of thermotherapy to treat CL caused by *L.tropica* in Kabul, Afghanistan in a randomized controlled trial. There were three groups: Group 1. Single application of RFHT for 50^{o}C for 30 seconds on anesthetized lesion using a ThermoMed Model 1.8; Group 2.Intralesional sodium stibogluconate (SSG) 2-7ml once a week for 5 weeks; Group 3. Intramuscular SSG 20mg/kg for 21 days.401 patients older than 5 years with a single lesion were included in the study. Parasitological diagnosis was carried out by dermal scrapings or biopsy, Giemsa stained, and examined under a microscope. A subset of 60 samples in each group were tested by PCR to confirm *L. tropica.* Patients were followed to measure size of lesion and to note side effects during 1, 4, 8, 16, 24 weeks post therapy (wpt). Cure was complete re-epithelialization by 100 days post therapy (dpt) and no relapse by 24 wpt. Failure was incomplete re-epithelialization by 100 dpt, or relapse by 24 wpt. Cure rate after 100 days was RFHT 69% (75/108) patients, Intralesional 75% (70/93) and Intramuscular 45% (26/58) (Figure 8). Healing time after start of treatment was RFHT 53 days, Intralesional 75 days,

and Intramuscular >100 days. Between the RFHT and the Intralesional group, no statistical association was shown between age, sex, body weight, lesion size, lesion location or lesion duration and trial outcome. No statistical difference was observed between cure by RFHT and Intralesional therapy. The study showed that a single treatment of RFHT was as effective as the administration of intralesional SSG and more effective than intramuscular SSG in the treatment of CL due to *L.tropica*. The time to cure was shorter with RFHT than with SSG in a Kaplan-Meier analysis.

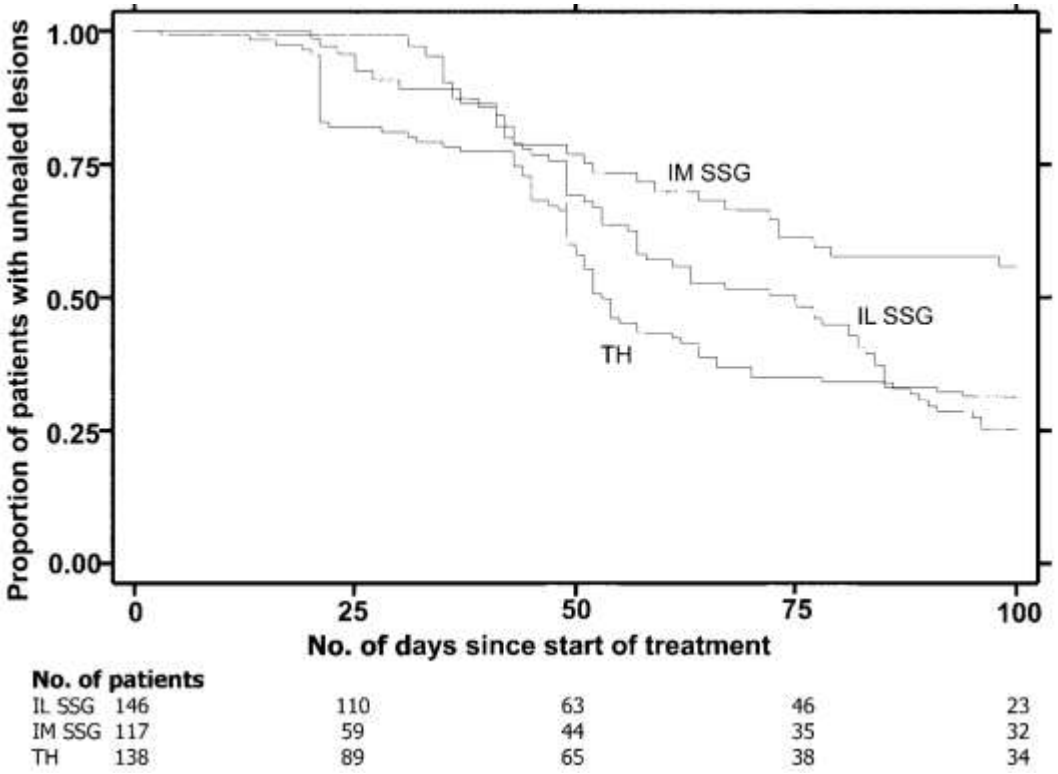

Figure 8. Survival analysis of time to healing of cutaneous leishmaniasl lesion, with data on number of patients enrolled in the trial at baseline and 4 other time points. IL, intralesional; IM intramuscular; SSG sodium stibogluconate; TH thermotherapy. From Reithinger et al. ClinInfecDis 2005; 40; 1148-1155

3.13 Willard *et al*. in2005 [13] reported on CL in soldiers from Fort Campbell, Kentucky returning from Operation Iraqi Freedom .*L. major* was the main species. 26 soldiers (24 men, 2 women), were treated with ThermoMed. There was one failure. 11 patients had 1 lesion, 7 had 2 lesions, 5 had 3 lesions, 1 had 4 lesions, and 2 had 5 lesions. They concluded that all soldiers expressed general satisfaction with the RFHT and all dermatology providers deemed the treatment safe and well tolerated and effective. Among the treated lesions, including those on dark skinned persons, no exaggerated scarring or color changes occurred beyond those previously described in CL.

3.14 Aronson at al.in 2010 [14] reported a randomized controlled trial of RFHT versus intravenous SSG for the treatment of *L. major* in military personnel who

had been infected in Iraq or Kuwait. There were 27 patients in each group. Diagnosis of *Leishmania* species was by PCR and isoenzyme analysis. RFHT was administered on an anesthetized lesion at 50^{o}C for 30 seconds and compared to SSG 20 mg/kg/day administered IV for 10 days, infused over 10-50 minutes for a total of 10 doses. Patients randomized to RFHT received oral antibiotics for secondary bacterial infections of their lesions prior to treatment. The results can be seen on (Fig 9), showing that the cure rates were similar. Side effects for the RFHT group were the result of the expected secondary burn, which were statistically significant compared to SSG such as oozing and blistering, whereas side effects for SSG were statistically significant compared to RFHT. These side effects were gastrointestinal symptoms, abdominal discomfort or pain, and musculoskeletal and nervous system symptoms. The conclusion of the trial was that skin lesions due to *L. major* treated by heat delivered by the ThermoMed device healed at a similar rate and with less associated systemic toxicity than lesions treated with intravenous SSG.

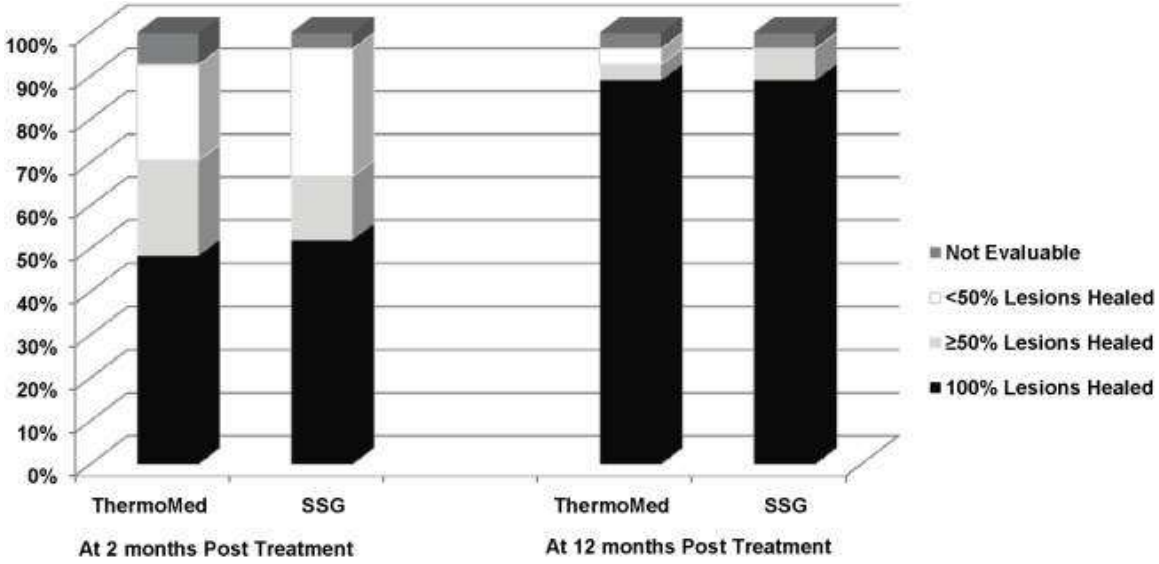

Figure 9. Consensus treatment efficacy at two and twelve months follow-up. From Aronson et al, PloSNeg Trop Dis2010; Mar 9;4(3) e628

3.15 Prasad et al. in 2011 [15] reported on thermotherapy on a 34 year old truck driver with HIV infection. He also had 6 month-old red plaques on his hand, which were biopsied and showed *L, tropica*by restriction-fragment length polymerization PCR. HIV/AIDS was confirmed by HIV ELISA TRO-DOT and HIV COMB. His viral load was 145,000 and his CD4^{+}T cell count was 180/µl. The HIV infection was treated with zidovudine, lamivusine and nevirapine. The CL was treated with SSG intralesionally, 0.5 ml (100g/Liter) twice a week for 6 weeks. There was no improvement of the CL at 24 weeks despite the rise of CD4+T cells to 240/ul. He was then treated with RFHT using a ThermoMed1.8 instrument and showed complete healing in 12 weeks. In addition to this patient, RFHT was also effective in a 28 year old HIV-

infected man with CL who did not responded to SSG and subsequent rifampicin for 3 months. Both patients have remained free of CL for a year after treatment. The authors conclude that RFHT should be considered as the first-line treatment for CL in HIV-infected patients.

3.16 Lopez *et al*. in 2012 [16] reported Thermotherapy as an alternative to the treatment of American CL in five military health centers in Columbia. There were 292 volunteers with parasitology, diagnosed CL by Giemsa stained smears and PCR, were randomly divided into two groups, 149 receiving a single application of thermotherapy at 50^{o}C for 30 seconds on the anesthetized lesion, 134 getting Glucantime 20 Sb^{5}/kg/day IM for 20 days. The healing response in the Glucantime group among patients with *L.(V) panamensis* and *L. (V) braziliensis* was 72% and 65% respectively. In the thermotherapy group the healing response in the L. (V) *panamensis* and L. (V) *braziliensis* patients was 58% and 53% respectively. The treatment with Glucantime was statistically superior to thermotherapy for treatment of CL in Columbia; however, Glucantime treatment was associated with severe side effects including myalgia and arthralgia, fever, headaches and toxicity to organs such as the kidney, the pancreas and the hematologic and cardiovascular systems. These side effects were not associated with thermotherapy, which only caused local pain four days after the initial treatment. Considering the side effects and increase in costs and treatment adherence problems with Glucantime, they consider that thermotherapy should be the first line of treatment for CL. Thermotherapy is also a valid alternative in patients with renal, hepatic and cardiac illnesses who cannot receive Glucantime.

3.17 Bumb*et al*. in 2013 [17] reported on the long-term efficacy of a single dose of RHFT vs. intralesional antimonials for CL in India. One hundred patients were randomly assigned. Fifty received RHFT at 50^{o}C for 30-60 seconds on the anesthetized lesion using a ThermoMed 1.8 instrument. All these patients received oral non-steroidal anti-inflammatory drugs and topical antibacterial cream for 5 days. The other 50 received intralesional injections of SSG 50mg cm^{-2} of lesion, twice a week for seven injections. Patients that had secondary bacterial infections of the lesions were treated with systemic or topical antibiotics without anti-leishmanial activity. Lesions were monitored every 15 days for 4 months and then at 5, 6, 9, 12, and 18 months post-treatment. Lesions were healed in 47 of the 50 patients (94%) in the RFHT group and 46 of the 50 patients (92%) in the SSG group at week 12. At 6 months post treatment cure rates in the RHFT and SSG groups were 98% and 94% respectively. Age, sex, and lesion size had no effect on cure rates. No relapse of infection was recorded in cured patients in either group up to 12-18 months after initiating treatment (Fig. 10). Skin biopsies of cured lesions in 8 out 8 from the RFHT group and 3 out of 3 from SSG group at 12 months showed minimal fibrosis and were negative for *Leishmania* by polymerase chain reaction test. Further, RFHT induced less scaring compared to SSG (Fig 11). They concluded that a single application of RHFT is safe, cosmetically acceptable and effective inducing long-term cure for CL. An editorial by this group was printed in 2011 [18].

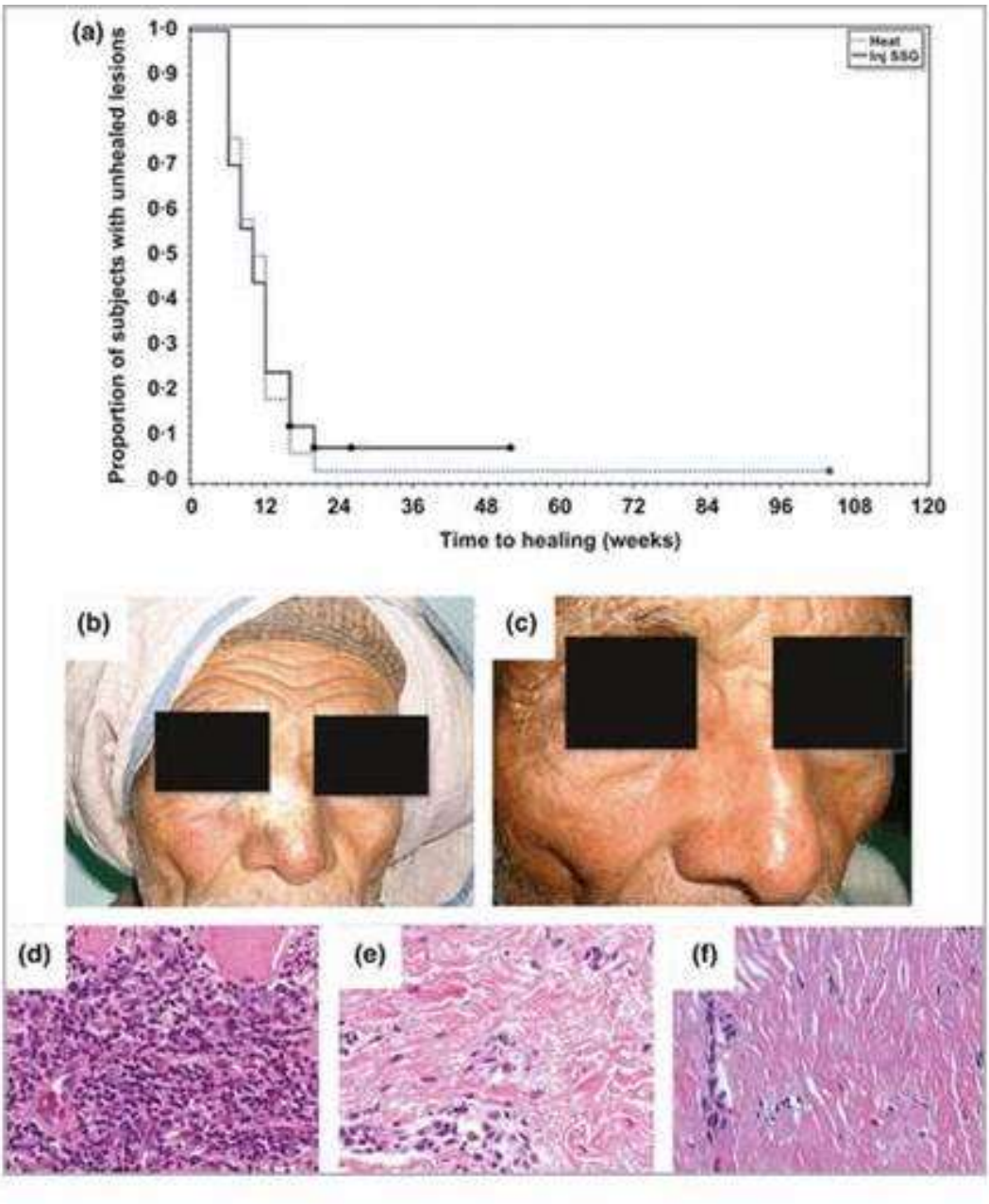

Figure 10. Efficacy of radiofrequency-induced heat therapy (RFHT) vs, intralesional sodium stibogluconate (SSG) in the treatment of cutaneous leishmaniasis (CL). (a) Survival analysis of time to heal after heat therapy (dotted blue) or intralesional SSG-injection (straight black). (b) A 79 year-old man with a lesion on the face/nose and was administered RFHT under local anesthesia. (c) The same patient 6 months post-treatment showing compete healing of the lesion with fine scarring. (d-f) Histopathology of the arm lesion from another patient prior to RFHT (d) and after 6 months (e) and 12 months (f) post-treatment. Original magnification: X40. From Bumb et al. Brit J Derm.2006; 168(5) 1114-1119.

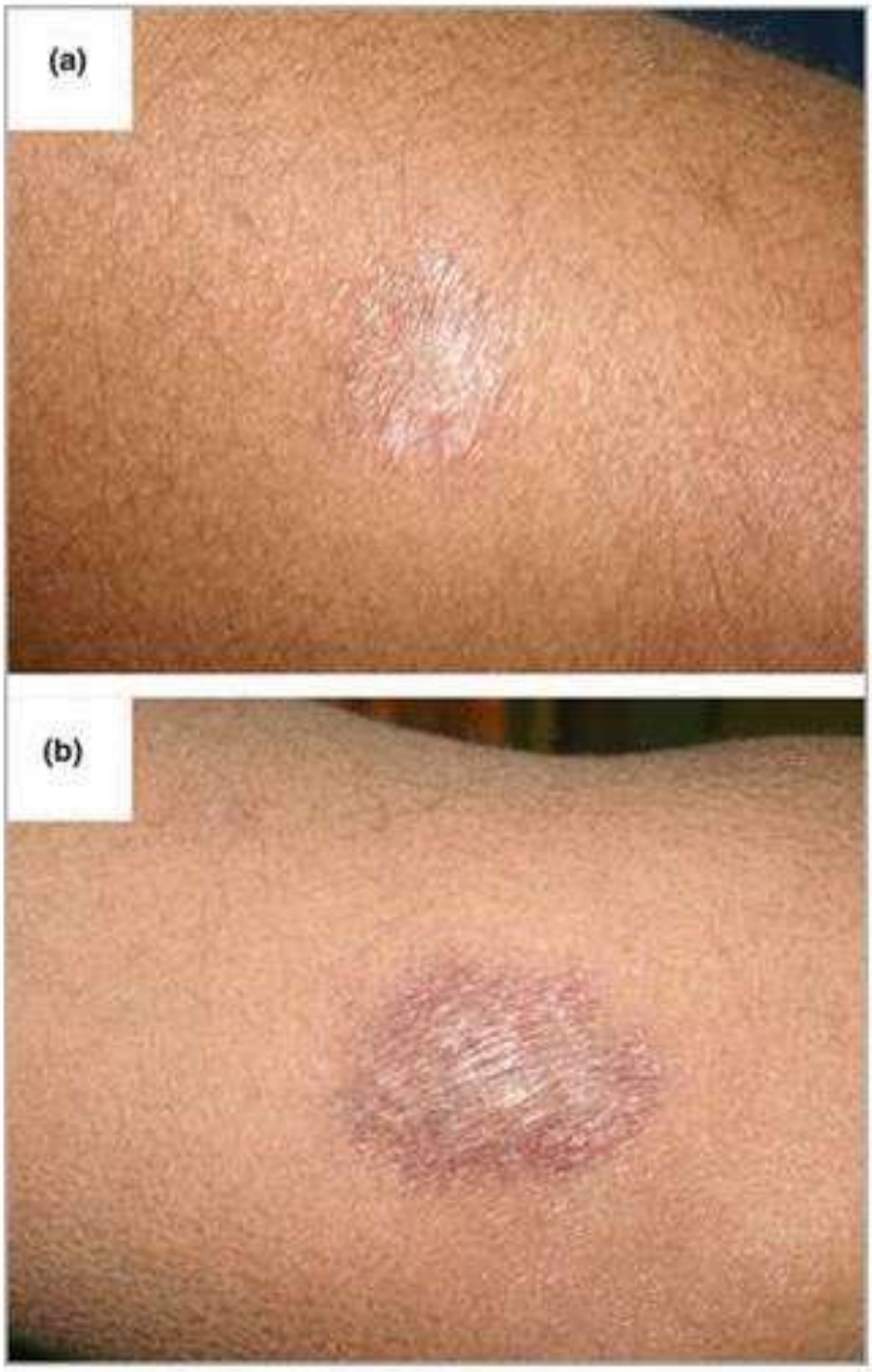

Figure11. Scarring associated with radiofrequency-induced heat therapy (RFHT) is less than with intralesional sodium stilbogluconate (SSG). (a) A cured lesion from a patient treated with RFHT; (b) a cured lesion from a patient treated with intralesional SSG injections. Lesions were located on the upper extremity in both patients. Note that RFHT results in fine scarring and minimal pigmentation compared to intralesional SSG. From Bumb et al as in Fig 6.

3.18 Ahuja et al.in 2012 [19] reported the successful treatment of canine CL using RFHT in two pet dogs using a single application on the anesthetized lesion from a ThermoMed 1.8 instrument. They found that RFHT induced complete clinical cure, lesions healing within 45 days and the dogs remained disease free for the last 16 months of observation. This is the first report that showed that RFHT worked in canine cutaneous leishmaniasis,

3.19 Safi et al. in 2012 [20] carried out a control study of patients with CL in Kabul, Afghanistan caused by *L. tropica.* Three hundred and eighty two patients were randomly assigned to a single localized treatment of heat therapy or 5 days of intralesional injection of Glucatime. The cure rate of the heat therapy group was 82.5% compared to 74% in the Glucantime group. The authors concluded that heat therapy was more effective than 5 days intralesional injection of Glucantime, and that heat therapy was more cost effective, with fewer side effects, of shorter duration and with better patient compliance than intralesional Glucatime.

3.20 Reveiz *et al*. in 2013 [21] reported a systemic review update, using meta-analysis of interventions for American cutaneous and mucocutaneous leishmaniasis. They included, however only one paper on RFHT, the Lopez et al (2012) paper sited above with the same conclusions. They mention that the rational for administrating local treatment such as RFHT is that the risk of developing the mucosal form is low, not necessarily prevented by systemic treatment, and localized treatments are better tolerated and have less frequent and severe adverse effects as compared to systemic treatments.

3.21 Valencia *et al*. in 2013 [22] reported on a low-cost thermotherapy for CL in Peru. They used a low-technology device named Hand–held Exothermic Crystallization Thermotherapy for CL (HECT-CL), a sodium acetate heating pad, invented by R. Witzig, which delivers a safe, reliable and renewable conduction heat. 25 patients with parasitologically confirmed CL by Giemsa staining, PCR, cysteine proteinase C gene, and Heat-shock-protein 70, used to distinguish *L. (V) braziliensis* and *L. (V) guyanensis* from each other and from non *L. (V) braziliensis* and *guyanensis* parasites. 25 patients completed the study, 16 males and 9 females. The initial temperature was 50^{o}C to 54^{o}C and applied to each lesion, some without anesthesia, for 3 minutes repeated daily for 7 days, and followed for 6 months by direct observation. Overall definite cure was 60%. 13 patients meeting minimally significant exclusion criteria had a cure rate of 68%, and of these 75% had experienced CL relapse after prior antimonial treatment.

3.22 Lopez *et al*. in 2013 [23] reported that RFHT was effective and safer than miltefosine for CL in Columbia using a controlled open randomized phase III clinical trial with patients from the Columbian army. 145 patients received 50 mg of miltefosine three times a day for 28 days. 149 patients received a single application of RFHT to the lesions using a ThermoMed instrument at 50^{o}C for 30 seconds. Both groups were comparable with respect to sociodemographic, clinical, and parasitological characteristics. In 56% of the patients, the *Leishmania* species was isolated and identified. In 81 patients

treated with miltefosine in whom 30 were *L.(V) panamensis* and 51 were *L. (V) braziliensis.* In 83 patients treated with RFHT, 24 were *L. (V) panamensis* and 59 were *L. (V) braziliensis*. No significant difference was found for treatment efficacy between the species responsible for infection. For the miltefosine group definitive cure at 6 months follow up was 59%, failure rate was 26% and lost to follow up was 14%. For RFHT, the definit8ve cure at 6 months was 59%, failure rate 33% and lost to follow up 9%. Midway through treatment, miltefosine was associated with greater occurrence of headache, vomiting, nausea and anorexia, and at the end of treatment with greater frequency of myalgia, arthralgia, headache, vomiting, and anorexia. RFHT was associated with pain at the lesion site following application of treatment. In Columbia, the authors do no think it is necessary to treat all patients infected with the *Viannia* species with systemic drugs because the incidence of MCL is less than 0.5%, and systemic treatment does not guarantee the absence of MCL.

3.23 Agrawal*et al*. in 2014 [24] reported on pediatric CL in an endemic region of India situated in the Thar Desert in Rajasthan State. 151 patients with 217 lesions were reported in the study period. The ages were from 0.25 to 5 years, with 41.7% of case between 2-4 years. The face was the most common site involved, the lesions being plaque-type or papulonodular. Smears were positive for *Leishmania* in 70% of 130 cases. Parasites were identified in 13 randomly selected cases as *L. tropica* by PCR. 58 patients received intralesional SSG, RFHT was used in 9 patients, 50 received oral rifampicin, 3 received oral dapsone, 11 received both dapsone and rifampicin, and 12 patients received both intralesional SSG and oral rifampicin. Nine patients were lost to follow up. Complete cure of the lesions was obtained within an average period of 9.7 weeks with a range of 4-20 weeks. Skin slits from 80 of 84 completely cured cases that were positive at the time of diagnosis were negative in all cases. Complete cure was seen in 125 (82.78%) of patients at 20 weeks. Complete sure for SSG patients was 84.4%, for RFHT it was 91.8%, for oral rifampicinit was 82%, for oral dapsone it was 66.67%, and for the combination of dapsone and rifampicin it was 90.1%. All 12 patients receiving a combination of intralesional SSG and oral rifampicin were cured. They concluded that all methods were effective and that RFHT is a good alternative because of its minimal systemic toxicity, and only a single treatment session is required.

3.24 Shah *et al*. in 2014 [25] reported in low-cost thermotherapy of CL in Sindh, Pakistan using the HECT-CL method described in the paper by Valencia *et al* [22], administered for 3 minutes for 7 days, Twenty- three patients could be evaluated for full treatment. By the final 180-day evaluation, 19 (83%) had been cured and the application was well tolerated with no side effects.

3.25 Lakhal-Naouar*et al*. in 2015 [26] reported on the immunologic healing response in CL treatment with localized heat using RFHT or systemic antimonial therapy. They studied the peripheral blood immune cells in a cohort of 54 cutaneous *L. major* subjects treated with SSG and RFHT. Multiparameter flow cytometry, proliferative assays and cytokine production was analyzed in order to investigate the differences in immune response before and after

treatment. Healing CL led to a significant decline of circulating T and NKT-like cells, with an expansion in NK cells regardless of the treatment modality. There was a decrease in antigen specific $CD4^+$T cell proliferation seen with $CD8^+$T cell depletion. In the healing and healed state, fewer circulating regulatory T cells were seen as well as reduced IFN-γ production and an overall contraction in polyfunctional $CD4^+$T cells. The authors conclude that healing of CL alters the circulating lymphocyte populations and subsets of T, NK and NK-like cells. The immunologic healing, through either local or systemic treatment, culminates in similar changes in frequency, quality and antigenic specific responsiveness with immunomodulation possible by a $CD8^+$ T cell dependent mechanism.

3.26 Cardona-Arias *et al*. in 2105 [27] reported on the efficacy of treating leishmaniasis using a meta-analysis of controlled clinical trials in 12 data bases. The results included 622 patients who underwent thermotherapy, with an efficacy of 73% (confidence intervals (Cl) = 69.6-78.7%, and 667 patients who underwent systemic therapy with an efficacy of 70.6% (95% Cl=67.1%. 1-74.1%) (Fig 12). Heterogeneity between studies, good sensitivity for the combined methods, and no publication bias were observed. The relative risk of the treatment was 1.02 (95% Cl =0.91, 1.15), showing that the effectiveness of thermotherapy is equal to that of pentavalent antimonial drugs. They conclude that due to efficacy, greater safety and lower cost, thermotherapy should be the first treatment option for CL in areas where the prevalence of the mucocutaneous form is low and in patients with contraindications for systemic therapy, such as kidney, liver and heart disease, as well as in pregnant women, infants and patients with immunodeficiency virus infections and acquired immunodeficiency syndromes.

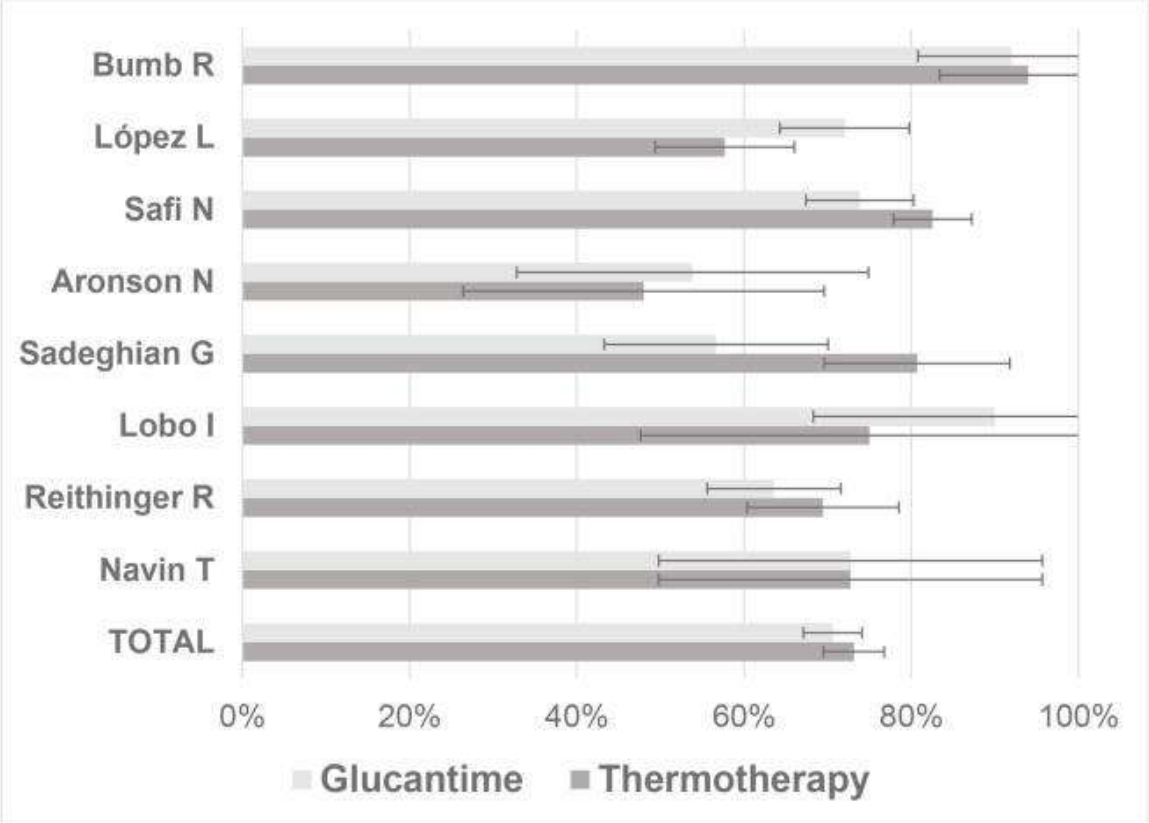

Figure 12. Efficacy of Glucantime and thermotherapy for the treatment of cutaneous leishmaniasis (proportion with 95% confidential intervals. From Cardona-Arias et al. PLos One 2015; 10 (5) e0122569

3.27 Refai*et al*. in 2017 [28] reported the Efficacy, Safety and Cost-Effectiveness of RFHT in the treatment of *L.donavani*-induced CL in a randomized controlled clinical trial in Sri Lanka. They mention that the standard treatment is the multiple painful doses of intralesional SSG, and as treatment failures were increasingly reported, the investigation of an alternative treatment was needed. A single blinded noninferiority randomized control trial was conducted. Laboratory confirmation of the diagnosis was made based on microscopy and culture of lesions before enrolment in the study. The thermotherapy group, containing 98 patients with single lesions, received a single session of RFHT given at 50^{o}C for 30 seconds using ThermoMed 1.8. The control group of 115 patients received 1-3 ml SSG intralesionally weekly until cure or up to 10 doses. Patients were followed every two weeks. Cost of treatment was assessed using scenario building technique. Cure rates at 8 weeks was 44,5% for RFHT, 28% for SSG, at 10 weeks was 56.5% for RFHT, 40.8% for SSG, and at 12 weeks 65.9% for RFHT, 59.4% for SGG, with no major adverse effects. Cure rates for RFHT were significant higher than SSG at 8 weeks (P=0.009) and 10 weeks (P=0.03) but comparable after. Cost for RFHT was 7 times less (USD = 1.54/patient) than SSG (USD = 11.09/patient). From this trial, they conclude that a single application of RFHT is safe, cost-effective and convenient compared to

intralesional SSG in the treatment of *L. donovani* CL, and thus RFHT should be considered with multiple benefits to the patient and the national health care system.

4.1 DISCUSSION

The ThermoMed™ device remains the most supported by randomized clinical trials and is recommended by WHO as an alternative therapy for all American CL species [1].It has been approved by the FDA for use for Cutaneous Leishmaniasis (FDA 510K number K021117). It is used by the WHO and Center for Disease Control and Prevention. Cost of treatment with antimonials is between $100 to $200 per patient depending on the country. The ThemoMed™ now costs $6500, so in a country where antimonial cost $100, the instrument will have paid for itself after 65 patients, and if $200, after 33 patients.

The ability to obtain a cure with just one application of treatment is especially useful in rural areas where compliance is often poor as it may be difficult for patients to be seen regularly by medical professionals administering the drugs. The observation that RFHT gives a systemic response, as measure by the cytokine response reported by Lobo *et al*.(2005) and Lakhal-Naouar*et al*. (2015) and by changes in the lymphocytes reported by the latter, are similar to the systemic administration of pentavalent antimonials, which is important in considering RFHT in areas where mucocutaneous leishmaniasis caused by *Leishmania* of the *Viannia* species is low. The observation that treatment of one lesion may be followed by the cure of an untreated lesion on the same patient, as reported by Junaid (1986), and by Lobo *et al*. (2005), appears to confirm the systemic response to heat therapy. This observation should be confirmed in future trials involving patients with multiple lesions, by treating half of the lesions and observing whether or not the untreated lesions cure. The mechanism for such a systemic effect is unknown. The secondary burn caused by the therapy results in the destruction of parasites releasing antigen that may stimulate the incoming lymphocytes and macrophages to produce an anti-*Leishmania* immune response similar to a vaccine. The burn may also induce pro-inflammatory cytokines such as TNF-α, and migration inhibitory factor (MIF) known to be involved in the immunity to *Leishmania* parasites.

5.1 SUMMARY

The conclusion of this review is similar to the conclusion of these many clinical trials, namely that RFHT is safe, cost effective and is at least as effective as pentavalent antimonial therapy and other drugs for treatment of cutaneous leishmaniasis.

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