



UNIVERSITY OF LEEDS

This is a repository copy of *Efficacy of Thermotherapy to Treat Cutaneous Leishmaniasis Caused by Leishmania tropica in Kabul, Afghanistan: A Randomized, Controlled Trial* .

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/1379/>

Article:

Reithinger, R., Mohsen, M., Wahid, M. et al. (5 more authors) (2005) Efficacy of Thermotherapy to Treat Cutaneous Leishmaniasis Caused by *Leishmania tropica* in Kabul, Afghanistan: A Randomized, Controlled Trial. *Clinical Infectious Diseases*, 40 (8). pp. 1148-1155. ISSN 1058-4838

Reuse

See Attached

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Efficacy of Thermo-therapy to Treat Cutaneous Leishmaniasis Caused by *Leishmania tropica* in Kabul, Afghanistan: A Randomized, Controlled Trial

R. Reithinger,^{1,4} M. Mohsen,¹ M. Wahid,² M. Bismullah,² R. J. Quinnell,³ C. R. Davies,⁴ J. Kolaczinski,^{1,4} and J. R. David⁵

¹Malaria and Leishmaniasis Control Program, HealthNet International, University Town, Peshawar, Pakistan; ²Afghan Ministry of Health, Kabul, Afghanistan; ³School of Biology, University of Leeds, Leeds, and ⁴Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom; and ⁵Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts

(See the editorial commentary by Wortmann on pages 1156–8)

Background. Pentavalent antimony is the agent recommended for treatment of cutaneous leishmaniasis (CL). Its use is problematic, because it is expensive and because of the potential for drug-associated adverse effects during a lengthy and painful treatment course.

Methods. We tested the efficacy of thermo-therapy for the treatment of CL due to *Leishmania tropica* in a randomized, controlled trial in Kabul, Afghanistan. We enrolled 401 patients with a single CL lesion and administered thermo-therapy using radio-frequency waves (1 treatment of ≥ 1 consecutive application at 50°C for 30 s) or sodium stibogluconate (SSG), administered either intralesionally (a total of 5 injections of 2–5 mL every 5–7 days, depending on lesion size) or intramuscularly (20 mg/kg daily for 21 days).

Results. Cure, defined as complete reepithelialization at 100 days after treatment initiation, was observed in 75 (69.4%) of 108 patients who received thermo-therapy, 70 (75.3%) of 93 patients who received intralesional SSG, and 26 (44.8%) of 58 patients who received intramuscular SSG. The OR for cure with thermo-therapy was 2.80 (95% confidence interval [CI], 1.45–5.41), compared with intramuscular SSG treatment ($P = .002$). No statistically significant difference was observed in the odds of cure in comparison of intralesional SSG and thermo-therapy treatments. The OR for cure with intralesional SSG treatment was 3.75 (95% CI, 1.86–7.54), compared with intramuscular SSG treatment ($P < .001$). The time to cure was significantly shorter in the thermo-therapy group (median, 53 days) than in the intralesional SSG or intramuscularly SSG group (median, 75 days and >100 days, respectively; $P = .003$).

Conclusions. Thermo-therapy is an effective, comparatively well-tolerated, and rapid treatment for CL, and it should be considered as an alternative to antimony treatment.

World-wide, the largest focus of cutaneous leishmaniasis (CL) is in Kabul, Afghanistan, where *Leishmania tropica* is anthroponotically transmitted by the sand fly *Phlebotomus sergenti* and where the estimated annual case load has been 67,500–200,000 patients during the past decade [1–3]. Because of limited resources available during and after the Afghan civil war, the treatment

of patients with CL by the Afghan Ministry of Health and by nongovernmental organizations is the only strategy to control the epidemic.

Pentavalent antimonials—namely, sodium stibogluconate (SSG) and meglumine antimoniate—are the mainstay of anti-leishmanial therapy [4–6]. A leishmaniasis vaccine does not exist [7]. In countries where leishmaniasis is endemic, antimonials are typically administered intramuscularly (at a dosage of 20 mg/kg/day for 20–28 days) or intralesionally (at a dosage dependent on the lesion size) [4, 5]. However, antimonials can have serious (usually reversible) adverse effects (e.g., pancreatitis, hepatotoxicity, and cardiotoxicity) when given intramuscularly [4,5], and they are expensive [8]. Moreover, the invasiveness of the stan-

Received 11 November 2004; accepted 7 December 2004; electronically published 16 March 2005.

Presented in part: Annual Meeting of the American Society of Tropical Medicine and Hygiene (Philadelphia), 7–11 December 2003.

Reprints or correspondence: Dr. R. Reithinger, 807 S. Overlook Dr., Alexandria VA 22305 (rreithinger@yahoo.co.uk).

Clinical Infectious Diseases 2005;40:1148–55

© 2005 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2005/4008-0012\$15.00

dard procedure—a lengthy course of painful inoculations—often leads patients to default on their full treatment course. Low compliance appears to be the principal reason behind the emergence of drug-resistant parasite strains, especially in areas where there is anthroponotic leishmaniasis; for example, in India, Sudan and Nepal [9]. Hence, research is focusing on the development of alternative treatments that use different dosage schedules, drugs, or methods of treatment [6].

Surprisingly, despite its regional importance, there is a dearth of clinical data on CL caused by *L. tropica*, and there are only limited data on natural or treatment-induced cure rates [10]. We evaluated the efficacy of thermotherapy as treatment for CL due to *L. tropica* in Kabul and compared it with standard intramuscular and intralesional SSG treatment in a controlled, randomized trial.

METHODS

Study location and participants. The study was carried out at the HealthNet International Khair Khana clinic in Kabul, Afghanistan. This clinic has been operational since 1995 and is the main leishmaniasis treatment center in Kabul [2, 3], with 4751 new and 25,783 follow-up patients treated in 2003. Eligible patients were those who attended the clinic for leishmaniasis treatment and who had only 1 suspected CL lesion. Inclusion criteria were age of >5 years; the presence of a single, parasitologically confirmed CL lesion; and no prior history of disease and/or antimonial treatment. Exclusion criteria were the presence of a CL lesion located on or immediately adjacent to the nose, lips, or eyes; pregnancy; breast-feeding; major surgery in the previous 3 months; presence of any uncontrolled medical condition; and anticipated unavailability for follow-up. Most patients were current Kabul residents.

Study design and procedures. The study was a randomized, controlled trial. There was no placebo group, because this would have been unethical due to the severity of CL that *L. tropica* causes and the social stigma associated with the disease [2]. The London School of Hygiene and Tropical Medicine Ethics Committee and the Afghan Ministry of Health approved the study protocol and the consent form. According to HealthNet International policy, all medical services provided during the study were free of charge.

To detect a 20% difference in the cure rate between the SSG and thermotherapy groups, assuming an 80% cure rate in the SSG groups [4–6], with a 90% power and a 5% 2-sided type I error, 98 subjects were needed in each group. To compensate for anticipated loss to follow-up, 40% more patients were enrolled in each group. Eligible patients coming to the clinic for treatment were briefed about the study, its aims, and the protocol. Patients were enrolled in the study after written consent had been given. Patients then proceeded to pick 1 of 3 identical cardboard pieces out of a hat (the cardboard had been labeled

with different treatment codes on one of its sides, the codes being nonvisible to the patient). After patients were randomly assigned to receive a treatment, the cardboard piece picked was returned to the hat. The assigned treatments were as follows: (1) intralesional administration of generic SSG (Albert David Ltd., Calcutta, India), 5 injections of 2–5 mL (depending on lesion size) every 5–7 days for a total of up to 29 days; (2) daily intramuscular administration of SSG 20 mg/kg (up to a maximum daily dose of 850 mg) for 21 days; and (3) a single thermotherapy treatment (≥ 1 consecutive application of 50°C for 30 s, depending on lesion size).

Both SSG regimens are standard World Health Organization–recommended treatment for CL in Afghanistan [11]. For intralesional treatment, SSG was infiltrated around the lesion until complete blanching of the lesion and its margin was obtained [11]. For thermotherapy, the lesion and a 15–20-mm border of healthy skin around the lesion were cleaned with stabilized 0.1% chlorine dioxide solution, anesthetized with 1% lidocaine HCl, and moistened with sterile saline solution; then heat was applied locally with a portable, battery-operated, localized current field radio-frequency generator (ThermoMed 1.8; Thermosurgery Technologies), according to the manufacturer's instructions. The generator has received 501K clearance by the US Food and Drug Administration for CL treatment. It produces a 6.78-MHz frequency, applied with a handset that includes an applicator gauge with 2 electrodes that are placed onto the diseased skin. The area between the electrodes covers 49–73 mm², depending on the applicator gauge size used; therefore, several thermotherapy applications may be required to cover a lesion. Once treatment begins, the temperature is measured by a thermistor embedded in one of the electrodes, ensuring that the applied temperature remains constant. The applied radio frequencies excite the tissue molecules, producing heat that evenly penetrates the upper dermis, exposing *Leishmania* amastigotes to high temperature without injuring the healthy underlying tissue. After all treatments, a chlorine dioxide gel was applied to lesions, and lesions were covered with gauze to prevent secondary infections.

Before the first treatment, all patients received a full physical examination. The location and duration (prior to treatment) of the lesion were recorded; its diameter was measured with a caliper. The status of each lesion was evaluated during 4 patient follow-up visits; the trial end point was 100 days after start of therapy. Lesions with a secondary bacterial infection before, during, or after treatment were treated with topical antibiotics. If systemic treatment was required, patients received treatment with an antibiotic that has no activity against *Leishmania* (e.g., erythromycin). The occurrence of adverse effects was evaluated blindly by means of patient interviews and physical examinations during follow-up visits.

Treatment efficacy was measured by the percentage of pa-

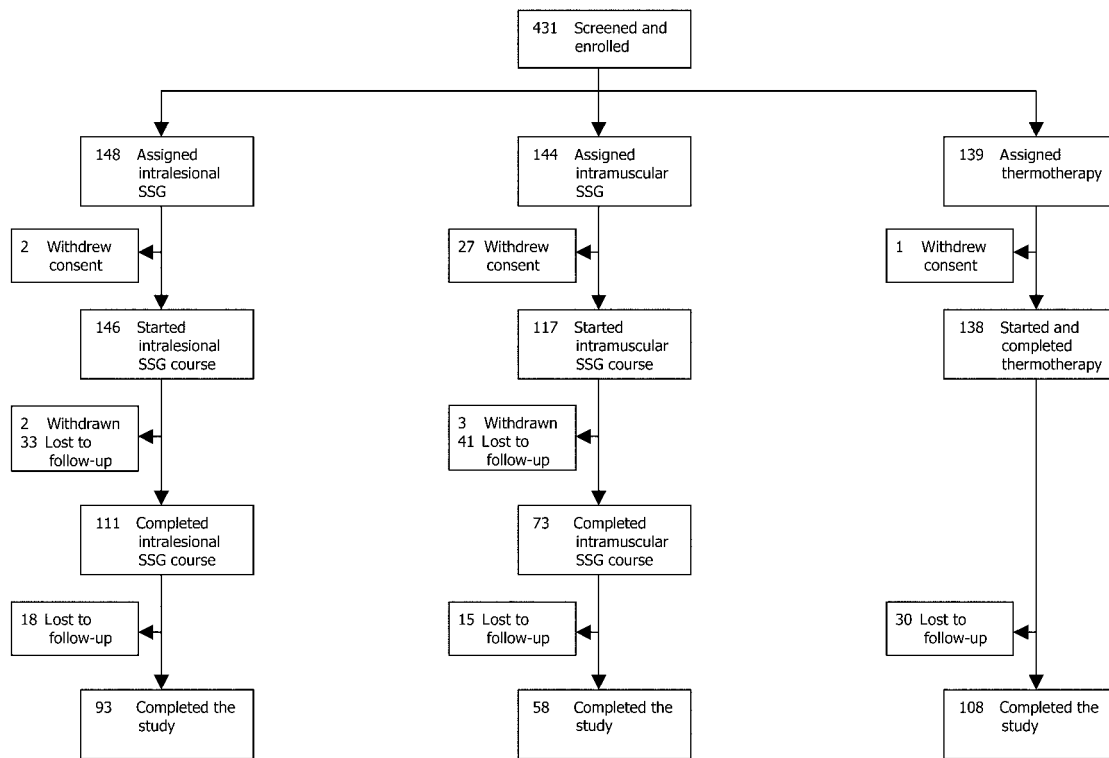


Figure 1. Flow chart summarizing the enrollment and randomization of patients in a trial of thermotherapy for cutaneous leishmaniasis and listing reasons for exclusion or withdrawal from the study. All values are no. of patients.

tients cured at 100 days after treatment initiation and by time to cure. Cure was defined as the complete reepithelialization of the CL lesion, with no evidence of papules, inflammation, or induration. Patients that did not experience cure after 100 days were offered intralesional or intramuscular SSG, as appropriate.

Parasitological studies. Parasitological confirmation of CL was by microscopic examination in Kabul and parasite identification by PCR at Leeds University (Leeds, United Kingdom). Microscopic examination was performed blindly. Scrapings from the lesion edge were smeared onto a slide, and the slide was dried, fixed with methanol, Giemsa-stained, and examined under the microscope at $\times 100$ magnification for presence of *Leishmania* amastigotes. For PCR, lesion scrapings were preserved in ethanol at -20°C prior to DNA extraction using a QIAamp DNA mini kit (Qiagen). Samples were amplified in a nested PCR with *Leishmania*-specific kinetoplast minicircle primers, under conditions published elsewhere [12]. This protocol differentiates between the major *Leishmania* species in Central Asia, namely *L. tropica*, *Leishmania major*, and *Leishmania infantum*. Each PCR included appropriate negative and positive controls. To evaluate sample degradation or PCR inhibition, sample DNA was also amplified for a 740-bp fragment of the human *TNFB* gene [13].

Statistical analysis. All patient data were entered into Excel software (Microsoft). A χ^2 test was used to test for significance ($P < .05$) between proportions (e.g., sex and loss to follow-up). All other analyses were done with Stata software, version 6.0 (Stata). A Kruskal-Wallis test was used to test for significance between pretrial characteristics (e.g., age, body weight, lesion size, and lesion duration) of treatment groups. The effects of the treatments on the proportion of patients cured by 100 days were tested by logistic regression. The analyses incorporated the effect of explanatory variables (discussed above) and treatment type. The significance of each variable was tested by backwards deletion; that is, by observation of whether these variables explained a significant ($P < .05$) proportion of the deviance remaining after removal from the model. Variables were removed from the models in order of least significance until only significant variables (those with $P < .05$) were retained in the minimum adequate model. The Kaplan-Meier method was used for the time-to-healing analysis; to compare the healing curves for the 3 treatment types, the log-rank test was used.

RESULTS

A total of 431 patients were enrolled in the study between January and September 2003. After random treatment alloca-

Table 1. Demographic and clinical characteristics of patients before treatment for cutaneous leishmaniasis.

Variable	All patients	Intralesional SSG group	Intramuscular SSG group	Thermotherapy group	P ^a
No. of patients	401	146	117	138	
Sex, no. male/female	200/201	67/79	63/54	70/68	
Age, median years (IQR)	13 (10–20)	13 (8.25–22)	13 (10–22)	14 (10–20)	.75
Body weight, median kg (IQR)	39 (24–51)	36 (22–50)	38.5 (26–51.25)	40 (24–51)	.70
Lesion diameter, median mm (IQR)	12 (7–20)	12.75 (7–20)	13.75 (8–22.5)	10.25 (7–20)	.11
Lesion duration, median months (IQR)	6 (3–7)	6 (3–7)	5.5 (3–7)	6 (3.75–8)	.19

NOTE IQR, interquartile range; SSG, sodium stibogluconate.

^a A Kruskal-Wallis rank test was used to compare difference in pretreatment patient characteristics between treatment groups.

tion, 30 patients decided to withdraw from the study (figure 1); 146 patients received intralesional SSG, 117 received intramuscular SSG, and 138 received thermotherapy treatment.

Baseline patient characteristics. All patients had lesions parasitologically confirmed by microscopy. For a subset of 39 patients, lesion scrapings were obtained for PCR-based parasite identification. All samples yielded amplification products for the human *TNFB* gene fragment. Of these 39 samples, 27 (69%) were PCR-positive for *Leishmania* DNA; for all 27, *L. tropica* was identified. Demographic and clinical characteristics of patients are presented in table 1. No statistically significant differences were observed between treatment groups with respect to sex, age, body weight, lesion size, or lesion duration. The lesions were primarily located on the face (43.4% of patients), as well as on the hands (38.2%), legs (15.9%), and arms (2.4%). The median times of follow-up visits for patients who completed the trial were day 13, day 21, day 49, and day 85, for the first, second, third, and fourth visit, respectively.

Efficacy. A total of 259 patients (63.8%) completed treatment and completed the 4 visits and 100 days of follow-up. Of these 259 patients, 108 were treated with thermotherapy, 93 were treated with intralesional SSG, and 58 were treated with intramuscular SSG (figure 1). In the intramuscular SSG group, 27 patients (47%) had their SSG dose limited by the protocol ceiling of 850 mg/day. Thermotherapy-treated patients were shown to be least likely to be lost to follow-up either during or after the end of treatment (table 2).

Complete cure by 100 days was observed in 69.4% of patients treated with thermotherapy, 75.3% of patients treated with intralesional SSG, and 44.8% of patients treated with intramuscular SSG (table 3). None of the patients with complete healing had relapse during the 100 days of the study. No statistically significant association was shown between age, sex, body weight, lesion size, lesion location or lesion duration and trial outcome. The OR for cure with thermotherapy was 2.80 (95% CI, 1.45–5.41), compared with intramuscular SSG treatment ($P = .002$). No statistically significant difference was observed between the odds of cure with intralesional SSG or thermo-

therapy treatment (OR, 1.34; 95% CI, 0.72–2.50; $P = .359$). The OR for cure with intralesional SSG treatment was 3.75 (95% CI, 1.86–7.54), compared with intramuscular SSG treatment ($P < .001$). An intention-to-treat analysis of the data (i.e., including the patients lost to follow-up, who were considered to have had treatment failure) yielded similar results for the comparison of the odds of cure for the different treatments (table 3).

According to the Kaplan-Meier survival analysis (which analyzes all available data, including those for patients who dropped out of the study during treatment), the time to cure was significantly shorter for patients treated with thermotherapy (median, 53 days) than for those who were treated with intralesional or intramuscular SSG (medians, 75 days and >100 days, respectively; $P = .003$, by the log-rank test) (figure 2).

Secondary infections were noted in 8 patients treated with thermotherapy (2 before and 6 after treatment), in 5 patients treated with intralesionally SSG (2 before and 3 after start of treatment), and in 2 patients treated with intramuscular SSG

Table 2. Rates of loss to follow-up of patients in the trial.

Period, treatment group	OR (95% CI)	
	Thermotherapy group	Intralesional SSG group
During treatment		
Intramuscular SSG	...	1.89 (1.06–3.38) ^a
Intralesional SSG
After the end of treatment		
Intramuscular SSG	0.93 (0.44–1.97)	1.34 (0.59–3.05)
Intralesional SSG	0.70 (0.35–1.39)	...
Throughout the study		
Intramuscular SSG	3.48 (1.94–6.24) ^b	1.78 (1.05–3.03) ^a
Intralesional SSG	1.97 (1.13–3.47) ^a	...

NOTE. ORs were estimated using the χ^2 test using data shown in figure 1. Excluded from the analyses are patients who withdrew from the study because of the adverse effects of treatment. SSG, sodium stibogluconate.

^a Not significant; $P < .05$.

^b Not significant; $P < .001$.

Table 3. Cure rates and odds of cure under different assumptions for the 3 treatment groups at the end of the trial.

Analytical assumption ^a	Proportion (%) of patients with cure at 100 days			OR (95% CI)		
	IL SSG group	IM SSG group	TH group	IL SSG vs. TH	IL SSG vs. IM SSG	IM SSG vs. TH
Per protocol	70/93 (75.3)	26/58 (44.8)	75/108 (69.4)
ITT	70/146 (47.9)	26/117 (22.2)	75/138 (54.3)	0.77 (0.47–1.27)	3.22 (1.81–5.77) ^b	0.24 (0.13–0.43) ^b
ITT var	105/146 (71.9)	70/117 (59.8)	75/138 (54.3)	2.15 (1.28–3.63) ^c	1.72 (0.99–2.98) ^d	1.25 (0.74–2.13)

NOTE Differences between per-protocol cure rates were analyzed using logistic regression (see Methods). IL, intralesional; IM, intramuscular; ITT, intention to treat; SSG, sodium stibogluconate; TH, thermotherapy.

^a Per protocol: analysis excluding patients that were lost to follow-up. ITT: analysis including patients lost to follow-up throughout the study, who were considered to have experienced treatment failure. ITT var: analysis including patients lost to follow-up during treatment, who were considered to have experienced cure, and including patients lost to follow-up after treatment completion, who were considered to have experienced treatment failure.

^b $P < .001$; pairwise comparison of ITT cure rates was done with a χ^2 test of proportions, with ORs given in the table.

^c $P < .01$.

^d $P < .05$.

(1 before and 1 after start of treatment), but the differences were not statistically significant. All secondary infections resolved with antibiotic treatment. Excluded from the study after treatment initiation were 2 patients treated with intralesional SSG, because of bradycardia and an undefined local reaction to the treatment; and 3 patients treated with intramuscular SSG, because of bradycardia, tachycardia, and palpitation. In the thermotherapy-treated group, the original CL ulcer often increased in size immediately after and up to 2 weeks after treat-

ment, with patients experiencing superficial second-degree burns where the electrodes were applied; thereafter, the lesion closed rapidly (figure 2). This observation may explain the low rate of follow-up among thermotherapy-treated patients in the first 2 weeks after treatment; 25 (83%) of the 30 patients lost to follow-up in the thermotherapy group were lost in the first 2 weeks. Patients may have become disheartened and unwilling to seek further medical advice when lesions became bigger. Though evaluation of scarring was not performed blindly, nei-

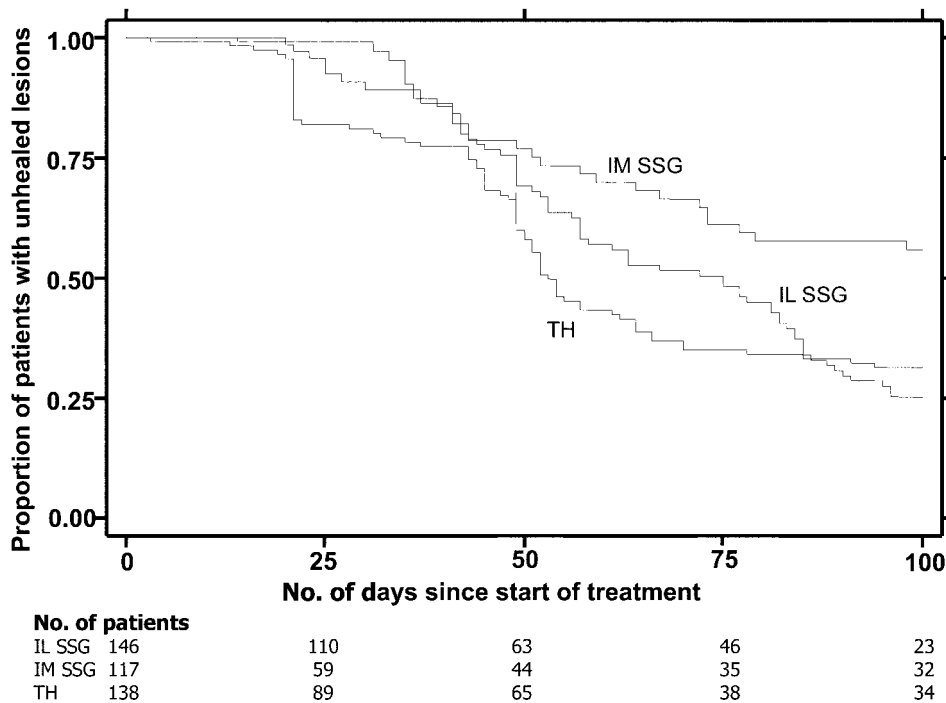


Figure 2. Survival analysis of time to healing of cutaneous leishmaniasis lesions, with data on the no. of patients enrolled in the trial at baseline and 4 other time points. IL, intralesional; IM, intramuscular; SSG, sodium stibogluconate; TH, thermotherapy.

ther the examining clinician nor patients noted a visible difference in the scarring between patient groups after successful treatment.

DISCUSSION

We demonstrate that a single treatment with accurately measured localized heat is as effective as the administration of intralesional SSG and more effective than the administration of intramuscular SSG for the treatment of CL due to *L. tropica*. The time to cure was shown to be shorter with thermotherapy than with SSG regimens in a Kaplan-Meier analysis of data for all study patients. We observed no significant effect of patient characteristics on the cure rate.

Because of the postconflict situation in Afghanistan, enrollment of patients was continuous throughout the study period. The reason the intramuscular SSG treatment group was smaller was that 27 patients who had been randomized to receive intramuscular SSG treatment refused to give consent (figure 1). Due to the social stigma associated with the disease, Kabul residents are very knowledgeable about leishmaniasis. They know that intramuscular SSG injections are painful and are usually given to patients with multiple lesions or lesions on sites where intralesional SSG administration will be difficult. These patients requested intralesional SSG or thermotherapy treatment and were excluded from the trial and given the treatment they requested. Further proof of patients' low acceptance of intramuscular SSG treatment was that the number of patients lost to follow-up during treatment was significantly greater in the intramuscular SSG group than in the intralesional SSG group ($P < .05$), but it was not significantly different after the end of treatment ($P = .58$) (figure 1 and table 2). Though the number of patients lost to follow-up after the end of treatment was not significantly different between treatment groups ($P = .54$) (figure 1), one caveat of our study is that we cannot exclude the possibility that patients dropped out during treatment because lesions were healing and, knowing that they had to face the remaining SSG injections, they did not want to attend further treatment visits. If one assumes that patients lost to follow-up during treatment experienced cure, the cure rate among patients treated with intralesional SSG would be significantly larger than that for patients treated with intramuscular SSG or with thermotherapy; the cure rates in the latter 2 groups would not differ significantly (table 3).

Laboratory studies showed that *Leishmania* parasites do not readily multiply in macrophages at temperatures $>39^{\circ}\text{C}$ in vitro [14, 15]. These observations led to studies investigating the efficacy of thermotherapy treatment of CL with hot-water baths [16], infrared light [17], direct-current electrical stimulation [18], ultrasound [19], and laser light [20–23]. Specifically, 3 studies suggested that thermotherapy with radio-frequency

waves could be effective for CL treatment. In a placebo-controlled trial, thermotherapy (3 treatments of 50°C for 30 s at 7-day intervals) was as effective as antimony therapy (meglumine antimoniate, 850 mg/day for 15 days) in treating *L. braziliensis* and *L. mexicana* infection [24]. Cure rates were identical—73% (16 of 22 patients), in each treatment group, compared with 27% (6 of 22 patients) in the placebo control group—13 weeks after treatment initiation [24]. In a second, uncontrolled study of thermotherapy (a single treatment of 50°C for 30 s) in *L. mexicana*-infected patients, cure rates of 95% (116 of 122 patients) and 90% (172 of 191 patients) were observed 4 and 8 weeks after treatment, respectively [25]. In a case report, a Sudanese patient with multiple *L. tropica* lesions was cured 6 months after receiving thermotherapy (a single treatment of 50°C for 30 s) [26].

However, it is difficult to draw conclusions from these studies. First, they are case studies or include small numbers of patients that preclude in-depth statistical analyses [16, 17, 19, 24, 26]. Second, some followed an undefined study protocol (e.g., they lacked either placebo or control treatment groups) [19, 25, 26]; one study had a short follow-up period that could have excluded relapses [25] and another had a long follow-up period that could have included cases of self-cure [26]. Third, one study included patient groups that were treated with suboptimal durations of antimony treatment (i.e., <20 – 28 treatment days) [24]. Fourth, one study included patients infected with different or unknown *Leishmania* species [24].

There are many reports of successful administration of intralesional antimony to cure Old World CL [4, 5, 27], but only one study in Saudi Arabia compared intramuscular versus intralesional administration of antimony [28]; cure rates were 68% and 73%, respectively, at 30 days after treatment (the difference was not statistically significant). Therefore, to our knowledge, our study is the first that shows that the intralesional route of SSG administration is more effective than the intramuscular route for treatment of Old World CL. This has practical relevance in terms of drug management because, on average, 10 times less drug is used when treating patients intralesionally instead of intramuscularly (R.R., unpublished data). Also, as observed here, patient compliance with intralesional treatment is better, because fewer clinic visits and injections are required. Surprisingly, comparable reported data on cure rates for the treatment of confirmed *L. tropica* infection with antimony are scarce: there is a single study reporting a 76% cure rate 10 weeks after intralesional meglumine antimoniate administration [29].

Localized heat could be an alternative to antimony for the treatment of CL and, in particular, would be very cost-effective in those areas of endemicity where the number of cases of *Leishmania* infection is high and focal (e.g., areas with anthro-

ponotic foci of CL). Reliable data on the cost of leishmaniasis treatment are difficult to obtain and depend on several factors (e.g., whether treatment is given on an inpatient or an outpatient basis and whether cheaper, generic SSG is used); the cost per patient treated range from US\$20 in Afghanistan (R.R. and P. G. Coleman, unpublished data) to US\$280 in Guatemala [30] to >US\$5500 in the United States (N. Aronson, personal communication). The retail price of the thermotherapy device used in the present study is US\$23,450. There are 2 main advantages to the tested thermotherapy protocol, compared with antimony treatment: (1) patient compliance rates are improved because of the lack of potentially serious adverse effects of treatment, because treatment is administered nonparenterally, and because the treatment schedule is shorter (i.e., 1 day, compared with 5–21 injection-days for antimony); and (2) the shorter administration schedule also increases the patient turnover rate, a prerequisite for controlling the patient case load and, hence, disease transmission. The tested thermotherapy method uses a handheld device and limited additional medical equipment, making it suitable for field conditions in areas with rudimentary medical infrastructure; the device, however, needs a power source to recharge the battery. Though we tested the efficacy of thermotherapy on patients with single CL lesions only, patients with multiple lesions could be treated in the same way. Patients with CL lesions adjacent to the eyes and lips will still have to be treated intramuscularly with SSG. Also, *L. tropica* is one of the more temperature-resistant *Leishmania* species [14, 15]. One would expect the thermotherapy method we tested to be more effective against less temperature-resistant *Leishmania* species; this awaits confirmation, for example for *L. major*.

Ultimately, the decision to use thermotherapy will depend on clinical factors (e.g., the location, size, and number of lesions, and the patient's responsiveness to antimony therapy) and patient management factors (e.g., patients' availability for follow-up and the total treatment time per patient). In conclusion, thermotherapy with the tested device proved to be effective, safe, and relatively noninvasive for treating patients with CL in the current postconflict context of Kabul, Afghanistan.

Acknowledgments

We are grateful to HealthNet International (HNI) Khair Khana Clinic staff for logistical support in the trial. We thank Harry Noyes, for the reference strains used in the PCR assays, and Anthony Bryceson, for making valuable comments on the manuscript.

Financial support. The HNI Malaria and Leishmaniasis Control Program is funded by the European Union. This study was supported by the United Nation Children's Fund/United Nation Development Program/World Bank/World Health Organization Special Program for Research and Training in Tropical Diseases, the Afghan Research Evaluation Unit, and the Leveen Family Fund. We are grateful to Thermosurgery Technologies for lending us the instruments for the study.

Potential conflicts of interest. Since March 2004, R. Reithinger has been a part-time employee of Thermosurgery Technologies. All other authors: no conflicts.

References

- World Health Organization. Cutaneous leishmaniasis, Afghanistan. *Weekly Epidemiological Record* **2002**;77:246.
- Reithinger R, Mohsen M, Aadil K, Sidiqi M, Erasmus P, Coleman PG. The burden of anthroponotic cutaneous leishmaniasis in Kabul, Afghanistan. *Emerg Infect Dis* **2003**;9:727–9.
- Reyburn H, Rowland M, Mohsen M, Khan B, Davies CR. The prolonged epidemic of anthroponotic cutaneous leishmaniasis in Kabul, Afghanistan: 'bringing down the neighbourhood.' *Trans R Soc Trop Med Hyg* **2003**;97:170–6.
- Berman JD. Human leishmaniasis: clinical, diagnostic and chemotherapeutic developments in the last ten years. *Clin Infect Dis* **1997**;24:684–703.
- Croft SL, Yardley V. Chemotherapy of leishmaniasis. *Curr Pharm Design* **2002**;8:273–301.
- Croft SL, Coombs GH. Leishmaniasis—current chemotherapy and recent advances in the search for novel drugs. *Trends Parasitol* **2003**;19:502–8.
- Handmann E. Leishmaniasis: current status of vaccine development. *Clin Microbiol Rev* **2001**;14:229–43.
- Boelaert M, Le Ray D, Van Der Stuyt P. How better drugs could change kala-azar control: lessons from a cost-effectiveness analysis. *Trop Med Int Health* **2002**;7:955–9.
- Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. *Trop Med Int Health* **2001**;6:928–34.
- Dowlati Y. Cutaneous leishmaniasis: clinical aspect. *Clin Dermatol* **1996**;14:425–31.
- Reyburn, H. A Guide to the treatment of cutaneous leishmaniasis. Kabul, Afghanistan: World Health Organization, **2000**.
- Noyes H, Reyburn H, Bailey JW, Smith D. A nested-PCR-based schizodeme method for identifying *Leishmania* kinetoplast minicircle classes directly from clinical samples and its application to the study of the epidemiology of *L. tropica* in Pakistan. *J Clin Microbiol* **1998**;36:2877–81.
- Messer G, Spengler U, Jung MC, et al. Polymorphic structure of the tumor necrosis factor (TNF) locus—an NcoI polymorphism in the first intron of the human TNF-beta gene correlates with a variant amino acid in position 26 and a reduced level of TNF-beta production. *J Exp Med* **1991**;173:209–19.
- Berman JD, Neva FA. Effect of temperature on multiplication of *Leishmania* amastigotes within monocyte-derived macrophages *in vitro*. *Am J Trop Med Hyg* **1981**;30:318–21.
- Sacks DL, Barral A, Neva F. Thermosensitivity patterns of Old vs. New World cutaneous strains of *Leishmania* growing within mouse peritoneal macrophages *in vitro*. *Am J Trop Med Hyg* **1983**;32:300–4.
- Neva FA, Petersen EA, Corsey R, Bogaert H, Martinez D. Observations on local heat treatment for cutaneous leishmaniasis. *Am J Trop Med Hyg* **1984**;33:800–4.
- Junaid AJN. Treatment of cutaneous leishmaniasis with infrared heat. *Int J Dermatol* **1986**;25:470–2.
- Sharquie KE, al-Hamamy H, el-Yassin D. Treatment of cutaneous leishmaniasis by direct current electrotherapy: the Baghdadin device. *J Dermatol* **1998**;25:234–7.
- Aram H, Leibovici V. Ultrasound-induced hyperthermia in the treatment of cutaneous leishmaniasis. *Cutis* **1987**;40:350–3.
- Rodriguez ME, Inguanzo P, Ramos A, Perez J. Treatment of cutaneous leishmaniasis with CO₂ laser radiation. *Rev Cubana Med Trop* **1990**;42:197–202.
- Babajev KB, Babajev OG, Korepanov VI. Treatment of cutaneous leishmaniasis using a carbon dioxide laser. *Bull World Health Organ* **1991**;69:103–6.

22. Meawad OB. Selective heat therapy in cutaneous leishmaniasis: a preliminary experience using the 585 nm pulsed dye laser. *J Europ Acad Dermatol Venereol* **1997**; 8:241–4.
23. Asilian A, Sharif A, Faghihi G, Enshaeieh Sh, Shariati F, Siadat AH. Evaluation of CO laser efficacy in the treatment of cutaneous leishmaniasis. *Int J Dermatol* **2004**; 43:736–8.
24. Navin TR, Arana BA, Arana FE, de Mérida AM, Castillo LA, Pozuelos JL. A placebo controlled clinical trial of meglumine antimoniate (Glucantime®) vs. localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *Am J Trop Med Hyg* **1990**; 42:43–50.
25. Velasco-Castrejon O, Walton BC, Rivas-Sanchez B, et al. Treatment of cutaneous leishmaniasis with localized field radio frequency in Tabasco, Mexico. *Am J Trop Med Hyg* **1997**; 57:309–12.
26. Levine N. Cutaneous leishmaniasis treated with controlled localized heating. *Arch Dermatol* **1992**; 128:759–61.
27. Tallab TM, Bahamdani KA, Mirdad S, et al. Cutaneous leishmaniasis: schedules for intralesional treatment with sodium stibogluconate. *Int J Dermatol* **1996**; 35:594–7.
28. Alkhwajah AM, Larbi E, al-Gindan Y, Abahussein A, Jain S. Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. *Ann Trop Med Parasitol* **1997**; 91:899–905.
29. Harms G, Chehade AK, Douba M, et al. A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-gamma in the local treatment of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* **1991**; 85:214–6.
30. Arana BA, Mendoza CE, Rizzo NR, Kroeger A. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. *Am J Trop Med Hyg* **2001**; 65:466–70.