The efficacy of thermotherapy to treat cutaneous leishmaniasis caused by Leishmania tropica in Kabul, Afghanistan: a randomised, controlled trial.

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Abstract

Background: Although pentavalent antimony is the recommended treatment for cutaneous leishmaniasis, its use is problematic because it is expensive and because of potential side-effects associated with the drug during a lengthy and painful course of administration.

Methods: We tested the efficacy of thermotherapy for the treatment of cutaneous leishmaniasis due to Leishmania tropica in a randomized, controlled trial carried out between January and September 2003 in Kabul city, Afghanistan. 401 patients with a single cutaneous leishmaniasis lesion were enrolled and administered thermotherapy using radio frequency waves (one treatment of one or more consecutive 30sec, 50°C applications) or either intralesionally (a total of five, 2-5ml injections every 5-7 days depending on lesion size) or intramuscularly (20mg/kg bodyweight daily for 21 days) with sodium stibogluconate (SSG).

Results: Cure, i.e. complete re-epithelialization at 100 days after the start of treatment, was observed in 69.4% (75/108), 75.3% (70/93) and 44.8% (26/58) of patients receiving thermotherapy, intralesional and intramuscular SSG treatment, respectively. The odds of cure using thermotherapy treatment were 2.80 [95% CI 1.45-5.41] times greater than using SSG intramuscular treatment [p=0.002]. No statistically significant difference was observed in the odds of cure when comparing intralesional SSG and thermotherapy treatments. Odds of cure using intralesional SSG treatment were shown to be 3.75 [95% CI 1.86-7.54] times greater than using intramuscular SSG treatment [p<0.001]. The time to cure was significantly shorter in thermotherapy than in intralesionally or intramuscularly SSG-treated patients (median, 53 days, 75 days, >100 days, respectively; p=0.003).

Conclusions: Thermotherapy is an effective, comparatively well tolerated and rapid treatment for cutaneous leishmaniasis due to L. tropica and should be considered as an alternative method of treatment to antimony.

Keywords:

Leishmaniasis, Leishmania tropica, treatment, sodium stibogluconate, thermotherapy, radio frequency, control, Afghanistan.

INTRODUCTION

The leishmaniases are a group of diseases, transmitted to humans by the bite of phlebotomine sand flies. In terms of global burden of disease, they are the third most important vector-borne disease after malaria and lymphatic filariasis, with an estimated 2.1 million Disability Adjusted Life-Years and 51,000 deaths per annum [1]. There has been a dramatic increase in the number of human leishmaniasis cases not only in leishmaniasis-endemic countries [2], but also in people originating from non-endemic areas, such as tourists [3], humanitarian aid workers [4], or soldiers [5].

The world-wide largest focus of cutaneous leishmaniasis (CL) is in Kabul city, Afghanistan, where Leishmania tropica is anthroponotically transmitted by Phlebotomus sergenti and where the estimated annual case load has been between 67500 and 200000 patients over the past decade [6-8]. Due to the limited resources available during and after the civil war in Afghanistan, the treatment of CL patients by the local Ministry of Health (MoH) and non-governmental organizations still remains the only strategy to control the epidemic.

Pentavalent antimonials, i.e. sodium stibogluconate (SSG) and meglumine antimoniate, are the mainstay of anti-leishmanial therapy [9-11]. A leishmaniasis vaccine does not exist [12]. In leishmaniasis-endemic countries, antimonials are typically administered intramuscularly (at a dosage of 20mg/kg/day for 20-28 days) or intralesionally (dosage dependent on lesion size) [9,10]. However, antimonials can have serious –though usually reversible- side-effects (e.g. pancreatitis, hepato- and cardiotoxicity) when given intramuscularly [9,10] and are relatively expensive even in countries were generic anti-leishmanial drugs have been registered (e.g. in Afghanistan the cost per CL patient treated with generic SSG is $US20 [Reithinger, unpublished]; the total health expenditure by the MoH is $US2 per person-year) [13].

Moreover, the invasiveness of the standard procedure, a lengthy course of painful inoculations, means that patients are prone to default their full treatment course. Low compliance appears to be the principal reason behind the observed emergence of drug-resistant parasite strains, especially in areas of anthroponotic leishmaniasis transmission, e.g. India, Sudan and Nepal [14]. Hence, research is now focusing on the development of alternative treatments using different dosage schedules (e.g. 10mg/kg daily antimony), drugs (e.g. fluconazole, miltefosine, paromomycin) or methods of treatment (e.g. immunotherapy) [11]. One promising approach maximizing patient compliance and minimizing treatment duration is thermotherapy using radio frequency waves, with cure rates of >73% in clinical trials with L. mexicana and L. braziliensis [15,16]. Because of the high purchasing cost of the thermotherapy device (US$23450), this treatment is of limited use in endemic areas where Leishmania transmission is zoonotic (i.e. case numbers tend to be moderate and geographically dispersed, e.g. L. mexicana). However, such a treatment could be cost-effective in areas where Leishmania transmission is anthroponotic (i.e. case numbers tend to be large and focalized, e.g. L. tropica).

We evaluated the efficacy of thermotherapy against 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 (HNI) Khair Khana clinic in Kabul, Afghanistan. This clinic has been operational since 1995 and is the main leishmaniasis diagnosis and treatment centre in Kabul [7,8], with 4751 new and 25783 follow-up patients treated in 2003. Eligible patients were patients attending the clinic for leishmaniasis treatment and who had only one suspected CL lesion. Inclusion criteria were an age of more than five years; the presence of one, parasitologically confirmed CL lesion; and no prior history of the disease and/or antimonial leishmaniasis treatment. Exclusion criteria were a CL lesion located on or immediately adjacent to the nose, lips or eyes; pregnancy; breast feeding; major surgery in the last three months; presence of any un-controlled medical condition; and anticipated unavailability for follow-up. Most of the patients were current Kabul residents.

Study Design and Procedures

The study was a randomized, controlled trial. There was no placebo group, as this would have been unethical due to the severity of CL that L. tropica can cause and the social stigma associated with the disease [7,8]. The London School of Hygiene and Tropical Medicine Ethics Committee and the Afghan MoH approved the study protocol and consent form. According to general HNI policy, all medical services provided during the study were free-of-charge.

To detect a 20 percent difference in the cure rate between the SSG and thermotherapy groups, assuming a 80 percent cure rate in the SSG groups [9-11], with a 90 percent power and a 5 percent two-sided type I error, 98 subjects were needed in each group. To compensate for anticipated loss to follow-up, 40 percent more patients were enrolled in each group. Patients

coming to the clinic for single CL lesion treatment were briefed about the study, its aims and protocol. A patient was enrolled into the study after written consent had been given. The patient then proceeded to pick one of three identical pieces of cardboard out of a hat (the cardboard had been labeled with different treatments codes on one of its sides, the codes being non-visible to the patient); after a patient was randomly assigned a particular treatment, the picked cardboard was returned to the hat. The assigned treatments were: (i) intralesional administration of a total of five, 2-5ml injections (depending on lesion size) of generic SSG (Albert David, Calcutta, India) every 5-7 days for a total of up to 29 days; (ii) daily intramuscular administration of 20mg/kg bodyweight (up to a maximum daily dose of 850mg) SSG for 21 days; (iii) a single thermotherapy treatment (one or more consecutive 30sec, 50°C applications depending on lesion size).

Both intramuscular and intralesional administration of SSG are the standard WHO-recommended CL treatment in Afghanistan [17]. For intralesional treatment, SSG was infiltrated around the lesion until complete blanching of the lesion and its margin was obtained [17]. For thermotherapy, the lesion and a 15-20mm border of healthy skin around the lesion was cleaned with stabilised 0.1% chlorine dioxide solution, anaesthetised with 1% lidocaine HCl and moistened with sterile saline solution prior to application of localised heat with a portable, battery-operated, localised current field radio frequency generator (ThermoMed 1.8^{TM}, Thermosurgery Technologies Inc., Phoenix, U.S.A.) according to the manufacturer's instructions. The generator has a 501K clearance by the United States Food and Drugs Administration for the treatment of CL. It produces a 6.78mHz frequency, which is applied via a handset including an applicator gauge with two electrodes that are placed onto the diseased skin. The area between the electrodes covers between 49 and 73mm^2 depending on the applicator gauge size used. Thus, several consecutive thermotherapy applications may be

required to cover a whole lesion. Once treatment begins, the temperature is measured by a thermistor embedded in one of the electrodes; it ensures 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.

Prior to 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 calliper. The status of each lesion was evaluated during 4 patient follow-up visits, the trial end point being 100 days after start of therapy. Lesions with a secondary bacterial infection before, during or after treatment were treated with topical antibiotics; if systemic antibiotic treatment was required, patients received treatment with antibiotics with no anti-leishmanial activity (e.g. erythromycin). The rates of side-effects were evaluated blindly by patient interviews and physical examinations during each follow-up visit.

Treatment efficacy was measured by the percentage of patients cured at 100 days after the start of therapy, and by time to cure. Cure was defined as the complete re-epithelialization of the CL lesion with no evidence of papules, inflammation or induration. Patients that failed to 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. Microscopic examination was performed blindly, on scrapings from the edge of the lesion that had been smeared onto a slide. The slide was dried, fixed with methanol, stained with Giemsa and then examined under the microscope at x100

171 magnification for presence of Leishmania amastigotes. For PCR, lesion scrapings were
172 preserved in ethanol at -20°C prior to DNA extraction using a QIAamp DNA mini kit (Qiagen,
173 Crawley, U.K.). Samples were amplified in a nested PCR with Leishmania-specific kinetoplast
174 minicircle primers according to published conditions [18]; this protocol differentiates the major
175 Leishmania spp. in Central Asia, i.e. L. tropica, L. major and L. infantum, by amplification
176 product size. Amplification products were analysed by electrophoresis on 2% agarose gels. Each
177 PCR included negative (no DNA, DNA from an uninfected person) and positive (water-lysates of
178 reference strain cultures) controls. To evaluate sample degradation or PCR inhibition, sample
179 DNA was also amplified for a 740 bp fragment of the human TNFB gene [19]. Separate areas
180 were used for DNA extraction, PCR preparation and product analysis to avoid cross-
181 contamination.
182
183 **Statistical Analysis**
184 All patient data was entered into Microsoft Excel (Microsoft Corporation, Seattle, U.S.A.)
185 at the end of the trial. A Chi square test was used to test for significance ($p<0.05$) between
186 proportions (e.g. gender, patients lost to follow-up). All other analyses were done in STATA 6.0
187 (Stata Corporation, College Station, U.S.A.). A Kruskal-Wallis test was used to test for
188 significance between pre-trial (e.g. age, body weight, lesion size, lesion duration) characteristics
189 of treatment groups. The effects of the different treatments on the proportion of patients cured
190 by 100 days were tested by logistic regression. The analyses incorporated the effect of
191 explanatory variables such as gender, age, lesion size, lesion location along with treatment
192 type. The significance of each variable was tested by backwards variable deletion, i.e. by
193 observing whether these variables explained a significant ($p<0.05$) proportion of the deviance
194 remaining after their removal from the model. Variables were removed from the models in

order of least significance until only significant variables ($p<0.05$) were retained in the minimum adequate model. The Kaplan-Meier method was used for the analysis of time to healing; to compare the three treatment healing curves, the log-rank test was used.

RESULTS

A total of 431 patients were enrolled into the study between January and September 2003. After random allocation of treatment, 30 patients decided to withdraw from the study (Figure 1). A total of 401 patients started treatment: 146, 117 and 138 patients received intralesional, intramuscular and thermotherapy treatment, respectively.

Baseline Patient Characteristics

All treated patients had lesions that were parasitologically confirmed by microscopy. A subset of lesion scrapings (n=39) was taken from patients for parasite identification using PCR. All samples yielded amplification products for the human TNFB gene fragment. 27/39 (69%) samples were PCR-positive for Leishmania DNA; all 27 were identified as L. tropica from the size of the PCR product. Of all patients, 200 and 201 were male and female, respectively; median age was 13 years (interquartile range: 10 to 20), median body weight was 39 kg (24 to 51), median lesion diameter was 12 mm (7 to 20) and median lesion duration was 6 months (3 to 7) (Table 1). The lesions were primarily located on the face (43.4%), then hands (38.2%), legs (15.9%) and arms (2.4%). No statistically significant differences were observed in gender, age, body weight, lesion size, or lesion duration between the treatment groups. Follow-up for patients completing the trial was a median 13, 21, 49, 85 days for the first, second, third and fourth follow-up visit, respectively.

Efficacy

A total of 259 (63.8%) patients completed treatment and the four-visit, 100 days follow-up period: 108, 93 and 58 patients, respectively, had been treated with thermotherapy, intralesional and intramuscular SSG (Figure 1). When compared with the thermotherapy cohort, the odds of patients lost to follow-up either during or after the end of treatment was 2.04 times (95% CI 1.18–3.57; p<0.01) and 3.70 times (95% CI 2.04–6.67; p<0.001) greater in the intralesional and intramuscular treatment groups, respectively. Intramuscularly-treated patients were 1.78 times more likely to be lost to follow-up than those treated intralesionally (95% CI 1.05–3.03; p<0.05).

Complete re-epithelialization of the CL lesion by 100 days was observed in 75/108 (69.4%), 70/93 (75.3%) and 26/58 (44.8%) of patients treated with thermotherapy, intralesional or intramuscular SSG, respectively. None of the patients with complete healing relapsed during the 100 days study duration. No statistically significant association of age, sex, body weight, lesion size, lesion location or lesion duration was shown on trial outcome. Odds of cure using thermotherapy were 2.80 [95% CI 1.45-5.41] times greater than using intramuscular treatment [p=0.002]. No statistically significant difference was observed between the odds of cure using intralesional or thermotherapy treatment [OR=1.34, 95% CI 0.72-2.50, p=0.359]. Odds of cure using intralesional treatment were 3.75 [95% CI 1.86-7.54] times greater than using intramuscular treatment [p<0.001].

According to the Kaplan-Meier survival analysis (which analyses all available data, including patients who dropped out during treatment), the time to cure was significantly shorter in thermotherapy than in intralesionally or intramuscularly-treated patients (median, 53 days, 75 days, >100 days, respectively; p=0.003 by the log-rank test) (Figure 2).

Secondary infections were noted in 8 thermotherapy-treated (2 before and 6 after treatment), 5 intralesionally-treated (2 before and 3 after start of treatment) and 2 intramuscularly-treated (1 before and 1 after start of treatment) patients, but the differences were not statistically significant; all secondary infections resolved with antibiotic treatment. Excluded from the study after the start of treatment were two intralesionally-treated patients because of bradycardia and an undefined local reaction to the treatment respectively, and three intramuscularly-treated patients because of bradycardia, tachycardia and palpitation respectively. In the thermotherapy-treated patients, the ulceration immediately and up to two weeks after treatment was often greater than the original ulcer, with patients suffering superficial second degree burns where the electrodes were applied; thereafter, the lesion closed rapidly (Figure 2). This observation may explain the low follow-up rate in thermotherapy-treated patients in the first two weeks after treatment (83% [25/30] of the total thermotherapy patients lost to follow-up were lost in the first two weeks), as patients may have become disheartened to seek further medical advice when lesions became bigger. Though not done blindly, neither 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 in Afghanistan. The time to cure was shown to be shorter with thermotherapy than with intralesional or intramuscular SSG

regimens in a Kaplan Meier analysis of all study patients. There was no significant effect of the patient characteristics on the cure rate.

Due to the present post-conflict situation in Afghanistan, enrolment of patients had to be continuous throughout the study period. The reason why the patient group given intramuscular SSG treatment was smaller was that 27 patients that had been randomly allocated intramuscular SSG treatment refused to give consent and participate in the study (Figure 1). Due to its potentially stigmatizing impact, Kabul residents are very knowledgeable about leishmaniasis, so-called saldana ('one-year sore'). They know that the 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 to be treated with intralesional SSG or thermotherapy, and were excluded from the trial and treated accordingly. Further proof for the low patient acceptance of the intramuscular SSG treatment is that, whereas not significantly different after the end of treatment ($p=0.58$), the number of patients lost to follow-up during treatment was significantly greater in the intramuscular SSG than in the intralesional SSG treatment group (OR 1.89; 95% CI 1.06-3.38; $p<0.05$) (Figure 1). Though the number of patients lost to follow-up after the end of treatment was not significantly different between the three treatment groups ($p=0.11$) (Figure 1), one caveat of our findings is that we cannot exclude the possibility of patients dropping out during treatment because lesions were healing and –knowing that they had to face remaining intralesional or intramuscular injections- they did not want to attend further treatment. If one assumes that all patients lost to follow-up cured (Figure 1), the number of patients that cured when treated with intralesional SSG or thermotherapy would not be statistically different (OR 1.68; 95% CI 0.89-3.17; $p=0.11$) as would the number of patients treated with intramuscular SSG and thermotherapy (OR 0.83; 95% CI 0.46-1.52; $p=0.63$). Based on this scenario, the number of patients cured when treated

289 with intralesional SSG would be significantly larger than those treated with intramuscular SSG
290 (OR 2.01; 95% CI 1.06-3.85; p<0.05).

291 Early laboratory studies showed that Leishmania parasites do not readily multiply in
292 macrophages at temperatures >39°C in vitro [20,21]. These observations led to several studies
293 investigating the efficacy of thermotherapy in treating CL using either hot water baths [22],
294 infrared light [23], direct current electrical stimulation [24], ultrasound [25], and laser [26-28].
295 In particular, three studies suggested that thermotherapy using radio frequency waves could be
296 effective for CL treatment. In a placebo-controlled trial, thermotherapy (three treatments of
297 50°C for 30sec at seven day intervals) was shown to be as effective as antimony (meglumine
298 antimoniate, 850mg/day for 15 days) in treating L. braziliensis and L. mexicana-infected
299 patients, with identical 73% (16/22) cure rates for each treatment compared to 27% (6/22) for
300 the placebo control 13 weeks after start of treatment [15]. In a second, uncontrolled study,
301 cure rates of 95% (116/122) and 90% (172/191) were observed in L. mexicana-infected
302 patients four and eight weeks post-treatment with thermotherapy (single treatment of 50°C for
303 30sec), respectively [16]. In a case report, a Sudanese patient with multiple L. tropica lesions
304 was cured at six months post-thermotherapy (single treatment of 50°C for 30sec) [29].
305 However, it is difficult to draw any conclusions from above studies as they (i) are case studies
306 or include small numbers that do not allow for in-depth statistical analyses [15,22,23,25,29]; (ii)
307 followed an undefined study protocol (e.g. lack either placebo or control treatment groups
308 [16,25,29]; short follow-up period could exclude relapses [16]; long follow-up period could
309 include self-cure [29]); (iii) included patient groups that were treated with sub-optimal dosages
310 of antimony (i.e. <20-28 days of antimony administered) [15]; and (iv) included patients
311 infected with different or unknown Leishmania spp. [15].

Many reports exist of successful intralesional antimony administration to cure CL [9,30], but only one study compared intramuscular versus intralesional antimony administration [31], with 68% and 73% cure rates at 30 days post-therapy, respectively. Our study, therefore, is the first to show that the intralesional route of SSG administration is more effective than the intramuscular route. This has practical relevance in terms of drug management as, on average, ten times less drug is used when treating patients intralesionally instead of intramuscularly (Reithinger, unpublished). Also, as observed here, patient compliance with intralesional treatment is better, as fewer clinic visits and injections are required. Surprisingly, comparable reported data on cure rates for the treatment of confirmed L. tropica cases with antimony is scarce, with one single study reporting a 76% cure rate ten weeks after intralesional meglumine antimoniate administration [32].

Localized heat could be an alternative to antimony in the treatment of CL and, in particular, would be very cost-effective in those endemic areas where the number of Leishmania cases is high. Reliable leishmaniasis treatment costs are difficult to obtain and depend on several factors (e.g. in- or out-patient basis treatment; use of cheaper, generic SSG), ranging from US$20 in Afghanistan (Reithinger et al., unpublished) to US$280 in Guatemala [33] to >US$5500 in the U.S.A. (Aronson, personal communication) per CL patient treated. The retail price of the thermotherapy device used here is US$23450. There are two main advantages of the tested thermotherapy protocol compared to antimony treatment: (i) patient compliance rates are improved due to the lack of potentially serious treatment side-effects, non-parenterally administered treatment and shorter treatment schedule (i.e. a one-day treatment compared to 5 to 21 injection-days for antimony); and (ii) the shorter administration schedule would also increase patient turnover rates, a pre-requisite for controlling the patient case load and, hence, disease transmission. Tested thermotherapy used a handheld device and

limited additional medical equipment, which makes this form of therapy suitable for field conditions or in areas with rudimentary medical infrastructure; the device, however, needs a power source to re-charge 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 have to be continued to be treated intramuscularly with SSG. Also, L. tropica is one of the more temperature-resistant Leishmania spp. [20,21]. One would expect tested thermotherapy to be more effective against less temperature-resistant Leishmania spp., such as L. major; however, future studies will have to confirm this hypothesis. Ultimately, the decision to use thermotherapy will depend on clinical (e.g. lesion location, size and number; patient responsiveness to antimony) as well as patient-management factors (e.g. patient availability for follow-up; total treatment time per patient).

In conclusion, thermotherapy with the tested device proved to be effective, safe, and relatively non-invasive to the patient with single CL lesions. Future studies to further develop current thermotherapy protocol (e.g. efficacy of thermotherapy on patients with multiple lesions) will be carried out before using thermotherapy as alternative to SSG in HNI operational programs for treating CL patients in Afghanistan.

Authors Contributions

R Reithinger, C R Davies and J R David designed the study; M Mohsen managed patient recruitment, treatment randomization and patient case recording forms; M Wahid managed patient care throughout the study; M Bismullah carried out the microscopic examination and lesion scrapings; R J Quinnell carried out the PCR; R Reithinger, M Mohsen and J Kolaczinski supervised the study; R Reithinger and C R Davies analysed the data; all authors contributed to writing the paper.

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The authors designed the study and had full access to the data. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. Thermosurgery Technologies Inc. provided HNI two thermotherapy devices on a loan-basis for the study. Reported results were presented at the Annual Meeting of the American Society of Tropical Medicine and Hygiene, Philadelphia, December 7-11, 2003.

Conflict of Interest

Since March 2004, R Reithinger is part-time employee of Thermosurgery Technologies Inc.

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TABLE 1. PRE-TREATMENT PATIENT CHARACTERISTICS.

	Intralesional SSG	Intramuscular SSG	Thermotherapy	P ‡
Number of patients	146	117	138	
(Males, Females)	(67, 79)	(63, 54)	(70, 68)	
Age*	13	13	14	0.75
	(8.25 – 22)	(10 – 22)	(10 – 20)	
Body weight in kg*	36	38.5	40	0.70
	(22 – 50)	(26 – 51.25)	(24 – 51)	
Lesion size in mm*	12.75	13.75	10.25	0.11
	(7 – 20)	(8 – 22.5)	(7 – 20)	
Lesion duration in months*	6	5.5	6	0.19
	(3 – 7)	(3 – 7)	(3.75 – 8)	

*Median and interquartile range in brackets. ‡ A Kruskal Wallis rank test was used to compare difference in pre-treatment patient characteristics.

FIGURE 1. TRIAL PROFILE

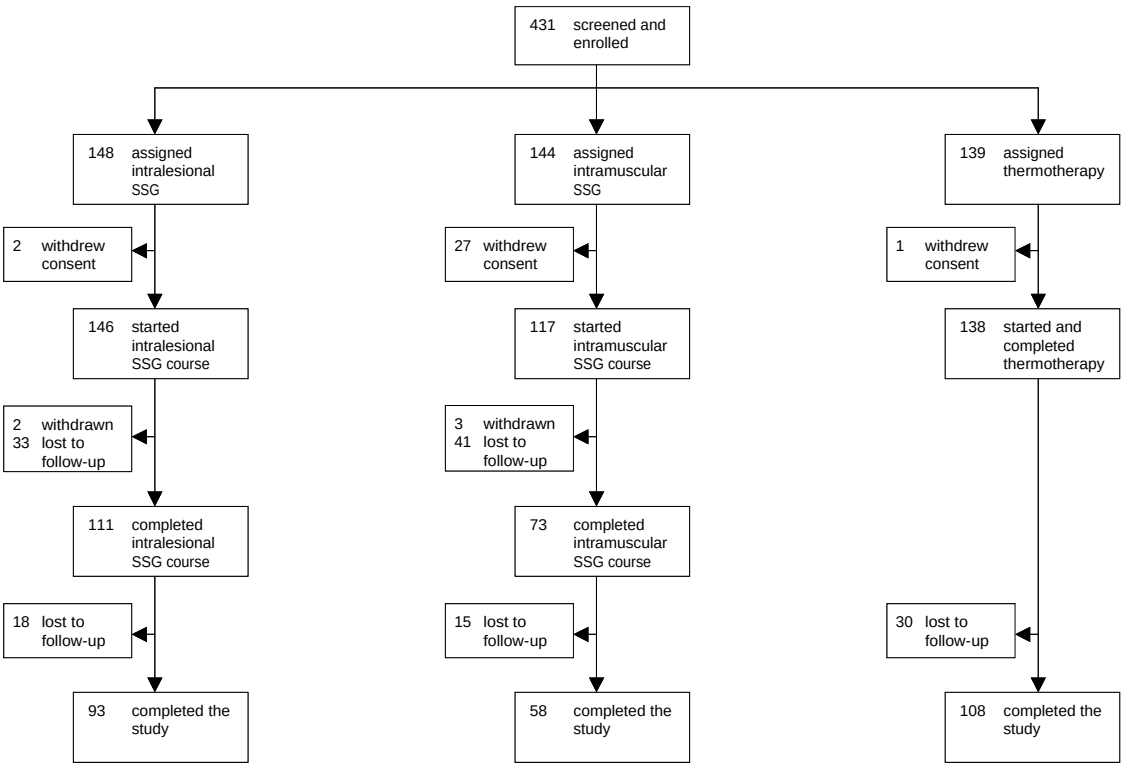
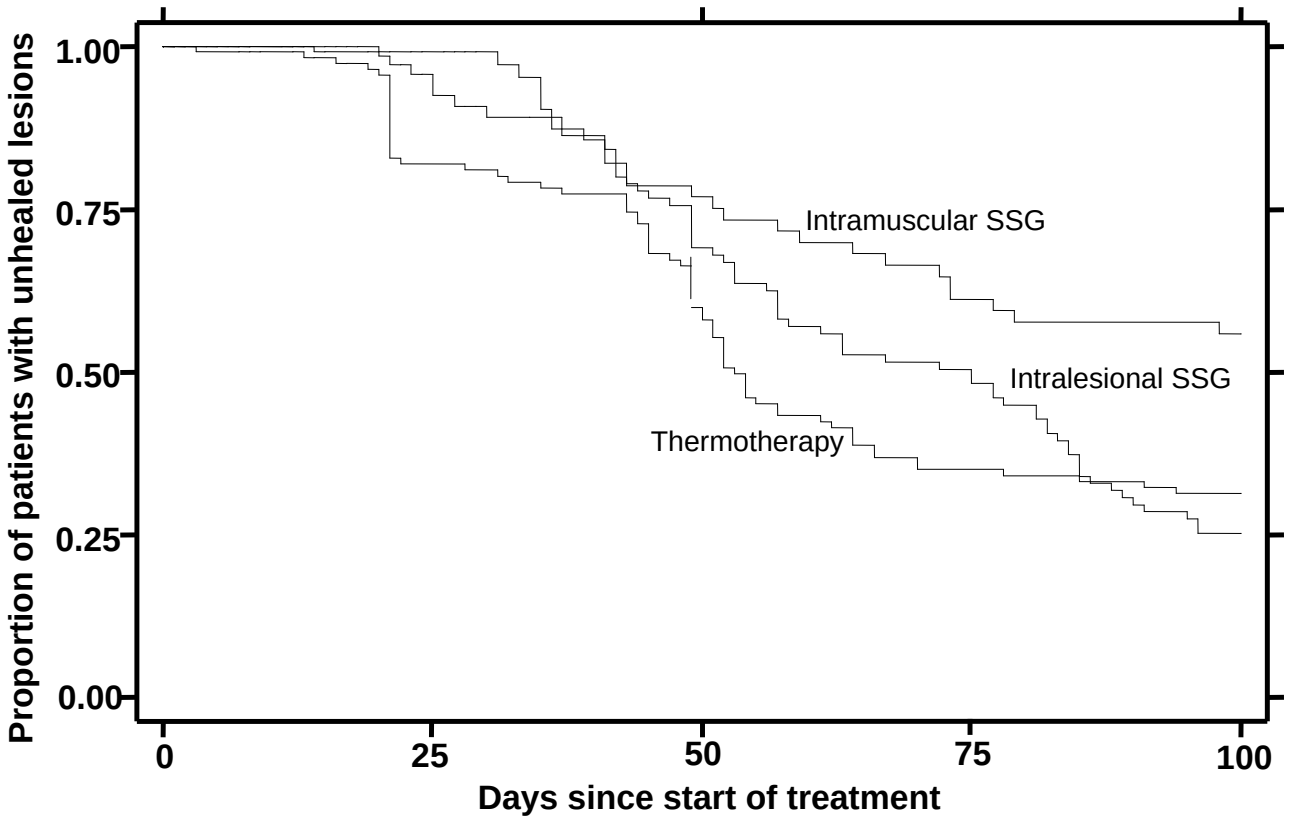


FIGURE 2. SURVIVAL ANALYSIS OF TIME TO HEALING



At risk					
IL	146	110	63	46	23
IM	117	59	44	35	32
TH	138	89	65	38	34

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