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# THERMOTHERAPY EFFECTIVE AND SAFER THAN MILTEFOSINE IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS IN COLOMBIA

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## SUMMARY

In Colombia, pentavalent antimonials and miltefosine are the drugs of choice for the treatment of cutaneous leishmaniasis; however, their toxicity, treatment duration, (treatment adherence problems), cost, and decreased parasite sensitivity make the search for alternative treatments of American cutaneous leishmaniasis necessary. Based on the results found in a controlled, open, randomized, phase III clinical trial, the efficacy and safety of miltefosine was compared to that of thermotherapy for the treatment of cutaneous leishmaniasis in Colombia. Adult patients from the Colombian army participated in the study; they received either 50 mg of miltefosine three times per day for 28 days by the oral route (n = 145) or a thermotherapy (Thermomed®) application of 50 ºC for 30 seconds over the lesion and surrounding area (n = 149). Both groups were comparable with respect to their sociodemographic, clinical, and parasitological characteristics. The efficacy of miltefosine by protocol and by intention to treat was 70% (85/122 patients) and 69% (85/145 patients), respectively. The adverse effects were primarily gastrointestinal for miltefosine and pain at the lesion site after treatment for thermotherapy. No statistically significant difference was found in the efficacy analysis (intention to treat and protocol) between the two treatments. ClinicalTrials.gov: NCT00471705**.**

**KEYWORDS:** Thermotherapy; Cutaneous leishmaniasis; Miltefosine; Treatment; Efficacy; Safety.

## INTRODUCTION

Leishmaniasis is a disease produced by parasites of the genus *Leishmania*; it is transmitted by female insects of the genus *Lutzomyia* in the Americas or *Phlebotomus* in the Old World, and it affects humans and domesticated and wild mammals[2,4,17]. It is endemic in over 95 countries, the majority of which are classified as developing. It is estimated that worldwide, around 12 million individuals are infected with *Leishmania*[35]. Cutaneous Leishmaniasis (CL) is the clinical manifestation presented by the majority of cases around the world, and there is approximately 1 to 1.5 million new cases every year[2,17,35]. In Colombia, a re-emergence of leishmaniasis has been seen since 2005, making the country second in the Americas for highest number of cases. From 2005-2008, there were 61,120 cases diagnosed, of which 34,262 (56.1%) occurred in military personnel of the National Army.

Since the 1940's, pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) have been the drug of choice for the treatment of CL; however, their toxicity, treatment period of 20 days that leads to treatment adherence issues, high cost, and progressively decreasing therapeutic response make necessary the search for alternative treatments[8,27].

In the search for therapeutic alternatives, various oral medications have been evaluated, such as dapsone[18], ketoconazole[12,21], mefloquine[9], and allopurinol[31], none of which were shown to be adequately effective. An additional difficulty in the interpretation of results of clinical trials is the lack of methodological unity, which hinders their comparison[3,8].

Miltefosine (hexadecylphosphocholine) is an oral medication initially developed as an anti-tumoral agent[28] that later showed *in vitro* and *in vivo* activity against *Leishmania* spp[5,6,15,28,37]. In India, where resistance to antimonial agents is very high, miltefosine has been used since 1998 for the treatment of Visceral Leishmaniasis (VL) produced by *L. donovani*[7,24]. This has motivated its evaluation for the treatment of other leishmaniasis[25]. In Colombia, two studies have been conducted for the treatment of CL. The first is a phase I-II study with a reported cure rate by protocol of 66% in individuals who received a dose of 50-100 mg/day and of 95% in individuals who received a dose of 133-150 mg/day[23]. The second study was a multicenter study (Colombia and Guatemala) where miltefosine was compared against a placebo; this study showed contradictory results. In Colombia, the cure rate by protocol was 91%, but in Guatemala, the rate was 53%. Even though the sample size was small and the number of strains very small, the difference in the therapeutic response between both countries was attributed to the predominant *Leishmania* species of each country: *Leishmania (Viannia) panamensis* in Colombia, but *L. (V.) braziliensis* and *L. (L.) mexicana* in Guatemala. However, recent studies conducted in Colombia show

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that *L. (V.) braziliensis* and *L.* (*V.*) *panamensis* are the two species that produce the majority of cases in Colombia and that they occur in a similar proportion; however, *L.* (*V.*) *panamensis* predominates in the northeast of the country (Andean region) and *L. (V.) braziliensis* predominates in the southeast (PECET. Unpublished data). Based on the previous study, the Ministry of Social Security of Colombia authorized the registry and use of miltefosine, and it has been used for the treatment of different clinical forms of leishmaniasis.

On the other hand, studies conducted in different countries have shown that the localized application of heat by using Thermomed® equipment may achieve a cure rate that varies from 70 to 94%. The Thermomed® is an operator, with special devices which achieve and maintain a temperature of 50 ºC. The electrodes are placed locally in the lesion for 30 seconds, the device produces heat waves through radio frequency technology, which extends them to deeper layers of the skin, causing destruction of the amastigotes[10,11,16,19,30]. In Colombia, there has only been one report of the use of thermotherapy in the treatment of CL in a study that focused on patients with an *L. guyanensis* from the Andean region; however, the elevated number of participant follow-up losses (81%) decreased the power of the study and did not allow for a conclusive efficacy result[29].

This data analysis from a controlled phase III clinical trial was conducted with the aim of comparing the efficacy and safety of miltefosine with that of a single thermotherapy application in the treatment of CL in Colombia. The trial evaluated the efficacy and safety of miltefosine and thermotherapy as compared to meglumine antimoniate for the treatment of cutaneous leishmaniasis.

## MATERIALS AND METHODS

**Study design.** The study was an open, randomized, phase III clinical trial, in which the efficacy and safety of miltefosine and thermotherapy were compared. Register ClinicalTrials.gov: code number NCT00471705.

**Population and study site.** The study was conducted between June 2006 and April 2008. The study subjects were adult males who were part of the Colombian army. The study was conducted at five military health care establishments located in the northeast, center, and south of Colombia.

**Inclusion criteria.** Patients who were included had: a) a confirmed parasitological diagnosis of leishmaniasis; b) no previous history of receiving treatment for the current infection; c) normal renal, hepatic, pancreatic, and hematologic tests; and d) voluntarily accepted participation in this study.

**Exclusion criteria.** Patients with a) serious concomitant diseases; b) lesions with mucosal involvement; c) 10 or more cutaneous lesions and a negative Montenegro test; and/or d) cutaneous lesions located less than 2 cm from the nasal, oral, lip border, eyes, urogenital orifice, and/or anal mucosa.

**Interventions.** Miltefosine (Impavido®, Zentaris Frankfurt-Germany) in a 50 mg capsule was administered orally three times per day after meals for 28 days for a total dose of 4,200 mg per patient. A single thermotherapy (Thermomed®, Thermosurgery inc. Phoenix-USA) session was administered, consisting of applications at 50 ºC over the lesion and surrounding areas for 30 seconds with prior asepsis and local 2% lidocaine anesthesia without epinephrine. The number of applications depended on the lesion size, and each time, heat was applied to the entire lesion area. Following thermotherapy, an antibiotic ointment (fucidic acid) was applied to the lesions and dressed with sterile gauze to prevent secondary infections over the next 10 days.

**Data collection, clinical samples, and strain identification of *Leishmania*.** After signing voluntary participation consent, all of the patients were assigned a clinical record with demographic information, lesion data, and review of inclusion/exclusion criteria. A photographic registry of all the lesions was obtained, and clinical samples were taken for the identification of *Leishmania* species via PCR-RFLP, following previously published protocols[13,20].

**Treatment group assignment.** Assignment to each treatment group was randomized. A list of randomly generated treatments, in blocks of eight, was made (EpiInfo 3.1). Only the study coordinator had access to the list and was in charge of assigning the treatments.

**Follow-up and outcome.** During the study, the participants who received miltefosine were evaluated by research personnel at the beginning, middle (day 15), and end of treatment (day 29), as well as six weeks, three months, and six months post treatment. Patients who received thermotherapy were evaluated at the beginning, day 10, and day 20, as well as six weeks, three months, and six months post treatment. Renal, hepatic, pancreatic, and hematologic function tests were obtained before treatment, in the middle, and at the end of treatment. Evaluation of adverse events was conducted based on the usual criteria for the evaluation of adverse reactions in cancer therapy v.3 (CTCAE)[26].

Response to treatment was clinically evaluated. The following definitions were used for each lesion:

*Initial cure:* Complete re-epithelization of all ulcers and the complete disappearance of induration up to three months following the termination of treatment.

*Definitive cure*: Initial cure plus the absence of recurrence at six months after completing treatment.

*Treatment failure*: a) Increase in lesion size greater than 50% by the end of treatment; b) Absence of clinical response at six weeks, which is a decrease in the lesion area to less than 50% upon final treatment evaluation; c) any sign of lesion activity at three months after completing treatment; or d) development of mucosal leishmaniasis (ML).

*Relapse*: Reactivation of the lesion at the original site after scar formation.

Rescue therapy for all participants who experienced treatment failure was the administration of meglumine antimoniate (Glucantime®, Aventis, Paris, France) with a dose of 20 mg/Sb5/K/d for 20 days, as established by MOH Colombia guidelines.

**Statistical analysis**: Data entry and analysis were performed using ACCESS and SPSS version 15, respectively. Participant characteristics were tabulated and analyzed by treatment group. The efficacy of treatments was calculated by intention to treat and by protocol. The relative risk was calculated using 2 x 2 tables. The $X^2$ test or Fisher's

exact test were used for hypothesis testing on dichotomous variables. Taking into account the distribution of variables, the Student's t-test or Mann-Whitney U-test were used to analyze continuous data. Potential confounding factors and interactions were controlled using a stratified analysis of species of the parasite responsible for the infection, number, anatomical location, type of lesion, and geographical location of the infection. Survival analysis methods (Kaplan-Meier and Log-rank test) were used to compare disease-free times between the two treatments. A $p < 0.05$ was considered significant for all analyses, and a confidence of 95% was used for the construction of all intervals.

## RESULTS

There were 294 patients who accepted voluntary participation and were included in the study and randomly assigned; 145 received miltefosine and 149 received thermotherapy. In the miltefosine group, two patients (1%) did not complete treatment due to side effects, and 21 (14%) were lost by the 6-month follow-up; for this reason, at the end, only 122 (84%) completed the study. In the thermotherapy group, two patients (1%) decided not to participate in the study after randomization, 18 (13%) were lost by the 6-month follow-up, and 134 (90%) completed the study (Fig. 1).

**Baseline analysis:** As observed in Table 1, the demographic, clinical, and parasitological characteristics of the participants were similar between both study groups, except for type of lesion.

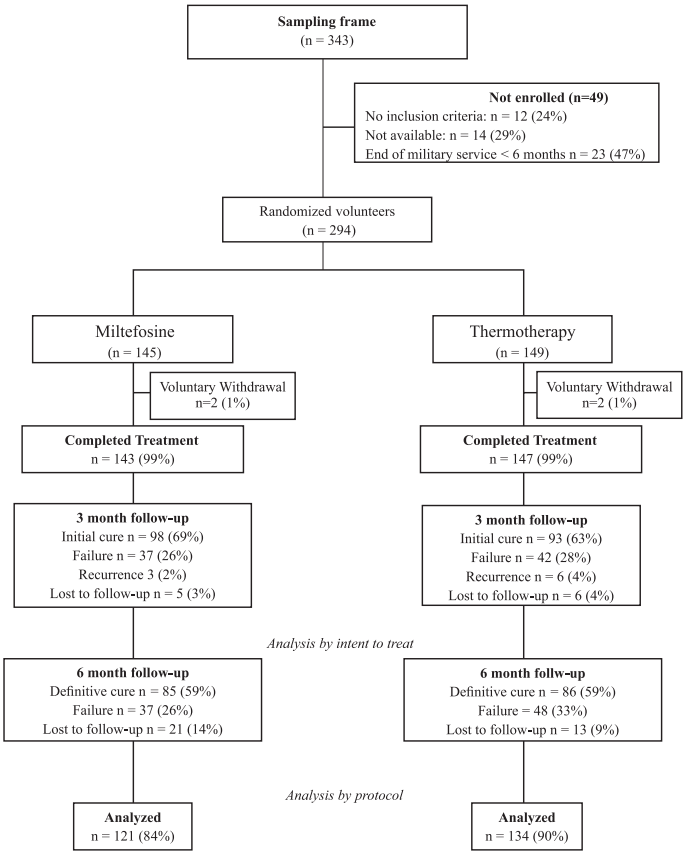


**Fig. 1 -** Flow diagram of the volunteer study participants.

### Therapeutic response

*Initial cure:* Three months after completion of treatment, 98 (68.5%) and 93 (63.2%) of the patients treated with miltefosine and thermotherapy were cured, respectively.

*Definitive cure:* the number of patients who were cured is shown in Table 2, which is organized by treatment and by type of analysis.

At six months after completion of treatment, 85 (69.5%) and 86 (64.5%) of the volunteers receiving miltefosine and thermotherapy, respectively, had a complete cure from all lesions (analysis by protocol). By intention to treat, the efficacy was 59.4% for the group that received miltefosine and 58.5% for the group treated with thermotherapy. There were not found differences between the scars of patients who received miltefosine or thermotherapy.

**Analysis by group:** In 164 (56%) patients, the *Leishmania* species responsible for infection was isolated and identified; 81 of the patients were treated with miltefosine, in whom 30 (37%) and 51 (63%) of the isolated strains were identified as *L. (V.) panamensis* and *L. (V.) braziliensis,* respectively. Of the group treated with thermotherapy, the strain was identified in 83 patients, in whom 24 (29%) and 59 (71%) of the strains were *L. (V.) panamensis* and *L. (V.) braziliensis*, respectively.

Cure rates in the miltefosine group were 60% for *L. (V.) panamensis and* 49% for *L. (V.) braziliensis*. The cure rate for the thermotherapy group was 58% for *L. (V.) panamensis* and 53% for *L. (V.) braziliensis.* No significant difference was found for treatment efficacy between the species responsible for infection (miltefosine $p = 0.3$, thermotherapy $p = 0.6$).

Also, there was no association found between treatment efficacy and characteristics, such as number, anatomical location, lesion type, or geographical location in Colombia where the infection occurred (Table 3).

**Recurrence:** Three (2.1%) and six (4.1%) of the patients treated with miltefosine and thermotherapy, respectively, had recurrences.

**Safety:** Localized and systemic adverse events seen in our study are summarized in Table 4.

Mid-way through treatment, miltefosine was associated with a greater occurrence of headache, vomiting, nausea, and anorexia, and at the end of treatment with a greater frequency of myalgia, arthralgia, headache, vomiting, nausea, and anorexia. Thermotherapy was associated with pain at the lesion site following the application of treatment.

We were able to determine that there is no association of either of the two treatments with changes in renal (Creatinine and BUN), hepatic (AST and ALT), and blood (hemoglobin, hematocrit, erythrocytes, leukocytes, and platelets) tests, neither mid-way through the treatment nor at the end. However, the proportion of changes in lab results for hepatic and pancreatic tests was greater in the miltefosine group.

**Serious adverse events:** One volunteer from the miltefosine group developed hematemesis, which was medically treated until the patient's recovery.

**Table 1**
Baseline characteristics of volunteers

| Characteristics | | **miltefosine n = 145** | **Thermotherapy n = 149** | ***p*-value*** |
|---|---|---|---|---|
| Age (years) (Median [min - max]) | | 23 (19 - 37) | 23 (19 - 39) | 0.9† |
| Race (%) | White | 14 (10) | 22 (14) | 0.25 |
| | Black | 9 (6) | 13 (9) | |
| | Mestizo‡ | 116 (80) | 104 (70) | |
| | Mulatto§ | 6 (4) | 10 (7) | |
| Weight (Kg) (Median [min - max] ) | | 64 (47 - 90) | 65 (42 - 104) | 0.8† |
| History of leishmaniasis (%) | Yes | 63 (43) | 67 (45) | 0.79 |
| | No | 82 (57) | 82 (55) | |
| Geographical place of infection | Northeast | 15 (10) | 16 (11) | 0.91 |
| | Southeast | 130 (90) | 133 (89) | |
| Number of lesions (%)** | 1 | 101 (70) | 115 (77) | 0.14 |
| | 2 or more | 44 (30) | 34 (23) | |
| Type of lesion (%) | Nodule | 9 (5) | 19 (11) | 0.04 |
| | Ulcer | 182 (95) | 161 (89) | |
| Anatomical location of lesion | Upper body | 117 (81) | 123 (83) | 0.68 |
| | Lower body# | 28 (19) | 26 (17) | |
| Evolution time (days) (Median [min – max] ) | | 60 (15 - 1080) | 85 (10 - 690) | 0.7† |
| Species (%) | *L. (V.) panamensis* | 30 (37) | 24 (29) | 0.27 |
| | *L. (V.) braziliensis* | 51 (63) | 59 (71) | |

* Chi square test; † Mann Whitney test; ‡ person who is born from one white parent and one indian parent; § person who is born from one white parent and one black parent; ** According to number of lesions;# This category includes 18 volunteers who presented with lesions to the upper and lower body; 8 and 10 from the miltefosine and thermotherapy groups, respectively

**Table 2**
Efficacy of miltefosine and thermotherapy. Analysis by protocol and by intention to treat

| Analysis | Miltefosine | | Thermotherapy | | *p*-value* |
|---|---|---|---|---|---|
| | Cure / Total | Efficacy (%) CI 95% | Cure / Total | Efficacy (%) CI 95% | |
| Intention to treat | 85/145 | 59 (50 - 67) | 86/149 | 58 (49 - 66) | 0.9 |
| By protocol | 85/122 | 70 (61 - 78) | 86/134 | 64 (55 - 73) | 0.4 |

*Chi square test.

**Survival analysis:** The time free of disease for both treatments is shown in Figure 2. No difference was found between the cumulative survival rates of patients who received miltefosine and those who received thermotherapy ($p = 0.2$).

## DISCUSSION

The efficacy of miltefosine, 70% by intention to treat and 59% per protocol, differs with previous studies conducted in Colombia where the efficacy of the protocol was 91%, but it is similar to that found in Guatemala where it was 53%[22].

The differences in therapeutic response in the previous study in Colombia and Guatemala were attributed to the species of *Leishmania* predominant in each country[22]. The data for Colombia, however, was mainly based on historical records, given that only seven isolated strains were identified in the study from the 73 study participants, and all were identified as *L. (V.) panamensis*. In this study, we included a larger number of patients than previous studies. Additionally, both species of *Leishmania* causing the majority of leishmaniasis cases in the country were present, and there were no significant differences in treatment response between the species responsible for the infection. However, we did observe a decreased therapeutic response in patients with *L. (V.) braziliensis*, of whom 49% were cured versus 53% of patients with *L. (V.) panamensis*. A similar situation was observed for thermotherapy treatment.

Thermotherapy showed an efficacy of 58% and 64% in the analysis by intention to treat and by protocol, respectively. This result was comparable to that obtained in Kabul, Afghanistan, where the efficacy by protocol was found to be 69.4%[19] and less than that found in other studies where localized heat was applied in various dosages.

The Thermomed® equipment gives and maintains localized heat of 50 degrees Celsius at the application site[1] and has the advantage of being completed in one to four sessions, decreasing the adherence problems faced by other treatments. Also, it does not have systemic side effects, so

**Table 3**
Efficacy of miltefosine and thermotherapy stratified by parasite species, anatomical location, number and type of lesion, and geographical location of infection

| Characteristics | Efficacy/total volunteers (%) Miltefosine | *p*-value** | Efficacy/total volunteers (%) Thermotherapy | *p*-value** |
|---|---|---|---|---|
| Overall efficacy | 85/145 (59) | - | 86/149 (58) | - |
| **History of leishmaniasis** | | | | |
| Yes | 45/63 (71) | 0.04 | 45/67 (67) | 0.05 |
| No | 39/82 (48) | | 42/82 (51) | |
| **Species** | | | | |
| *L. (V.) panamensis* | 18/30 (60) | 0.3 | 14/24 (58) | 0.6 |
| *L. (V.) braziliensis* | 25/51 (49) | | 31/59 (53) | |
| **Number of lesions** | | | | |
| 1 | 60/101 (59) | 0.5 | 70/115 (61) | 0.3 |
| 2 or more | 24/44 (55) | | 17/34 | |
| **Anatomical location of lesions** | | | | |
| Upper body | 66/117 (56) | 0.4 | 73/123 (59) | 0.6 |
| Lower body† | 18/28 (64) | | 14/26 (54) | |
| **Geographical place of infection** | | | | |
| Northeast | 10/15 (67) | 0.5 | 6/16 (38) | 0.08 |
| Southeast | 74/130 (57) | | 81/133 (60) | |

** Chi square test; † This category includes 18 volunteers who presented with lesions on the upper and lower parts of the body; 8 and 10 from the miltefosine and thermotherapy groups, respectively.

**Table 4**
Incidence and relative risk of local and systemic adverse events presented at the end and middle of treatment

| Test/Event | | Middle of treatment Miltefosine | Middle of treatment Thermotherapy | RR (CI 95%) | End of treatment Event or Test/Total volunteers (%) Miltefosine | End of treatment Event or Test/Total volunteers (%) Thermotherapy | RR (CI 95%) |
|---|---|---|---|---|---|---|---|
| Adverse Events | Fever | 8/130 (6) | 4/124 (3.22%) | 1.91 (0.59 - 6.18) | 8/129 (6) | 4/132 (3) | 2.05 (0.63 – 6.63) |
| | Myalgia | 9/130 (7) | 3/124 (2.41%) | 2.86 (0.79 - 10.33) | 16/129 (12) | 4/132 (3) | 4.1 (1.41 – 11.91)* |
| | Arthralgia | 9/130 (7) | 3/124 (2.41%) | 2.86 (0.79 - 10.33) | 13/129 (10) | 3/132 (2) | 4.43 (1.29 – 15.2)* |
| | Headache | 23/130 (18) | 10/124 (8.1%) | 2.19 (1.09 - 4.42) | 30/129 (23) | 13/132 (10) | 2.36 (1.29 – 4.32)* |
| | Vomiting | 29/130 (22) | 3/124 (2.41%) | 9.22 (2.88 - 29.50)** | 44/129 (34) | 2/132 (2) | 22.51 (5.57 – 90.9)** |
| | Nausea | 38/130 (29) | 5/124 (4.03%) | 7.25 (2.95 - 17.82)** | 59/129 (46) | 4/132 (3) | 15.1 (5.65 – 40.34)** |
| | Anorexia | 19/130 (11) | 5/124 (4.03%) | 3.62 (1.40 - 9.41)* | 37/129 (29) | 6/132 (5) | 6.31 (2.76 – 14.44)** |
| | Diarrhea | 0/130 (0) | 0/124 (0%) | - | 6/129 (5) | 1/132 (2) | 6.14 (0.75 – 50.29) |
| | Abdominal pain | 0/130 (0) | 0/124 (0) | - | 9/129 (7) | 0/132 (0) | - |
| | Lesion pain | 14/130 (9) | 27/124 (22) | | 11/129 (9) | 18/132 (14) | 0.63 (0.31 – 1.27) |
| | Lesion infection | 5/130 (4) | 9/124 (7) | 0.53 (0.18 - 1.54) | 5/129 (4) | 11/132 (8) | 0.47 (0.17 – 1.3) |
| | Lesion vesicles | 0/130 (0) | 4/124 (3) | - | 0/129 (0) | 5/132 (4) | - |
| | Pruritus | 0/130 (0) | 0/124 (0) | - | 3/125 (2) | 4/125 (3) | 0.75 (0.17 – 3.28) |
| Blood chemistry | ↑ Creatinine | - | - | - | 1/103 (2) | 0/80 (0) | - |
| | ↑ BUN | - | 1/83 (2) | - | 3/103 (3) | 2/80 (3) | 1.17 (0.2 – 6.81) |
| | ↑ AST | 1/114 (2) | 1/93 (2) | 0.82 (0.05 - 12.98) | 5/103 (5) | 2/75 (2.67) | 1.82 (0.36 – 9.13) |
| | ↑ ALT | 1/114 (2) | 1/93 (2) | 0.82 (0.05 - 12.87) | 10/104 (10) | 5/73 (6.84) | 1.4 (0.5 – 3.94) |
| | ↑ Amylase | 15/111 (14) | 6/87 (7) | 1.96 (0.79 - 4.84) | 11/102 (7) | 7/70 (10) | 1.08 (0.44 – 2.65) |
| Hematology | ↓ Hemoglobin | - | - | - | 1/102 (2) | 1/78 (1.28) | 0.76 (0.05 – 12.04) |
| | ↓ Erythrocytes | 1/105 (2) | 4/82 (5) | 0.20 (0.02 - 1.71) | 1/102 (2) | 1/75 (1.33) | 0.74 (0.05 – 11.57) |
| | ↓ Leukocytes | 2/115 (2) | 0/96 (0) | - | 1/105 (2) | 0/79 (0) | - |
| | ↓ Platelets | - | - | - | - | 1/79 (1.27) | - |

* < 0.05; ** < 0.001.

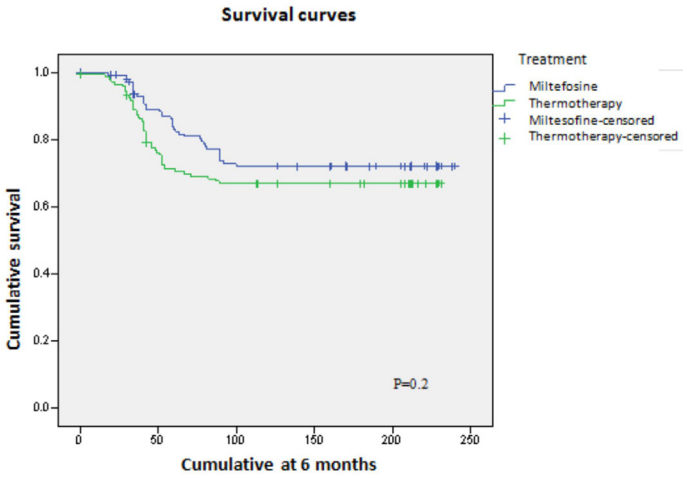


**Fig. 2 -** Cumulative survival estimates for absence of disease for each treatment.

it does not require paraclinical analysis, patients need not be in treatment or in convalescence for extended periods of time, and it can also be used in patients with renal, hepatic, or cardiac alterations, as well as in women who are pregnant, breastfeeding, or of child-bearing age, all of whom are disqualified from conventional treatment with pentavalent antimonials or miltefosine.

In addition, ethno-medical studies in indigenous and farming communities in Latin America show extensive and empirical use of locally applied caustic agents (gunpowder, hot sugar cane, silver nitrate, petroleum, and battery acid) or cauterization with hot metallic instruments, such as spoons or the edge of an ax, which they apply over the lesions, achieving, in many cases, lesion scarring[14,33,34].

The association between miltefosine and gastrointestinal adverse events, such as nausea, vomiting, anorexia, abdominal pain, and diarrhea, reported in previous studies was confirmed[24,32]. With respect to safety in the thermotherapy group, the only reported adverse event was pain at the site of heat application, which was controlled with common analgesics and did not persist for longer than one week after heat application.

In India, Miltefosine is the first oral agent that has shown a good efficacy for the treatment of visceral leishmaniasis caused by *L. (L.) donovani*, or Kala-azar. However, it´s use for CL treatment in the New World is limited. Some of its inconveniences are as follows: current cost (about 670 USD), which is greater than that of antimonials, long treatment period (28 days) leading to adherence problems, lack of adherence leading to strain resistance, teratogenicity, which complicates its administration to women of child-bearing age because adequate contraception must be guaranteed during treatment and up to three months after treatment, gastrointestinal adverse effects in over 30% of patients, and finally, as seen in this study, efficacy inferior to that of pentavalent antimonials, which continue to have an efficacy rate of 85.1% in Colombia[32].

The results of this study show that the efficacy of thermotherapy in single doses is similar to that of oral miltefosine with a duration of 28 days for the treatment of CL in Colombia ($p = 0.9$), and its toxicity is lower.

One of the criticisms against the use of local therapy in the treatment of patients with CL caused by species of the *Viannia* subgenre is the possibility of developing ML. In the case of Colombia, the necessity for prescribing systemic treatment to all patients is debatable, given that the incidence of ML in the country is less than 0.5%, despite the fact that the great majority of patients with CL who reside in rural areas far away from a health care center are empirically treated with caustic agents. In these populations, it is estimated that only 10% of patients with CL receive treatment with antimonials, and even then, the incidence of ML is very low. In addition, systemic treatment does not guarantee the absence of ML[14,33,34,35].

However, the cure rate seen in our study with one dose of thermotherapy is not sufficiently large enough to recommend it as treatment. In the clinical studies where greater cure rates have been seen, the patients received two or three heat therapy sessions.

We believe that further clinical studies should be conducted with thermotherapy using an increased number of heat application sessions or in combination with other local medications.

In American CL, the dissemination of parasites through the lymphatic system happens early at the beginning of the lesion. In patients with less than three months of disease evolution, 90% present with lymphadenopathies; however, ML cases are rare. In any case, all local treatments should be accompanied by patient education regarding early detection of lesion reactivation signs and possible mucosal complications so that they may consult their physician and reserve systemic treatments for these cases.

## FUNDING

This study was financed by the Ministry of Social Protection of the Republic of Colombia, which did not participate in the design, execution, or report.

## CONFLICTS OF INTEREST

None declared.

## ETHICAL APPROVAL

The protocol was approved by the Committee of Bioethics for human research of the University Research Headquarters (CBEIH-SIU) of the University de Antioquia and by the Ethics Committee of the Directorate General of Health of the Colombian army. The clinical trial was developed following the international guidelines for good clinical practice (GCP).

## RESUMEN

### Termoterapia efectiva y más segura que la miltefosina en el tratamiento de la leishmaniasis cutánea en Colombia

En Colombia antimoniales pentavalentes y miltefosina son los medicamentos de primera elección para el tratamiento de la leishmaniosis cutánea; sin embargo**,** su toxicidad, duración (que lleva a problemas de adherencia), costo y la disminución de la sensibilidad de los parásitos a los mismos, hacen necesaria la búsqueda de nuevas alternativas de tratamiento para la leishmaniosis cutánea americana. A partir de resultados derivados de un ensayo clínico controlado abierto,

aleatorizado, fase III, se comparó la eficacia y seguridad de la miltefosina con la de la termoterapia, para el tratamiento de la leishmaniosis cutánea en Colombia. Adultos pertenecientes al Ejército de Colombia participaron el estudio. Miltefosina, una cápsula de 50 mg tres veces día durante 28 días, vía oral (n = 145). Termoterapia (Thermomed®) aplicación de 50 ºC/30´´ sobre la lesión y el área circundante (n = 149). Ambos grupos fueron comparables en características sociodemográficas, clínicas y parasitológicas. Eficacia de la miltefosina por protocolo 70% (85/122 pacientes) y 69% (85/145 pacientes) por intención a tratar. Termoterapia eficacia por protocolo 64% (86/134 pacientes) y 58% (86/149 pacientes) por intención a tratar. En miltefosina los eventos adversos fueron principalmente de tipo gastrointestinal y en termoterapia se encontró dolor en el sitio de la lesión luego del tratamiento. En el análisis de eficacia (intención a tratar y protocolo) no se encontró diferencia estadísticamente significativa entre los tratamientos evaluados. ClinicalTrials.gov: NCT00471705**.**

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