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Jaiberth Antonio Cardona-Arias, Liliana López-Carvajal, Mery Patricia Tamayo Plata, Iván Darío Vélez

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ARTICLE

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Cost-effectiveness analysis of thermotherapy versus pentavalent antimonials for the treatment of cutaneous leishmaniasis

Jaiberth Antonio Cardona-Arias[1,2] | **Liliana López-Carvajal**[3] | **Mery Patricia Tamayo Plata**[4] | **Iván Darío Vélez**[3]

[1]School of Medicine, Cooperative University of Colombia, Medellín, Colombia

[2]School of Microbiology, University of Antioquia, Medellín, Colombia

[3]PECET, University of Antioquia, Medellín, Colombia

[4]School of Economics and Finance, EAFIT University, Medellin, Colombia

Correspondence
Iván Darío Vélez, PECET, University of Antioquia. Calle 62 No. 62-59, Lab 632- Medellin, Colombia.
Email: idvelez@pecet-colombia.org

Abstract

Objective: The treatment of cutaneous leishmaniasis is toxic, has contraindications, and a high cost. The objective of this study was to estimate the cost-effectiveness of thermotherapy versus pentavalent antimonials for the treatment of cutaneous leishmaniasis.

Methods: Effectiveness was the proportion of healing and safety with the adverse effects; these parameters were estimated from a controlled clinical trial and a meta-analysis. A standard costing was conducted. Average and incremental cost-effectiveness ratios were estimated. The uncertainty regarding effectiveness, safety, and costs was determined through sensitivity analyses.

Results: The total costs were $66,807 with Glucantime and $14,079 with thermotherapy. The therapeutic effectiveness rates were 64.2% for thermotherapy and 85.1% for Glucantime. The average cost-effectiveness ratios ranged between $721 and $1275 for Glucantime and between $187 and $390 for thermotherapy. Based on the meta-analysis, thermotherapy may be a dominant strategy.

Conclusion: The excellent cost-effectiveness ratio of thermotherapy shows the relevance of its inclusion in guidelines for the treatment.

KEYWORDS

Antimony sodium gluconate, Colombia, cost-effectiveness analysis, cutaneous leishmaniasis, thermotherapy

1 | INTRODUCTION

Leishmaniasis is a disease caused by protozoan parasites of the genus *Leishmania*, family Trypanosomatidae, with three main clinical forms: cutaneous, mucosal, and visceral. From an epidemiological standpoint, the disease is characterized by being endemic in 99 countries. A total of 12 million infections, with 2 million incident cases per year, are estimated. Regarding visceral leishmaniasis, the estimated lethality rate is 10%, with between 20,000 and 40,000 deaths per year. These figures are underestimated due to underdiagnosis, the lack of active surveillance, the high number of asymptomatic infections, and the fact that most endemic countries do not have a mandatory notification system.[1–4]

Cutaneous leishmaniasis is the most frequent worldwide; 75% of cases occur in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, and Peru.[4] This form of the disease characteristically starts with papules that become nodules and ulcers, which are related to disability, scars, stigmatization, psychosocial problems, and economic losses from an inability to work and lost work days.[1,5,6]

The standard treatment of cutaneous leishmaniasis is based on pentavalent antimonials, mainly sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®), although there are various therapeutic resources, such as thermotherapy and topical, local, and systemic treatments.[7] Treatment with pentavalent antimonials has been questioned due to the recording of multiple adverse consequences, such as cardiac, liver, kidney, and hematological

toxicity, sometimes leading to patient death, pancreatitis, myalgia, and arthralgia, along with problems of therapeutic adherence.[8,9] Antimonial treatment is contraindicated in multiple populations, such as infants, pregnant women, and children and in patients with chronic problems, and contraindicated due to the high cost associated with the treatment itself and the management of the medication's side effects.[10–19]

Faced with the above problems, multiple local treatments have been explored, among which thermotherapy stands out due to certain advantages, such as the low number of adverse effects and contraindications and good adherence; it is safer than pentavalent antimonials, as it results in fewer side effects and has good effectiveness in empirical applications in rural communities, controlled clinical trials, and meta-analyses.[20–26] In addition, thermotherapy significantly reduces the cost entailed in the management of cutaneous leishmaniasis for the Social Security Health System. The cost per patient with Glucantime (treatment of choice) is $38, whereas the cost is less than $20 with thermotherapy.[2] However, it is clear that these values do not include the cost of personnel, diagnostic aids, and other resources required to provide treatment and to monitor patient safety.

The background outlined above supports the hypothesis that thermotherapy may be the most cost-effective strategy for the treatment of cutaneous leishmaniasis, as it has a similar therapeutic effectiveness but with significantly lower costs. Indeed, unlike the first-line treatment, its implementation does not include diagnostic aids, such as electrocardiograms and laboratory tests for hematological, kidney, pancreatic, and liver profiles. Thermotherapy requires fewer visits by the medical team and reduces the costs associated with the management of adverse effects of pentavalent antimonials.

Notwithstanding the above, a full economic assessment for thermotherapy in the treatment of cutaneous leishmaniasis has not been conducted; based on a review of economic assessments, the lack of research on this topic was corroborated. In this regard, a search on EBM Reviews - NHS Economic Evaluation Database generated 11 results on leishmaniasis, two of which do not correspond with economic assessments; the remaining nine were based on comparing the cost of medication against the visceral form of the disease,[27] costs of active case detection,[28] cost-effectiveness analysis of prevention strategies,[6] analysis of the combination of therapies for visceral leishmaniasis in India,[29,30] the implementation of a treatment program against the cutaneous form of the disease,[31] a medication policy against the visceral form of leishmaniasis,[32] a vaccine for the visceral form in India,[33] and a vaccine for cutaneous leishmaniasis in seven American countries.[34] From this search, it was concluded that in the economic assessments on leishmaniasis, seven correspond to cost-effectiveness studies, only two assessments were conducted on the cutaneous form, three have compared treatments, and none have analyzed thermotherapy. This search was extended to PubMed, ScienceDirect, Web of Science, Wiley, Scielo, Lilacs, and OVID, with the inclusion criterion that the terms "*Cutaneous leishmaniasis*" & "*Thermotherapy*" were in the title, abstract or keywords; but no difference in results was observed.

The aim of this research was to estimate the cost-effectiveness ratio of thermotherapy compared with pentavalent antimonials for the treatment of cutaneous leishmaniasis in Colombia from an institutional standpoint.

2 | MATERIAL AND METHODS

2.1 | Type of study

Cost-effectiveness analysis.

PICO question: Population, Intervention, Comparison, and Outcome.[8]

2.1.1 | Population

Soldiers from five health centers of the armed forces of Colombia in the Northeast, South, and Central regions of the country, with confirmed diagnosis of cutaneous leishmaniasis, without mucosal involvement, without previous treatment for this infection, and with normal kidney, liver, and hematological function tests, were included in this study. Patients with comorbidities, with 10 or more lesions, and with involvement of sites close to the nasal or oral mucosa, eyes, and anal or urogenital openings (less than 2 cm) were excluded. A total of 255 patients participated and were randomly assigned to each arm of the study based on a calculation of the sample size with effectiveness rates of 78% for thermotherapy and 90% for meglumine antimoniate, a confidence interval of 95%, a power factor of 80%, and a sampling correction of 20%.[8]

In addition, the population of eight studies of a meta-analysis of controlled clinical trials assessing the effectiveness of thermotherapy in the treatment of cutaneous leishmaniasis[26] was included in this study.

2.1.2 | Intervention

Thermotherapy involved the local application of heat (radiofrequency) at 50°C for 30 sec three in a single session using ThermoMed® (Thermosurgery Inc., Phoenix, AZ, USA) on the active center and edges until the entire lesion was covered. Prior asepsis and local anesthesia were applied with Xylocaine 2%, followed by fusidic acid treatment for 10 days.[8]

2.1.3 | Comparison

Pentavalent antimonials, sodium stibogluconate, and meglumine antimoniate.

2.1.4 | Outcomes

The primary outcome was effectiveness or proportion of cured patients, ie, with the disappearance or re-epithelialization of lesions and complete loss of indurated lesions until three months after treatment ended, without reactivation of the lesion or appearance of mucosal involvement for six months following the completion of treatment. The secondary outcomes included data on treatment safety, consisting of local side effects, such as pain, burning, itching, erythema, edema, and swelling at the site of administration, and systemic side effects, such as myalgia, fever, anorexia, headache, arthralgia, generalized rash, and laboratory abnormalities in blood counts, blood chemistry, and liver function tests.[8]

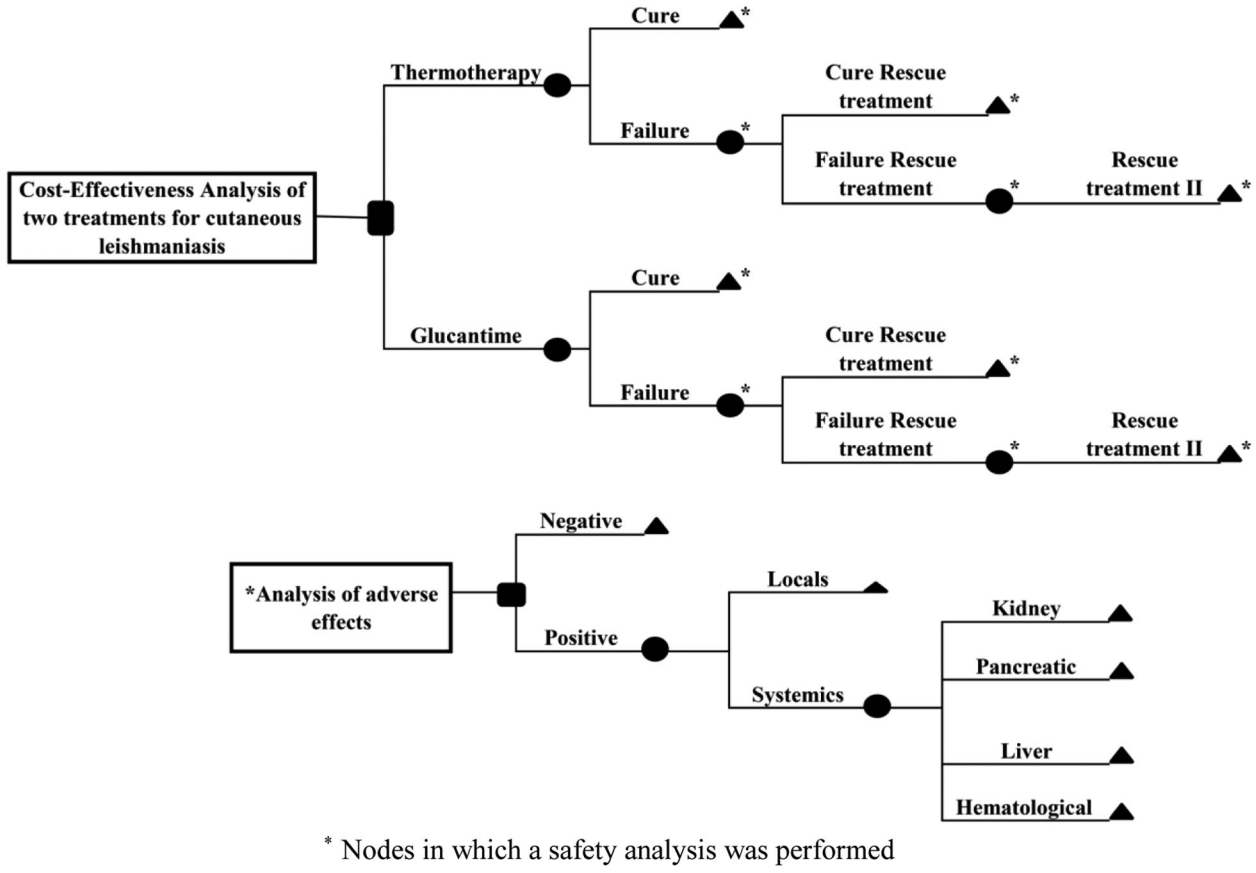

FIGURE 1 Decision tree for the analysis of therapeutic effectiveness and safety

2.2 | Analytical decision model

The decision tree presents different clinical courses that can occur with both treatments. The first tree includes the comparison of therapeutic effectiveness; a binary result of cure or therapeutic failure is presented in the following tree. Where a failure occurred, a rescue treatment with meglumine antimonate was provided according to the guidelines for treatment of leishmaniasis of the Ministry of Health of Colombia. The decision tree is finalized at that point because the probability of failure in a second rescue treatment approaches zero. The assessment of secondary outcomes was performed for every decision node and at the end of each possible course of action described in Figure 1. The base year was 2015, assuming a duration of one year for the follow-up of patients requiring rescue treatments.

The safety analysis assessed adverse effects according to the Common Terminology Criteria for Adverse Events v.3 (CTCAE).[35] It should be noted that in the thermotherapy arm, there are no systemic effects attributable to the treatment; however, they were included in this assessment so as not to skew the monitoring of those effects within the clinical trial.

2.3 | Data sources

Secondary data source was used to measure the effectiveness and safety of the intervention; the data were collected from a randomized controlled phase III clinical trial developed by PECET.[8] Additionally, the group of researchers performed a meta-analysis to provide additional data on the effectiveness of thermotherapy.[26]

The costing was conducted from an institutional perspective through two methods validated by two clinical studies: (i) standard costing, including only the prices of the intervention (medication, doctor, nurse, and diagnostic aids) and the management of side effects (without considering costs associated with patients undergoing rescue treatment), and (ii) costing based on patient monitoring; this form includes intervention prices, the management of side effects, rescue treatments, and the management of their adverse effects.

For myalgia, arthralgia, fever, and headache, the price of analgesic and antipyretic treatment was included, usually for six days, with three pills of acetaminophen per day. In case of abdominal pain, two pills of omeprazole were provided for 6 or 10 days according to the patient's symptoms. However, for the treatment of vomiting, nausea, anorexia, and diarrhea, three pills of metoclopramide for two days and oral rehydration salts three times a day for two days were provided. The following were included among systemic effects: the cost of tests, such as blood urea nitrogen (BUN); creatinine blood tests for patients with renal effects; amylase test for pancreatic effects; aspartate and alanine transaminase tests (AST and ALT) for liver effects; and hemoglobin, red blood cells, leukocytes, and platelet count for hematological effects. However, it should be noted that these tests are normally performed to monitor the toxicity of antimonials and to choose a treatment if toxicity occurs.

Unit prices of standardized pricing manuals for Colombia, such as SOAT (Compulsory Traffic Accident Insurance - Seguro Obligatorio de Accidentes de Tránsito) and SISMED (Drug Price Information System - Sistema de Información de Precios de Medicamentos), were used. In the case of Glucantime, experts who validated the protocol considered that its price was higher than the price included in this study.

The costs were converted to US dollars, estimated from the exchange rate projected for 2013 of $1 = $1900 COP, without applying any annual discount rate, given that the time period of the study was less than a year.

2.4 | Cost-effectiveness analysis

The summary measure used for cost-effectiveness analyses was the cost-effectiveness ratio, in terms of the average (cost/effects) for each intervention and in terms of incremental costs to estimate the additional cost per effectiveness unit reached.[36]

$$\text{Incremental Cost Effectiveness Ratio (ICER)} = \frac{\Delta C}{\Delta E}$$

$$= \frac{\text{A Costs} - \text{B Costs}}{\text{A Effectiveness} - \text{B Effectiveness}}$$

2.5 | Sensitivity analysis

To analyze the inherent uncertainty of the parameters and the way they affect the outcomes, one-way and multivariate sensitivity analyses were performed based on the limits of the confidence intervals obtained in therapeutic effectiveness and safety, whereas price adjustments for the procurement of healthcare services in Colombia were used to analyze costs. Four univariate sensitivity analyses were developed: (i) according to changes in the therapeutic effectiveness of the controlled clinical trial (limits of the confidence interval), (ii) based on the effectiveness reported in the meta-analysis, (iii) with the variation in the results of safety (proportion of adverse effects), and (iv) with the variations in prices used in the procurement of health services in Colombia of 25%, 30%, and 48%; thus, the findings shown are adjusted to the reality of the country's payment and procurements.[37] Subsequently, the multivariate sensitivity analysis was conducted based on the combinations of effectiveness, safety, and reported costs.

2.6 | Ethical aspects

The principles of the Declaration of Helsinki, Resolution 8430 of 1993 of the Colombian Ministry of Health, and Resolution 2378 of 2008 were taken into account.

3 | RESULTS

3.1 | Cost measurement

In the group treated with pentavalent antimonials, the costs of the medication, nursing assistance, medical checkups, and laboratory tests represented a cost of $65,412, with an average cost (per patient) of $540.6, whereas the average cost of the management of adverse effects was $11.5 (Table 1).

In thermotherapy, medical consultations and nursing care represented an average cost of $99.3, and the management of adverse effects represented an average cost of $5.8. Although adverse effects were included as a way to unify the groups of clinical trials, thermotherapy does not actually generate them (Table 2).

In accordance with the above, the total cost of treatment with pentavalent antimonials was $66,807.2 (Table 1), and the total cost with thermotherapy was $14,079.2 (Table 2). Subsequently, patients receiving rescue therapy were monitored, and costs associated with providing Glucantime and managing adverse effects in both groups were added, resulting in a total cost of $76,521.6 for the 121 patients who were provided with Glucantime, 18 individuals who required rescue therapy, and one patient who received two rescue treatments (Table 1). However, for the 134 patients who received thermotherapy and 48 who required rescue treatment, the total cost was $39,981.6 (Table 2). It should be noted that in previous studies on leishmaniasis and in other assessments of cost-effectiveness, the costs associated with the management of patients with treatment failure were not included. In this sense, if the cost of patients who received rescue therapy had not been included, the thermotherapy cost-effectiveness ratio would be much better.

When taking into account the lower limit of the confidence interval of the proportion of adverse effects (maximum safety level), a total cost of $66,257.2 was obtained for the group treated with pentavalent antimonials, and a total cost of $13,572.1 was obtained for the thermotherapy group. In the second scenario, the upper limit of the proportion of side effects was taken, so the costs increased to $67,529.3 for the group with pentavalent antimonials and to $14,684.3 for the thermotherapy group (Table 3). In addition, according to the percentages of procurement of health services in Colombia, the cost of pentavalent antimonials increased, ranging between $83,509.0 (25% adjustment) and $98,874.7 (48% adjustment), whereas the cost of thermotherapy was between $17,599.1 (25% increase) and $20,837.3 (48% increase) (Table 3).

3.2 | Safety measures and clinical effectiveness

In the safety analysis, among the 121 patients treated with pentavalent antimonials, the major local effects were 74% vomiting, nausea, anorexia, and diarrhea, followed by 55% myalgia, 54% arthralgia, and 43% headache. The most frequent systemic effects included 20% pancreatic disorders and 17% liver disorders (Table 1). Among patients undergoing thermotherapy, the proportion of adverse effects was significantly lower, with greater occurrences of vomiting, nausea, diarrhea, anorexia, and local effects (10%), and the highest systemic effects were pancreatic and liver disorders (5%) (Table 2). In patients receiving rescue therapy, statistically similar probabilities to those obtained for patients treated with pentavalent antimonials were found.

In terms of therapeutic effectiveness, 48 out of the 134 patients treated with a single thermotherapy application showed treatment failure, which is equivalent to 64.2% effectiveness (86/134); among the 48 patients who underwent rescue treatment, no treatment

TABLE 1 Costing protocol of patients treated with pentavalent antimonials

	L	#	Unit cost *	Total*
Glucantime: approximately 70 ampules	1.00	121	2.37	20,060.5
Nurse (treatments): 20 applications	1.00	121	7.34	17,770.4
Medical consultation: five visits	1.00	121	12.41	7508.4
Paraclinical tests				
Creatinine: three times	1.00	121	5.79	2102.3
BUN: three times	1.00	121	4.14	1501.7
AST/ALT: three times	1.00	121	18.00	6532.5
Amylase: three times	1.00	121	6.72	2440.3
CBC: three times	1.00	121	15.00	5443.7
ECG: once	1.00	121	16.96	2052.3
Side effects				
Myalgia	0.55	67	0.71	47.6
Arthralgia	0.54	65	0.71	46.2
Headache	0.43	52	0.71	36.9
Abdominal pain	0.02	2	1.77	3.5
Fever	0.24	29	0.71	20.6
Vomiting, nausea, anorexia, diarrhea	0.74	90	2.73	245.8
Infection of the lesion	0.04	5	44.06	220.3
Effects in kidney	0.01	1	9.93	9.9
Pancreatic effects	0.20	24	6.72	161.3
Effects in liver	0.17	21	18.00	377.9
Hematological effects	0.12	15	15.00	224.9
Total standard costing				66,807.2
Average cost with standard costing				552.1
Rescue therapy I: 18 patients, to whom the same protocol was applied.				
Rescue therapy II: one patient				
Total cost costing per patient				76,521.6
Average cost costing per patient				632.4

L: Likelihood of development.
*US dollars, exchange rate $1 = $1900 COP.

failures were recorded. Treatment failure was also recorded in 18 patients treated with pentavalent antimonials, equivalent to 85.1% effectiveness (103/121). Among those who underwent rescue treatment, one case of therapeutic failure occurred. Table 3 shows the results of therapeutic effectiveness, as described in the previous paragraph, with the minimum and maximum values of their 95% confidence intervals. Additionally, therapeutic effectiveness was calculated in a meta-analysis conducted by researchers on thermotherapy and pentavalent antimonials.[26]

3.3 | Cost-effectiveness ratio and sensitivity analysis

The average cost-effectiveness ratio derived in the standard costing was $785.0 for pentavalent antimonials and $219.3 for thermotherapy. Based on the univariate and multivariate sensitivity analyses, the variation for pentavalent antimonials ranged between $721.0 and $1274.8, whereas the average cost-effectiveness ratio for thermotherapy ranged from US $186.7 to US $390.2 (Table 4).

On the basis of the costing per patient (which, unlike the standard costing, includes costs associated with rescue treatments), the average cost-effectiveness ratios were $632.4 (ranging from $590.7 to $721.1) for prevalent antimonials and $298.4 (ranging from $245.9 to $352.2) for thermotherapy. The incremental cost-effectiveness ratio was $2523 (ranging from $2323 to $4073) (Table 4).

In the sensitivity analyses, the final decision is subject to the cost-effectiveness threshold established by the authorities in charge of assigning the intervention, in this case the Ministry of Health and Social Protection (Ministerio de Salud y de Protección Social). In this sense, if a threshold of $400 per patient treated is set, all of the combinations of costs and effectiveness and the safety measures analyzed provide a basis for concluding that thermotherapy is more cost-effective than treatment with pentavalent antimonials.

It is worth mentioning that when using the meta-analysis data in which pentavalent antimonials and thermotherapy were similar in terms of effectiveness, the incremental cost-effectiveness ratio showed a negative result, given that thermotherapy showed an

TABLE 2 Costing protocol of patients treated with thermotherapy

	L	#	Unit cost*	Total*
ThermoMed	1.00	134	22.55	3021.1
Medical consultation: five visits	1.00	134	12.41	8315.1
Nurse (treatments): two visits	1.00	134	7.34	1968.0
Side effects				
Myalgia	0.03	4	0.71	2.8
Arthralgia	0.02	3	0.71	2.1
Headache	0.10	13	0.71	9.2
Abdominal pain	0.00	0	1.77	0.0
Fever	0.03	4	0.71	2.8
Vomiting, nausea, anorexia, diarrhea	0.10	13	2.73	35.5
Infection of the lesion	0.08	11	44.06	484.6
Effects in kidney	0.01	2	9.93	19.9
Pancreatic effects	0.05	7	6.72	47.1
Effects in liver	0.05	7	18.00	126.0
Hematological effects	0.02	3	15.00	45.0
Total standard costing				14,079.2
Average cost with standard costing				105.1
Rescue therapy I: 48 patients, to whom the Glucantime protocol (Table 1) was applied				
TOTAL COST costing per patient				39,981.6
AVERAGE COST costing per patient				298.4

L: Likelihood of development. US dollar exchange rate $1 = $1900 COP.

TABLE 3 Synthesis of the analyses of effectiveness and costs of treatments

		Pentavalent antimonials	Thermotherapy
Effectiveness of the PECET Study	Mean	85.1%	64.2%
	Minimum	78.4	55.7
	Maximum	91.9	72.7
Effectiveness meta-analysis	Mean	70.6%	73.2%
	Minimum	6.17	69.6
	Maximum	74.1	76.7
Costs according to safety results*	Mean	$66,807.2	$14,079.3
	Minimum	66,257.4	13,572.1
	Maximum	67,529.3	14,684.3
Costs according to procurement prices in Colombia*	+25%	83,509.0	17,599.1
	+30%	86,849.4	18,303.0
	+48%	98,874.7	20,837.3

*US dollars, exchange rate projected for 2013 of $1 = $1900 COP.

incremental cost of $52,728.0 (lower incremental cost than pentavalent antimonials) and an incremental therapeutic effectiveness of 2.6%. This finding indicates that the increasing effectiveness of thermotherapy in a percentage compared with pentavalent antimonials may generate cost savings between $40,560 and $43,940. In other words, thermotherapy is a dominant strategy, as it has a lower cost and a slightly higher therapeutic effectiveness (Table 4). The sensitivity analysis indicated that the conclusion is robust under variations in the assessed parameters, namely, effectiveness, safety, and costs.

4 | DISCUSSION

In this study, data were collected regarding thermotherapy effectiveness from the clinical trial of López et al.[8] and a meta-analysis.[26] Both studies concluded that this therapy could be applied to patients with cutaneous leishmaniasis, which is consistent with studies that have shown favorable results of the use of heat or caustic treatments in Latin American rural and indigenous populations.[23–25] Furthermore, thermotherapy effectiveness gains greater relevance in the treatment of the cutaneous form of the disease, as the following advantages are

TABLE 4 Cost-effectiveness ratio and sensitivity analysis

	Pentavalent antimonials *	Thermotherapy *
Average cost-effectiveness ratio (standard costing)	**785.0**	**219.3**
Sensitivity analysis	**Range**	
Univariate analysis for costs depending on safety analysis	778.6 to 793.5	211.4 to 228.7
Univariate analysis for procurement costs in Colombia	981.3 to 1161.9	274.1 to 324.6
Univariate analysis for effectiveness of the PECET study	727.0 to 852.1	193.7 to 252.8
Univariate analysis for Meta-analysis effectiveness	872.2 to 972.4	181.0 to 201.1
Multivariate analysis	721.0 to 1274.8	186.7 to 390.2
Average cost-effectiveness ratio (costing per patient)	632.4	298.4
Sensitivity analysis	Range	
Univariate analysis for costs depending on safety analysis	627.34 to 641.6	292.0 to 306.3
Univariate analysis for procurement costs in Colombia	784.2 to 948.7	365.0 to 453.3
Univariate analysis for effectiveness of the PECET study	595.9 to 668.7	252.4 to 344.1
Univariate analysis for meta-analysis effectiveness	678.4 to 721.1	224.9 to 267.0
Multivariate analysis	590.7 to 721.1	246.6 to 352.2
Incremental cost-effectiveness ratio	2523	
Sensitivity analysis	Range	
Univariate analysis for costs depending on safety analysis	2521 to 2,528	
Univariate analysis for procurement costs in Colombia	2904 to 4,064	
Univariate analysis for effectiveness of the PECET study	2323 to 2,746	
Univariate analysis for meta-analysis effectiveness	−40,560; −43,940	
Multivariate analysis	2323 to 4073	

*US dollars, exchange rate $1 = $1900 COP.

given: shorter duration; greater adherence[38]; does not require paraclinical examinations; and can be used in patients with kidney, liver, or heart problems, in pregnant women, children, and other groups in which pentavalent antimonials or miltefosine are contraindicated.[39] Moreover, in the systemic therapy, effectiveness can be reduced, and resistance based on incomplete administration or poor adherence can grow day by day.[21]

Despite the existing evidence of the effectiveness and safety of thermotherapy in the treatment of cutaneous leishmaniasis and the fact that this is the most prevalent form of the disease in the world, most studies from an economic standpoint have focused on the visceral form of the disease. The economic analyses conducted on cutaneous leishmaniasis differ from those developed in this study; therefore, it is difficult to make a comparison of the cost-effectiveness found. However, it is worth mentioning the results of the following research studies: (i) Orellana et al. in Argentina found an incremental cost-effectiveness ratio of $156.46 per DALY (Disability Adjusted Life Years) avoided for an early diagnosis strategy and a ratio of $13,155.52 per DALY avoided for the use of clothes and curtains impregnated with insecticide,[6] (ii) Vega et al. in 1 524 patients treated with intramuscular antimonials during an outbreak in Colombia, reported a cost per patient treated and cured with antimonials in US$ 345 (CI 277 to 488) and the cost for DALY avoided in US$ 15 215 (IC 12,226 to 21,532),[40] and iii) Reithinger et al. reported a cost of standard treatment US$ 27 (IC 20 to 36) per patient cured and US$ 1200 (761 to 1827) per DALY avoided.[31] However, the World Health Organization no longer considers Meglumine Antimoniate as a treatment of choice for this clinical form of the disease.

Unlike other economic assessments on leishmaniasis, final outcomes such as mortality or DALYs were not used in this research for the following reasons: low lethality from the cutaneous form of the disease and inherent difficulties in estimating DALYs. Indeed, these metrics were used in leishmaniasis on the basis of an extrapolation of the measurement of disability resulting from diseases such as leprosy.[6] The metrics were also used for taking arbitrary measures on the duration of the disease, similar to some previous studies that estimate DALYs as the product of the incidence, the disability weight for cutaneous leishmaniasis (taken from a global report and not from a unique context), and disease duration.[31] Instead, the cure proportion was used as an outcome, as this measure directly reflects the epidemiological features of the disease.

However, the treatment of cutaneous leishmaniasis has wide variations in cost due to the price of the medication, the protocol of application (intralesional or intramuscular, the latter being approved by the Ministry of Health of Colombia), the type of patient care,[31] and the social security system to which the patient belongs. To tackle this contingency, this study took a wide range of costs, and the sensitivity analysis showed the model robustness to establish the greater cost-effectiveness of thermotherapy. In this vein, research studies that have recommended the use of pentavalent antimonials for their low cost generally do not include costs associated with the management of adverse effects.[32]

In the case of equipment not included in the costing guides, there are challenges about how to include in the algorithm the estimation of the costs of every health unit currently providing treatment for CL with Anitmonials would need to invest have their own ThemoMed machine. The cost of ThemoMed is just one time payment; however, it is an initial cost that need to be include to convince the health regulators that even when at the beginning, the cost of using thermotherapy is going to probably higher, this cost is going to be dramatically less for the subsequent years. In relation to this, possible limitation must bear in mind that the sensitivity analysis shows that changes in cost parameters do not affect the conclusion.

In relation to other physical treatments of CL, specifically cryotherapy, previous studies have generated evidence showing a statistically similar efficacy to that obtained with pentavalent antimonials; however, its application requires attention by a specialist physician and other facilities that derive in high costs and low feasibility for its application in endemic areas for CL, in Colombia, they are characterized by being rural areas, with low presence of institutions that provide services of health, with barriers to access to the social security system, with difficulties for specialized medical care, among other factors that would limit their cost-effectiveness.[41]

According to the sensitivity analyses, the average cost-effectiveness ratios ranged from $590.7 to $1274.8 for pentavalent antimonials and from $186.7 to $390.2 for thermotherapy; the incremental cost-effectiveness ratio was $2523 (range from $2323 to $4073). This ratio is subject to the threshold set by the decision maker; with this regard, the WHO has indicated that a strategy is very cost-effective when cost-effectiveness is lower than the gross domestic product (GDP) per capita in the country and is cost-effective when cost-effectiveness is lower than three times the GDP per capita, while higher values are not considered cost-effective.[36] In the current study, we found a cost-effectiveness ratio close to one-third of the GDP per capita, which was $7826 in Colombia in 2013.[42] This finding qualifies thermotherapy as a highly cost-effective strategy for the treatment of cutaneous leishmaniasis in all scenarios generated in the sensitivity analysis, that is, the same conclusion is found when individually and simultaneously changing the costs, safety, and effectiveness of the assessed treatments.

Several motives have expanded the use of cost-effectiveness analyses according to the WHO: (i) to prioritize the funding of interventions, to reduce health inequalities, and to address the well-being of future generations, (ii) to identify the best way to allocate health resources or to optimize health budgets, (iii) to avoid or overcome inefficiencies of many countries in gaining health conditions, (iv) to base health policy on costs and effects of different health interventions, particularly in middle- and low-income countries, and (v) to improve clinical practice guidelines.[36]

Despite the advantages set forth, some limitations remain, such as the inclusion of items in the costs and the way their prices are determined, eg, the inclusion of out-of-pocket expenses and costs associated with informal health care and extra costs for the years of life gained due to an intervention. In addition, there is variability in implementing interventions in different contexts or regions, and the valuation that no effect is observed when health processes are interrelated. Other challenges in costing include classification, such as salaries, medicine, capital, management, planning, monitoring, or costs at the organizational level (ie, national, district, or hospital level).[36] Some of the aforementioned limitations are overcome in this study, as assistance to control leishmaniasis in Colombia is standardized. Therefore, items related to direct costs are also standardized. Regarding pricing, national standard sources were used, and an uncertainty analysis was performed by taking the percentage increase handled for the procurement of services in Institutions Providing Health Services (IPS).

In addition, from a social perspective, it would be relevant to include nonmedical costs associated with transportation to the IPS or to the place of treatment, out-of-pocket expenses for outpatient services, indirect costs associated with loss of productive activities of the patient and his or her family (due to the disease itself or to transportation to the place of treatment), among others, which would be much higher for systemic treatment compared with thermotherapy, as the former requires more medical visits and higher social costs associated with the treatment itself and the management of any adverse effects. In this respect, a cost-effectiveness assessment from a social perspective may improve thermotherapy outcomes for the treatment of cutaneous leishmaniasis.

The main advantages of this study are that unlike other economic assessments, costing not only included analysis per patient and standard costing but also took actual monitoring data from a controlled clinical trial. This strategy allowed for overcoming constraints from previous studies that do not include the management of side effects, analyzing cost-effectiveness regardless of the results of therapeutic safety (ie, costs associated with the management of side effects) or taking clinical effectiveness data from observational studies. This study also took into account broad ranges of effectiveness, safety, and costs, providing greater comprehensiveness to the model, as it represents different contexts, possible variations in outcomes attributable to the infecting species, the number, size and type of lesions, and the excellent internal and external validity of the clinical trial that was used for measuring effectiveness and safety.

5 | CONCLUSIONS

The multiple benefits of thermotherapy, including its low cost, high safety, and ease of implementation, show the relevance of its incorporation into the treatment of cutaneous leishmaniasis as a first-choice treatment. The excellent cost-effectiveness ratio of thermotherapy is a key feature for guiding decisions for disease management in Colombia and other countries with similar epidemiological patterns. The evidence generated in this study is useful for prioritizing interventions and public policies regarding this disease, efficiently allocating health resources and orienting researchers and professionals interested in this issue and mitigating costs generated by the disease for the Colombian System of Social Security in Health (Sistema de Seguridad Social en Salud).

CONFLICT OF INTEREST

None.

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