Articulos Originales

Is intralesional treatment of cutaneous leishmaniasis safe against the risk of mucosal complications?

El tratamiento intralesional de Leishmaniasis cutánea es seguro frente al riesgo de complicaciones mucosas?

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Abstract: Transitional zone cancer represents 20-25% of the cases (in radical prostatectomy specimens), its diagnosis is frequently incidental, being clinically identified as presumed adenomas.
Objetive: to determine the incidence of adenocarcinoma in the transitional zone of the prostate and identify precancerous stages in patients with clinical BPH.
Methods: retrospective longitudinal study from 2013-2018 in the city of Cochabamba-Bolivia; study population: patients submitted to simple, retropubic and/or transvesical prostatectomy. Data collection: based on medical records, patients with clinical symptoms of benign prostatic hyperplasia and total PSA < 4ng/ml.
Results: 76 patients were identified, of which 5 were found to have Adenocarcinoma and 9 with: High Grade Prostatic Intraepithelial Neoplasia 2.6%, Atypical small acinar proliferation 7.9%, thus representing 10.5%. As for invasion, 5.3% represented perineal invasion, 2.6% lymphovascular invasion and none with extravascular invasion.
Discussion: patients with transitional zone prostate cancer, present a high prostate specific antigen suspicious to adenocarcinoma. However, this study found high-risk prostate adenocarcinoma with total prostate specific antigen less than 4 ng/ml. In spite of the clinical instruments and indications for surgical therapy of a presumed benign prostatic hyperplasia, the incidence of Adenocarcinoma in the Transitional Zone was 6.5%, with a 10.5% incidence of precancerous forms, and 17.1% of the patients were at risk of lethality from the disease.

Keywords: mucosal leishmaniasis, intralesional treatment, systemic treatment, treatment safety.

Resumen: Objetivo: evaluar la seguridad a largo plazo frente al riesgo de complicaciones mucosas del uso intralesional de antimoniales pentavalentes en pacientes con Leishmaniasis cutánea comparado con el uso sistémico de los mismos.
Métodos: estudio observacional, cuantitativo de tipo longitudinal retrospectivo. Se analizó un total de 66 registros clínicos de pacientes, con diagnóstico de Leishmaniasis cutánea del parque Isiboro Secure durante el periodo 2012 a 2016. Se evaluó un total de 46 tratamientos sistémicos y 20 intralesionales.

Resultados: la evaluación clínica realizada entre 4 y 7 años posteriores a la cicatrización de las lesiones cutáneas de Leishmaniasis mostró la ausencia de desarrollo de lesiones mucosas. Así mismo no se reportó fallas terapéuticas, recidivas ni efectos adversos a corto plazo.
Conclusiones: el tratamiento intralesional fue seguro y eficaz a largo plazo y es una opción confiable para el tratamiento de Leishmaniasis cutánea evitando las complicaciones futuras de la enfermedad.

Palabras clave: leishmaniasis mucosa, tratamiento intralesional, tratamiento sistémico.

Leishmaniasis is a parasitic, non-contagious disease caused by different species of protozoa of the genus Leishmania[1]. The WHO estimates the incidence of Leishmaniasis at approximately 2 million new cases per year[2], with deaths from Leishmaniasis reaching 67,000 per year worldwide[3]. In South America, the disease is present in almost all countries except Chile and Uruguay[3]. Leishmaniasis has three clinical forms: visceral, cutaneous and mucocutaneous. The cutaneous form is the most common and consists of chronic ulcers that leave lifelong scars, and the mucocutaneous form is more aggressive and causes partial or complete destruction of the mucous membranes of the nose, mouth and larynx[3]. In Bolivia, the most frequent species responsible for 85% of cases of cutaneous Leishmaniasis is L. braziliensis[4]. This species is also responsible for mucosal leishmaniasis, which generally occurs after an episode of cutaneous leishmaniasis due to systemic dissemination of the parasite[5].

Pentavalent antimonials are the first-line drugs for the treatment of cutaneous leishmaniasis and are administered systemically (intravenously or intramuscularly) at a dose of 20 mg/kg/day for 20 days. According to a meta-analysis conducted in 2008, this treatment has a clinical cure efficacy of 76.5%[7]. However, the disadvantage of this therapy is the use of multiple injections and large volumes of drug, causing adverse effects such as myalgia, arthralgia, gastrointestinal symptoms and significant cardiac, hepatic, pancreatic and renal toxicity. Adverse reactions and toxicity associated with this treatment are responsible for treatment abandonment by the patient, as well as partial or total treatment interruptions by medical staff, situations that give rise to problems of therapeutic failure that are much more complicated to manage[8,9].

Intralesional application of pentavalent antimonials is a widely used technique to treat Leishmaniasis worldwide with a clinical cure rate of 70%[7], which is why it is currently recommended by PAHO/WHO[6]; this is why Brazil, which has the same strain responsible for mucosal Leishmaniasis, has included a management manual for the use of intralesional antimonials for the disease[10]. Additionally, in Bolivia, our working group has developed its own experiences in this type of treatment[4], however, this treatment has not yet been sufficiently accepted or implemented in Bolivia by the authorities of the Ministry of Health, due to excessive mistrust regarding the success of this treatment, arguing that there is little evidence to support the safety of the treatment[11]. In the interest of contributing more evidence on this issue, the aim of this study was to evaluate the safety of intralesional treatment with pentavalent antimonials for cutaneous leishmaniasis against the risk of long-term mucosal complications.

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Material and methods

This is a retrospective longitudinal quantitative observational study. Exclusion criteria for the study included having received treatment other than intralesional or systemic treatment and the impossibility of post-treatment follow-up. On the other hand, inclusion criteria included having received pentavalent antimonial-based treatment (intralesional or systemic) within the follow-up period and their acceptance to voluntarily participate in the study.

Sixty-six clinical records were selected for the study of patients with a laboratory-confirmed diagnosis of cutaneous leishmaniasis who received intralesional treatment or systemic treatment with pentavalent antimonials during the period 2012 to 2016 and who corresponded to a community in the Isiboro Sécure Park in the Municipality of Villa Tunari. Of the 66 patients, 46 received systemic treatment and 20 received intralesional treatment. The latter consisted of the local application of 3 and 6 doses of pentavalent antimonials at the edge of the lesion every other day. The amount of drug applied was calculated by multiplying the width by the length of the lesion and by a constant factor of 0.008, according to the Bolivian operational guide[4]. Intralesional treatment was performed on the basis of two schedules: nine patients received three applications in a first clinical trial in 2012-2013 with a 7-year follow-up, and the other 11 received six applications as part of a second clinical trial conducted in 2014-2015 with a 4-year follow-up[4,5].

Data collection

Clinical information on study participants was collected from records available at health centres throughout the Isiboro Sécure Park territory, in conjunction with a new on-site clinical assessment of patients previously notified for this purpose.

Post-healing clinical evaluation participants were evaluated by means of a complete physical examination in search of complications that could occur after the completion of the treatment. Specifically, participants were assessed for: 1) the presence of parasitic activity (characterised by recurrence of the ulcer or inflammation of the scar edges); 2) the occurrence of a new episode in areas of the skin other than where the healed lesion was located; and 3) the presence of mucosal ulcers in the nose, mouth, changes in voice tone as a sign of mucosal complication.

Ethical considerations

The study was approved by the Bolivian Ethics Committee of the Faculty of Medicine of the Universidad Mayor de San Simón. All study participants gave their voluntary written consent agreeing to participate in the study.

Results

Sixty-six patients with cutaneous leishmaniasis who received systemic or intralesional treatment between 2012 and 2016 were contacted. Of this total, the highest percentage were women and the age range was between 4 and 67 years of age, with a mean of 26 years(Table 1).

Variables		Systemic Treat. n=46	Intralesional treat. A n=11	Intralesional treat. B n=9
Age (years) *		28 (4 - 67)	29 (14 - 52)	22 (6 - 36)
Gender	M	22 (47,8)	2 (18,2)	5 (55,6)
	F	24 (52,2)	9 (81,8)	4 (44,4)
Occupation	Agriculture	19 (41,3)	2 (18,2)	5 (55,6)
	Student	16 (34,8)	4 (36,4)	4 (44,4)
	Household chores	9 (18,6)	4 (36,4)	¬
	Other	2 (4,3)	1 (9,1)	¬
Anatomical region involved	Head/neck	5 (10,8)	¬	¬
	Upper extremity	9 (19,6)	1 (9,1)	1 (11,1)
	Lower extremity	32 (4,3)	10 (90,9)	8 (88,9)
Number of lesions	One	36 (78,3)	9 (81,2)	7 (77,8)
	Two	7 (15,3)	2 (18,2)	2 (22,2)
	> than two	3 (6,5)	¬	¬
Treatment start delay in weeks *		10 (2 - 39)	5 (1 - 13)	11 (3 - 34)
Concomitant disease	Yes	1 (2,2) (anemia)	1 (9,1) (Chagas)	¬
	No	45 (97,8)	10 (90,9)	9 (100)

*Average(Range); Systemic Treat. = Conventional treatment for 20 days of intramuscular application dosage/kg/weight; Intralesional treat.(A) = Six applications of intralesional medication; Intralesional treat. (B) = Three applications of intralesional medication

TABLE 1

Demographic and clinical data of patients with cutaneous leishmaniasis who received systemic or intralesional treatment with pentavalent antimonials. Data presented as frequencies (%).

All of them achieved healing of their skin ulcers within 6 months of follow-up after completion of treatment, regardless of the type of treatment received (Figure 1). It should be noted that the ulcer area was less than 900 mm^2 (30x30 mm) in all cases included in the study (systemic or intralesional treatment). The time in which the lesions reached healing, according to the reports reviewed, was in the range of 6 months after completion of treatment.

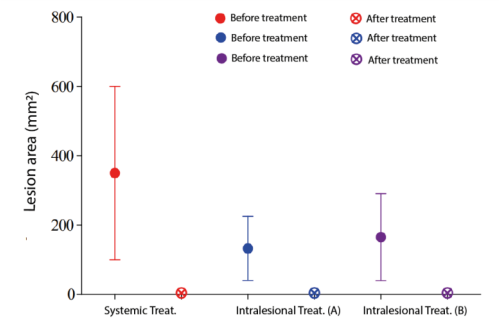

FIGURE 1.

Area of the lesion of patients with cutaneous leishmaniasis before and after therapeutic intervention. Tx. Systemic = Conventional treatment for 20 days of intramuscular application dose /kg/weight (n=46); Tx. Intralesional (A) = Six Intralesional drug applications (n=9); Tx. Intralesional (B) = Three Intralesional drug applications (n=11). Data expressed as Median (RIC)

Regarding post-treatment clinical follow-up, both for those who received systemic and intralesional treatment (3 and 6 applications respectively), the clinical review showed the absence of mucosal lesions after completion of treatment for cutaneous leishmaniasis regardless of treatment (Figure 2), as well as the absence of other cutaneous involvement compatible with therapeutic failure, the presence of relapses and/or the occurrence of new episodes (Table 2).

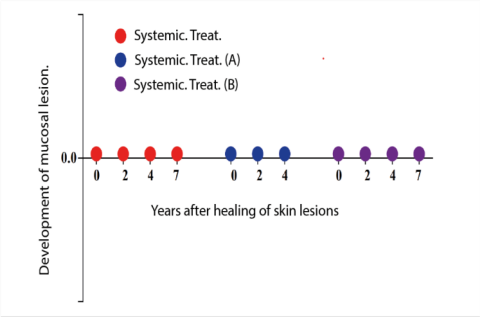

FIGURE 2.
Clinical follow-up for Leishmania mucosal lesions, after clinical cure (scar) of cutaneous leishmaniasis. Systemic Tx = Conventional treatment for 20 days of intramuscular application dose /kg/weight (n=46); Intralesional Tx (A) = Six applications of intralesional drug (n=9); Intralesional Tx (B) = Three applications of intralesional drug (n=11).

Variables		Systemic. treat n=46	Intralesional Treat A n=9	B n=11
Therapeutic failure	Yes	1 (2.2)	¬	¬
	No	45 (97.8)	11 (100)	9 (100)
Relapse	Yes	1 (2.2)	1 (9.1)	¬
	No	45 (97.8)	10 (90.9)	9 (100)
New Infection	Yes	1 (2.2)	¬	2 (22.2)
	No	45 (97.8)	11 (100)	7 (77.8)
New Treatment for leishmaniasis	Yes	2 (4.4)	¬	2 (22.2)
	No	44 (95.6)	11(100)	7 (77.8)

Systemic treat. = Conventional treatment for 20 days of intramuscular application dose/kg/weight; Intralesional treat. (A) = Six applications of intralesional medication; Intralesional treat. (B) = Three applications of intralesional medication.

TABLE 2.
Clinical involvement following treatment with pentavalent antimonials in patients with cutaneous leishmaniasis. Data are expressed as frequency of cases. Data are expressed in frequency (%).

Finally, regarding adverse effects caused by systemic or intralesional treatments, the most frequent was pain at the site of application for both treatments used (systemic or intralesional). However, cases receiving systemic treatment also presented with myalgia, fever and headache in about 11% of patients (Table 3). No data on liver, cardiac and pancreatic alterations are available because laboratory tests were not available in the medical services where the treatments were performed.

Type of adverse effects		Systemic treat. n=46	Intralesional. treat A n=11	Intralesional. treat B n=9
Local Pain	Yes	45 (97.8)	9 (81.8)	9 (100)
	No	1 (2.2)	2 (18.2)	¬
Myalgia	Yes	5 (10.9)	¬	¬
	No	41 (89.1)	11 (100)	9 (100)
Fever	Yes	5 (10.9)	¬	¬
	No	41 (89.1)	11 (100)	9 (100)
Headache	Yes	6 (13)	¬	¬
	No	40 (87)	11 (100)	9(100)
Anorexia	Yes	1 (2.2)	¬	¬
	No	45 (97.8)	11 (100)	9 (100)
Fatigue/Asthenia	Yes	2 (4.4)	¬	¬
	No	44 (95.6)	11 (100)	9 (100)
Nausea	Yes	1 (2.2)	¬	¬
	No	45 (97.8)	11 (100)	9 (100)
Hives	Yes	2 (4.4)	¬	¬
	No	44 (95.6)	11 (100)	9 (100)
Burning sensation	Yes	1 (2.2)	¬	¬
	No	45 (97.8)	11 (100)	9 (100)
Itching	Yes	1 (2.2)	¬	¬
	No	45 (97.8)	11 (100)	9 (100)

Systemic = Conventional treatment for 20 days of intramuscular application dose/kg/weight; Intralesional treat. (A) = Six applications of intralesional medication; Intralesional treat. (B) = Three applications of intralesional medication.

TABLE 3.
Adverse effects presented during treatment with pentavalent antimonials in patients with cutaneous leishmaniasis. Data are expressed in frequency of cases. Data are expressed in frequency (%).

Discussion

Long-term clinical evaluation of patients treated with systemic and intralesional pentavalent antimonials showed the absence of mucosal complications of Leishmaniasis in all cases, regardless of the treatment regimen administered. Although there are few studies in Latin America that perform long-term follow-up of patients treated with systemic or intralesional pentavalent antimonials, the few that exist showed similar results to this study, highlighting the absence of development of mucosal lesions[12-14]. Although the reasons for the development of mucosal complications are not sufficiently clear, different evidence points to dysregulation of the individual's immune system as an important factor for this development[15-18]. In this respect, the immunomodulatory effect of pentavalent antimonials is as important as their leishmanicidal effect. Pentavalent antimonials modify the specific immune response by favouring the activation of macrophages and thus facilitating phagocytosis of intracellular parasites[19]. On the other hand, in the absence of a functional immune system, the response to pentavalent antimonials is reduced for ulcer healing and the likelihood of mucosal complications increases[20], due to the modification of the cell-mediated immune response[21,22] of the individual with Leishmaniasis. Another important finding was the absence of relapses or reinfections in the group of patients who received three intralesional applications of the drug, and although new skin lesions were identified in other anatomical regions, these corresponded to a new episode.

The adverse effects produced by the drugs were more frequent among patients who received systemic treatment (Table 3), the most common being myalgia, fever and headache, which are probably due to the toxicity of the antimony or of the additives contained in the pharmaceutical formulation[23,24]. In contrast, these types of adverse effects in intralesional application are considered rare[25]. Local pain was present in all cases regardless of whether treatment was by systemic or intralesional application due to local hypersensitivity of the inflamed tissue due to antimony toxicity[26,27] and in the case of intralesional application the inflammation also responds to the activity of the parasite present at the edge of the lesions[28,29].

The results presented in this study have two limitations related to sample size, due to the difficulties of access to the communities, and the follow-up time (4-7 years), which, although long-term, is not long enough to completely rule out the risk that these patients may develop mucosal leishmaniasis in a period longer than that evaluated as a result of changes in the behaviour of their immune system,[15] which could be triggered by

multiple causes. However, despite these limitations, this is the first study with a follow-up longer than four years for this type of treatment in Latin America.

Conclusions

This study is the first in Bolivia to explore the effect of intralesional and systemic treatment with a clinical follow-up of more than four years in all patients evaluated.

Treatment with intralesional pentavalent antimonials is a reliable option in relation to future complications of the disease, as well as in terms of its clinical efficacy, since it achieves a similar percentage of cure to that obtained with systemic treatment. Its long-term safety, characterised by its low toxicity, minimal risk of relapses and reinfections and the absence of mucosal complications, reinforces the conclusions that it is a more cost-effective alternative for health systems in the management of cutaneous leishmaniasis.

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