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ORIGINAL ARTICLE

Metronidazole *versus* Pentostam for treatment of cutaneous leishmaniasis

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ABSTRACT

BACKGROUND: The cutaneous leishmaniasis of old world is a skin distorting disease and considered as a social stigma in countries of the Asia, Mediterranean and Middle East including Iraq. Many drugs nowadays have been reported to have a clinical efficacy against cutaneous leishmaniasis but only a few have been proven worthy. In this study, we aim to compare the efficacy and safety of Intralesional sodium stibogluconate (Pentostam® 100 mg/mL) and Intralesional metronidazole (flagyl® 5 mg/mL) solutions in the treatment of cutaneous leishmaniasis.

METHODS: A clinical trial was done in Dermatology Consultancy Clinic of Al-Hussain Teaching Hospital, Nassiriah (Thi Qar Province Center), Iraq, during the period from June 2015 to June 2016 on a convenient sample of 100 patients with cutaneous leishmaniasis. Those patients were assigned randomly into two groups according to type of localized treatment (50 patients on Pentostam) and (50 patients on Metronidazole) and seen weekly for a maximum of 8 weeks.

RESULTS: Patients treated with Pentostam were significantly associated with a higher complete response rate than patients treated with Metronidazole (P<0.001). Complications of treatment were significantly detected among patients treated with Pentostam (P<0.001). Pain at injection site was significantly perceived as severe among patients treated with Pentostam (P<0.001).

CONCLUSIONS: Pentostam solution has a higher efficacy in the treatment of cutaneous leishmaniasis than Metronidazole solution but with higher rates of complications and pain at injection site.

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Key words: Cutaneous leishmaniasis - Antimony sodium gluconate - Metronidazole.

Leishmaniasis represents a group of chronic infections affecting humans and several animal species. The responsible micro-organisms are more than 20 species of the genus Leishmania that is a flagellated protozoon belonging to the order *Kinetoplastidae* transmitted by sandflies.[1] The cutaneous leishmaniasis (CL) of old world is a skin disfiguring disease which is considered as a social stigmata in countries of the Asia, Mediterranean and Middle East including Iraq.[2]

More than 90% of leishmaniasis cases in Iraq are cutaneous. In Iraq, incidence rate of cutaneous leishmaniasis is ranging from 2.3/100,000 to 45.5/100,000 [3] with CL cases of 3218 in 2004 and declined in 2012 to reach 2045 cases.[4] Geographical distribution of CL in Iraq covered the Southern East provinces such as Diala, Wasit, Missan, Thi Qar and Basrah.[5] However, due to displacement crises at 2014, CL outbreak occurs in northern areas of Iraq (Kurdistan) affecting thousands of internally displaced persons and host communities.[6] Two *Lieshmania* species are present: *L. tropica*

(anthroponotic cutaneous leishmaniasis) and *L. major* (zoonotic cutaneous leishmaniasis).[7]

Until now, no immunization has been approved for leishmaniasis and the preventive strategy is based on fighting the sandflies bite. At present, about 25 drugs were reported to have a clinical efficacy against leishmaniasis, but only a few have been proven worthy. The first line treatment for leishmaniasis is the pentavalent antimonials. Other drugs like amphotericin B, pentamidine, miltefosine and aminosidine are also showing good efficacy.[8] All these reported drugs have many side effects such as high toxicity and other problems that result in treatment withdrawal and development of resistant strains. Leishmaniasis is a disease of poor developing communities, so the high cost of treatment increases the burden of the disease.[9] In addition, high relapses were reported after use of anti-leishmaniasis drugs.[10]

Cutaneous leishmaniasis of small, non-inflamed and localized lesions is treated locally by many modalities such as intralesional antimonial (Pentostam®),[11, 12] cryotherapy,[13] intralesional metronidazole,[14] hypertonic sodium chloride,[15] topical or intralesional zinc sulfate,[16] etc. while systemic therapy is used for complicated cutaneous leishmaniasis.[17] Many authors in and outside Iraq were studying the effect of intralesional injection for metronidazole (Flagyl®) as an alternative for Pentostam in treatment of CL with variability in outcome.[18, 19] Increasing number of CL cases with numerous outbreaks due to displacement caused by disastrous events and wars in Iraq and cost burden of Pentostam on Ministry of Health pushed the dermatologists to find acceptable alternatives. Our study aimed to compare the efficacy and safety of Intralesional sodium stibogluconate (Pentostam® 100 mg/mL) and Intralesional Metronidazole (Flagyl® 5 mg/mL) solutions in the treatment of cutaneous leishmaniasis.

Materials and methods

This study is a clinical trial that was done in Dermatology Consultancy Clinic of Al-Hussain Teaching Hospital, Nassiriah (Thi Qar Province Center), Iraq, over the period from June 2015 to June 2016. Inclusion criteria were patients with single lesion of cutaneous leishmaniasis irrespective of age and gender. Exclusion criteria were lesions of more than 12 weeks' duration, with surface area more than 10 cm^2 or lesions close to the eyes, inflamed lesion, patients who received local or systemic anti-leishmanial treatment during the last 6 weeks, pregnancy, chronic diseases (like diabetes mellitus, peripheral neuropathy and poor peripheral circulation) and prolonged corticosteroid therapy. A convenient sample of 100 patients with single lesion of cutaneous leishmaniasis was selected from patients who were visiting the clinic. An informed written consent was obtained from each patient and/or their parents before instituting the treatment and the patients with their data were handled according to Helsinki Declaration.

The data were collected by the researcher through direct interview and fulfilling a prepared questionnaire designed by the researcher. In All 100 patients, the diagnosis of cutaneous leishmaniasis were made on the clinical basis of a typical, non-healing, painless, indurated papule, nodule, or plaque, etc. with or without crust in patients coming from geographic areas previously delineated as endemic areas of leishmaniasis. For this study, a single typical cutaneous leishmaniasis lesions from each patient had been labelled by writing its number on a piece of adhesive plaster and put above or below the lesion, then the numbers were mixed and assigned by lottery into two groups according to type of treatment (Pentostam 100 mg/mL) or (metronidazole solution 5 mg/mL) and 50 patients were selected for each group, then the lesions length and width is measured by a ruler and documented and photographed by a Samsung mobile camera. During each visit for a total of eight visits, the lesion and perilesional area of the lesion is sterilized by povidone iodine 10% and then 0.2 mL of sodium stibogluconate solution (Pentostam; 100 mg/mL) was infiltrated through the surrounding normal skin into the lesion for each 1 cm^2 area of the lesion resulting in a blanching and this procedure was

repeated to cover the whole lesion. On the other hand, the other labelled lesion was infiltrated by 0.2ml of metronidazole solution (Flagyl; 5 mg/mL) for each 1 cm^2 area of the lesion and this procedure was repeated until blanching of the whole lesion had occurred. This procedure was done weekly for a maximum of 8 weeks' duration and during each visit the lesions' induration was measured in size and photographed again and documented.

By the end of 8th week, the response to therapy was graded according to the following scale: complete improvement (full re-epithelialization of the lesions), partial improvement (decrease in induration size between 50% and 75%) and no improvement (decrease in induration size <25%). During the visits, we evaluated side effects of the two treatment options. All patients' data were entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) v. 21 was used.

Results

A total of 100 patients with CL were included (50 CL patients treated locally with pentostam and 50 patients were treated locally with metronidazole). No significant differences were observed between two study groups regarding patients age and gender (P=0.9, P=0.6, respectively) (Table I).

No significant difference in CL duration was observed between two study groups (P=0.8). Cutaneous leishmaniasis lesions types, sites and diameter were not significantly different between two study groups (P=0.5, P=0.06, P=0.6, respectively) (Table II).

Treatment sessions were not significantly different between two study groups (P=0.8). Patients treated with Pentostam were significantly associated with a higher complete re-

TABLE I.—*Distribution of demographic characteristics of leishmaniasis patients according to treatment types (N.=50 for each group).*

Variable	Leishmaniasis patients		
	Pentostam N. (%)	Meronidazole N. (%)	P value
Age			
<10 years	25 (50.0%)	26 (52.0%)	0.9**
10-19 years	17 (34.0%)	17 (34.0%)	
20-29 years	4 (8.0%)	3 (6.0%)	
≥30 years	4 (8.0%)	4 (8.0%)	
Gender			
Male	32 (64.0%)	30 (60.0%)	0.6*
Female	18 (36.0%)	20 (40.0%)	

*χ^2 test; **Fisher's exact test.

TABLE II.—*Distribution of lesions characteristics of leishmaniasis patients according to treatment types (N.=50 for each group).*

Variable	Leishmaniasis patients		
	Pentostam N. (%)	Meronidazole N. (%)	P value
Duration			
≤2 months	29 (58.0%)	26 (60.0%)	0.8*
>2 months	21 (42.0%)	17 (40.0%)	
Lesion type			
Dry	45 (90.0%)	47 (94.0%)	0.5**
Wet	5 (10.0%)	3 (6.0%)	
Lesion site			
Face	18 (36.0%)	8 (16.0%)	0.06**
Neck	6 (12.0%)	4 (8.0%)	
Upper limbs	16 (32.0%)	27 (54.0%)	
Lower limbs	10 (20.0%)	11 (22.0%)	
Lesion diameter			
≤2 cm	35 (15.0%)	33 (66.0%)	0.6*
>2 cm	15 (30.0%)	17 (34.0%)	

*χ^2 test; **Fisher's exact test.

TABLE III.—*Distribution of treatment outcome of leishmaniasis patients according to treatment types (N.=50 for each group).*

Variable	Leishmaniasis patients		
	Pentostam N. (%)	Meronidazole N. (%)	P value
Treatment sessions			
≤6 sessions	37 (74.0%)	38 (76.0%)	0.8*
>6 sessions	13 (26.0%)	12 (24.0%)	
Outcome			
No response	6 (12.0%)	27 (54.0%)	<0.001**
Partial response	0 (0%)	5 (10.0%)	
Complete response	44 (88.0%)	18 (36.0%)	
Complications			
No	10 (20.0%)	39 (78.0%)	<0.001**
Hyperpigmentation	30 (60.0%)	6 (12.0%)	
Scarring	6 (12.0%)	3 (6.0%)	
Hyperpigmentation and scarring	4 (8.0%)	2 (4.0%)	
Pain at injection			
Mild	0 (0%)	20 (40.0%)	<0.001*
Moderate	7 (14.0%)	29 (58.0%)	
Severe	43 (86.0%)	1 (2.0%)	

*χ^2 test; **Fisher's exact test.

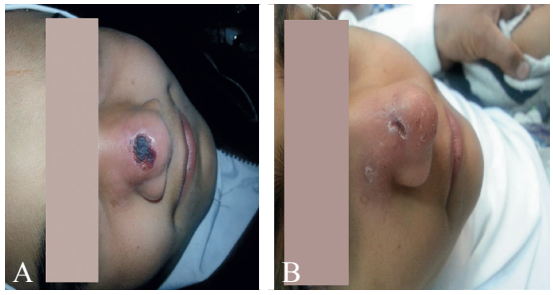

Figure 1.—A, B) 8-year-old female child with CL treated with Metronidazole (complete response after 6 sessions).

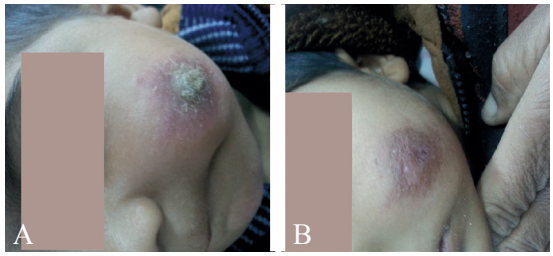

Figure 2.—A, B) 5-year-old male child with CL treated with Metronidazole (partial response after 8 visits).

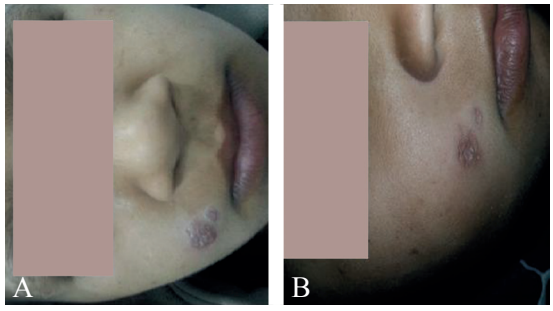

Figure 3.—A, B) Atrophic scarring and hyperpigmentation after treatment with Pentostam (5 sessions).

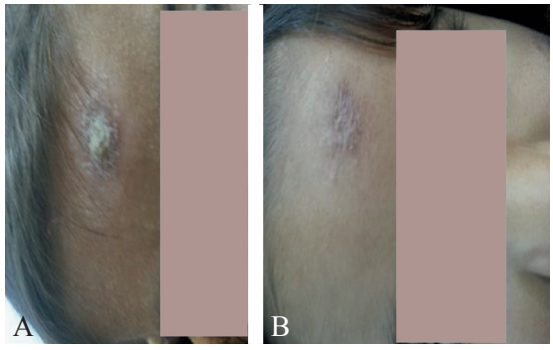

Figure 4.—A, B) 5-year-old child treated with Pentostam (complete response after 7 sessions).

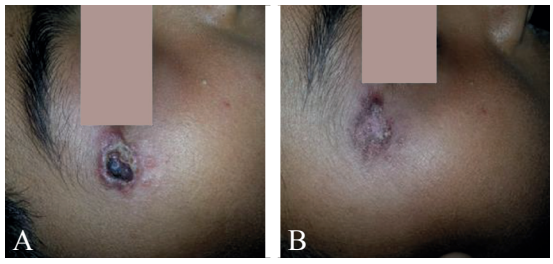

Figure 5.—A, B) Hyperpigmentation after treatment with Pentostam (6 sessions).

sponse than patients treated with Metronidazole (P<0.001). Complications of treatment (hyperpigmentation and scarring) were more frequently detected among patients treated with Pentostam (P<0.001). Pain at injection site was significantly perceived as severe among patients treated with Pentostam (P<0.001) (Table III, Figure 1, 2, 3, 4, 5).

Discussion

Cutaneous leishmaniasis is not a severe disease; however, it may be hardly tolerated by patients because of many reasons. Therefore, therapeutic abstention is rarely accepted despite the high rate of spontaneous recovery specially seen with old world cutaneous leishmaniasis.[2]

In the present study, cutaneous leishmaniasis treated with Pentostam solution had significantly higher response and better improvement (88%) in comparison to patients treated with Metronidazole solution (36%) (P<0.001). This finding is consistent with the results of Kellapatha *et al*.[18] study in Sri Lanka who reported that the standard treatment of Pentostam solution shows superior efficacy to Metronidazole in treating cutaneous leishmaniasis. Sharquie *et al*.[20] study in Iraq recommended intralesional Pentostam solution as a safe and effective treatment of acute cutaneous leishmaniasis. Pentavalent antimony compounds, the "best drug of a bad bunch" still remain the mainstay of treatment in the majority of cases.[20] However, Pentostam has a disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions. Other treatment

options are Pentamidine and imidazole compounds given systemically.[21] Drugs such as allopurinol, rifampicin, dapsone, chloroquine and Nifurtimox have showed favorable results in some studies.[22] Our findings are also similar to the results of Mapar *et al*.[19] study in Iran which stated that intralesional Metronidazole injections have little effect for the treatment of cutaneous leishmaniasis.

Inconsistent with our findings, Al-Waiz *et al*.[14] study in Iraq which showed that intralesional Metronidazole injection was significantly effective; and 85-87% of patients were cured with 1-3 injection. The difference between the result of this study and ours is noticeable, these differences may be due to different method of drug preparation, or different criteria for determining the cure, or may be due to different sensitivities of different geographical variants of the parasite species to Metronidazole solution.[14]

Many studies have shown that Metronidazole solution may be considered as a therapeutic option for old world cutaneous leishmaniasis leading to 66% recovery.[23, 24] Considering the self-limiting aspect of *Leishmania tropica* and *Leishmania major*, there is a need for more controlled studies to confirm the real contribution of Metronidazole solution to cutaneous leishmaniasis healing.[2] Our study showed that a complete response to Metronidazole was observed more in CL lesions of face than those of the upper and lower limbs. This fact might be attributed to many reasons that need further studies for analysis.

The most common complications reported in the present study for Cutaneous Leishmaniasis patients treated with Pentostam solution were hyperpigmentation and scarring which were significantly higher than complications seen among patients treated with Metronidazole (P<0.001). This is similar to the results of Oliveira et al study in Brazil.[25] However, there are concerns about cost, toxicity and the development of drug resistance to Pentostam. Pain at injection site was significantly more severe among patients treated with pentostam (P<0.001). Pain at the site of the injection was greater when administered intralesionally than IV/IM.[26, 27]

Limitations of the study

The main limitations of the present study were loss of follow-up to monitor the relapse rate and absence of culture testing.

Conclusions

This study concluded that Pentostam solution has a higher efficacy in the treatment of cutaneous leishmaniasis than Metronidazole solution but with higher rates of complications and pain at injection site. We recommend use of Pentostam as a first line treatment of cutaneous leishmaniasis. However, Metronidazole solution may be used as an alternative treatment of cutaneous leishmaniasis especially in case of sodium stibogluconate solution scarcity owing to cost and other reasons and in case of resistance to Pentostam.

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