Intralesional injection of 2% zinc sulfate solution in the treatment of acute Old World cutaneous leishmaniasis: a randomized, double-blind, controlled clinical trial

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Comparison of topical paromomycin sulfate (twice/day) with intralesional meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by *L. major*

This is an open study to compare the cure rate of cutaneous leishmaniasis caused by *L. major* and treated with either paromomycin sulfate or intralesional injection of meglumine antimoniate. Sixty parasitologically proven cases with 1-3 lesions were included and divided randomly into two equal groups; one group received 1 ml of meglumine antimonate intradermally every other day for 20 days, the other group received the ointment containing 15% parmomycin sulfate in urea twice daily for 20 days. The patients were clinically evaluated at 1 and 6 weeks after treatment was completed. The results of clinical evaluation at 1 week after treatment completed showed a cure rate of 18 out of 27 (66%) in the meglumine antimonate injected group and 20 out of 29 (68%) in the paromomycin sulfate treated group. The chi square test was used to compare the cure rate between the two groups and showed no significant difference (p = 0.85).

Key words: cutaneous leishmaniasis, meglumine antimoniate, paromomycin sulfate

Leishmaniases are among the major public health problems in many countries of Asia.

Cutaneous leishmaniasis (CL) is the most common form of leishmaniases. Control strategies have almost all failed especially in regard of zoonotic forms of the diseases [1]. Presently there is no vaccine available against leishmaniases [2]. There are two types of CL in Iran; zoonotic CL (ZCL) caused by *L. major* and anthroponotic CL (ACL) caused by *L. tropica*, and many modalities are used for the treatment of leishmaniasis [3]. Pentavalent antimonial is the current standard WHO recommended treatment for leishmaniasis which requires multiple injections, and has parenteral disadvantages such as local pain, toxicity and high cost which have led to the search for alternatives. The WHO recommendation for ZCL is no treatment except in patients with multiple lesions, lesions close to a vital organ and large lesions [1, 4]. Paromomycin ointment has been shown to be effective in experimental models of murine leishmaniasis [5-7]. Local paromomycin was considerd for use in cutaneous leishmaniasis and in a double blind controlled cross-over trial, 20 days topical treatment with 15% paromomycin in a soft paraffin showed a rate of 77% cure over 27% cure in the placebo group [8]. A two week course of 15% paromomycin plus 10% urea treatment in Iran showed a significantly higher parasitological cure in the treated group [9]. Later on a 4 week course of the same formula in Iran showed a significantly higher cure rate than two weeks (74%) or placebo (59%) [10].
In this open study the efficacy rate of paromomycin sulfate and intralesional injection of meglumine antimoniate in the treatment of CL caused by *L. major* was compared.

Materials and methods

Study design

This study was designed as a randomized, open, comparative clinical trial to evaluate the efficacy of paromomycin sulfate in comparsion with intralesional injection of meglumine antimonate.

Study population

This study was performed in Mousian, Dehloran; a ZCL endemic area, located in western Iran.

Ethical considerations

The study was approved by the Army Ethical Committee. The objective and procedure of the trial were explained in a simple language to potential candidates and only those volunteers who signed the informed consent were included in the study.

Recruitment

This study was performed in a Military Base Clinic from January to October 2001. Three hundred male CL suspected cases were refered to the clinic. Sixty parasitologically proven cases of CL, healthy apart from CL, lesions not in close proximity to a vital organ or joint were included. Number of lesions 1-3, ulcer size less than 5 cm in diameter, onset of the lesion less than 3 months, no previous standard anti-*Leishmania* treatment, and no history of allergy to the paromomycin family were recruited. Each patient was interviewed and physically examined before initiation of the

treatment. A photograph of each patient's lesion was taken before and at week 1 after the treatment was completed.

Diagnostic criteria

Cutaneous leishmaniasis was approved by direct smear. One to three scrapings were taken from the border of the lesion(s) of each patient, stained with Giemsa stain [11].
Sixty male patients with proven CL were divided randomly into two equal treatment groups. One group received 1 ml of meglumine antimoniate intradermally every other day for 20 days. Each lesion was injected in the upper and mid-dermis using a 30-gauge needle. Infiltration was thorough and produced a complete blanching at the base of the lesion [3]. In order to avoid any bias all injections were performed by the same physician. The second group of patients was treated with paromomycin sulfate (0.5 mg/mm^2/day) after cleaning the lesion(s) with soap and water twice a day for 20 days and treated lesions were left uncovered [9, 10]. The ointments were used under the observation of medical staff.

Paromomycin sulfate ($C_{23}H_{45}N_5O_{14}$. xH2SO4) and meglumine antimoniate

Paromomycin ointment used in this trial contained 15% paromomycin sulfate (MW = 615.65) and 10% urea in 30 gram of white soft paraffin in a collapsible tube. Paromomycin ointment was purchased from Razak Laboratories Co., Tehran, Iran.
Meglumine antimoniate (Rhone-Poulenc Rorer, Paris, France) was kindly donated by Ministry of Health and Medical Education.

Follow up

Follow up and clinical evaluation of the patients were performed at week 1 and week 6 after the treatment was completed. The patients were visited once at 6 months after treatment was completed. Parasitological evaluation was performed at week 6 only in patients with active lesion(s).

Responses to treatment

Complete cure was defined as complete re-epithelization of all lesions at one week after cessation of treatment. Patients with multiple lesions were considered to be cured if all the lesions were healed.
Partial cure (parasitological cure) was defined when clinical cure had not occurred in any lesion in a patient but no *Leishmania* amastigote was found in a direct smear of the lesion(s), 3 slides were prepared, and stained from each active ulcer and 1,000 fields were checked (aproximately 3 slides) [11].
Failure of treatment was defined as no clinical cure and no parasitological cure at one week after cessation of treatment.
Relapse was defined as a reappearance of the lesion after complete cure.

Statistical analysis

Epi-Info Version 6 was used for data entry and satistical analysis. Student's t-test was used to compare the means and chi-square was used to compare the proportion. All statistical tests were two tailed. A ρ-value of < 0.05 was considered as a significant difference.

Results

Patient characteristics

Sixty parasitologically proven cases were selected and randomly assigned to receive either meglumine antimoniate or paromomycin sulfate, there was no statistical difference between the age, weight and lesion characteristics of the two groups *(table 1)*.

Treatment efficacy

Three of 30 patients in the meglumine antimoniate treatment group and one of the patients in the paromomycin sulfate group were withdrawn from the study because of cutaneous reactions like erythematosis, urticaria or lymphadenitis with pain, the withdrawn patients were put on systemic meglumine antimonate and were all cured; 20 mg/kg for 14 days. No systemic toxic reaction attributable to the drug was observed.
The results as shown in *table 2*, indicates a complete cure in 18 out of 27 (67%) in the meglumine antimoniate group and 20 out of 29 (69%) in the paromomycin sulfate group which statistically is not significant (p = 0.85). The partial cure rate was 7 out of 27 (26%) in the meglumine antimoniate group and was 3 out of 29 (10%) in the paromomycin

Table 1. Initial characteristics of patients recruited for the treatment with either paromomycin sulfate ointment or intralesional injection of meglumine antimoniate

Characteristic	Paromomycin sulfate (N = 30)	Meglumine antimoniate (N = 30)	ρ-value
Age (year)	20.6 ± 1.2	21.7 ± 2	0.32
Lesion size (mm)	21.7 ± 2.3	25 ± 7	0.21
Lesion duration (days)	37.8 ± 3.5	39 ± 5.1	0.24
No. of lesions per patient	2	2.4	0.10
No. of lesions	60	76	0.035
One lesion	11	3	
Two lesions	8	8	
Three lesions	11	19	
Location of the lesion(s)			
Head & neck	15	10	0.36
Upper extremities	25	36	
Lower extremities	19	28	
Trunk	1	2	
Type of lesions			
Papular	9	14	0.65
Nodular	5	9	
Ulcerative	46	53	

Table 2. Results of evaluation at one week after completion of the treatment

Outcome	Paromomycin sulfate No. (%)	Meglumine antimoniate No. (%)	ρ-value
Cure	20 (69)	18 (67)	0.85
Partial cure	3 (10)	7 (26)	0.24
Failure	6 (21)	2 (7)	0.65
Total	29 (100)	27 (100)	

sulfate group (not significant). The failure rate was 2 out of 27 (7%) in the meglumine antimoniate group and 6 out of 29 (21%) in the paromomycin sulfate group (not significant).

Discussion and conclusion

Leishmaniasis caused by intracellular protozoan of the genus *Leishmania*, depends upon the host immune response and the *Leishmania* species, leishmaniasis presents a wide spectrum of clinical manifestations. Based on the diversity of epidemiological characteristics, specific to each species and its environment, vector and reservoir control are impractical, costly and usually require political commitment and infrastructures beyond the means of the countries suffering most from this disease [1, 4, 12]. Antimonials are still the first line of treatment for leishmaniasis [3]. Treatment of CL with antimonials is expensive, needs multiple injections, is acompanied by side effects and moreover variations in efficacy and drug resistance are reported [4, 12, 13]. In Iran only meglumine antimoniate is available, and usually when a patient has a limited number of lesions, intralesional injection of meglumine antimoniate is used. Intralesional injection of meglumine antimoniate is as effective as systemic [14] and even leads to a faster improvement of the lesion [15], but multiple intralesional injections around the ulcer is very painful and not all patients tolerate it, intralesional injection also needs special medical services which are not available in most endemic areas. In this study intralesional injection of meglumine antimoniate was compared with paromomycin sulfate.

Paromomycin, like all the aminoglucoside antibiotics, inhibits protein biosynthesis in sensitive organisms [16]. Most reports have shown successful topical treatment of CL with paromomycin containing 12% methylbenzethonium chloride (MBCL) [5-8, 17, 18]. Regarding the fact that local pain and inflammation are frequently reported with MBCL, in contrast to the use of paromomycin containing 10% urea [9, 10], in this formulation, urea was replaced for MBCL. The result of a study in Iran showed that a 4 week course of treatment is more effective than a two week course [10].

In summary, paromomycin sulfate has been shown to be safe and as effective as intralesional injections of meglumine antimonate in the treatment of ZCL caused by *L. major*. The rate of self healing varies from case to case and depends on various factors such as the duration of the lesion, charecteristics of the lesion etc. Patient memory is the only way to estimate the lesion(s) duration, there is a report that showed paromomycin ointment is effective on ulcerated lesions [19]. WHO recommended not to treat uncomplicated cases of ZCL or postpone the treatment for a few weeks until enough immune response is generated [1]. This strategy is very difficult to implement especially in new endemic areas in which the residents are not sure of the self healing nature of the disease. The least beneficial use of topical paromomycin in endemic areas is to postpone the use of antimonials for a few weeks, with increasing antimonial resistance in leishmaniasis, the first line anti-*Leishmania* drug should be reserved only for complicated cases of CL. ■

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