Research Articles

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A double blind, randomised placebo controlled trial of rifampicin with omeprazole in the treatment of human cutaneous leishmaniasis

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Abstract

Background & objectives: This study was conducted on 50 patients of Anthroponotic cutaneous leishmaniasis (oriental sore) to assess the efficacy of rifampicin and omeprazole through a double blind, randomised placebo control study.

Methods: The diagnosis of Anthroponotic cutaneous leishmaniasis (ACL) caused by *Leishmania tropica* was done by demonstration of *Leishmania tropica* (LT) bodies from the painless, dry ulcerative lesion. Each patient was assessed clinically in the beginning of the study, at the end of 2 ,4 and 6 weeks and all observations were compared in both the groups. Twenty-five patients received rifampicin with omeprazole (Group A) whereas other 25 patients received placebo (Group B) for a period of six weeks.

Results: Altogether 23 cases in group A and 21 cases in group B completed the study. About 16 (69.7%) cases in group A and 3 (14.29%) cases in group B had complete healing, whereas 3 patients (13.04%) of group A and 4 patients (19.05%) of group B had partial response and 4 patients (17.93%) of group A and 14 patients (66.67%) of group B had no response at the end of study. The difference of two groups was statistically highly significant ($p<0.00025$). All patients tolerated the drug and placebo very well and no side effect was reported.

Interpretation & conclusion: In our opinion rifampicin and omeprazole is a highly effective, less toxic and cheaper alternative for the management of cutaneous leishmaniasis.

Key words Anthroponotic cutaneous leishmaniasis – *Leishmania tropica* – oriental sore – rifampicin

Introduction

Cutaneous leishmaniasis is a vector borne parasitic disease caused by a number of different *Leishmania* species. Following the bite of an infected sandfly the clinical manifestations of the disease are largely governed by the characteristics of the infecting *Leishmania* species. Infection can be limited to the skin or mucous membrane in localised cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL) or mucosal leishmaniasis (ML)[1].

Cutaneous leishmaniasis is prevalent in different parts of India, but distribution of the disease is not uniform. It has been reported from Bikaner (in the northwest India) at endemic levels[2-5]. Studies carried

out in Rajasthan during 1971–73 revealed the existence of two clinicoepidemiological types—(i) Anthroponotic cutaneous leishmaniasis (ACL) restricted to urban areas, and (ii) zoonotic cutaneous leishmaniasis (ZCL) restricted to rural areas. A long-term follow-up study carried out during 1973–76 in these foci revealed that ACL is caused by *L. tropica* where man is a reservoir and man-to-man transmission is maintained by *Phlebotomus sergenti*. The disease is characterised by dry type of ulcer and ZCL is caused by *L. major*, a naturally occurring infection of *Meriones hurriannae*, a desert gerbil species maintained by *P. salehi*, a sandfly breeding in rodent burrows. Human infections are occupational hazards and are characterised by wet type of ulcers[5,6]. A clinical study carried out in S.P. Medical College & PBM Hospital, Bikaner during 1981–82 identified that cases coming from Bikaner city area are only of dry type and caused by *L. tropica*[7]. Recently Himachal Pradesh has also been identified as a new endemic focus of this disease in India[8]. The lesions are usually seen on the exposed parts of body such as face, hands and legs and recovery after the treatment usually leaves a disfiguring dark coloured scar and pitted area over the affected body parts[9,10].

Different treatment regimens are available for the management of cutaneous lesions. Many authors have also advocated no treatment because of spontaneous healing which usually occurs after 6 months from the onset of disease[11,12]. For many years, patients had been treated with sodium stibogluconate, a pentavalent antimonial compound but this treatment is less than adequate because of prolonged intravenous therapy, drug toxicity, and frequent need of hospitalisation for the complete treatment course (usually 20 days). Pentamidine is also used as an alternative to sodium stibogluconate. Intralesional berberine sulphate is also used but is more painful and leaves scars after healing[4].

Various oral medications such as ketoconazole, itraconazole, metronidazole, allopurinol, dapsone, etc. have been used but their effects are not consistent. As the prolonged injectable treatment modalities for oriental sore are not well accepted by patients, and other available oral drugs are not uniformly effective, many workers have studied the effect of rifampicin as an oral treatment for oriental sore and it had shown some promising results[13-17]. Moreover, omeprazole has been found to be effective against *Plasmodium falciparum in vitro*[18]. Rapid influx of H^+ into the everted vesicles of *Leishmania* species was found to be dependent on the simultaneous presence of adenosine-tri-phosphate (ATP) and Mg^{++}. H^+ entry into the everted vesicles is strongly inhibited by omeprazole[19]. Taking these observations into account we tried to assess the effect of combination of rifampicin and omeprazole in the treatment of oriental sore.

Material & Methods

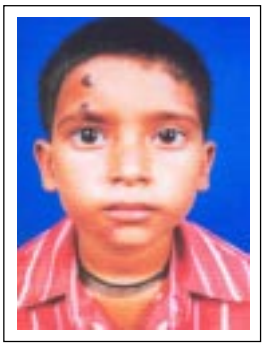
This study was conducted on randomly selected 50 cases of Anthroponotic cutaneous leishmaniasis. Biopsies were taken from the edge of the skin lesions, and were stained with Giemsa stain. The diagnosis was confirmed by demonstration of LT bodies (amastigote stage of *L. tropica* under oil immersion). Informed consent was obtained from all adult participants and from parents or legal guardians of minors. The protocol was approved by the ethical committee of the unit. One group of patients received rifampicin (1200 mg/day) in two divided doses plus omeprazole 20 mg, whereas another group of patients received placebo in a double blind controlled fashion for 6 weeks. Detailed history and clinical examination including duration of disease, site, number, type and distribution of lesions were noted in a proforma. Laboratory investigations including haemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), serum bilirubin, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) were done in every patient before starting the treatment and at the end of 2, 4 and 6 weeks after initiating treatment. All these data were collected on special proforma and the study was kept dou-

ble blind. At the end of 6 weeks, the files were decoded, and the patients were divided into two groups—Group A, receiving rifampicin and omeprazole and group B receiving placebo. Clinical and parasitological evaluations of the patients were performed again at the end of the treatment period. The data were collected on special proforma and MS-Excel was used to tabulate the findings. Statistica 5.0 was used to analyse the data. A cure was defined as complete healing and disappearance of the lesion or reversible hypopigmentation at the site of lesion. Incomplete or partial healing was defined as a reduction in the size of a lesion and the absence of parasites on smear.

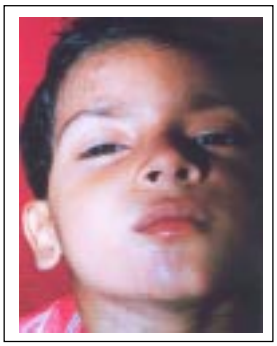
Results

The present study was conducted on 50 cases of Anthroponotic cutaneous leishmaniasis caused by *L. tropica* who attended the associated group of hospital, Bikaner. The diagnosis was confirmed by demonstration of *Leishmania tropica* (LT) bodies from the lesion. The LT bodies are the amastigotes form of parasite in the Giemsa stained smear. It was observed that the amastigotes were heavily packed in the mononuclear leucocytes, the cytoplasm was light blue, nucleus appeared purple and the kinetoplast appeared reddish purple. The nuclei in mononuclear leukocyte were oval or globular in shape.

The details of cases of two groups are depicted in Flow chart and Table 1. The ratio of male to female was 2.13 : 1. Male predominance was probably due to the habit of sleeping in open space outside the house without mosquito nets and improper clothing during night when the sandflies are active. Regarding the type of lesion, erythematous nodular was the most common type (40%) followed by erythematous plaque (16%), erythematous ulcerative (14%), nodular (12%), ulcerative (10%) and nodular ulcerative (8%). Maximum cases were presented with 1–2 months of duration of disease. The differences in the healing rates at the end of study between the two groups were statistically significant. The Peto and Peto Wilcoxon test compared two samples for the entire period of the study. The patients who did not show healing till the end of the study were censored. About 20% patients had unhealed lesions in the group receiving rifampicin and omeprazole whereas over 82% of patients had unhealed lesions at the end of 6 weeks in the group receiving placebo. Other details are given in Table 1.



Patient having multiple lesions on the face (Nodular type)



Same patient showing complete healing after treatment

Discussion

Cutaneous leishmaniasis is being reported from almost every part of the world but it is commonly re-

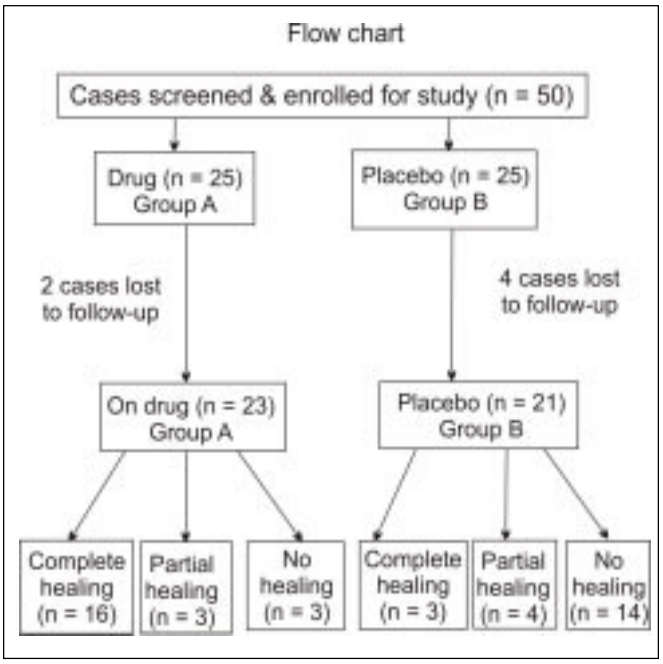


Table 1. Clinical characteristics of patients with cutaneous leishmaniasis

	Group A (Rifampicin + Omeprazole)	Group B (Placebo)	Total no. of patients	
Male	17	17	34	(68%)
Female	8	8	16	(32%)
Age in years				
16–20	12	10	22	(44%)
21–30	5	4	9	(18%)
31–40	4	5	9	(18%)
41–50	2	3	5	(10%)
51–60	2	2	4	(8%)
61–70	0	1	1	(2%)
Type of lesion				
Erythematous nodular	11	9	20	(40%)
Erythematous plaque	3	5	8	(16%)
Ulcerative	3	2	5	(10%)
Erythematous ulcerative	2	5	7	(14%)
Nodular	4	2	6	(12%)
Nodular ulcerative	2	2	4	(8%)
Duration of disease in months				
0–1	2	6	8	(16%)
1–2	8	7	15	(30%)
2–3	5	5	10	(20%)
3–4	2	3	5	(10%)
4–5	1	0	1	(2%)
5–6	4	3	7	(14%)
6–8	1	0	1	(2%)
8–12	1	1	2	(4%)
>12	1	0	1	(2%)
Number of lesions				
1	14	14	28	(56%)
2	5	7	12	(24%)
3	5	4	9	(18%)
>3	1	0	1	(2%)
*Distribution of lesions**				
Face	4	11	15	(30%)
Neck	3	2	5	(10%)
Arms	6	3	9	(18%)
Hand	9	6	15	(30%)
Back	2	2	4	(8%)
Abdomen	1	3	4	(8%)
Buttock	1	1	2	(4%)
Legs	4	3	7	(14%)
Foot	3	4	7	(14%)
Response to therapy				
Complete healing	16	(69.57%)	3	(25.29%)
Partial response	3	(13.04%)	4	(19.05%)
No response	4	(17.39%)	14	(66.67%)
P-value	0.0007			
Chi-square value	14.532			

(*contd...*)

*Patients were having lesions at two anatomical locations.

ported from the area in and around Bikaner. Clinical diagnosis is sometimes difficult, because occasionally it resembles other skin diseases and the definitive diagnosis is possible only by demonstration of organisms from the lesion. Serological and leishmanian skin tests become positive in 4–6 weeks, but they may demonstrate cross-reactivity with other parasitic diseases[17]. Serological testing is an insensitive means for diagnosing cutaneous leishmaniasis because antibody titres are only minimally elevated, except in patients who have diffuse cutaneous leishmaniasis[20]. Depending on the availability of laboratory backup, the species should be identified by molecular methods. All the cases in this study were diagnosed only by demonstrating LT bodies from skin biopsy specimen.

There are very few options for the treatment of cutaneous leishmaniasis, and the commonly used treatment with antimonial compounds that require daily parenteral administration and frequent need of hospitalisation. It is also associated with many adverse effects, including those related to musculo-skeletal symptoms, liver, bone marrow toxicity, pancreatitis and electrocardiographic abnormalities. Intravenous catheter related complications were also observed in patients who were administered intravenous sodium stibogluconate for 20 days[21]. A recent study of parenteral sodium stibogluconate therapy for cutaneous leishmaniasis revealed complete healing of the lesions without scaring at the end of treatment. All patients developed transient musculoskeletal symptoms and asymptomatic hepatitis[17]. Sodium stibogluconate and berberine sulphate are also given locally, however, these are painful and not acceptable to patients with multiple lesions[4]. Drug toxicity is also very common with the use of pentamidine and amphotericin B for the treatment of cutaneous leishmaniasis.

In an earlier study, the use of metronidazole did not show major clinical improvement in cutaneous leishmaniasis[22,23]. A study from northern Algeria observed good results with ketoconazole, but in other studies it was almost entirely ineffective in patients with CL caused by *L. tropica* and *L. aethiopica*[24–27].

Rifampicin was used by various workers for management of cutaneous leishmaniasis and showed some promising results[13,14,16]. In one study, rifampicin (1200 mg/day) was used in 46 patients and 41 patients showed complete healing[13]. However, many other workers have questioned the efficacy of a short-term course of rifampicin therapy[28]. The effect of rifampicin is through its property of blocking RNA synthesis by specifically binding and inhibiting DNA dependent RNA polymerase. In a study from this institution on 46 patients in which 23 patients received rifampicin 1200 mg/day in two divided doses and another 23 received placebo for a period of 4 weeks, those receiving drugs 17 (73.9%) had complete healing, 2 (8.6%) had partial healing and 4 (17.3%) had no response, whereas in the placebo group 1 (4.3%) had complete healing, 8 (34.8%) had partial healing and 14 (60.9%) had no healing or exacerbation of lesion. The difference was statistically significant and the drug was well tolerated[16].

Among the benzamidazoles, the omeprazole had shown promising effect against *Plasmodium falciparum in vitro*[18]. It remains a possible and promising therapeutic agent either alone or in combination, but its effect on the *Leishmania* parasite was not available even after extensive internet search. The rapid influx of H^+ into everted vesicles of *Leishmania* species was found to be dependent on the simultaneous presence of ATP (1 mM) and Mg^{++} (1 mM). H^+ entry into everted vesicle was strongly inhibited by SCH28080 (IC_{50} = approximately 40 μM) and by omeprazole (IC_{50} = approximately 50 μM), both of which were characteristic inhibitors of mammalian gastric H^+, K^+ ATPase[19]. On this observation we thought to combine rifampicin with omeprazole for the management of cutaneous leishmaniasis.

At the end of the study we observed that out of 23 patients receiving rifampicin, 16 (69.6%) cases had complete healing, 3 (13.04%) had partial healing and 4 (17.4%) had no healing whereas in the placebo group 3 (14.2%) cases had complete healing, 4 (19.05%) had partial healing and 14 (66.7%) had no healing. The difference was statistically significant ($p<0.05$).

Thus, from the result of the present study it can be safely concluded that rifampicin with omeprazole was very effective, cheap, easily available and well-tolerable oral alternative treatment for cutaneous leishmaniasis. This short-term preliminary study provided some useful data about the efficacy of rifampicin and omeprazole in cutaneous leishmaniasis and thus provided the basis for further studies with larger group of patients.

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