Research Article

Rifampicin and Trimethoprim\Sulfamethoxazole plus intralesional antimony compared with antimony alone in treatment of cutaneous leishmaniasis.

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ABSTRACT

The present study was conducted to evaluate the efficacy of Rifampicin and Trimethoprim plus sodium stibogluconate antimony and sodium stibogluconate antimony in treatment of cutaneous leishmaniasis. This study was carried out on 89 patients were enrolled in the study and were divided into two groups; group A included 43 patients treated with Rifampin and Trimethoprim plus sodium stibogluconate antimony of them 19 males and 24 females, while group B included 46 patients(24 males and 22 females) treated with sodium stibogluconate antimony, all were treated and evaluated weekly. The cure rate in complete response for patients in group A in six week 35(81.39%) and less rate was in one week 1(2.23%) when as compared with group B which recorded high rate in six week 31(67.39%) while did not show any response in one week. The highest rate of partial response was observed in the first week 16(37.20%) and then reduced in the third week 12(27.90%) and sixth week 7(16.27%) while the percentage of partial response in group B was reduced when as compared with group A. The present study recorded that the poor response of combination therapy in group A was 26(60.46%) in the first week then gradually reduced in third and sixth week 4(9.30%) and 1(2.32%) respectively while the poor response in group B was high especially in the first week 45(97.82%) and third week 20(43.47%).The present study showed that using adjunct drug such as Rifampin and Trimethoprim plus sodium stibogluconate antimony increase the therapeutic activity in treatment of cutaneous leishmaniasis when as compared with sodium stibogluconate antimony alone.

Key Words: Cutaneous Leishmaniasis, Rifampicin and Trimethoprim,Antimony, Therapeutic Efficacy.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a parasitic infection of skin macrophages that is caused by different leishmania species with L.tropica (40%) and L.major (60%) are being the most prevalent species in Iraq as proved by PCR technique[1].According to the WHO, 1.5 million cases are diagnosed with cutaneous leishmaniansis each year globally , and about 350,000,000 people are at risk of acquiring the disease in the 88 endemic countries ,including Iraq , where CL is considered a major health problem[2] .Although CL is a self-limiting disease , there are many justification for treatment including the duration of disease which might last for months or years with risk of complications as secondary bacterial infection, cosmetically important sites as the face with risk of serious disfigurement ,immune suppression and psychological impact on patient [3].Many treatment options are available for CL some are given systemically as sodium stibogluconate but it is limited by the painful injections ,systemic toxicities and resistance in some cases[4,5] , for those reasons other systemic agents have been used as ketoconazole [6,7], zinc sulfate [8] and dapsone[9]. on the other hand, the limited CL is preferred to be treated either topically by promomycin[10] and 50% trichlore acitic acid[11] , or by physical methods as cryotherapy[12] ,heat application and cauterization[13] or by intralesional injection of sodium stibogluconate [14], zinc sulfate 2%[15] among others. Although the intralesional sodium stibogluconate is the main stay for the treatment of CL ,there are indications for systemic therapy : an immune suppressed host; more than four lesions of substantial size (e.g. >1 cm) or individual lesion(s) measuring ≥5 cm; markedly enlarged regional lymph nodes; and involvement of the mucosa, face, ears, genitalia ,fingers, toes, or skin overlying a joint[16,17,18], but the intralesional therapy has a drawback of pain, erythema and swelling after treatment session[19] which might be problematic specially in children. For that reason ,the present study was designed to estimate the effectiveness of inralesional sodiumstibogluconate augmented by orally administered trimethoprim\sulfamethoxazole and Rifampin aiming to decrease the number of injection sessions and it's complications, increase the efficacy of pentavalent antimony, shorten the therapy duration and minimize or prevent the resultant scar.

Patients and methods

Patients population

The present study was carried out on 89 patient with typical cutaneous leishmanasis were involved in this study who visit the outpatients of dermatology and venerologyin Al-Hussein Teaching hospital in Thi-

Qar province / Iraq and AL-Yarmok Teaching hospital in Baghdad province. The period of study is conducted from September 2017 to the end of 2018. The diagnosis of each case based on the clinical examination, direct smear and a histopathological examination for the query cases in whom the smear was negative. A questionnaire for demographic and clinical data was designed to include the patients age, gender, address emphasizing on whether they live in rural or urban areas, number of lesions and it's sites, duration, any previous systemic, topical or intralesional therapy taken, past medical, surgical and drug history specially allergy to the drug used in this study. An examination was done to evaluate each lesion regarding the size in centimeters, induration, color, whether it is of dry or wet type, any signs of secondary bacterial infection and regional lymphadenopathy. Any patient with an indication for systemic pentavalent antimony (the mentioned indications above in the introduction) or with chronic debilitating disease, age less than 5 years, pregnancy or lactation were excluded. An interrogation and explanation were done to each patient or their next of kin (for children) regarding their disease and it's natural history, prognosis, possible complication and available treatment options. lastly,a formal consent was taken from each participant.

Table 1: participants'' characteristics of the two study groups.

Clinical features	Group A (trial) N=43	Group B (control) N= 46	P. value
Average age (year, mean ± SD)	27±12	29±14	--
Duration of lesions (mean±SD)	1.9±0.5	1.7±0.6	
Gender			
Male	19 (44.18%)	24 (52.17%)	0.451
Female	24 (55.81%)	22 (47.83%)	
Total	43 (100%)	46 (100%)	
Site of lesions			
Face	34 (35.41%)	41 (39.04%)	0.605
Upper extremities	25 (26.04%)	26 (24.76%)	
Lower extremities	21 (21.87%)	24 (22.85%)	
Trunk	16 (16.66%)	14 (9.52%)	
Total	96 (100%)	105 (100%)	
Clinical presentation			
Plaque	58 (60.41%)	52 (49.52%)	0.291
Nodule	24 (25%)	32 (30.47%)	
Papule	14 (14.58%)	21 (20%)	
Total	96 (100%)	105 (100%)	

P. value ≤ 0.05 Significant

Study design

The diagnosis was established by history, examination and The sample was divided into two groups regarding the type and size of the lesions:group A received intralesional sodium stibogluconate (0.1ml per 1 cm^2 of 100mg per ml vial)weekly plus oral 600mg Rifampicin and 160mg/800mg trimethoprim/sulfamethoxazole in two divided doses given twelve hourly (or 10 mg/Kg/day not to exceed 600mg/day Rifampin and 8mg/Kg/day trimethoprim for children) and group B whom received intralesional sodium stibogluconate (0.1ml per 1 cm^2 of 100mg per ml vial) weekly alone. a photograph was taken each visit and the lesion's dimensions, color and induration were recorded, the following parameters were checked at zero time then weekly until healing which are lesion size, color,induration and ulceration, also the patients were asked and examined for any possible

adverse drug reactions. Weekly, the patients evaluated according to the following criteria: cure was defined as no induration, reappearance of epidermal creases and no ulceration or crustation, partial improvement was defined as decrease the lesion's size, flattening, change of color from bright red to dusky red or brown but no epidermal creases seen, no and poor responses were defined as no change in color, size or induration. Also, a biochemical assessment of all participants was conducted at zero time, then at first week and monthly thereafter in form of complete blood count, liver function test and renal function test.Chi-squaretest was used in analysis of the results using SPSS programme, version 20.

Results

A total of 89 patients were enrolled in the study and were divided into two groups; group A included 43 patients of them 19 males and 24 females with total number of lesions was 96 , while group B included 46 patients (24 males and 22 females) and the total number of lesions was 105, all were treated and evaluated weekly. The mean patients' age was 27±12 years for group A and 29±14 years in group B, while the mean disease duration was 1.9±05, 1.7±06 months for group A,B respectively. The most observed clinical presentation was plaque type in both groups (60.41% in group A and 49.52% in group B), followed by nodular type (25% in group A and 30.47% in group B) and ,lastly, the papular type (14.58% in group A and 20% in group B) with no significant differences (P= 0.261). 57% of patients had more than one lesion. The most common site of involvement was the face in both groups (35.41% in group A and 39.04% in B) followed by upper and lower extremities and the least frequent site was the trunk for both groups with no significant differences (P= 0.605)..Weekly the patient was evaluated(till healing) for complete, partial and poor responses to the given therapy. The present study recorded that high rate of complete response in group A in six week 35(81.39%) and less rate was in one week 1(2.23%) when as compared with group B which recorded high rate in six week 31(67.39%) while did not show any response in one week. The complete response in both group A and B was relatively equal 40(93.02%) and 42(91.3%) respectively in third month. The highest rate of partial response was observed in the first week 16(37.20%) and then reduced in the third week 12(27.90%) and sixth week 7(16.27%) while the percentage of partial response in group B was reduced when as compared with group A. The poor response of combination therapy in group A was 26(60.46%) in the first week then gradually reduced in third and sixth week 4(9.30%) and 1(2.32%) respectively while the poor response in group B was high especially in the first week 45(97.82%) and third week 20(43.47%). The present study showed that the percentage of complete, partial and poor response was relatively equal in third month. Table (2) and figure (1).

Table2: percentage of response to therapy in both study groups (A and B) in 1st,3rd and 6th week and 3rd month.

Response	Week 1		Week 3		Week 6		Month 3	
	Group A N=43	Group BN=46	Group A N=43	Group BN=46	Group A N=43	Group B N=46	Group AN=43	Group B N=46
Complete	1 (2.23%)	0 (0.0%)	27 (62.79%)	8 (17.39%)	35 (81.39%)	31 (67.39%)	40 (93.02%)	42 (91.3%)
Partial	16 (37.20%)	1 (2.17%)	12 (27.90%)	18 (39.13%)	7 (16.27%)	12 (26.08%)	2 (4.65 %)	3 (6.52%)
poor	26 (60.64%)	45 (97.83%)	4 (9.30%)	20 (43.47%)	1 (2.32%)	3 (6.52%)	1 (2.32%)	1 (2.17%)
Chi square	19.241		22.105		2.460		0.148	
P.Value	0.000**		0.000**		0.292		0.929	

**P.value ≤ 0.05 mean high Significant

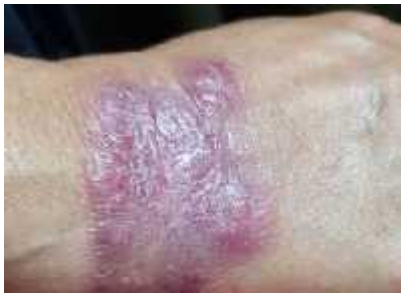
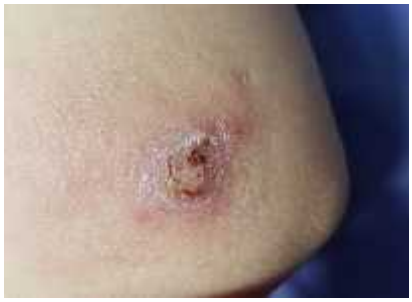
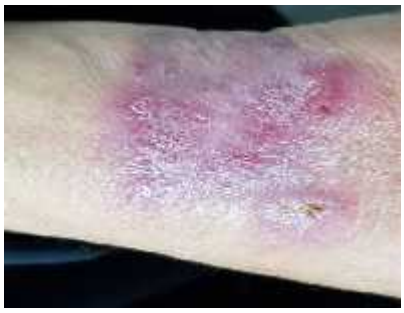
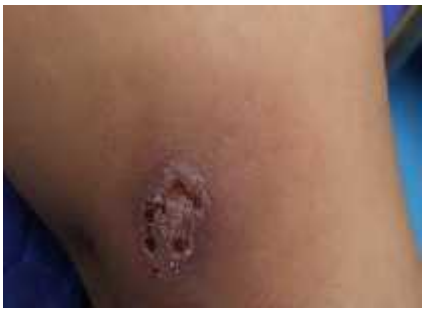
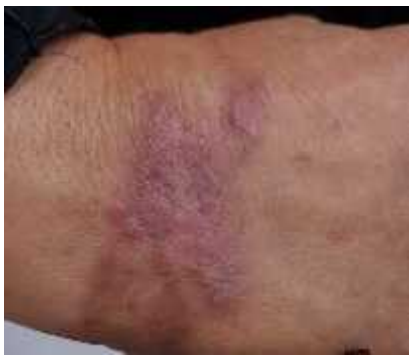
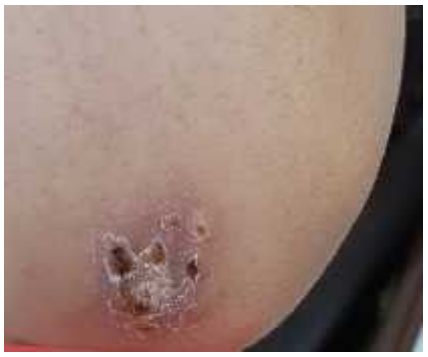
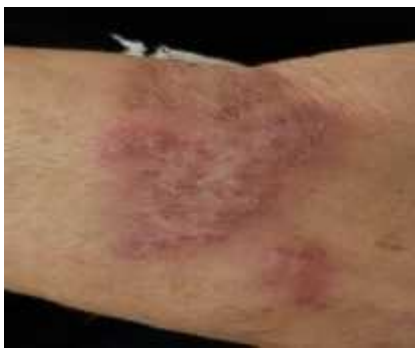
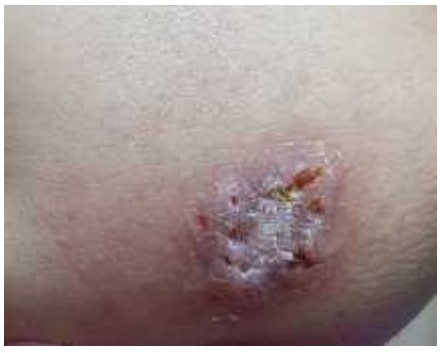
Time	A patient from group A	A patient from group B
At presentation		
First week		
Third week		
Sixth week		

Figure1: the findings of Combination therapy (systemic Rifampin and trimethoprim\ sulfamethoxazole) plus sodium stibogluconate with sodium stibogluconate in both group A and B.

Discussion

The pentavalent antimony is the most accepted treatment for cutaneous leishmaniasis[20] ,but the need for many painful injections, which is problematic particularly in children, increasing failure rate due to emergence of resistance and high cost[21][22] necessitate the seek for therapy augmentation to decrease number of treatment sessions with similar ,or even higher ,cure rate which ,in turn, shorten the disease duration, risk of secondary bacterial infection and local tissue destruction and ultimately minimize or prevent the resultant scar.The combination therapy may seem costlier than mono therapy in the short term, but when used appropriately, it causes significant savings such as lower treatment failure rate, lower case fatality ratio and fewer side effects than mono therapy, slower development of resistance and consequently, less money needed for the development of new drugs [25].The present study showed that the combination therapy (systemic Rifampin and Trimthoprim/sulfamethoxazole) plus sodium stibogluconate antimony giving effective therapeutic activity against the cutaneous leishmaniasis when as compared with sodium stibogluconate antimony alone. this study, which investigates the use of combination therapy (systemic rifampin and trimethoprim with weekly intalesional sodium stiboglocunat) in comparison with weekly intralesional sodium stiboglocunate demonstrate that the combination therapy was more effective and faster in clearing cutaneous leishmaniasis lesions with success rate (81.39%) as early as sixth week and a less treatment sections was required with better compliance and smaller, more shallow and more accepted scar. The reason of this activity may be using of antibiotic drugs such as Rifampin and Trimethoprim/sulfamethoxazole which is contribute in cure from cutaneous leishmaniasis within short therapeutic period by destruction of leishmanial stages by antimony and stopping the growth of bacterial infection associated for cutaneous leishmaniasis using the Rifampin and Trimethoprim/sulfamethoxazole.Rifampin[23] and Trimethoprim[24] had been used previously as a sole systemic treatment forcutaneous leishmaniasis with variable success rates. The parasitic infection always causes secondary infections represented by bacterial infection and this were confirmed by previous studies. When nodules due to infection with leishmania parasite ulcerate, they become susceptible to colonization with the number of microorganisms, such as pathogenic bacteria and fungus that could provoke secondary infection[26], therefore using the combination therapy may be contribute in killing of bacterial growth associated with parasitic infection in addition to attack of leishmanial bodies (amastigotes).[27] showed that the high concentration of Rifampin decreased the viable counts of leishmania promastigote. There are no reports in the published literature on the activity of systemic Rifampin and Trimthoprim/sulfamethoxazole plus sodium stibogluconate antimony on cutaneous leishmaniasis for comparison but there are many studies used the combination therapy such as [28]who refer to the cure rate for patients treated with stibogluconate was 39% while the addition of allopurinol increased this rate to 71%. [29]showed that the efficacy of ivermectin was highest followed by rifampicin, amphotericin B and nystatin in treatment of Balb/c mice infected with cutaneous leishmaniasis. In conclusion, the use of systemic Rifampin and(Trimthoprim/sulfamethoxazole) as an adjunct to antimony or another oral agent is leading to complementary role in the treatment of cutaneous leishmaniasis during shorten the duration of healing or prevent the scarring. The present study is recommended by the mentioned drug as primary drug especially if was the number of lesions is more or in special sites of body and using as complementary therapy in the cases which is did not respond for local injection by pentostam.

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