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Effect of using azithromycin and sodium stibogluconate in the treatment of cutaneous leishmaniasis

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Abstract:
This study was conducted on 50 patients with cutaneous leishmaniasis in Libya, and the patients were divided into two groups. Group A received sodium stibogluconate only by injection into the infection area and group B received combination therapy of sodium stibogluconate and azithromycin 500 mg orally. Follow-up was done to observe the recovery of the cases in the sixth week and at the end of the eighth week of treatment. The majority of the infections in patients were nodular (60%) and ulceration (40 %). After 6th week treatment, in group A, complete healing of the infection was found in 11(44%) patients and very good response found in 6(24%) patients, while inn group B, complete healing was found in18 (75%) patients and very good response was found in 4 (16%). It could be concluded that, oral azithromycin in combination with intral-lesional sodium stibogluconate could achieve earlier healing of the lesion and less possibility of resistant cases.

Keywords: Cutaneous leishmaniasis, intra-lesional sodium stibogluconate, azithromycin.

تأثير استخدام أزيثرومايسين وستيبوجلوكونات الصوديوم في علاج داء الليشمانيا الجلدي

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الملخص
أجريت هذه الدراسة على 50 مريض بداء الليشمانيا الجلدية في ليبيا، وتم تقسيم المرضى إلى مجموعتين، تلقت المجموعة (أ) ستيبوجلوكونات الصوديوم فقط عن طريق الحقن في المنطقة المصابة والمجموعة (ب) تلقت العلاج المركب من ستيبوجلوكونات الصوديوم وأزيثروميسين 500 ملجم عن طريق الفم. تمت المتابعة لملاحظة شفاء الحالات في الأسبوع السادس وفي نهاية الأسبوع الثامن من العلاج. وقد توصلت الدراسة إلى حدوث دمامل (عقد) لأغلب العدوى الجلدية بنسبة 70.5 % بينما وصلت نسبة القروح في هذه العدوى إلى 50 %.متوسط الوقت للعلاج يتراوح بين 2.7 اسبوع إلى 3.6 اسبوع لكل من المجموعة الأولى والثانية على التوالي. المجموعة الأولى (أ): في الأسبوع السادس وصل عدد المرضى الذين تم شفائهم بشكل كامل من العدوى الجلدية إلى 11 مريض (بنسبة 44 %) بينما وصلت حالات الشفا من المرض في المجموعة الثانية (ب) إلى 18 مريض (بنسبة 72%). في نهاية الأسبوع الثامن وصل عدد المرضى الذين تم شفائهم بشكل كامل من العدوى الجلدية في المجموعة الأولي إلى 16 مريض (بنسبة 64 %) بينما وصلت نسبة الشفاء في المجموعة الثانية إلى 20 مريض (بنسبة 80 %). النتائج المستنبطة من هذا البحث توصي بعلاج المرضى المصابون بالليشمانيا الجلدية بالمضاد الحيوي ازثرومايسين (جرعة فموية) مع الحقن بالصوديوم ستبوكلوكونيت لأن ذلك يعطي فعالية علاجية أكثر مقارنة بالحقن بالصوديوم ستبوكلوكونيت فقط.

الكلمات المفتاحية: داء الليشمانيات الجلدي، ستيبوغلوكونات الصوديوم داخل الآفة، أزيثروميسين.

Introduction

Cutaneous leishmaniasis is the parasitic infection that has different treatment options but no one was found to have satisfactory for both clinician and patient, in which resistance to treatment was the main problem that face therapy introduction [1,2]. Sodium stibogluconate still the treatment number one in management of cutaneous leishmaniasis (CL) , but emergence of difficult cases makes to think about alternative ways of treatment [3]. leishmaniasis is a parasitic infection caused by Leishmania species and transmitted to human by sand-fly vector. Cutaneous leishmaniasis (CL) was an endemic infection, self-limited but its course may prolong for one year or more and could have negative impact on various aspects of the patients as physical, psychological, social and economic [4,5]. Skin infection usually appear weeks to months after insect bite as papules, plaques and nodules and may be indurate, crusts, ulcerate accordingly [6] and the last healing residue usually was disfiguring scar [5]. Treatment of CL with pentavalent antimony, especially sodium stibogluconate SSG (pentostam) intra-lesionally for non-disseminated cases was successfully used [7]. Other drugs like azoles, rifampicin, metronidazole, paromomycin etc. were used for its treatment, but still SSG remains the first line of the treatment of Cutaneous leishmaniasi (CL) despite its side effects and cost [7,8]. Many studies were conducted to optimize treatment of cutaneous leishmaniasis (CL) because resistant cases to the above-mentioned treatments were going to grow up [9,10]. Bacterial super-infection to infection of cutaneous leishmaniasis (CL) was considered to be one of the complications of this disease which was incriminated to be the cause of the resistant cases to proven therapy. So that combating this super-infection was thought to be very helpful to reduce the possibility of resistance and better response to the treatment plan. Macrolides especially azithromycin and clarithromycin had been studied to be effective against Leishmania species of old world, but these studies were not conducted on the infection of human being [11,12]. Azithromycin due to its property of achieving high concentration in macrophages is promising in treatment of infection of cutaneous leishmaniasis (CL) [12,13].

In the Bani Walled area, Libya, after the outbreak of cutaneous leishmaniasis (CL), we were tried to conduct this study to compare the combination therapy of azithromycin (oral) and sodium stibogluconate (SSG) intra- lesionally.

Patients and Methods

This study was conducted from September 2021 up to March 2022 in the Bani Walled area in Lybia. Fifty patients with leishmaniasis were selected for this study. Patients were diagnosed clinically by two separate dermatologists and then confirmed parasitologically through detection of Donovan's bodies in the smears taken from patients' infection. The study sample randomly divided into 2 groups. The first group was 25 patients who received sodium stibogluconate within the infected area (IA) only, each infected area was injected with 0.5 - 1 ml and repeated every two weeks, The second group (B) was 25 patients who were injected with sodium stibogluconate intralesionally at the same dose as group (A) and repeated every two weeks, while took azithromycin tablets orally 500 mg three consecutive days a week for up to two months. Patients were followed up to monitor clinical improvement in the sixth week from the start of treatment and the second monitoring was at the end of the eighth week of treatment.

Statistical analyses

The statistical analyses of the data were done by using the software SPSS program version 22.

Results

This study was included 50 patients (males) suffering from cutaneous leishmaniasis (CL). The age of patients ranged between 27-30 years (mean of 28.5 ± 0.5 years). There were no significant ($P < 0.05$) differences between ages of both groups A and B ($P < 0.05$) as shown in Table 1.

Table 1. Main characteristics of patients in both groups

Characteristic	Groups		P Value
	Group A	Group B	
	SSG	SSG + Azithromycin	
Number of patients	20	25	> 0.05
Age / years	27	30	
Sex	Male	Male	
Duration of infection / weeks	3.6	2.7	

The majority of the infections in patients were nodular 60%. Ulceration was dominant characteristic of the infection found in 40 % of the infection as shown in table 2. The duration of the infections at the time of presentation was ranged between 3 and 9 weeks (mean of 3.6 ± 1.1 and 2.7 ± 1.8 weeks) in patients of group A and B respectively.

Table 2. Type and number of infection (ulcer or nodule)

Number of patients	Type of infection	Number of infections
20	Ulceration	40%
30	Nodule	60%

At 6th week follow up: in group A, complete healing of the infection was found in 11(44%) patients and very good response found in 6(24%) patients. In group B, complete healing was found in18 (75%) patients and very good response was found in 4 (16%). At the end of 8th week, in group A complete healing of the infection was increased and number of patients become 16 (64%) patients, while in patients of group B complete healing found in 20 (80%) as shown in Table 3.

Table 3. Response of the patients in both groups for therapy (during 6 week and after 8 weeks)

Follow up	8th week		6th week	
	Gr. B (N=25)	Gr. A (N=25)	Gr. B (N=25)	Gr. A (N=25)
Poor response	1 (4%)	2 (8%)	2 (8%)	5 (20%)
Good response	2 (8%)	3 (12%)	1 (4%)	3 (12%)
Very good response	2 (8%)	4 (16%)	4 (16%)	6 (24%)
Complete healing	20 (80%)	16 (64%)	18 (72%)	11 (44%)
Total	25	25	25	25

Discussion

Azithromycin has antiprotozoal and antileishmanial effect (Prata et al., 2003). Amer et al. (2016) tried oral azithromycin in combination with multifosine for the treatment of Leishmania major infection in mice and they proved the effectiveness of this combination of drugs. Secondary bacterial infection of CL infection in some case could complicate course of the disease, so that, the synergistic effect of both azithromycin and sodium stibogluconate could be due to the antibacterial effect of azithromycin which could eliminate secondary bacterial infection [2,12]. In our study, there were some cases that did not heal after 8 weeks therapy in patients receiving intra-lesional (IL) SSG (poor response 8 % and good response 12 %). During the course of therapy, no significant side effects of drugs had been observed apart from pain during intra-lesional injections.

Conclusion

According to the results of this study, it could be concluded that, oral azithromycin in combination with intral-lesional sodium stibogluconate could achieve earlier healing of the lesion and less possibility of resistant cases. Further studies need to be conducted to see the effect of these combination therapies on different species of cutaneous leishmaniasis (CL) in Libya to identify the species which is sensitive to the suggesting treatment. These need to provide identification of Leishmania species in all case of cutaneous leishmaniasis (CL) before the introduction of therapy which will provide more cost and time effective therapy; also, it will reduce probability of non- responding cases.

Recommendations

The results drawn from this research recommend treatment of patients with Leishmania dialis with the antibiotic azithromycin (oral dose) with injections of sodium stabugluconate, because this gave more therapeutic effectiveness compared to injections of sodium stabugluconate only.

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