Evaluation of intralesional 0.2% ciprofloxacin as a treatment for cutaneous leishmaniasis

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تقييم المعالجة الداخلية لآفات الليشمانيا الجلدية بالسيبروفلوكساسين 0.2٪

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الخلاصة: بالرغم من أن آفات الليشمانيا الجلدية تشفى في العادة تلقائياً إلا أنها تسبب ندبة سيئة المنظر. وتقيّم هذه الدراسة علاجاً جديداً محتملاً لـ 38 مريضاً لديهم 70 آفة، اختيروا عشوائياً لتجربة الحقن الداخلي بالسيبروفلوكساسين 0.2٪، أو معالجة الآفات داخليا بمحلول كلوريد الصوديوم المفرط التوتر (7٪). وبعد استبعاد المرضى الذين لم يواظبوا على العلاج، شفيت تماماً الآفات التي تلقت العلاج بمحلول كلوريد الصوديوم (وعددها=21) في 76.2٪ من الحالات، وعندما استمر وجود الندبة فإن حجمها قد انخفض بنسبة 66٪ مقارنة بحجم الآفة الأصلي. أما الآفات التي عولجت بالسبروفلوكساسين (وعددها=27) فكان معدل الشفاء فيها 81.5٪، وكان متوسط انخفاض حجم الندبة 68.6٪. إن العلاج الداخلي بالسيبروفلوكساسين 0.2٪ كان فعالاً مثل العلاج بالمحلول الملحي المفرط التوتر بالنسبة لآفات الليشمانيا الجلدية.

ABSTRACT Although cutaneous leishmaniasis lesions usually heal spontaneously they cause unsightly scarring. This study evaluated a possible new therapy in 38 patients, with 70 lesions, randomly assigned to intralesional injection of ciprofloxacin (0.2%) or intralesional sodium chloride hypertonic solution (7%). After excluding patients who defaulted on treatment, lesions assigned to sodium chloride treatment (*n* = 21) were completely healed (with or without scarring) in 76.2% of cases, and, when a scar remained, the scar size was reduced 66.0% compared with the original lesion. Lesions assigned to ciprofloxacin (*n* = 27) showed an 81.5% healing rate with an average scar size reduction of 68.6%. Intralesional 0.2% ciprofloxacin was as effective as hypertonic saline in the treatment of cutaneous leishmaniasis infection.

Évaluation de la ciprofloxacine en injection intralésionnelle à 0,2 % comme traitement de la leishmaniose cutanée

RÉSUMÉ Bien que les lésions causées par la leishmaniose cutanée guérissent en général spontanément, elles laissent une cicatrice disgracieuse. Cette étude a évalué une possible nouvelle thérapie chez 38 patients présentant 70 lésions, soumis de façon aléatoire à une injection intralésionnelle de ciprofloxacine (0,2 %) ou à l'administration intralésionnelle d'une solution de chlorure de sodium hypertonique (7 %). Après exclusion des patients qui n'avaient pas suivi le traitement, les lésions soumises au traitement par le chlorure de sodium (*n* = 21) avaient complètement guéri (avec ou sans cicatrice) dans 76,2 % des cas et lorsqu'il restait une cicatrice, sa taille avait diminué de 66,0 % par rapport à la lésion d'origine. Les lésions soumises à la ciprofloxacine (*n* = 27) montraient un taux de guérison de 81,5 % avec une réduction moyenne de la taille de la cicatrice de 68,6 %. L'administration intralésionnelle de ciprofloxacine à 0,2 % était aussi efficace que le soluté salin hypertonique dans le traitement de la leishmaniose cutanée.

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Introduction

Cutaneous leishmaniasis is a parasitic disease transmitted by biting insects (sandflies) [*1,2*]. The disease is endemic in Iraq [*3*] and in other neighbouring countries such as Kuwait, Saudi Arabia and the Islamic Republic of Iran [*4*]. In Iraq there are 2 main species of the genus *Leishmania* causing the infection: *L. tropica* and *L. major* [*5*].

Lesions usually heal spontaneously within several weeks or months [*6*], but it is reasonable to treat the lesions since they may persist for a long time leaving unsightly scars on healing [*7,8*]. Although antimony is the first choice of treatment, it is an unstable and toxic drug [*9*]. This has led many workers to try other drugs, such as sodium chloride hypertonic solution, zinc sulfate and metronidazole in local studies [*5,10,11*]. Good results were also obtained with ciprofloxacin, a wide-spectrum antibiotic, used topically in an experimental study on BALB/c mice infected with *L. major* [*12*].

The aim of this study was to evaluate intralesional ciprofloxacin (0.2%) as a new therapy for cutaneous leishmaniasis in humans and compare its efficacy with sodium chloride hypertonic solution (7%).

Methods

The study sample was all patients with cutaneous leishmaniasis who were diagnosed clinically by the same dermatologist in the outpatient clinic of Basra teaching hospital, south Iraq, from April 2004 to March 2005.

Information was taken from each patient, including the number of lesions, sites, history of infections and whether lesions had been treated previously or not. Thin blood films were made from the edge of the lesion and stained by Giemsa stain [*13*] and then examined microscopically. Exudates from lesions were also sampled and injected into semi-solid culture medium which was incubated at 26 °C and examined after 5–6 days to detect parasites.

The 38 patients had a total of 70 cutaneous leishmaniasis lesions. The patients were randomly divided into 2 groups with equal numbers of lesions in each: group 1 lesions (n = 35) were treated with hypertonic sodium chloride solution (7%) (7 g dissolved in 100 mL distilled water and autoclaved) and group 2 lesions (n = 35) were treated with ciprofloxacin solution (2 mg/mL). Both drugs were injected into the lesions in amounts of 0.1–0.5 mL according to the size of the lesion.

In order to measure the effect of each treatment, the diameter, erythema and induration of the lesions were assessed at the start and again at 2-week intervals after treatment for 8 weeks. A scoring system was specially designed as follows. The diameter of lesions was recorded in millimetres using a ruler and scored as: 0 (total healing); 1 (0–< 0.5 cm); 2 (0.5–< 1 cm); 3 (1–< 1.5 cm); 4 (1.5–< 2 cm); 5 (2–< 2.5 cm); or 6 (≥ 2.5 cm). The degree of induration was assessed by palpation in comparison with the patient's normal skin and given the following scores: 0, 0.5, 1, 1.5, 2 or 3. The degree of erythema was assessed by naked eye and scored as: 0, 0.5, 1, 1.5, 2 or 3. Ulceration was scored as: 1 (present) or 0 (absent). All parameters scores were converted to percentages, and then the mean and standard deviation (SD) % score were calculated. The scores of these 4 parameters were added to give a total score for each lesion.

The changes in total score between weeks 0–2, weeks 2–4, weeks 4–6 and weeks 6–8 were compared. Follow-up continued for 8 weeks until complete healing took place (i.e. resolution of active lesion with or without scarring). After healing, the scar size for each group was recorded and compared with the original lesion size to evaluate the efficacy of drugs in reducing scar size.

Statistical analysis was done by analysis of variance (ANOVA) and Student t-test test with significance at $P < 0.05$.

Results

A total of 38 patients with 70 cutaneous leishmaniasis lesions were treated and followed up during this study. The lesions were on different parts of the body but predominantly on the upper and lower extremities. The age of patients ranged from 1.5 to 64 years (1.5–45 years in group 1 and 3–64 years in group 2) with a mean of 21.1 years. There was no significant difference in the sex of the patients (52.5% males, 47.5% females). The duration of lesions before the study started ranged from 1 month to 5 years (Table 1).

Group 1 lesions were treated with hypertonic sodium chloride solution while group 2 lesions were treated with ciprofloxacin. After excluding patients who defaulted on treatment, a total of 21 lesions were analysed in group 1 and 27 in group 2. In both groups 1 and 2 marked reductions were seen in the total % scores of lesions after 2, 4, 6 and 8 weeks of treatment, with significant improvements within each group in the % scores between weeks 0–2 and weeks 2–4 (ANOVA test, $P < 0.05$) but not between weeks 4–6 and 6–8 (Table 2). After 8 weeks there was no significant difference in the mean total % scores between groups 1 and 2 (1.8% versus 5.4%).

At the end of the 8 weeks follow-up the mean % scores for diameter, induration and erythema separately showed some differences between the 2 groups but none were significant (Table 3).

After 8 weeks, 16/21 (76.2%) lesions were completely healed (with or without scarring) in group 1 and 22/27 (81.5%) in group 2 (Table 4). Healing was mostly achieved by 6 weeks. There were 5 lesions in both groups that showed no response. One lesion had been treated previously with pentostam

Table 1 Characteristics of cutaneous leishmaniasis lesions in each treatment group before the start of the study

Variable	Group 1 Sodium chloride	Group 2 Ciprofloxacin
No. of lesions treated at start of study	35	35
No. of lesions/patient		
1	7	7
2	5	8
3	1	2
> 3	7	5
No. of lesions by site		
Face and neck	8	3
Upper limbs	19	10
Lower limbs	7	18
Trunk	1	4
Mean lesion size before study (cm)	1.74	1.70
Range of lesion duration before study	1 month–1 year	1 month–5 years

Table 2 Total lesion scores during the 8 weeks of treatment

Time (weeks)	Group 1 Sodium chloride (21 lesions)	Group 2 Ciprofloxacin (27 lesions)
	Mean (SD) % score	Mean (SD) % score
0	100.0	100.0
2	70.2 (17.3)	62.1 (20.4)
4	33.3 (25.3)	39.3 (29.2)
6	9.5 (15.6)	9.3 (19.0)
8	1.8 (4.9)	5.4 (12.9)

SD = standard deviation.

Table 3 Mean percentage reduction in parameter scores after 8 weeks of treatment

Parameter	Group 1 Sodium chloride (*n* = 21 lesions)	Group 2 Ciprofloxacin (*n* = 27 lesions)
	Mean (SD) % score	Mean (SD) % score
Diameter	31.1 (35.9)	37.1 (36.4)
Induration	30.3 (29.7)	30.8 (30.1)
Erythema	44.9 (38.0)	32.7 (34.2)

SD = standard deviation.

with no healing but, when treated with the hypertonic solution, healed within 4 weeks.

In group 1, 4/21 (19.0%) lesions healed without scarring and 7/21 (33.3%) left a scar of < 40% of the original lesion size. In group 2, 5/27 (18.5%) of the lesions left no scar on healing while 13/27 (48.2%) lesions were < 40% of the original. No significant differences in scar size were recorded between the groups.

Table 4 summarizes the outcome of treatment. Scar size at the end of the study for lesions which healed with a scar was greatly reduced in comparison with the original size of the lesion: in group 1 the mean reduction in scar size was 66.0%, while in group 2 the mean reduction was 68.6%.

Discussion

Treatment of cutaneous leishmaniasis lesions is recommended since their duration cannot be predicted in an individual case [*14*] and in order to ameliorate ugly scars left after healing. Many drugs have been tried for treating the infection, but most are not available in our country, in addition to their high cost and side-effects that may result when they are used systemically [*8*].

Intralesional injection of leishmaniasis sores is a traditional method of treatment recommended by the World Health Organization in endemic areas, where many drugs have been tried by this method [*5,10,15–17*]. It is reasonable to treat these infections individually since the lesions persist locally and the parasite does not migrate [*15*]. Only a small amount of the drug is used but the effect is local and direct with slow absorption [*15*].

To evaluate the efficacy of the drugs in this study, 2 weeks were left between each visit, as was done in other studies with local therapy [*5,18,19*]. The follow-up scoring system depended on 4 parameters (diameter, erythema, induration and ulceration) and a final total score was devised and used for the first time in this study. Using multiple parameters is a good feature in any study, where it minimizes mistakes in measurement and gives a more precise assessment of the lesion. Other studies estimated only lesion diameter and erythema, depending mainly on the reduction in size as a sign for healing [*5*] or depended on the area of ulceration multiplied by the area of induration for evaluation during the treatment and followed cases until re-epitheliazation

Table 4 Summary of outcome of treatment after 8 weeks of treatment

Variable	Group 1 Sodium chloride (*n* = 21 lesions)	Group 2 Ciprofloxacin (*n* = 27 lesions)
Lesions unhealed [No. (%)]	5 (23.8)	5 (18.5)
Lesions healed, with or without scarring [No. (%)]	16 (76.2)	22 (81.5)
Lesions healed, without scarring [No. (%)]	4 (19.1)	5 (18.5)
Healing time (weeks) (No.)		
2	1	2
4	5	8
6	7	9
8	3	3
Mean reduction in lesion size (%)	66.0	68.6

occurred [*20*]. The cases were followed up mostly for 8 weeks.

Al-Shaikhly and Sayidmarie used hyperthermia for treating cutaneous leishmaniasis [*18*] and, as in the present study, most lesions were healed by 6 weeks. Najim recorded cure in 6 weeks also with local application of zinc sulfate and hypertonic saline solution [*5*]. Hypertonic sodium chloride solution has not been previously evaluated in south Iraq. In the present study, hypertonic saline showed a 76.2% healing rate after 8 weeks, mostly by 6 weeks after 2–3 injections, while Najim in Iraq recorded 85% cure (mean time 4 weeks) with zinc sulfate [*5*]. Ciprofloxacin showed a cure rate of 81.5%. The results are difficult to compare, however, as there are different species or strains of the parasite present in south Iraq as well as differences in host reaction, immune status of patients and age of lesions that may affect treatment.

Both the antibiotic and hypertonic solution were effective in reducing scar size after healing. Hypertonic saline gave an average 66.0% reduction, while the ciprofloxacin gave an average 68.6% reduction compared with the original size of the lesions. If lesions are left to heal spontaneously, we would expect a scar that is similar in size to the original lesion [*14*].

Ciprofloxacin is effective against intracellular pathogens such as *Brucella* and *Legionella* spp., where it inhibits the enzyme DNA gyrase which is responsible for DNA replication [*21*]. Ciprofloxacin was also found to be active against some protozoa including *L. donovani*. Others have recorded a reduction in lesion size and induration of *L. major* lesions after treatment with ciprofloxacin as a topical paste (250 mg) [*12,22*]. The mode of action of ciprofloxacin in the treatment of *Leishmania* infection is not well established, but it may exert its effect by the same mechanism mentioned above, and local injection leaves the drug in contact with the pathogen for as long as possible where it may act directly.

In conclusion, intralesional 0.2% ciprofloxacin was as least as effective as hypertonic sodium chloride solution in the treatment of cutaneous leishmaniasis infection. Further studies using this drug on a large sample and for other clinical forms of infection are suggested.

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Innovative and Intensified Disease Management (IDM)

Innovative and Intensified Disease Management (IDM) focuses on diseases for which cost-effective control tools do not exist and where large-scale use of existing tools is limited. The diseases include Buruli ulcer, Chagas disease, human African trypanosomiasis and leishmaniasis and they share the following characteristics:

- they are difficult and costly to manage – diagnosis, treatment and follow up;
- the burden is poorly understood;
- there is a lack of appropriate control tools;
- there has been relatively lower investment in research and development;
- people affected often live in remote rural areas with limited access to diagnosis and treatment.

The goal of IDM is to allow these diseases to be easily managed within the primary health-care system and ultimately eliminated as a public health problem. The objectives are to: intensify disease management using existing tools; encourage the rapid development and implementation of better control tools and to ensure the full involvement of national control programmes; and advocate for health service development in affected areas.

Further information about IDM can be found at: http://www.who.int/neglected_diseases/disease_management/en/index.html