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Original Article

Response to treatment of cutaneous leishmaniasis with intralesional chloroquine vs intralesional meglumine antimoniate

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Abstract

Background In Pakistan, cutaneous leishmaniasis (CL) is mostly caused by *Leishmania major*. For simple lesions which are few in number and where there is no risk of disfigurement or joint mobility restriction, topical application or local treatment e.g. intralesional antimony compounds are valuable.

Objective To compare the effect of intralesional chloroquine with meglumine antimoniate in the treatment of CL.

Patients and methods Patients and methods In this quasi experimental study, 60 patients of CL with 1 to 3 lesions and aged >3years were divided into 2 treatment groups to receive either intralesional chloroquine (treatment group) or meglumine antimoniate (control group). Both drugs were used 1cc per cm^2 of lesion, once weekly for 8 weeks (8 injections). 8 more injections were given to those who showed partial response.

Results
Both treatments showed 100% response; however, greater number of injections was required with meglumine antimoniate ($p<0.05$). Both drugs were well tolerated.

Conclusion
Intralesional chloroquine appears to be an effective, safe and cheap alternative to meglumine antimoniate in the treatment of CL.

Key words
Cutaneous leishmaniasis, intralesional, chloroquine, meglumine antimoniate.

Introduction

As we enter the new millennium, many important strides have been made in cutaneous leishmaniasis (CL) treatment and control. Paradoxically, however, there are still approximately 1.5 million new cases of CL each year worldwide, with the bulk reported from Afghanistan, Iran, Iraq, Algeria, Saudi Arabia, Peru, and Pakistan. According to the World Health Organization (WHO), leishmaniasis is endemic in 88 countries, with a total of 350 million people at risk. It is believed that worldwide 12 million people are currently infected by leishmaniasis.

Most CL lesions are self limiting and may heal in 1-5 years. In spite of this, treatment is justified in a variety of cases, namely early lesions, multiple lesions, lesions involving cosmetically sensitive sites, mucosal lesions and patients with significant immunosuppression. In addition psychological impact of the disease

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cannot be ignored. The aims of therapy are two-fold, namely clinical healing and disappearance of parasites. The disease still presents a therapeutic problem in several parts of the world. Unfortunately to date there is no safe, simple, cheap and effective ambulatory treatment for CL. Pentavalent antimony compounds, 'the best drug of a bad bunch' still remain the mainstay of treatment in the majority of cases. However, these have the disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions. Other treatment options are pentamidine given systemically and imidazole compounds.[6,7,8] Drugs such as allopurinol, rifampicin, dapsone, chloroquine and nifurtimox have found favor in some studies.[9] Cryotherapy and intralesional meglumine antimoniate are also found to have beneficial role.[10] Physical methods to control transmission of CL as a preventive measure have also been tried with some success.[11] For simple lesions which are few in number and where there is no risk of disfigurement or joint mobility restriction, the treatment options, parenteral antimony compounds, because of their untoward effects, inconvenience and cost, are not recommended. Topical application or local treatment of cutaneous lesions, therefore, would be valuable option. Local therapy is of value if it is simpler to administer and less toxic than systemic ones.

Previously, intralesional sodium stibogluconate and meglumine antimoniate have been used with success but keeping in mind its toxicity, cost and availability other treatment options have been tried. One of these is the use of intralesional chloroquine which has shown very encouraging results. Chloroquine is an antiprotozoal drug primarily used in malaria which has much less side effects and cost as compared to antimony compounds. In a pilot study of 10 patients, intralesional chloroquine showed 100% response.[12] To exploit its therapeutic potential in CL, the trial was carried out on a large scale. The objective of this study was to compare the effect of intralesional chloroquine with intralesional meglumine antimoniate in the treatment of cutaneous leishmaniasis.

Patients and methods

This quasi-experimental study was conducted at Department of Dermatology, Pakistan Institute of Medical Sciences, Islamabad. The inclusion criteria for the study were patients with 1 to 3 lesions, age more than 3 years and both genders. Patients were excluded from the study if lesions were larger than 5cm or if they were already getting any systemic or local antileishmaniasis treatment.

The history and examination findings of patients were noted. Diagnosis was confirmed by staining with Giemsa/Leishman's stain and histopathological examination of skin lesion biopsy. After confirmation of diagnosis informed consent was taken. Two groups were formed by using random number table. Then intralesional chloroquine was given to 30 patients of group A, while the rest of 30 patients (group B) were given intralesional meglumine antimoniate. Injections were given once a week for 8 weeks i.e. 8 injections. 8 more injections were given to those who showed partial improvement. The dose used for both drugs was 1cc per cm^2 of the lesion.

At each follow up patients were examined for clinical improvement of lesions and inquired about any local or systemic side effects. Response to treatment was based on clinical resolution of lesions with residual pigmentation/scarring or without scarring.

The data were analyzed by SPSS version 10. Descriptive statistics were used to calculate mean, standard deviation for age and regression in lesion size. Frequencies and percentages were calculated for categorical variables e.g. response to treatment. Chi-square test was used to compare response (categorical variables) while t-test was used to compare numerical variables.

Results

A total of 60 patients were enrolled in the study, which belonged to both sexes and aged over 3 years. Both group A (chloroquine) and group B comprised of 30 patients each and they were well matched in terms of age, sex and clinical parameters. **Table 1** shows the details of demographic and clinical data. The majority in both groups had single lesion. About half of patients in both groups had lesions measuring 3 cm^2. Most patients had crusted variety of lesions, while plaque and ulcerated lesions were less frequent.

Regarding number of injections required (**Table 2**), there was a significant difference in two groups. In group A (chloroquine), 1 (3.3%) patient required 3 injections, 5 (16.6%) required 4 injections, 10 (33.3%) required 5 injections, 9 (30%) required 6 and 5 (16.6%) patients required 8 injections while in group B, 1 (3.3%) patient required 4 injections, 6 (20%) required 5 injections, 12 (40%) required 6, 4 (13.3%) required 8 and 1 (3.3%) patient required 9 injections (p<0.001) i.e. in group B number of injections required was greater as compared to group (A).

In both the groups, all patients were cured (**Figure 1**). In chloroquine group (A) the rate of cure was 100% (all 30 patients) after 8 injections and in meglumine antimoniate group (B) it was 97% (29 patients). One patient in the latter group having lesion size of 4cm^2 required 9 injections, while other patients of same size of lesion required less number of injections. the patients with ulcerated form of lesion required greater number of injections in both groups except that the patients with ulcerated lesion which were comparatively of smaller size required less number of injections. No linear relationship was found between duration of lesion and number of

Table 1 The demographic and clinical data in two groups.

	Group A Chloroquine N=30	*Group B Meglumine antimoniate N=30*
Age	25.93±13.53	27.80±12.79
Gender		
Male	16 (53.3%)	21 (70%)
Female	14 (46.6%)	9 (30%)
No. of lesions		
1	23 (76%)	23 (76%)
2	4 (13%)	4 (13%)
3	3 (10%)	2 (6%)
4		1 (3%)
Morphology		
Plaque	12 (40%)	12 (40%)
Crusted lesions	14 (47%)	15 (50%)
Ulcer	3 (7%)	3 (7%)
Nodule	1 (3%)	-
Size of the lesion cm^2		
1.5	1 (3%)	
2	4 (13%)	2 (7%)
2.5	4 (13%)	3 (10%)
3	15 (50%)	17 (57%)
3.5	3 (10%)	4 (13%)
4	4 (13%)	7 (23%)

Table 2 Number of injections required to clear lesions in two groups.

No. of injections	*Chloroquine group N=30*	*Meglumine antimoniate group N=30*
3	1 (3.3%)	
4	5 (16.6%)	1 (3.3%)
5	10 (33.3%)	6 (20%)
6	9 (30%)	12 (40%)
8	5 (16.6%)	4 (13.3%)
9	-	1 (3.3%)

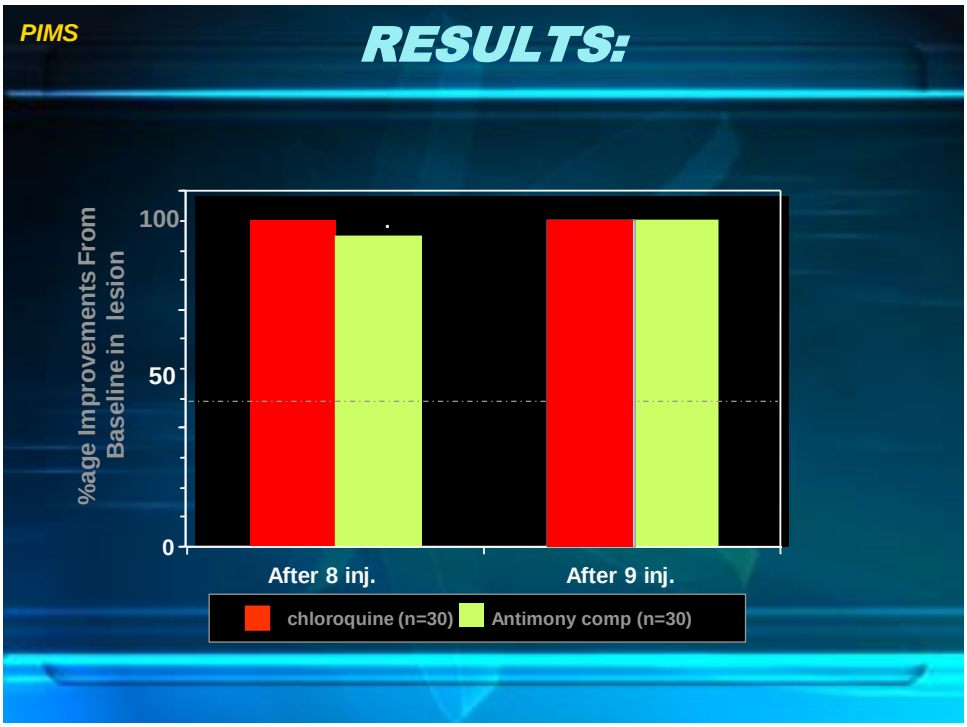

Figure 1 Comparison of results in two groups.

injections required. Some patients with shortest duration required greater number of injections and other ones with shorter duration required less number of injections and vice versa.

No side effect was noted in both groups except for local hyperpigmentation, scab formation or mild degree of scarring in some patients. In most of the patients these complaints also settled over the period of time. 2 patients in group A and 3 patients in group B had secondary infection of lesion after the start of therapy which was treated with oral antibiotics.

Discussion

Regarding the treatment of CL, pentavalent antimonials are the mainstay of treatment. These compounds have the disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions where they have been used for a long time. The other well known problems with these compounds are increasing frequency and severity of adverse events, and increasing cost, which is especially important in underdeveloped countries like Pakistan. Another important problem is availability of drug. Most of the rural areas do not have drug available, an important cause of which again is cost. Even in developed areas of Pakistan like Islamabad has to face the problem of shortage of drug very often. Common adverse effects of antimonials are myalgias, arthralgias, increase in liver function enzymes, arrhythmias and repeated parenteral injections. These events can be particularly a problem in old age group when people are already friable and are suffering from many systemic illnesses. These limitations have stimulated the search for new drugs to treat this disease. In the past decade, there have been several advances with the introduction of new therapies liposomal amphotericin, paromomycin and oral miltefosine. Chloroquine is an antimicrobial drug which was used as intralesional injection on a small number of patients and was found very effective in curing

the skin lesions.[23] The response rate was 100%. Based on this pilot study, a large scale study was planned to find out the effectiveness of the drug, and to compare the results with antimonials compounds.

Our present trial in immunocompetent patients, older than 3 years of age shows that intralesional chloroquine is an effective and safe treatment of cutaneous leishmaniasis. At the end of 8 injections, all of 30 patients had healing of lesion in terms of clinical features like disappearance of signs of inflammation and healing with or without scar formation. None of patients developed any side effects except that 2 of patients had got their lesions secondarily infected which were treated effectively with antibacterial. We compared chloroquine with conventional antimonials and found it equally effective to antimonials. Response rate in antimonial group after 8 injections was 96% while it was 100% in chloroquine group (p=0.857). Although on comparing 2 groups size of lesion was slightly greater in antimonials group, which can be a possible cause of increased number of injections required in this group. But only 1 patient which required 9 injections had a size of 4cm^2, while other patients with same size of lesions required less number of injections, however, it was an insignificant observation (p=0.8). On the whole the patients with ulcerated form of lesions required greater number of injections in both groups except those patients with ulcerated lesions comparatively of smaller size required less number of injections. Similarly, no linear relationship was found between duration of lesion and number of injections required. Some patients with shorter duration required greater number of injections and other ones with shorter duration required less number of injections and vice versa implying that duration of therapy does not affect the therapeutic response.

Therapeutic agents may be compared with respect to efficacy, tolerance, convenience and cost of administration. Very high cure rate of 100% in our study clearly surpasses the efficacy of other antileishmanial drugs and side effects profile also shows that intralesional chloroquine is as tolerable as other agents used in the treatment of leishmaniasis. Moreover, chloroquine is free of any side effects as compared with antimonials. Cost effectiveness is another important plus point of chloroquine especially in underdeveloped counties like Pakistan. Intralesional treatment is also safe during pregnancy because only small amount of drug is absorbed which does not seem to be enough to cause fetal damage which is not the case with antimonials. Regarding availability of drug it is easily available in big cities, small towns and villages because of its low cost.

Conclusion

However, intralesional chloroquine appears to be a safe and effective alternative to currently available therapies. It may also be helpful in areas where parasites are resistant to current agents.

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