COMPARATIVE EFFICACY OF INTRA LESIONAL SODIUM STIBOGLUCONATE AND INTRA LESIONAL CHLOROQUIN IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS IN A TERTIARY CARE TEACHING HOSPITAL: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Pentavalent antimonials are the agents recommended for treatment of cutaneous leishmaniasis (CL). Its use is problematic, because it is expensive, not easily available and because of the potential for drug-associated adverse effects during a lengthy and painful treatment course. **Objective:** The objective of this study was to compare the effect of intra-lesional chloroquine with intra-lesional sodium stibogluconate in the treatment of cutaneous leishmaniasis. **Material and Methods**: In this randomized controlled trial, we tested and compared the efficacy of Intralesional Chloroquine with that of intralesional sodium stibogluconate (SSG) for the treatment of CL. We enrolled 50 patients of CL with a single to multiple lesions of various sizes, divided them in group A and B and randomly administered chloroquine or sodium stibogluconate (SSG), intralesional twice weekly (total number of injections and duration of treatment depending on the size and number of lesions). Duration of Study: This study was conducted from1st March, 2010 to 31st September, 2010. **Results**: Cure occurred in 100 % patients in both groups towards end of the treatment. Mean cost of the treatment per patient in the present study was found to be very high for SSG group (Rs. 5664± 186), as compared to chloroquine group (Rs. 68.4±9) with a p value of <0.000. Mean number of inj. given in SSG group was 14±4.6 as compared to13.6±5.5 in chloroquine group. (P=0.1) Mean duration of treatment in SSG group was 55.3±23 days compared with 51.24±22 days in chloroquine group (p=0.9). **Conclusion**: Intra lesional chloroquine is an effective, well tolerated, easily available and economical treatment for CL, and it should be considered as an alternative to antimony treatment.

Key words: Cutaneous leishmaniasis, Chloroquine, Sodium stibogluconate

INTRODUCTION

Leishmanias is a group of diseases, caused by a single celled parasite called leishmania that is transmitted by sand fly bites.[1] Cutaneous leishmaniasis is the most common form of leishmaniasis. It is endemic to many parts of the world including Pakistan. It has been occurring in American & Canadian troops coming back from Afghanistan.[2] There are four types of cutaneous leishmaniasis depending upon the species of the parasite involved.[1] Cutaneous leishmaniasis, is due to L. major also known as 'wet, rural or zoonotic cutaneous leishmaniasis, cutaneous leishmaniasis due to L. tropica, also known as 'dry, urban or anthroponotic cutaneous leishmaniasis, cutaneous leishmaniasis due to L. aethopica, and cutaneous leishmaniasis due to L. donovani infantum. Diagnosis is based on characteristic clinical appearance of slow healing, raised, scaly lesions that may ulcerate & become secondarily infected in someone who has returned from an endemic area. Diagnosis is confirmed by the presence of one or more of the following criteria including:[1] History of exposure to an endemic area in the previous weeks or months; History of sand fly bites in the previous weeks or months; History of high-risk activities such as sleeping outdoors, jungle or desert visit, Non-healing chronic nodular, voilaceous ulcer for 4-6 weeks or longer; Demonstration of amastigotes in Giemsa-stained smears from infected skin by direct microscopy; Demonstration of intracellular amastigotes in the dermis of H & E stained sections of skin; Presence of leishmanial granulomas in the dermis in H & E specimens; Growth of promastigotes in Nicolle-Novy-MacNeal (NNN) culture medium from lesional specimens and the gold standard for diagnosis is demonstration of leishmanial DNA by PCR.[3] In the present century, many important advances have been made in treatment & control of cutaneous leishmaniasis, but the disease still presents a therapeutic problem in several parts of the world. Unfortunately, to date, there is no safe, simple, cheap & effective ambulatory treatment for cutaneous leishmaniasis. Different treatment options available include: Topical such as; Heating at 40-42C,[4] Freezing with carbon dioxide snow,[5] Curettage under

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local anesthesia,[6] and infiltration with 1-2ml sodium stibogluconate or meglumine antimoniate,[7] and Systemic such as; I/M or I/V sodium stibogluconate or meglumine antimoniate and oral ketoconazole.[10] Pentavalent antimony compounds still remain the mainstay of treatment in majority of the cases. These drugs, however, have the disadvantages of toxicity, resistance,[8] availability & cost in certain regions.[7-9] Drugs such as allopurinol, rifampicin, dapsone, chloroquine & nifurtimox have also been used in some studies.[10] For simple lesions which are few in number & where there is no risk of disfigurement or joint mobility restriction, the treatment options like parenteral antimony compounds, because of their untoward effects, inconvenience & cost, are not recommended. Physical modalities or local treatment of cutaneous lesions in such cases, therefore, is a preferred option. Previously, intra-lesional sodium stibogluconate & meglumine antimoniate have been used with success.

Sodium stibogluconate is an antileishmanial drug which acts by suppressing glycolysis and fatty acid synthesis in glycosomes and also by diminishing ATP & GTP generation.[11] But keeping in mind its toxicity, cost & availability, other treatment options have been tried. One of these is the use of intra-lesional chloroquine which has shown very encouraging results.[12] Chloroquine, is an anti-protozoal drug, primarily used in malaria, which has much less side effect profile, is cost effective and easily available as compared to antimony compounds. In both oral and intralesional routes it has given encouraging results in the treatment of cutaneous leishmaniasis.[12, 13, 14] In a pilot study of 10 patients, intra-lesional chloroquine showed 100% response.[12] In a comparative study with 30 patients, orally administered chloroquine showed 100% response compared with 93% in injectable pentavalent antimony, without any complication in either group.[13]

To explore therapeutic potential of chloroquine further, in cutaneous leishmaniasis, the trial was carried out in our setting. The objective of this study was to compare the effect of intra-lesional chloroquine with intra-lesional sodium stibogluconate in the treatment of cutaneous leishmaniasis.

MATERIALS AND METHODS

The randomized controlled study was carried out at Department of Dermatology, Sheikh Zayed Hospital, which is a tertiary care teaching hospital affiliated to Shiekh Zayed Medical College, Rahim Yar Khan. Patients were diagnosed on the basis of history of exposure to endemic areas of Pakistan, bite of the sand fly, high risk activities and clinical examination showing chronic dusky red papules / plaques, voilaceous nodules and ulcerated lesions for greater than 4 - 6 weeks on exposed body parts, confirmed by demonstration of amastigotes in Giemsa-stained smears from involved skin by direct microscopy. Inclusion criteria were: age between 5 and 60 years; the presence of a single or multiple parasitologically confirmed CL lesions with no past history of disease and any kind of treatment. Exclusion criteria were: extremes of age (below 5 and above 60), presence of any uncontrolled medical condition and the patients who had received any kind of treatment.

The study was a randomized, controlled trial. There was no placebo group. Patients coming to the OPD clinic for treatment were briefed about the study, its aims, and the protocol. They were then enrolled in the study after written consent had been given. Patients then proceeded to pick one of two, identical cardboard pieces out of a hat (the cardboard had been labeled with treatment codes A and B on one of its sides, the codes being non visible to the patient). After patients were randomly assigned to one of the treatment groups the cardboard piece picked was returned. The assigned treatments were as follows: Group A, intralesional administration of SSG and Group B, intralesional administration of chloroquine, both twice weekly until disappearance of the lesions and / or complete re-epitheliazation of ulcers.

Before the first treatment, all patients had a full physical examination. The location, duration and size of the lesion were recorded prior to treatment. The size was measured with a caliper. The status of each lesion was evaluated at each follow-up visit. Lesions with a secondary bacterial infection before, during, or after treatment were treated with topical antibiotics. If systemic treatment was required, patients received treatment with an antibiotic that has no activity against Leishmania (e.g., erythromycin). Cure was defined as the complete re epitheliazation of the ulcerated lesions, with no evidence of papules, inflammation, or induration. All patients' data were entered in SPSS version 15 and analyzed.

RESULTS

A total of 50 patients were enrolled in the study, with 25 in each group. Group A was given inj. Sodium Stibogluconate (SSG) and group B was given inj. Chloroquine. Overall the mean number of lesions was 2.68 ± 1.9. The size of the lesions in cm^2 was 6.86 ± 6 in both groups. In SSG group the size of the lesion was 6.88±3.1cm^2 and in chloroquine group it was 6.85±8.6cm^2. Overall, the lesions of ≤ 4 cm^2 were noted in 18 (36%) patients, whereas lesions of >4 cm^2 were seen in 32 (64%) patients. All the patients in both groups were treated successfully and all patients gave history of visit to the endemic areas. In both groups no local side effect of either drug was observed. It was noted that 18 (72%) patients in SSG group had multiple lesions compared to 12 (48%) in chloroquine group. Overall 74% of the patients had lesions on exposed body parts and 60% had multiple lesions. In SSG group 84% had lesions on exposed body parts compared to 66% in Chloroquine group (p=0.1). In SSG group 48% had lesions of ≤ 4cm^2 compared to 24% in Chloroquine group.

Figure I: Number of injections given in both treatment groups. (N=50)

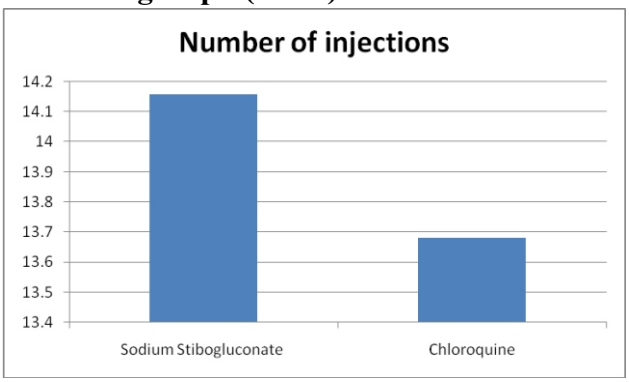
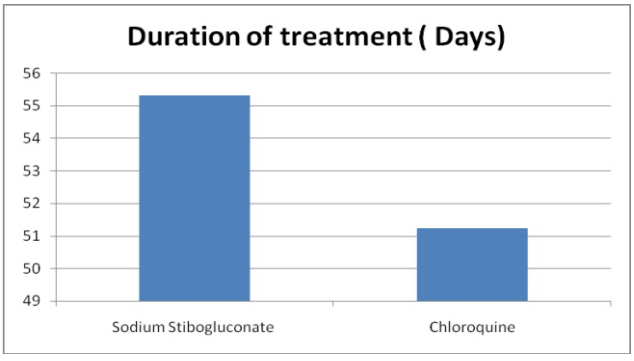


Figure II: Duration of treatment (days) in both groups. (N=50)



Mean number of injections given in SSG group was 14±4.6 as compared to13.6±5.5 in chloroquine group. (P=0.1) (Figure I) Mean duration of treatment in SSG group was 55.3±23 days compared with 51.24±22 days in chloroquine group (p=0.9). (Figure II)

As far as, the availability of these drugs was concerned, chloroquine was readily available from all pharmacies, whereas, SSG was only available minimum after two weeks of prior booking. The mean cost of the treatment per patient was very high for SSG group (Rs. 5664± 186), as compared to chloroquine group, (Rs. 68.4±9) with p value of <0.000.

DISCUSSION

In a disfiguring disease like cutaneous leishmaniasis, which is fairly common and endemic in certain areas of a developing country like Pakistan the mainstay of the treatment until recent past has been antimonial compounds. It is not only the side effects of these compounds (arthralgia, myalgia, disturbance of the liver enzymes and cardiac arrhythmias to name a few amongst others) which make them unsuitable; they are costly and not easily available too. This requires finding out a safer, cheaper and easily available alternative treatment for such common problem.

In our RCT, a total of 50 patients were enrolled in the study with 25 in each group. Group A was given inj. Sodium Stibogluconate (SSG) and group B was given inj. chloroquine. Mean duration of treatment in SSG group was 55.3 ± 23 days compared with 51.24 ± 22 days in chloroquine group (p=0.9). Mean number of inj. given in SSG group was14 ± 4.6 as compared to13.6 ± 5.5 in chloroquine group. The mean cost of the treatment per patient was very high for SSG group Rs. 5664± 186, as compared to chloroquine group Rs. 68.4±9 (p <0.000). As far as the availability of these drugs was concerned, chloroquine was readily available from all pharmacies in country; whereas SSG was only available minimum after two weeks of prior booking. All the patients in both groups were treated successfully. In both groups no local or systemic side effect of either drug was observed and there was no relapse after 3 months of treatment in either group. These results clearly showed that chloroquine is a safer, and easily available alternative to antimonials in the treatment of cutaneous leishmaniasis. It is reported that, pentavalent antimonials have a high incidence of side effects, but the latter are reversible.

In a study,[13] 96 subjects with leishmaniasis (83 cases were cutaneous) were treated for 20 to 28 days and followed for one year. Side effects included aching, arthralgia, fatigue, gastrointestinal upset, elevation of amylase, lipase, and liver enzyme levels, leukopenia, anemia, and electrocardiographic abnormalities. This is in contrast to our study, where no side effect was noted in SSG group. In a previous study, in which SSG was given, cure rates were 100%, in the 10-day group and 95% in the 20-day group. Side effects were more common among patients who received 20 days of therapy.[14]

Overall, the mean number of lesions was 2.68 ±1.9. The size of the lesions in cm^2 was 6.86 ± 6 in both groups. In SSG group the size of the lesions was 6.88±3.1cm^2 and in chloroquine group it was 6.85 ±8.6 cm^2. Overall, it was noted that the lesions of ≤ 4 cm^2 were in18 (36%) of the patients, whereas lesions of >4 cm^2 were in 32 (64%) of the patients. In a study,[15] conducted on comparatively smaller number of patients comparing oral chloroquine (250 mg thrice daily) for 20 days with intramuscular antimonial (20 mg/Kg) for 28 days where majority of the patients had only one lesion; the cure rate in chloroquine group was 100% with no relapse as opposed to antimonial group in which cure rate was 97% and in one patient (7%) the lesions relapsed. In present study, however, the cure rate was comparable to this study but there was no relapse in either group. In both groups no local or systemic side effect of either drug was observed,[15] which is comparable to present study.

In another study conducted,[15] on a comparable number of patients the number of lesions was restricted to 1-3 and patients having lesions greater than 5 cm were excluded from study. This is in contrast to our study where no restriction was placed on the number and size of the lesions and where overall the mean number of lesions was 2.68 ±1.9. The size of the lesions in cm^2 was 6.86 ± 6 in both groups. Moreover, in that study, the injections were given once weekly for 8 weeks and 8 more injections were given to those who showed partial response thus making the total duration of treatment considerably longer (8-16 weeks). In the present study, a documented regimen of twice weekly injections was followed and the mean duration of treatment in SSG group was 55.3± 23 compared with 51.24 ± 22 days in chloroquine group (p=0.9). In previous study,[16] more number of injections of the antimonial than chloroquine were required which is not comparable to our study where almost equal number of injections were given in SSG group i-e, 14 as compared to 13.6 in chloroquine group. Cure rate in the earlier study,[16] was 100% in chloroquine and 97% in antimonial group. In present study, however, it was 100% in either group. Mean cost of the treatment per patient in the present study was found to be very high for SSG group (Rs. 5664± 186), as compared to chloroquine group (Rs. 68.4±9) with a p value of <0.000. The cost, however has not been calculated in previous studies. The results of our study showed that chloroquine is comparable in its efficacy to antimonials in the treatment of cutaneous leishmaniasis.

CONCLUSION

All the patients in both groups were treated successfully. Chloroquine is a safer, economical and easily available alternative to antimonials in the treatment of cutaneous leishmaniasis. Further studies with larger sample are, however, required to substantiate these findings.

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