COMPARISON OF EFFICACY OF ORAL FLUCONAZOLE WITH INTRAMUSCULAR MEGLUMINE ANTIMONIATE IN TREATMENT OF CUTANEOUS LEISHMANIASIS

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ABSTRACT

Objective: To compare the efficacy of oral fluconazole with intramuscular meglumine antimoniate in patients of cutaneous leishmaniasis.

Study Design: Randomized Control Trial.

Place and Duration of Study: Study was conducted from 1st January 2013 to 30th June 2013, at Dermatology department, Military Hospital, Rawalpindi.

Patients and Methods: Eighty histopathologically diagnosed patients of cutaneous leishmaniasis were selected. Patients were randomly allocated into two groups. Group-A was given oral fluconazole 200mg/day for six weeks. Group-B was given intramuscular meglumine antimoniate 20 mg/kg/day for 21 days. Status of each lesion was regularly documented and efficacy of drugs was measured at the end of three months. The drug was considered efficacious if there is more than 75% regression in size and induration of lesions.

Results: Clinical efficacy was seen in 70% (n=28) in Group-A and 92.7% (n=37) in Group-B at end of three months. When compared by Chi-square test, these results were found to be statistically significant with *p*-value 0.010(< 0.05)

Conclusion: Efficacy of Intramuscular meglumine antimoniate is better than oral fluconazole in treatment of cutaneous leishmaniasis.

Keywords: Fluconazole, Leishmaniasis, Meglumine antimoniate.

INTRODUCTION

The leishmaniases are a group of diseases caused by several species of the genus Leishmania[1]. Globally, there are an estimated 1.5–2 million new cases and 70,000 deaths each year[2]. In Pakistan, prevalence has been estimated at 2.7% in the north-western part of the country with incidence at 4.6 cases/1000 persons/year over the last ten years.

Human leishmaniasis is usually classified as cutaneous, mucocutaneous or visceral. Cutaneous leishmaniasis (CL) includes 50-75% of all incident cases. Most lesions heal spontaneously within one year and are characterized as acute CL. Disease lasting more than 1 year is termed as chronic CL[1].

As most lesions of CL are likely to heal spontaneously approximately within a year, and an expectant approach should provide protective immunity, and so it is preferred. Multiple lesions, which are either progressive, or persistent or deep, sporotrichoid, and secondarily infected, or at cosmetically or functionally unacceptable sites, should, however, be treated.

Available treatment options for cutaneous leishmaniasis include various topical and systemic agents and choice of therapy depends upon type of leishmaniasis, site and number of lesions, cost, side effects and ease of administration. Pentavalent antimony compounds like meglumine antimoniate are the main therapeutic agents for various forms of leishmaniasis[1,3] with efficacy as high as 93% with standard intramuscular dose of 20mg of antimony/kg/day[4] However, because of requirement for parenteral administration, side effects, such as hepatotoxicity and cardiac toxicity, and emergence of resistant strains, there has been an intensive search for alternative therapies.

Certain antifungal drugs have activity against leishmania[5-7]. They inhibit growth of leishmania by inhibiting cytochrome P-450–

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mediated 14α-demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14α-methyl sterols. Fluconazole, which is a triazole, has been used to treat CL in various trials with variable results, efficacy ranging from 44 to 79 percent[5,6]. Its excellent safety profile and pharmacokinetic properties make it a suitable alternative therapy for CL[7]. It has a long half-life, high solubility in water, and a concentration in skin that is 10 times that in plasma.

We planned to conduct a randomized controlled trial to compare the efficacy of a six weeks course of oral fluconazole for the treatment of CL with 21 days course of meglumine antimoniate with rationale that if efficacy of both drugs was found comparable, then the results of this study can be applied on the patients with CL presenting in our outpatient department.

PATIENTS AND METHODS

This was a Randomized Control Trial (RCT), carried out after approval of hospital ethical committee, in dermatology department, Military Hospital, Rawalpindi, from 1st January 2013 to 30th June 2013. Histopathologically diagnosed patients of Cutaneous Leishmaniasis, with duration of disease less than 4 months, not previously using anti-leishmania therapies were selected. While pregnant patients, children less than 12 years of age, patients having history of liver or kidney disease or allergy to azole anti fungals or antimony compounds were excluded from the study. Sample size was 80 (40 in each group) and patients were selected through non-probability consecutive sampling.

After taking an informed written consent, name, age, gender, serial number and hospital record number, address and phone number of each individual were noted and all patients were subjected to physical examination, complete blood picture, urine examination, liver and renal function tests and ECG examination. These investigations were repeated at 2 weeks, 4 weeks and at the end of treatment. The number of leishmania lesions was charted, along with a description of their appearance, induration, size in millimeters and their location.

Then the patients were randomly allocated into two groups by using the random numbers table. Group A was given tablet fluconazole 200 mg daily orally for 6 weeks. Group B was given meglumine antimoniate 60 mg/kg body weight (equal to 20mgof antimony/kg body weight) in the form of deep intramuscular injections for 21 days. The status of each lesion was documented every two weeks for six weeks, and then at end of 2nd and 3rd month and efficacy of drug was measured at end of 3 months.

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the results. The two groups were compared for efficacy by Chi-square test. *p*-value <0.05 was considered as significant. Quantitative variables were first checked for normality and then independent t-test was applied.

RESULTS

In group A, most patients were in age group 21 ± 40 years, n=28 (70%), with mean age 30.48 ± 11.852, most were males, n=28 (70%), and 12 (30%) were females. Duration of illness varied from 43 to 118 days with mean duration 79.10 + 19.57. Number of lesions varied from 1 to 7 and maximum patients had single lesion, n=20 (50%) with mean 2.2 + 1.6.

In group B, most patients were in age group 21-40 years, n=21 (52.5%), with mean age 37.05 + 13.292, most were males, n=30 (75%) while 10 (25%) were females. Duration of illness varied from 40 to 116 days with mean duration 81.45 + 22.07. Number of lesions varied from 1 to 6 and maximum patients had single lesion, n=19 (47.5%) with mean 2.1 + 1.41. Both the groups were found comparable with respect to gender, with *p*-value of 0.617.

All the patients recruited for the trial completed full treatment period and follow-up at 3 months. No significant adverse effects were noted in any of the two groups, and both drugs were well tolerated.

Response to treatment in both groups was recorded at the end of the 3rd month in terms of efficacy of the drug, where efficacy was defined

as more than 75% regression in size and induration of lesions at end of three months. These results are presented in table-1.

Efficacy of intramuscular meglumine antimoniate (Group-B) was found significantly better than oral fluconazole (Group-A).

DISCUSSION

Cutaneous leishmaniasis, is a major health problem worldwide. Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate), discovered and marketed since 1940s, remain the first-line treatment for all clinical forms of leishmaniasis, despite the variable therapeutic response and the growing concern of treatment failure.

Nilforoushzadeh MA et al demonstrated complete response in 93% of CL patients treated with meglumine antimoniate for 21 days, while Neves LO et al demonstrated only 55.5% efficacy[4,8]. In a Brazilian series, cure rate was 51% of L. braziliensis cases.[9] However, clinical response to meglumine antimoniate in few studies conducted in Pakistan is quite favourable. Khan AA et al demonstrated 85.4% cure rate with 14 days therapy[10].

Mohapatra S, Hajjaran H et al and Thakur CP et al, alongwith several other investigators have demonstrated decreasing efficacy, emerging resistance, rising treatment failure rates with pentavalent antimony compounds in vivo and in vitro studies[11,12]. However, the role of drug resistance alone in treatment failure has been difficult to ascertain as the therapeutic response is multifactorial. Because of their potential toxic effects, cost, emerging drug resistance, and requirement of parenteral administration, the development of alternative therapeutic approaches for cutaneous leishmaniasis has received considerable attention in recent research.

Several studies have demonstrated in vitro and in vivo efficacy of certain azole antifungals including oral fluconazole in the treatment of cutaneous leishmaniasis, though data are limited and there are very few controlled trials worldwide[5-7]. To our knowledge, there is not a single previous trial that evaluated the clinical efficacy of fluconazole for cutaneous leishmaniasis in Pakistani population, which prompted us to conduct this study. In our study, we compared the efficacy of oral fluconazole with intramuscular meglumine antimoniate in patients of cutaneous leishmaniasis. As per results of our study, clinical efficacy, which was marked as more than 75% reduction in lesion size and induration, was seen in 92.7% in meglumine antimoniate group versus 70% in fluconazole group ($p < 0.05$).

Table-1: Comparison of efficacy in both groups (n=80).

Efficacy	Group-A (n=40)		Group-B (n=40)	
	No. of patients	percentage	No. of patients	Percentage
Yes	28	70	37	92.5
No	12	30	03	7.5
Total	40	100	40	100

There are a large number of previous studies demonstrating efficacy of meglumine antimoniate in different leishmania species, but, as far as fluconazole is concerned, there is paucity of data. There are very few controlled trials worldwide and not even a single trial in our population. Even among those few listed trials, treatment response is much variable, ranging from 44% to 79% or even upto 100% at higher doses of fluconazole than those used in our study.

Alraijhi et al conducted an RCT in Saudi Arabia on patients with CL treated with fluconazole 200 mg daily for 6 weeks which showed complete healing of lesions for 63/80 patients (79%) at 3 months follow-up. 13 Efficacy of fluconazole was evaluated in 35 travelers with Old World CL by Morizot G et al at same dose and duration, but clinical cure was demonstrated in just 44.4% of patients, which was similar to that of placebo group. This data

questioned the assumption that oral fluconazole is consistently effective for treatment of CL[6].

In another trial in Brazil, Sousa AQ et al reported the successful outcome from use of fluconazole to treat CL due to Leishmania braziliensis at doses of 5mg/kg and 8 mg/kg per day, with cure rates of 75% and 100% respectively[14]. Emad et al, also showed that the cure rate was dose dependent. In their study, 200 mg of fluconazole healed lesions in 48.3% (n=29) while 400 mg in 81% of CL patients (n=47). Though, they didn't compare the results between the two groups at 3 months. Furthermore, in the 400mg group, two patients discontinued the treatment after 2 weeks because of the rise of serum creatinine in one patient and the elevation of liver enzymes in the other patient, while 45 patients developed cheilitis and 10 patients developed nausea during treatment, and no such adverse effects were observed with 200 mg group[5].

As far as response to fluconazole is concerned, the results of my study are comparable with those conducted by Alraijhi AA and Sousa AQ et al (79% and 75% respectively). Though there is a significant difference in response between the two groups in our study, fluconazole can still be considered as an effective and safe alternative treatment option where meglumine antimoniate is either contraindicated, or not available, or the patients is having co morbidities or experiencing significant adverse effects with meglumine antimoniate. It's cheaper and potentially free of adverse effects at the dose used in my study. However, keeping in view the excellent treatment response, meglumine antimoniate will still remain the treatment of choice. Though there is emerging resistance worldwide, but meglumine antimoniate is still effective in our part of the world where L. major and L. tropica (old world cutaneous leishmaniasis) predominate.

CONCLUSION

Efficacy of Intramuscular meglumine antimoniate is better than oral fluconazole in the treatment of cutaneous leishmaniasis, but fluconazole can still be considered as safe and effective alternative option where meglumine antimoniate can't be given.

There is still room for further research and multi center studies should be undertaken to validate these results.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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