

COMPARISON OF EFFICACY OF ORAL ZINC SULPHATE WITH INTRAMUSCULAR MEGLUMINE ANTIMONIATE IN PATIENTS OF CUTANEOUS LEISHMANIASIS

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ABSTRACT

Objective: To compare the efficacy of oral zinc sulfate ($ZnSO_4$) with intramuscular meglumine antimoniate (MA) in the treatment of cutaneous leishmaniasis.

Study Design: Randomized controlled trial.

Place and Duration of Study: Dermatology Department, Military Hospital, Rawalpindi from 1st May 2013 to 1st Jan 2014.

Material and Methods: Eighty patients of cutaneous leishmaniasis from dermatology OPD fulfilling the inclusion criteria were selected after informed consent and permission from Hospital Ethical Committee. Using simple randomization patients were assigned into two treatment groups. Group A received oral zinc sulfate in a dose of 10 mg/kg/day during 45-day period in three divided doses, and group B received systemic MA (glucantime) 20 mg/kg/day intramuscularly for 20 days. The size and induration of lesions was measured by ruler and palpation respectively. Patients were followed up till the end of treatment. Three patients were excluded from the study due to discontinuation of treatment. Acceptable cure indicated efficacy at the end of treatment duration.

Results: In group A 14 (35.9%) patients had moderate improvement followed by total clearance in 12 (30.8%) patients. In group B, majority of the patients i.e. 26 (68.4%) patients had total clearance followed by moderate improvement in 9 (23.7%) patients. Group B had significantly better response as compared to group A. Efficacy of the drug was significantly higher in group B as compared to group A ($p = 0.001$).

Conclusion: Oral zinc sulfate 10mg/kg is not better than intramuscular MA in treatment of cutaneous leishmaniasis but can be considered as a treatment option if MA cannot be used.

Keywords: Cutaneous Leishmaniasis, Efficacy, Meglumine antimoniate, Oral zinc sulphate.

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INTRODUCTION

The term leishmaniasis encompasses cutaneous and visceral anthroponotic and zoonotic diseases caused by the vector-borne parasites of the genus leishmania. The infection is transmitted by bites from sand flies infected with the parasite. Cutaneous leishmaniasis is the most common form of the disease¹. It causes local inflammation, ulcers, and scars, which lead to disfiguration.

Cutaneous leishmaniasis is estimated to cause the ninth largest disease burden among individual infectious diseases². The stigma and the economic effects on households produce an

important impact on the estimates of disability-adjusted life years that increases the impact of the accounted burden of disease. The estimated annual incidence in Pakistan is from 21700 to 35700 cases². Scattered foci have been described in northern areas, in Lasbella and Makran, in Punjab and KPK³. It is endemic in Baluchistan, Interior Sind, and Multan^{4,5,6}. Wet-and dry-type lesions indicate the presence of both leishmania tropica and major respectively, in Pakistan⁹.

Although cutaneous leishmaniasis is a self-healing disease, but treatment is required to prevent disfiguring scars. Several therapies are available^{1,6} and meglumine antimoniate (glucantime)⁶ is most commonly used. Serious side effects, high costs and multiple injections make researchers look for newer therapeutic

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options. In 1998 zinc sulphate activity against *L. major* and *L. tropica* amastigotes were tested in vitro, in Iraq¹. Recently intra lesional injections and oral zinc sulphate treatment proved effective in vivo^{7,8}. Keeping in mind its minimal side effects, low cost, and ease of oral intake¹⁰ this study was designed to compare oral zinc sulphate with intramuscular meglumine in the treatment of cutaneous leishmaniasis.

MATERIAL AND METHODS

This randomized controlled trial was carried out at Dermatology Department, Military Hospital (MH), Rawalpindi from June 2013 to Jan 2014. Sample size was calculated by using WHO size calculator for two proportions

Lesions with duration more than 6 weeks but less than 6 months, with no treatment received so far, of both genders and all age groups were included in the study. Cases of pregnant or nursing women and those with history of hepatic, renal, heart diseases and anemia were excluded. Eighty patients were selected after informed consent and permission from Hospital Ethical Committee. Using simple randomization by lottery method, patients were assigned into two treatment groups. Group A received oral zinc sulfate in a dose of 10 mg/kg/day during 45-day period before meals in three divided times, and group B received systemic MA (glucantime) 20 mg/kg/day intramuscularly for 20 days with a maximum of three vials of

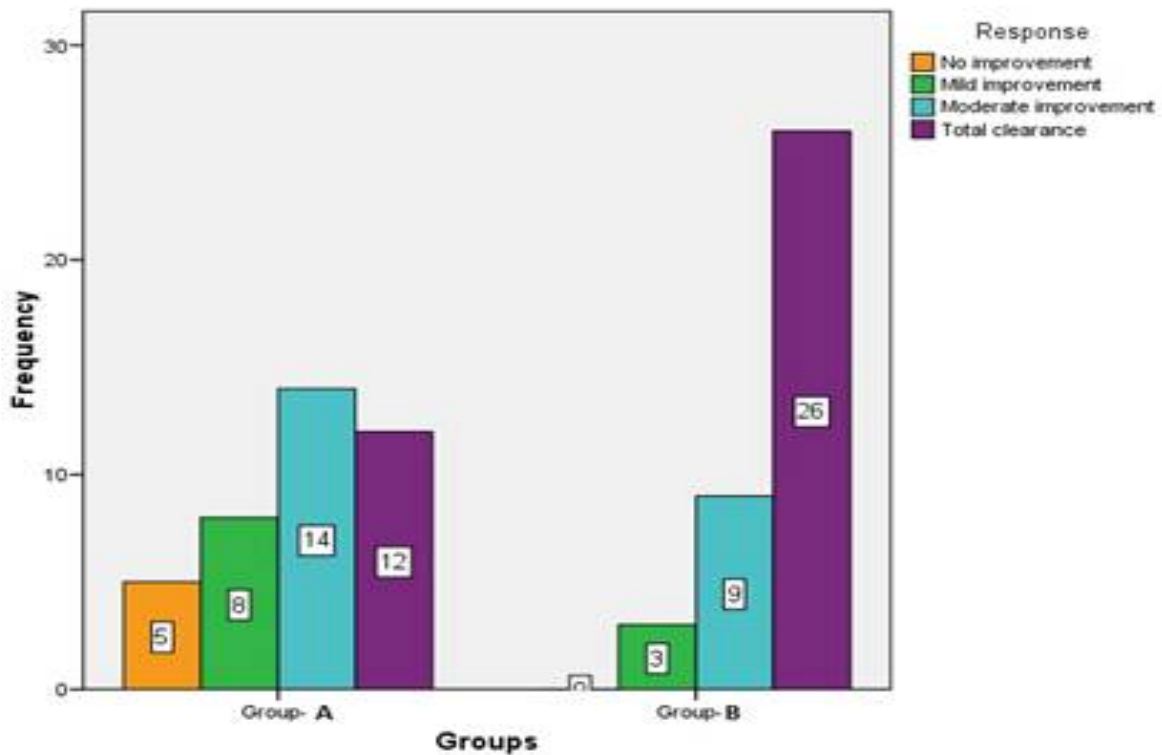


Figure-1: Comparison of the response to treatment between the groups.

based on outcome variables. Level of significance was 5%, power of test 90%, anticipated population proportion (P1) was = 96.9% and anticipated population proportion (P2) was =35.5%. Calculated sample size was 40 in each group. Non probability consecutive sampling was done. Diagnosis of cutaneous leishmaniasis was confirmed by skin biopsy.

glucantime. The size and indurations of lesions was measured by ruler and palpation respectively. Patients were regularly examined till the end of treatment. Response to treatment was graded as

1. Treatment failure- <25% reduction in size of; lesion with persisting induration or increase in size of lesion.

2. Mild improvement - 25 -50% reduction in size with persisting induration of lesion.
3. Moderate improvement - > 50% reduction in size but not complete healing with persisting induration of lesion.
4. Acceptable cure - complete re epithelialization without any induration.

Acceptable cure indicated efficacy at the end of 45 days with oral zinc sulphate and at the end of 20 days for intramuscular meglumine antimoniate.

SPSS version-17.0 was used to analyze the data. Mean and standard deviations were used to describe numeric variables like age and size of lesion at baseline. Frequencies and percentages were used to describe categorical variables like gender, efficacy and response. Chi square test was used to compare the efficacy (categorical variables) in two groups. A *p* value of less than 0.05 was considered significant.

RESULTS

Three patients were excluded from the study due to discontinuation of treatment¹, from group A and two from group B.

Average age of group A was 36.90 ± 14.11 years. Average age of group B was 31.72 ± 12.28 years. Most of the patients were male. The male to female ratio was 2.5:1 in group A and 3.75:1 in group B. Average size of the lesions in group A was $1195.68 \pm 909.02\text{mm}^2$ while in group B was $1405.87 \pm 977.34 \text{mm}^2$.

In group A, 23 (59%) patients had one lesion¹¹, (28.2%) patients had two lesions, 4 (10.3%) patients had 3 lesions and 1 (2.6%) patient had 4 lesions.

In group B, 25 (65.8%) patients had single lesion⁷, (18.4%) patients had two lesions, 3 (7.9%) patients had 3 lesions and 3 (7.9%) patients had 4 lesions (*p* = 0.551).

In group A, majority of the patients i.e. 14 (35.9%) patients had moderate improvement followed by total clearance in 12 (30.8%) patients. In group B, majority of the patients i.e. 26 (68.4%) patients had total clearance followed by moderate improvement in 9 (23.7%) patients. Group B had significantly better response as compared to group A (*p* = 0.004). (Fig-1)

In group A, drug was effective in 12 (30.8%) patients while in 27 (69.2%) patients drug was ineffective. In group B, drug was effective in 26 (68.4%) patients while in 12 (31.6%) patients drug was ineffective.

Efficacy of the drug was significantly higher in group B as compared to group A (*p* = 0.001) (fig-2).

DISCUSSION

Despite the high rate of spontaneous recovery in cutaneous leishmaniasis (specially noted with Old World CL) dermatologists still have to use different treatment modalities because of two reasons. First is its particular localization in uncovered areas which makes an esthetic issue for the patient especially when on the face. Second is the unbearable scarring caused particularly if left to selfheal.

Intramuscular meglumine antimoniate (MA) is the most commonly used treatment

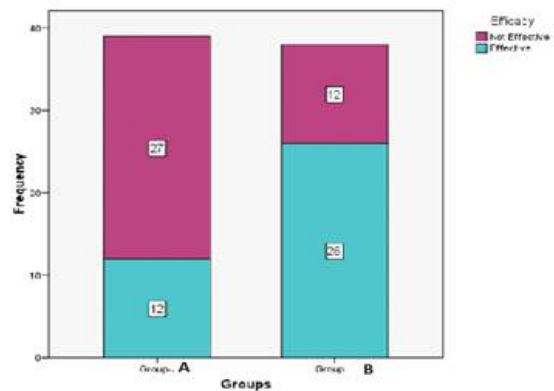


Figure-2: Comparison of efficacy of the treatment between the groups.

modality for CL in Pakistan for the last 2 decades. It is expensive, not widely available and requires monitoring and frequent visits to hospitals. Besides this it has numerous side effects⁶.

Current study was carried out as an attempt to find a cheaper, safer and preferable alternative to systemic meglumine antimoniate in treatment for CL in the form of oral zinc sulphate.

Zinc acts as an immunomodulator by increased generation of INF γ -producing T cells. INF γ activates infected macrophages to eliminate the parasite via reactive oxygen and reactive nitrogen. Experimental studies showed that zinc deficiency could change immune functions from cellular Th1 responses to humoral Th2 response¹¹. It was also known that there was a depression of helper T cell function in CL. It also has role in healing of ulcers.

Zinc sulphate is the inorganic compound with the formula ZnSO₄. It was historically known as "white vitriol"¹⁵.

Zinc is relatively nontoxic, particularly if taken orally. However, manifestations of overt toxicity symptoms (nausea, vomiting, epigastric pain, lethargy, and fatigue) will occur at amounts well in excess of the recommended dietary allowance i. e 15 mg Zn/d¹². There is induced copper deficiency with attendant symptoms of anemia and neutropenia. Even lower levels of zinc supplementation, closer in amount to the RDA, have been suggested to interfere with the utilization of copper and iron and to adversely affect HDL cholesterol concentrations.

Sharquie et al in 2001¹⁰ (Iraq) showed zinc sulphate was effective in treatment of cutaneous leishmaniasis at the dose of 10 mg/Kg/day with a mean of 28.32 \pm 1.35 days, was safe with 96.9 % cure rate.

Some studies have shown that CL responding to zinc sulphate was based on low body zinc levels in the affected patients. In a study carried out by Pourfallah et al¹³ in 2009, 60 patients with CL and the control group of 100 healthy volunteers from the same area, levels of serum Zn were significantly lower than the control group ($p < 0.001$). Serum Fe ($p < 0.05$) levels were also lower in patients with cutaneous leishmaniasis than the control group. They also found serum Cu concentration ($p < 0.05$) in the patient group was significantly higher than that of the control group. However, zinc/copper ratio ($p < 0.001$) was lower in patients with cutaneous leishmaniasis than in the control group.

Some studies have suggested the use of serum zinc levels as a tool for estimating the

prognosis of CL¹³. Yazdanpanah et al⁷ in 2011 in Iran, compared oral zinc sulfate with IM meglumine antimoniate in patients with CL. A total of 100 patients with CL were included and randomly divided into two groups. The first group was treated with oral zinc sulfate (10 mg/kg/day during 45 days period), and the second group was treated with systemic MA (20 mg/kg/day intramuscularly for 20 days). Acceptable cure after treatment occurred in 30.2% of lesions in first group, while this was 35.5% for the second group. There was no significant difference between the two treatment groups ($p = 0.42$).

In the above mentioned studies especially carried out in Iraq, oral zinc sulfate was proved to be more effective in treatment of CL cases caused by *L. Major*. We did not check the species in our patients and the endemic difference in species between Iraq, Iran and Pakistan may be the reason for difference in our results. Moreover differences in baseline size and duration of lesion can be a reason for the differences in our results.

In our study efficacy was significantly higher with 20 days of treatment with IM MA 20 mg/kg/day as compared to oral zinc sulfate 10mg/kg/day for 45 days ($p = 0.001$). In group A, drug was effective in 12 (30.8%) patients and in group B, drug was effective in 26 (68.4%) patients.

The above discussion revealed that oral zinc sulfate in the dose of 10mg/kg for 45 days can be considered as a safe treatment option in patients of CL. Although cure rate of systemic MA group was better treatment with zinc sulfate and is much easier, cost effective, convenient and safer.

Cutaneous leishmaniasis is a self-healing disease. It can be a source of bias in our study. The endemic types of cutaneous leishmaniasis in Pakistan are *L. major* and *L. tropica* healing on their own in 4-6 months and 3-24 months respectively¹⁴. But healing time with 45 days of oral zinc sulfate in our study is less than that of the self-healing duration. More studies are required in our settings to check the susceptibility on species specific basis of oral zinc sulfate.

CONCLUSION

Oral zinc sulfate in the dose of 10mg/kg for 45 days is not better than IM MA20mg/kg for 20 days. It is safe, cost effective and easily administered treatment option in patients, especially in those having comorbidities like old age, renal, hepatic and cardiac diseases limiting the use of systemic antimonials.

CONFLICT OF INTEREST

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

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