Efficacy of oral zinc sulphate compared with intralesional meglumine antimoniate injection (glucantime) in the treatment of cutaneous leishmaniasis

Farah Sattar, Shamshad Akram, Aliya Akhtar, Uzma Almas, Raheel Tahir, Shahid Nawaz
Dermatology Department, Nishtar Medical University, Multan.

Abstract

Introduction Leishmaniasis comprises of group of human infections which range in severity of disease from spontaneously healing skin ulcer to overwhelming systemic illness. Approximately 12 million patients are reported all over the world every year with this disease and it is associated with significant increase in morbidity. This study was conducted to compare the effectiveness of oral zinc sulphate with intralesional meglumine antimoniate injection in the treatment of cutaneous leishmaniasis.

Objective To compare the efficacy of oral zinc sulphate with intralesional meglumine antimoniate injection in patients presenting with cutaneous leishmaniasis at a tertiary care hospital.

Subjects and Methods The randomized control trial was carried out in the Outpatient Department of Dermatology, Nishtar Hospital Multan from 1-6-2016 to 30-11-2016. A total of 68 patients with cutaneous leishmaniasis were enrolled through Outpatient Department of Dermatology. The disease was diagnosed on clinical features with appearance of a papule or nodule at the feeding site of sandfly.

Results Mean age of the patients presenting with cutaneous leishmaniasis in group A was 26.76±16.71 years and in group B 26.02±15.15 years. Males were (52.9% vs. 58.8%) in group A and B respectively while females were (47.1% vs. 41.2%) in group A and B respectively. In group A, 30 patients (88.2%) showed effective response to therapy and 4 patients (11.8%) showed ineffective response. Effective response in terms of complete cure was seen in 20 patients (66.7%) while effective response in terms of partial improvement was seen in 10 patients (33.3%). In group B, effective response was seen in 26 patients (76.5%), with complete cure in 14 patients (53.8%) and partial improvement in 12 (46.1%) patients. Ineffective response was seen in 8 (23.5%) patients.

Conclusion There is no significant difference in the treatment of cutaneous leishmaniasis with oral zinc sulphate and intralesional meglumine antimoniate injection.

Key words Cutaneous leishmaniasis (CL), zinc sulphate, meglumine antimoniate (MA).
developing cutaneous Leishmaniasis.\textsuperscript{1,2}

In human beings, this disease is transmitted by the bite of infected female sand fly parasite that exists in two different forms: “an amastigote in the mammalian host and a flagellated promastigote in insect vector”.\textsuperscript{3} Human leishmaniasis can further be categorized into different forms such as cutaneous, mucocutaneous, diffuse cutaneous and visceral leishmaniasis.\textsuperscript{1} In the old world cutaneous Leishmaniasis most of the cases are caused by any one of the 2 species of related parasites which may involve; leishmania tropica that is traditionally an urban infection which produces comparatively benign “dry” ulcers and leishmania major, which is classically rural type that specifically develops into large and relatively more destructive type ulcers with “wet” type. Leishmania ethiopica is usually more prevalent in countries like Ethiopia and Kenya. In the “new world” most of the parasites are leishmania mexicana (which are more prevalent in countries like Mexico, Guatemala and South America) and leishmania braziliensis (primarily found in South and Central American countries). The incidence of cutaneous leishmaniasis is on the rise in Pakistan.\textsuperscript{4} The most prevalent type of this infection in Pakistan is urban or “anthroponotic leishmaniasis”.\textsuperscript{5} The various clinical presentations can be; paronychial, chancriform, annular, palmoplantar, zosteriform and erysipeloid form which may be difficult to diagnose.\textsuperscript{6,7} Although cutaneous leishmaniasis is usually believed to be a self-healing disease but can be associated with deforming scars.\textsuperscript{8}

Different modalities for the treatment of cutaneous leishmaniasis are available which may include curettage, surgical removal, grenz ray (in past), thermotherapy, cryotherapy, electrotherapy and laser. Topical treatment options include 15% paromomycin and intralosomal pentavalent antimonies injectable treatment. Systemic treatment options include antimony compounds, pentamidine, interferon, allopurinol, rifampicin, dapsone, azole antifungal drugs and immunotherapy. Different clinical trials have demonstrated the efficacy of various therapeutic modalities including photodynamic therapy (PDT), topical azole agents, herbal extracts and zinc sulphate showing varying proportions of efficacy to treat acute old world cutaneous leishmaniasis.\textsuperscript{9-13} However intralosomal treatment modalities as well as systemic route of administration of pentavalent antimonia such as sodium stibogluconate and meglumine antimoniate are still thought to be standard mode of treatment for the patients of cutaneous leishmaniasis. Cure rates of cutaneous leishmaniasis with meglumine antimoniate in different studies was 65–70%.\textsuperscript{2}

Zinc is an essential mineral which stimulates the activity of more than 100 enzymes which are substances that promote biochemical reactions in body. Deficiency of zinc can alter various immune responses primarily from predominantly cellular Th\textsubscript{1} to humoral Th\textsubscript{2} responses.

Inhibitory impacts of zinc sulphate on L. major as well as L. tropica amastigotes in vitro and involving animal studies have been shown\textsuperscript{14}. Zinc was postulated to act directly on enzyme system of parasite. Promising results are reported on treatment of cutaneous leishmaniasis with both oral and intralosomal administration of zinc sulfate.\textsuperscript{15,16} Cure rate with zinc sulphate reported from various studies was 90–96%.\textsuperscript{15}

Cutaneous Leishmaniasis is common presentation in our region and majority of these patients present to the OPD of our hospital. This study was done to compare the efficacy of oral zinc sulphate with intralosomal meglumine antimoniate injection in patients presenting with
Cutaneous leishmaniasis as Zinc Sulphate is easily available and cost-effective without injectable therapy. Zinc sulphate in the treatment of cutaneous leishmaniasis will provide our patients with significantly cheaper mode of treatment having good efficacy which will help to decrease burden of cutaneous leishmaniasis and improve quality of life of these patients.

**Materials and Methods**

The randomized control trial was conducted in the Outpatient Department of Dermatology, Nishtar Medical University and Allied Hospital, Multan from 1-06-2016 to 30-11-2016. A total of 68 patients with cutaneous leishmaniasis were enrolled through Outpatient Department of Dermatology. The disease was diagnosed on clinical features with appearance of a papule or nodule at the feeding site of insect assessed by a senior Dermatologist having more than 10 years experience. Diagnosis was confirmed by positive smear for LD bodies. Patients of either sex, age range 13 years to 60 years, with cutaneous Leishmaniasis were included in our study after taking informed consent from all these patients. Patients with recurrent disease, pregnant women, patients having known allergies to the drugs and malignancies were excluded from our study.

Patients were randomly divided in two equal groups. Group-A was given oral zinc sulphate in a dose of 10 mg/kg/day in divided doses and Group-B was given intraleisional meglumine antimoniate injection on weekly basis for 45 days of treatment in skin outdoor. Patients were followed up on 45th day of treatment in skin OPD to find out the effectiveness. All the data were recorded in a proforma specifically designed for the study.

SPSS version 20 was used for entry and analysis of our study data while mean and standard deviation was calculated for age of the patients having cutaneous leishmaniasis. Frequencies and percentages were calculated for gender and therapy outcome (effective or non effective response). Efficacy was defined as resolution of lesions on clinical examination and smear negative test for LD bodies. Chi-Square test was applied to compare the therapy outcome between two groups. *p*-value was considered significant if less than or equal to 0.05.

**Results**

Total 68 patients were studied with 38 (55.8%) male and 30 (44%) females. In group A, there were 18 males (52.9%) and 16 females (47.1%) while in group B, male patients were 20 (58.8%) and females were 14 (41.2%) as shown in Table 1. All patients presented with papulonodular lesions or plaques of variable sizes at feeding site of insect. In group A, 15 patients (44.1%) had lesions on upper limb, 10 (29.4%) had lesions on lower limb and (23%) had lesions on face. In group B 17 (50%) patients had lesions on upper limb, 11 (32%) had lesions on lower limb and (23%) had lesions on face.

All patients took the treatment for 45 days and followed up. Sixty eight patients were divided into two equal groups each containing 34 patients (50%). In group A, patients received oral zinc sulphate; 30 of them (88.2%) showed effective response to therapy and 4 patients (11.8%) showed ineffective response (Table 2).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (52.9%)</td>
<td>20 (58.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (47.1%)</td>
<td>14 (41.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective</td>
<td>30 (88.2%)</td>
<td>26 (76.5%)</td>
</tr>
<tr>
<td>Ineffective</td>
<td>04 (11.8%)</td>
<td>08 (23.5%)</td>
</tr>
</tbody>
</table>
Table 3: Effectiveness of response to therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>20 (66.7%)</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>Partial</td>
<td>10 (33.3%)</td>
<td>12 (46.2%)</td>
</tr>
<tr>
<td>Ineffective</td>
<td>04 (11.8%)</td>
<td>08 (23.5%)</td>
</tr>
</tbody>
</table>

Figure 1: Mean age of presentation was 26.76±16.71 and 26.02±15.15 years in group A and B respectively.

In group A, effective response in terms of complete cure was seen in 20 patients (66.7%) while effective response in terms of partial improvement was seen in 10 patients (33.3%) as shown in Table 3. In group B, patients were put on intralesional injection of meglumine antimoniate. Effective response was seen in 26 patients (76.5%) out of 34, with complete cure in 14 patients (53.8%) and partial improvement in 12 (46.1%) patients. Ineffective response was seen in 8 (23.5%) patients.

Chi-square test was applied to compare the effectiveness of therapy between group A and group B. p-value so obtained was 0.203 which was not significant (> 0.05) showing that there was no statistically significant difference between the effectiveness of two therapies.

Discussion

Cutaneous leishmaniasis is primarily caused by a parasite with significant morbidity. It is endemic in Pakistan. In Pakistan, urban leishmaniasis is more prevalent caused by leishmania tropica. The disease is self healing and mostly recovers in 6–12 months by scar formation. But lesions on cosmetically or functionally important sites like face or hands or those associated with lymphangitis, chronic and resistant lesions need to be given active treatment. There is no satisfactory and effective treatment for old world cutaneous leishmaniasis and there remains a pressing need for new anti-leishmania therapy with high cure rate, less side effect, better compliance and cheaper therapy.

During our study the effectiveness of zinc sulphate was found 88.2% as compared to intralesional injection of meglumine antimoniate with effectiveness of 76.5% in treatment of old world cutaneous leishmaniasis. However, statistically no significant difference was found between the effectiveness of two drugs. Results of our study are encouraging regarding the use of zinc sulphate as an alternate therapy in treatment of old world cutaneous leishmaniasis.

Effectiveness of zinc sulphate has been reported in acute old world cutaneous leishmaniasis in comparison with the effectiveness of intralesional route of administration of 2% ZnSO₄ with SSG or 7% sodium chloride solution. The results have shown that 84.8% of the lesions treated by 2 % ZnSO₄ showed cure after 1 injection and 94.7 % of the lesions were entirely cured after administering 2 injections at the interval of 10 to 15 days. Sharquie et al. studied 130 cases of acute CL and showed that oral ZnSO₄ had a dramatic effect on healing of the lesions. In this study, 83.90% of the patients’ lesions treated with oral ZnSO₄, 2.5 mg/kg per day, had healed after 31.8±1.8 days (mean±SD). The cure rate was 93.1% and 96.9% in the groups that were treated with oral ZnSO₄, 5 mg/kg per day for 29.9±1.7 days and 10 mg/kg per day for 28.3±1.4 days, respectively. They showed same effects of intralesional ZnSO₄.
injections in another study.\textsuperscript{19}

On the other hand, the study that compared 6 weekly intralesional injections of either 2% sterile ZnSO\textsubscript{4} solution or MA showed that 2% ZnSO\textsubscript{4} solution was less effective than MA in the treatment of acute Old World CL (P < 0.05).\textsuperscript{12}

Different randomized controlled trials have observed efficacy of pentavalent antimonials extensively as compared with any other drug. In fact, these drugs have been experimented in last 2 decades, on more than 1600 subjects presenting with old world cutaneous Leishmaniasis. In the treatment of cutaneous Leishmaniasis systemic pentavalent antimonies were extensively studied in the treatment of this infection since 1929.\textsuperscript{20,21} Today, SSG and meglumine antimonies (MA), Glucantime, are considered to be standard treatments for CL. Pentavalent antimonies are also commonly used as intralesional injections.

Interestingly, there has not been a single RCT performed to compare the efficacy of systemic pentavalent antimonies with placebo. In one open non randomized trial the efficacy of intralesionally injected SSG was evaluated in comparison with a control group, who received no treatments.\textsuperscript{22}

It was found that cure rates for oral zinc sulphate in terms of reduction in size of lesion up to 30% in 4.5% cases, 30%-60% in 9% cases. Only 9% cases were cured with > 60% reduction in size of lesion in the treatment of CL.\textsuperscript{23} In another study 10 mg/kg/day oral zinc sulfate was administered for 45 days to 31 patients with acute CL. Complete healing was only observed in two (9%) of the patients.\textsuperscript{24}

**Conclusion**

Zinc sulphate is an effective drug in treatment of cutaneous leishmaniasis with effective response of 88.2% in terms of percentage as compared to 76.5% response of intralesional meglumine antimoniate injection. However, no significant difference was found between therapeutic outcomes of two drugs statistically as p-value was 0.203.

**References**


