Journal of Pakistan Association of Dermatologists. 2020; **30(1)**: 111-116.

Original Article

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).

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 and it is associated with significant increase in morbidity. It is estimated that 10 % of world's population is at risk of

Address for correspondence
Dr. Aliya Akhtar, Assistant Professor,
Department of Dermatology,
Nishtar Medical University, Multan.
Email: draliyaakhtar@gmail.com

developing cutaneous Leishmaniasis.[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".[3] Human leishmaniasis can further be categorized into different forms such as cutaneous, mucocutaneous, diffuse cutaneous and visceral lesihmaniasis.[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.[4] The most prevalent type of this infection in Pakistan is urban or "anthroponotic leishmaniasis".[5] The various clinical presentations can be; paronychial, chancriform, annular, palmoplanter, zosteriform and erysipeloid form which may be difficult to diagnose.[6,7] Although cutaneous leishmaniasis is usually believed to be a self-healing disease but can be associated with deforming scars.[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 intralesional 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.[9-13] However intralesional treatment modalities as well as systemic route of administration of pentavalent antimonials 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%.[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_1 to humoral Th_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**[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 intralesional administration of zinc sulfate.[15,16] Cure rate with zinc sulphate reported from various studies was 90–96%.[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 intralesional 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 intralesional 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 6 (17.6%) 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)**.

Table1 Sex distribution

Sex	*Group*	
	A	*B*
Male	18 (52.9%)	20 (58.8%)
Female	16 (47.1%)	14 (41.2%)

Table2 Effectiveness of response to therapy

Response	*Group*	
	A	*B*
Effective	30 (88.2%)	26 (76.5%)
Ineffective	04 (11.8%)	08 (23.5%)

Table3 Effectiveness of response to therapy

Response	*Group*	
	A	*B*
Effective		
Complete	20 (66.7%)	14 (53.8%)
Partial	10 (33.3%)	12 (46.2%)
Ineffective	04 (11.8%)	08 (23.5%)

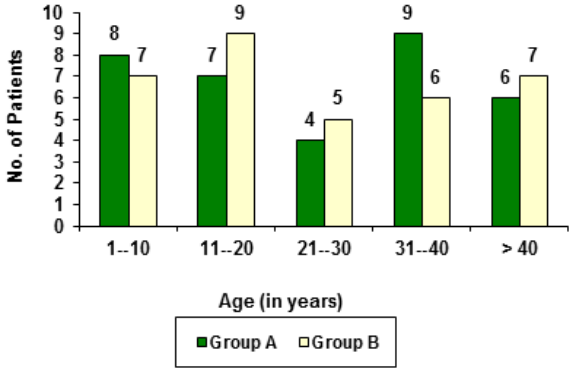

Figure 1 Mean age of presentation was 26.76±16.71 and 26.02±15.15 years in group A and B respectively.

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 lesishmaniasis 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-leshmania 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% $ZnSO_4$ with SSG or 7% sodium chloride solution.[17] The results have shown that 84.8% of the lesions treated by 2 % $ZnSO_4$ 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 $ZnSO_4$ had a dramatic effect on healing of the lesions.[18] In this study, 83.90% of the patients' lesions treated with oral $ZnSO_4$, 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 $ZnSO_4$, 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 $ZnSO_4$

injections in another study.[19]

On the other hand, the study that compared 6 weekly intralesional injections of either 2% sterile $ZnSO_4$ solution or MA showed that 2% $ZnSO_4$ solution was less effective than MA in the treatment of acute Old World CL ($P < 0.05$).[12]

Different randomized controlled trials have observed efficacy of pentavalent antimonies 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.[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.[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.[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.[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

1. Desjeux P. Leishmaniasis: current situation and new perspective. Comp Immunol Microbiol Infect Dis 2004; 27: 305-18.
2. Davies CR. Leishmaniasis: new approaches to disease control. BMJ 2003; 326: 377-82.
3. Crespo-Erchiga V, Florencio VD. Malassezia yeasts and pityriasis versicolor. Curr Opin Infect Dis 2006; 19(2): 139-47.
4. Bhutto AM, Soomro RA, Nonaka S, Hashiguchi Y. Detection of new endemic areas of cutaneous leishmaniasis in Pakistan. Int J Dermatol 2003; 42: 543-8.
5. Ayub S, Gramiccia M, Khalid M, Mujtaba G, Bhutta RA. Cutaneous leishmaniasis in Multan. J Pak Med Assoc 2003; 53: 445-7.
6. Iftikhar N, Bari I, Ejaz A. Rare variants of cutaneous leishmaniasis: whitlow, paronychia, and sporotrichoid. Int J Dermatol 2003; 42: 807-9.
7. Morishita N, Sei Y, Sugita T. Molecular analysis of malassezia microflora from patients with pityriasis versicolor. Mycopathologia 2006; 161(2): 61-5.
8. Piscopo TV, Mallia, Azzopardi C. Leishmaniasis. Postgrad Med J 2007; 83: 649-57.
9. Lurati M, Baudraz-Rosselet F, Vernez M, Spring P, Bontems O, Fratti M, et al. Efficacious treatment of non-dermatophyte mould onychomycosis with topical amphotericin B. Dermatol 2011; 223: 289-92.
10. Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of old world cutaneous leishmaniasis. Clin Exp Dermatol 2006; 31: 634-7.
11. Larbi EB, al-Khawajah A, al-Gindan Y, Jain S, Abahusain A, al-Zayer A. A randomized, double-blind, clinical trial of topical

clotrimazole versus miconazole for treatment of cutaneous leishmaniasis in the eastern province of Saudi Arabia. Am J Trop Med Hyg 1995; 52: 166-8.
12. Firooz A, Khatami A, Khamesipour A, Nassiri-Kashani M, Behnia F, Nilforoushzadeh M, et al. Intralesional injection of 2% zinc sulfate solution in the treatment of acute old world cutaneous leishmaniasis. J Drug Dermatol 2005; 4: 73-7.
13. Zerehsaz F, Salmanpour R, Handjani F, Ardehali S, Panjehshahin MR, Tabei SZ, et al. A double-blind randomized clinical trial of a topical herbal extract (Z-HE) vs. systemic meglumine antimoniate for the treatment of cutaneous leishmaniasis in Iran. Int J Dermatol 1999; 38: 610-2.
14. Ananda-Rajah MR, Grigg A, Slavin MA. Making sense of posaconazole therapeutic drug monitoring. Curr Opin Infect Dis 2012; 25: 605-11.
15. Iraji F, Vali A, Asilian A, Shahtalebi MA, Momeni AZ. Comparison of intralesionally injected zinc sulfate with meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. Dermatology 2004; 209: 46-9.
16. Moodahadu-Bangera LS, Martis J, Mittal R, Krishnankutty B, Kumar N, Bellary S, et al. Eberconazole--pharmacological and clinical review. Indian J Dermatol Venereol Leprol 2012; 78: 217-22
17. Türel O. Newer antifungal agents. Expert Rev Anti Infect Ther 2011; 9: 325-38.
18. Sharquie KE, Najim RA, Farjou IB. A comparative controlled trial of intralesionally administered zinc sulphate, hypertonic sodium chloride and pentavalent antimony compound against acute cutaneous leishmaniasis. Clin Exp Dermatol 1997; 22: 169-73.
19. Sharquie KE, Najim RA, Farjou IB. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. Clin Exp Dermatol 2001; 26: 21-6.
20. Iraji F, Vali A, Asilian A. Comparison of intralesionally injected zinc sulfate with meglumine antimoniate in treatment of acute cutaneous leishmaniasis. Dermatol 2004; 209: 46-9.
21. Das S, Barbhuniya JN, Biswas I, Bhattacharya S, Kundu PK. Studies on comparison of the efficacy of terbinafine 1% cream and butenafine 1% cream for the treatment of Tinea cruris. Indian Dermatol Online J 2010; 1: 8-9.
22. Keshtkar-Jahromi M, McTighe AH, Segalman KA, Fothergill AW, Campbell WN. Unusual case of cutaneous and synovial Paecilomyceslilacinus infection of hand successfully treated with voriconazole and review of published literature. Mycopathologia 2012; 174: 255-8.
23. Yazdanpanah MJ, Mostofi K, Soleimani M, Ebrahimirad M. Oral administration of zinc sulphate in treatment of acute cutaneous leishmaniasis. IRCMJ 2007; 9: 205-8.
24. YazdanPanah MJ, Mostoufi SK, Soleimani M. Oral zinc sulfate in the treatment of acute cutaneous leishmaniasis. Iranian J Dermatol 2003; 2: 20-4.