ORIGINAL ARTICLE

COMPARISON OF EFFICACY OF MILTEFOSINE VERSUS MEGLUMINE ANTIMONATE IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS

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Background: Cutaneous Leishmaniasis is a morbid condition that generates stigmatization and disfiguring scars. Pakistan is among the ninety-eight countries where cutaneous Leishmaniasis is endemic. Purpose of study was to compare the efficacy of miltefosine and meglumine antimoniate in the treatment of cutaneous Leishmaniasis. **Methods:** All patients with cutaneous Leishmaniasis (CL) who met the inclusion criteria were divided into two groups using the envelop method. Capsule Miltefosine 50 mg (2.5 mg/ kg) was given to group A, while intralesional Glucantime injection was given to group B. The treatment's efficacy was evaluated after four weeks and again after eight weeks. **Results:** Out of 74 patients, 37 patients were included in each group. In group A (miltefosine group), 56.75% were males, and 43.25% were females. In group B (meglumine antimoniate group), 62% were males, while 38% were females (p=0.63). The mean age was 32.81 years±12.09 SD, the mean duration of the disease was 5.4 months±2.3 SD and the mean number of lesions was 2.56±1.33 SD. The efficacy of Miltefosine and meglumine antimoniate (I/L) was 91.9% and 56.75%, respectively (p<0.001). **Conclusion:** Miltefosine was more effective than intralesional meglumine antimoniate in the treatment of cutaneous Leishmaniasis (p<0.001).

Keyword: Cutaneous leishmaniasis; Miltefosine; Meglumine antimoniate; Efficacy

Citation: Mohammad N, Sagheer F, Paracha MM, Khan AQ, Naseem S, Waseem M. Comparison of efficacy of miltefosine versus meglumine antimonate in the treatment of cutaneous leishmaniasis. J Ayub Med Coll Abbottabad 2022;34(4):849–53.

DOI: 10.55519/JAMC-04-11135

INTRODUCTION

Cutaneous Leishmaniasis (CL) is a significant public health concern in endemic countries with every 10th person at risk of infection for any type of Leishmaniasis.[1] The annual incidence of cutaneous Leishmaniasis is 1 to 1.5 million cases. Syria, Algeria, Brazil, Afghanistan, and Saudi Arabia account for over 90% of all cutaneous leishmaniasis cases.[2] In Pakistan, the prevalence ranges from 4.16–6.93%. Cutaneous Leishmaniasis is endemic in Pakistan's KPK, tribal areas, Baluchistan, and Punjab's southern districts. In Peshawar, a large number of cases have been discovered. The vast majority of cases have been found in Afghan refugees as well.

Cutaneous Leishmaniasis can be classified into three types: diffuse, intermediate, and localized forms. Males are more susceptible to parasitic illnesses than females.[3] It is a morbid condition that generates disfiguring scars and stigmatization. It is regarded as a serious health issue, with roughly 10% of cases resulting in severe manifestations. The gold standard for treatment these days in many countries is anti-parasitic injections of pentavalent antimonials, including meglumine antimoniate and sodium stibogluconate. Local treatments based on intralesional pentavalent antimonials, topical paromomycin, thermotherapy, or cryotherapy are also used for certain cases of cutaneous Leishmaniasis.[4,5]

Advancements in technology have allowed testing compounds against Leishmania parasites, although no new drugs have been registered so far. Antimony compounds remain the traditional treatment of choice for Leishmaniasis.[6] Parenteral and intralesional meglumine antimonite (Glucantime)are the first line of treatment.[6] However, each of these therapies presents important limitations, including long-term parenteral administration, toxic side effects, high cost in endemic countries, and a high number of resistance cases predominately associated with human immunodeficiency virus (HIV) co-infection. Miltefosine, a hexadecyl phosphocholine, was initially studied as an anti-tumor agent; more recently, it was described to exhibit both in vitro and in vivo activity against Leishmania parasites.[7]

In an experimental study conducted on the clinical efficacy of miltefosine, complete clearance of the lesions was observed in 39 (92.9%) patients and partial clearance in 1 (2.4%) patients. No significant derangements in the laboratory profile were noted before and after treatment. The mean duration of treatment was 23.47±SD 4.44 days. Sixteen patients

(38.1%) took Miltefosine for 28 days, 12 (28.6%) for 21 days and 9 (25%) for 25 days.[8] In a retrospective study, 31 patients over five years (2008 and 2013) were treated with intralesional M.A. (Glucantime). The initial (three months) and definitive (six months) cure rates were 70.9% and 67.7%, respectively.[9] In a randomized control trial, Rubiano LC *et al*. found that the efficacy of miltefosine was 68.96%, while intramuscular M.A. (Glucantime) efficacy was 82.8%.[10]

This study was designed to see the efficacy of miltefosine versus meglumine antimoniate as there are multiple issues with the availability of meglumine antimoniate in Pakistan. Based on the results of this study, clinicians will have another available option for the treatment of CL in Pakistan.

MATERIAL AND METHODS

A randomized controlled trial was conducted in Department of Dermatology, Lady Reading Hospital, Peshawar from 18th April to 18th October 2020 over period of 06 months after ethical approval from ethical review board. Data was collected from 74 (37 in each group) patients by non-probability consecutive sampling technique. The sample size calculation was done by WHO sample size calculation formula. Patients of either gender, age between 18 and 60 years with confirmed parasitological diagnosis of leishmaniasis who did not receive any treatment during the past six weeks with normal hepatic, renal, pancreatic and haematological functions were enrolled in the study. Patients with serious comorbids(hepatic/ cardiac/ renal disorders), with mucosal involvement and those with disseminated cutaneous leishmaniasis(more than 4 cutaneous lesions) were excluded from the study.

All the patients coming to the out-patient department of Dermatology fulfilling the inclusion criteria were included in the study.Informed written consent was taken from all the participants. Leishmania skin lesions were stained with Giemsa for Leishmania amastigotes under magnification (100x) to confirm the diagnosis. Study participants were randomly allocated to two groups by block randomisation method. Laboratory investigations like complete blood count, hepatic and renal function tests were done before starting the therapy. Group A was treated with Cap Miltefosine 50 mg (2.5 mg/kg), while group B was treated with intralesional Glucantime injection. Clinical response (efficacy) was assessed at four weeks then at eight weeks. The drug was considered effective when the complete clinical response was observed after four weeks. The drug was considered effective if complete re-epithelization of the ulcerated lesion occurs without residual inflammation & papular eruption. Photographs were taken before and after the therapy. All the data were collected through a predesigned *proforma*.

Data analysis was done with the help of SPSS software (version 19.0). All continuous variables like age, number of lesions & duration of disease were shown as mean±standard deviation (S.D.), and categorical data like gender & efficacy were presented based on frequency and percentage. The statistical analysis used was descriptive analysis. Effect modifiers like age, no of lesions, duration of the disease, and gender were controlled through stratification. The post-stratification chi-square test was applied, taking the *p*-value as ≤0.05 as statistically significant. All the results were presented in the form of tables and figures.

RESULTS

In this study, 74 patients were included, divided into two groups, i.e., 37 in each group.

Group A: In this group, 21 patients (56.75%) were males, and 16 patients (43.25%) were females.

Group B: In this group, 23 patients (62%) were male, while 14 patients (38%) were females.

The mean age was 32.81 years (18–60 years) ±12.09 SD. Patients were divided into two groups on the basis of the group.

Group A: Patients aged (18–40) were included in this group. Out of these 37 patients, 31 patients (83.7%) were aged 18–40 years.

Group B: Patients aged 41–60 years were included in this group. Out of these 37 patients, 26 patients (70.2%) were aged 18–40 years.

Group A (Miltefosine group): In this group, 91.9% of the patients responded well to the treatment, i.e., more than 75% clearance of the lesion.

Group B (Meglumine antimoniate group): 56.76% of patients showed more than 75% response to the treatment in this group.

By applying the Chi-square test, the p-value was statistically significant ($p<0.001$).

The frequency of efficacy of the treatment was stratified based on gender. In males, miltefosine and meglumine antimoniate were effective in 19 patients (90.4%) and 14 patients (60.8%), respectively, with a *p*-value ($p<0.023$). In female patients, miltefosine was effective in 15 patients (93.7%), while meglumine antimoniate was effective in 07 patients (50%) with a *p*-value <0.007.

The frequency of efficacy of the treatment was stratified on the basis of age.

Group A: Miltefosine was effective in 28 patients (90.3%), while meglumine antimoniate was effective in 15 patients (57.7%) of patients ($p<0.004$)

Group B: In patients aged 41–60 years, miltefosine was effective in 6 patients (100%) while meglumine

antimoniate was effective in 06 patients (54.5%) with a *p*-value <0.04.

The frequency of efficacy of the treatment was also stratified on the basis of the duration of the disease. Among patients with a disease duration of less than six months, miltefosine was effective in 20 patients (95.2%), while meglumine antimoniate was effective in 19 patients (59.4%) with a *p*-value <0.004. In patients with a disease duration of more than six months, miltefosine and meglumine antimoniate were effective in 14 patients (87.5%) and 02 patients (40%), respectively ($p<0.023$)

Based on the number of lesions, miltefosine and meglumine antimoniate were effective in 28 patients (93.4%) and 16 patients (57%), respectively in patients having ≤03 lesions ($p<0.001$). While in patients having a number of lesions more than three, miltefosine was effective in 06 patients (85.7%), and meglumine antimoniate was effective in 05 patients (55.6%) with a *p*-value of 0.19.

Table-1: Distribution of patients on the basis of gender (N=74)

Gender	Distribution on the basis of group		*p*-value
	Group A Miltefosine	Group B Glucantime	
Male	21 (56.75%)	23 (62%)	**0.63**
Female	16 (43.25%)	14 (38%)	
Total	37 (100%)	37 (100%)	

Table-2: Distribution of patients on the basis of age (n=74)

Age of patients	Distribution on the basis of group		*p*-value
	Group A	Group B	
18 to 40 years	31 (83.7%)	26 (70.2%)	**0.19**
41 to 60 years	06 (16.3%)	11 (29.8%)	
Total	37 (100%)	37 (100%)	

Table-3: Efficacy of the treatment (N=74)

Effectiveness of the drug	Distribution on the basis of group		*p*-value
	Group A Miltefosine	Group B Glucantime	
Effective	34 (91.9%)	21 (56.75%)	**0.001**
Not effective	03 (8.1%)	16 (43.25%)	
Total	37 (100%)	37 (100%)	

Table-4: Stratification of efficacy based on gender (n=74)

Gender	Efficacy	Group A	Group B	*p*-value
		Miltefosine	Glucantime	
Male	Effective	19 (90.4%)	14 (60.8%)	**0.023**
	No effective	02 (9.6%)	09 (39.2%)	
Total		21 (100%)	23 (100%)	
Female	Effective	15 (93.7%)	07 (50%)	**0.007**
	Non effective	01 (6.3%)	07 (50%)	
Total		16 (100%)	14 (100%)	

Table-5: Stratification of efficacy based on age (N=74)

Age	Efficacy	Group A	Group B	*p*-value
		Miltefosine	Glucantime	
18 to 40 Years	Effective	28 (90.3%)	15 (57.7%)	**0.004**
	Not effective	03 (9.7%)	11 (42.3%)	
Total		31 (100%)	26 (100%)	
41 to 60 Years	Effective	06 (100%)	06 (54.5%)	**0.04**
	Not effective	0 (0%)	05 (45.5%)	
Total		06 (100%)	11 (100%)	

Table-6: Stratification of efficacy based on duration of leishmaniasis (N=74)

Disease duration	Efficacy	Group A	Group B	*p*-value
		Miltefosine	Glucantime	
<6 months	Effective	20 (95.2%)	19 (59.4%)	**0.004**
	Not effective	01 (4.8%)	13 (40.6%)	
Total		21 (100%)	32 (100%)	
>6 months	Effective	14 (87.5%)	02 (40%)	**0.023**
	Not effective	02 (12.5%)	03 (60%)	
Total		16 (100%)	05 (100%)	

Table-7: Stratification of efficacy based on the number of lesions (N=74)

Gender	Efficacy	Group A	Group B	*p*-value
		Miltefosine	Glucantime	
≤ 3 Lesions	Effective	06 (85.7%)	05 (55.6%)	**0.19**
	Not effective	01 (14.3%)	04 (44.4%)	
Total		07 (100%)	09 (100%)	
>3 lesions	Effective	28 (93.4%)	16 (57%)	**0.001**
	Not effective	02 (6.6%)	12 (43%)	
Total		30 (100%)	28 (100%)	

DISCUSSION

Among 74 patients in this study, the mean age was 32.81 years±12.09 SD, the mean duration of the disease was 5.4 months±2.3 SD, and the mean number of lesions was 2.56±1.33 SD. In the study, 83.7% of the participants were aged 18–40 years, while 16.3% were aged 41–60 years (p=0.19). The efficacy of Miltefosine and meglumine antimoniate was 91.9% and 56.75%, respectively (p<0.001). (Table-3)

In experimental research on the efficacy of miltefosine in cutaneous leishmaniasis, Tahir M *et al*. found that 92.9 percent of patients had a complete clinical response, i.e., complete clearance of the lesions, which is similar to our findings.[8]

A retrospective study reviewed the experience of a Brazilian leishmaniasis reference centre using intralesional M.A. (Glucantime) to treat 31 patients over five years (2008 and 2013). The initial (three months) and definitive (six months) cure rates were 70.9% and 67.7%, respectively[9]. Rubiano LC *et al*. conducted a randomized control trial to compare the efficacy of miltefosine with meglumine antimoniate in the treatment of cutaneous leishmaniasis. The effectiveness of miltefosine was found to be 68.96% & the efficacy of intramuscular M.A. (Glucantime) was 82.8%.[10]

Intralesional meglumine antimoniate is effective, particularly in single lesions or lesions less than three in number. A case series of twelve patients with a parasitological diagnosis of CL (91% were single lesions) concluded that intralesional meglumine antimoniate was effective in 91.4% of cases even in recurrent CL in 1-5 sessions, pointing towards its therapeutic effectiveness in single lesions[11]. In our study, miltefosine and intralesional meglumine antimoniate were equally effective in lesions less than three in number (p=0.19).

Miltefosine in the oral formulation has better compliance and effective results. This study provides the best example in this regard. Even its efficacy is excellent in meglumine antimoniate-resistant cases of cutaneous leishmaniasis. Tayyebi M *et al*. found it effective (82%) in cases of MA resistant CL.

We found Miltefosine an effective drug for CL with prolong duration (p<0.023) and multiple lesions (p <0.001), emphasizing its coverage of all strains in KPK. Our results are endorsed by Ware JM et al. and Tayyabi M *et al*.[12,13] Ware JM concluded that miltefosine was effective (77%) against all strains of leishmania, while Tayyab M et al. found it effective (82%) against MA-resistant cases of CL. Mann S *et al*. reported successful treatment of two cases of L. panamensis, which is also consistent with our study results of our study.[14]

Miltefosine may be a better alternative for treating leishmaniasis due to its oral formulation and impressive cure rate. et al. found a cure probability (>2.0) of miltefosine than MA in the treatment of mucosal leishmaniasis and concluded it a better alternative to MA in the future[15].

CONCLUSION

This study concludes that miltefosine is more effective than intralesional MA in the treatment of cutaneous leishmaniasis. Its oral formulation makes it a better choice for the people and may be an impressive alternative to MA in the near future.

AUTHORS' CONTRIBUTION

NMA, FS: Literature search, conceptualization of the study design. MMP, AQK: Data collection, data analysis. SN, MW: Data interpretation, proof reading.

REFERENCES

1. Ali A, Ur Rehman T, Qureshi NA, Ur Rahman H. New endemic focus of cutaneous leishmaniasis in Pakistan and future epidemics threats. Asian Pac J Trop Dis 2016;6(2):155–9.
2. Alcantara LM, Ferreira TCS, Gadelha FR, Miguel DC. Challenges in drug discovery targeting TriTryp diseases with an emphasis on leishmaniasis. Int J Parasitol Drugs Drug Resist 2018;8(3):430–39.
3. Nezamzadeh-Ezhiyeh H, Mirhendi H, Jafari R, Veysi A, Rassi Y, Oshaghi MA, *et al.* An Eco-Epidemiological Study on Zoonotic Cutaneous Leishmaniasis in Central Iran. Iran J Public Health 2021;50(2):350–9.
4. Aronson NE, Joya CA. Cutaneous leishmaniasis: updates in diagnosis and management. Infect Dis Clin 2019;33(1):101–17.
5. Noor SM, Bhatti MZ, Paracha MM, Ullah GU. Efficacy of Combined Intralesional Meglumine Antimoniate and Cryotherapy Versus Cryotherapy alone for the Treatment of Cutaneous Leishmaniasis. J Postgrad Med Inst 2018;32(1):103–6.
6. Yesilova Y, Surucu HA, Ardic N, Aksoy M, Yesilova A, Oghumu S, *et al.* Meglumine antimoniate is more effective than sodium stibogluconate in the treatment of cutaneous leishmaniasis. J Dermatolog Treat 2016;27:83–7.

7. Peralta MF, Usseglio NA, Bracamonte ME, Guzmán ML, Olivera ME, Marco JD, *et al*. Efficacy of topical miltefosine formulations in an experimental model of cutaneous leishmaniasis. Drug Deliver Translat Res 2022;12(1):180–96.
8. Tahir M, Bashir U, Hafeez J, Ghafoor R. Safety and efficacy of miltefosine in cutaneous leishmaniasis: An open label, non-comparative study from Balochistan. Pak J Med Sci 2019;35(2):495–9.
9. Silva, Júnior AT, Senna MC, Rabello A, Cota1 G. Intralesional meglumine antimoniate for the treatment of localised cutaneous leishmaniasis: a retrospective review of a Brazilian referral centre. Mem Inst Oswaldo Cruz 2016;111(8):512–6.
10. Rubiano LC, Miranda MC, Muvdi Arenas S, Montero LM, Rodríguez-Barraquer I, Garcerant D, *et al*. Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. J Infect Dis 2012;205(4):684–92.
11. Arboleda M, Barrantes S, Úsuga LY, Robledo SM. Successful treatment of cutaneous leishmaniasis with intralesional meglumine antimoniate: A case series. Rev Soc Bras Med Trop 2019;52:e20180211.
12. Tayyebi M, Darchini-Maragheh E, Layegh P, Kiafar B, Goyonlo VM. The effect of oral miltefosine in treatment of antimoniate resistant anthroponotic cutaneous leishmaniasis: An uncontrolled clinical trial. PLoS Neglect Trop Dis 2021;15(3):e0009241.
13. Ware JM, O'Connell EM, Brown T, Wetzler L, Talaat KR, Nutman TB, *et al*. Efficacy and tolerability of miltefosine in the treatment of cutaneous leishmaniasis. Clin Infect Dis 2021;73(7):e2457–2562.
14. Mann S, Phupitakphol T, Davis B, Newman S, Suarez JA, Henao-Martínez A, *et al*. Case Report: Cutaneous Leishmaniasis due to Leishmania (Viannia) panamensis in Two Travelers Successfully Treated with Miltefosine. Am J Trop Med Hyg 2020;103(3):1081–4.
15. Sampaio RN, Silva JS, Paula CD, Porto C, Motta JD, Pereira LI, *et al*. A randomized, open-label clinical trial comparing the long-term effects of miltefosine and meglumine antimoniate for mucosal leishmaniasis. Rev Soc Bras Med Trop 2019;52:1–8.
16. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, *et al*. CONSORT for ReportingRandomized Controlled Trials inJournal and Conference Abstracts:Explanation and Elaboration. PLoS Med 2008;5(1):e20.

Submitted: July 5, 2022	*Revised: August 8, 2022*	*Accepted: August 12, 2022*

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