ORIGINAL ARTICLE

COMPARISON OF ORAL DAPSONE WITH INTRAMUSCULAR MEGLUMINE ANTIMONIATE IN CUTANEOUS LEISHMANIASIS

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Background: Many drugs are effective are used as second line treatment for cutaneous leishmaniasis. Dapsone therapy is tolerated well and cost effective. The aim of present study is to determine the efficacy of oral dapsone in comparison with intramuscular meglumine antimoniate in patients with cutaneous leishmaniasis and thus find out an effective second line treatment agent. **Methods:** This randomized controlled trial was carried out at dermatology department, of tertiary care centre Rawalpindi, Pakistan from November 2017 to June 2018. Hundred biopsy proven patients of cutaneous leishmaniasis completed the study with 50 patients in two group. Group A received intramuscular meglumine antimoniate (15 mg/kg/day). Group B received oral dapsone2.5 mg /kg/body weight /day (200 mg per day). Efficacy of therapeutic response was noted at the end of treatment. Data was analyzed with statistical analysis program (IBM-SPSS V22). Chi-square test was applied to compare efficacy, *p* value of ≤0.05 was significant. Stratification of data with respect to age, gender, duration of disease, number of lesions and weight was done to see their effect on treatment efficacy. Post stratification chi-square test for both groups was applied ($p \leq 0.05$ considered significant). **Results:** A total of 100 participants took part in the study. Duration of treatment (*p*-value <0.001) and the efficacy of the drugs (*p*-value=0.020) were significant. Meglumine antimoniate therapy group displayed a comparatively fast-paced recovery in (21–40 days) whereas Dapsone group showed better recovery in (41–60 days) in their lesions. **Conclusion:** Dapsone is an effective treatment for cutaneous Leishmaniasis.

Keywords: Cutaneous leishmaniasis; Meglumine antimoniate; Dapsone

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INTRODUCTION

Leishmaniasis is caused by a flagellated parasite, of genus *Leishmania*. It is present in America, Asia, Europe and Africa. More than 12 million patients are affected by leishmania and WHO reports more than two million new cases every year.[1] Epidemiology of disease is affected by environment, migration and climate. Clinical features include cutaneous, mucocutaneous and visceral forms, depending on the species of *Leishmania* involved.[2] Cutaneous leishmaniasis (CL) mimics many dermatoses. Smear, histopathology, culture, and polymerase chain reaction (PCR) can differentiate CL from its imitators.[3] Erythematous volcanic ulcer, lupoid, eczematous, erysipeloid, verrucous, dry, zosteriform, paronychial, sporotrichoid, chancriform and annular are atypical patterns. Subcutaneous and deep mycosis, cutaneous lymphoma, pseudolymphoma, basal and squamous cell carcinoma like lesions are other atypical presentations.[4] Ulcerative lesions were more common in immunosuppressed than in immunocompetent patients.[5] Pentavalent antimonial are standard drug of choice, although it is toxic and intolerable for patients. Efficacy of second line treatment options varies e.g., with azoles it is reported as 64%[6]. Systemic oral therapeutic options are an azole (fluconazole, itraconazole, ketoconazole)[7], Chloroquine[8], allopurinol[9], and dapsone[10].

Treatment response of second line drugs for CL varies. Dapsone is an old salt, economical and well tolerated.[11] Dapsone acts as an antileishmanial agent by inhibiting choline incorporation into lecithin decreasing phospholipid synthesis of the cell membrane, or by interfering folic acid synthesis. There is a desperate requirement of standardized trials and well conducted studies for favourable treatment of CL.[12] The aim of present study is to determine the efficacy of oral dapsone in comparison with intramuscular meglumine antimoniate in patients with cutaneous leishmaniasis and thus find out an effective second line treatment agent.

MATERIAL AND METHODS

This randomized controlled trial was carried out at dermatology department of tertiary care centre of Rawalpindi, Pakistan from November 2017 to June 2018. The sample size was calculated by WHO sample size calculator based on outcome variables with anticipated population proportion P1 of 85.4% and anticipated population proportion P2 of 56.5%. The sampling technique was non probability consecutive sampling. Hundred biopsy proven patients of CL were recruited in

the study with 50 patients in two groups. Written informed consent from patients and permission from hospital ethical committee was taken. Lottery method was used to divide patients in 2 groups. Group A received intramuscular meglumine antimoniate (15 mg/kg/day) not to exceed 15ml injection MA. While group B was treated with dapsone 2.5 mg /kg/body weight /day/per mouth (maximum200 mg per day). Each patient underwent complete medical examination and laboratory evaluation with complete blood count, hepatic and renal function tests, ECG, and serum for glucose 6-phosphate dehydrogenase (G6PD) deficiency. Patients with any co-morbid hepatic, renal or cardiac impairment, diabetes mellitus, pregnant females as well as those already taking treatment with any other anti-leishmanial agent in the last one month were excluded from the study. The duration of treatment was 40 days for Group A patients or earlier in case of complete healing occurring before 40 days or in case of intolerable side effects. This duration of treatment was chosen due to the fact that MA dose is considered to be 20mg/kg body weight/day for 28 days. This dosage has considerable side-effect profile and slightly lower dose with increase in duration was opted in this study. Group B received Dapsone for a maximum of 80 days or earlier, if complete healing was achieved earlier or due to intolerable side effects.

Efficacy of both treatments were noted at the completion of treatment by the researcher on specially designed proforma who was blinded to treatment modality of individual patient. The results were grouped into 'poor response' as being <50% response from the start of treatment, 'fair response' as 51–75% healing, 'good response' as 76–99% healing of the lesion from the baseline while complete healing (100%) was defined as complete disappearance of the induration or ulceration of the lesion. Data was analyzed by IBM-SPSS V22. Frequency and percentage were computed for qualitative variables like gender, number of lesions and efficacy. Mean±SD was presented for quantitative variables like age, duration of disease and weight. Chi-square test was applied to compare efficacy of both groups, taken $p \leq 0.05$ as significant. Stratification was done with regard to age, gender, duration of disease, number of lesions and weight to see the effect of these variables on efficacy. Post stratification chi-square test for both groups was applied ($p \leq 0.05$ considered significant).

RESULTS

Hundred participants completed study from November 2017 to June 2018. All patients were biopsy proven cases. The descriptive statistics of the age, gender, weight and number of lesions of patients are listed in Table-.

The comparison of two groups of patients on meglumine antimoniate and dapsone considering their clinical parameters of size of lesion, duration and efficacy of treatment is listed in Table-.

Four patients in Group A were continued with meglumine antimoniate therapy after 40 days as they were responding satisfactorily to treatment without demonstrating any side effects. Overall, nine patients reported to have side effects from the medicine (Four patients in group A and five in group B) in which case the treatment was stopped.

Patients age, weight, number of lesions, size, duration and efficacy of treatment of patients on meglumine antimoniate and dapsone **were** analyzed by Pearson chi-square test to calculate *p*-values (

Table-) for statistically significant findings.

Therapeutic response of dapsone in patient of cutaneous leishmaniasis. (Figure-1)

Duration of treatment (*p*-value <0.001) and the efficacy of the drugs (*p*-value=0.020) were statistically significant. The characteristics such as age, weight, number of lesions and size of lesions were obtained to be statistically insignificant with *p*-values greater than 0.05.

Table-1: Demographic variables of the patients with cutaneous leishmaniasis (CL)

		Meglumine antimoniate	Dapsone	Percentage	Mean±SD
Age	20–40 years	44	45	89	31±11.079
	41–60 years	5	3	8	
	61–80 years	1	2	3	
Gender	Male	50	50	100	
	Female	0	0	0	
Weight	45–60 kg	4	5	9	71.50±9.366
	61–75 kg	32	30	62	
	76–90 kg	13	15	28	
	91–105 kg	1	0	1	
Number of Lesions	1– 3	38	46	84	2.06±1.582
	4–6	10	4	14	
	7–9	2	0	2	

Table-2: Cutaneous leishmaniasis lesion size, treatment duration and efficacy between the two study groups

		Meglumine antimoniate	Dapsone	Percentage
Size of Lesions	0.1–3.0 cm	27	24	51
	3.1–6.0 cm	19	23	42
	6.1–9.0 cm	3	3	6
	9.1–12.0 cm	1	0	1
Duration of Treatment	21–40 days	46	15	61
	41–60 days	4	31	35
	61–80 days	0	4	4
Efficacy of Treatment	<50% improvement in size of lesion	4	5	9
	51–75% improvement in size of lesion	21	7	28
	75–100% improvement	21	33	54
	Medicine stopped due to side effects	4	5	9

Table-3: Stratification of groups on parameters of age, weight, number, size of lesion, duration and treatment response in two study groups

Variables		Group Names		Total	*p*-value
		Meglumine antimoniate	Dapsone		
Age	20-40 years	44	45	89	0.656
	41-60 years	5	3	8	
	61-80 years	1	2	3	
Weight	45-60 kg	4	5	9	0.725
	61-75 kg	32	30	62	
	76-90 kg	13	15	28	
	91-105 kg	1	0	1	
Number of Lesions	1 to 3	38	46	84	0.069
	4 to 6	10	4	14	
	7 to 9	2	0	2	
Size of Lesions	0.1-3.0 cm	27	24	51	0.669
	3.1-6.0 cm	19	23	42	
	6.1-9.0 cm	3	3	6	
	9.1-12.0 cm	1	0	1	
Duration of Treatment	21-40 days	46	15	61	0.001
	41-60 days	4	31	35	
	61-80 days	0	4	4	
Efficacy of Treatment	<50% improvement in size of lesion	4	5	9	0.020
	51-75% improvement in size of lesion	21	7	28	
	75-100% improvement	21	33	54	
	Medicine stopped due to side effects	4	5	9	

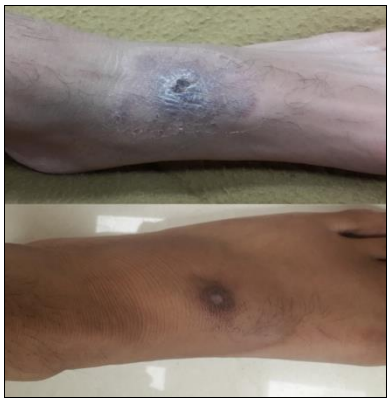

Figure-1: Efficacy of Dapsone in Cutaneous leishmaniasis Day 56

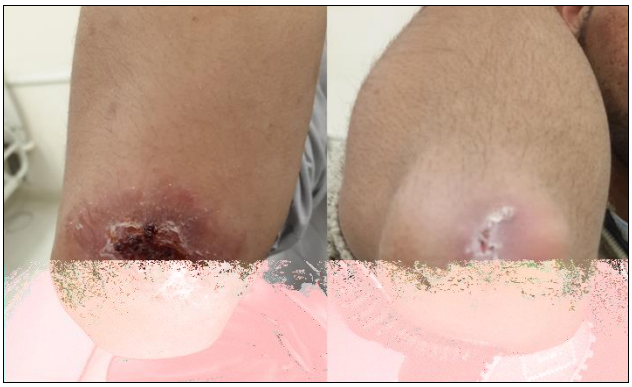

Figure-2: Efficacy of Meglumine antimoniate (Glucantime) in Cutaneous leishmaniasis Day 28

DISCUSSION

Cutaneous leishmaniasis is endemic in 98 countries. Pazoki *et al*. in their study in Herat at Afghanistan reported that males of 15–25 years are more commonly affected and average number of dermal lesions were 1.54+1.45.[13] Bashir et al. in their study on CL at in Pakistan reported it as being more common in young males.[14] This may be attributed to nature of job. Wijerathna T *et al*. in their study in Sri Lanka found that individuals residing in the areas appropriate for sand fly breeding and resting are at higher risk of infection.[15]

Dapsone can be considered as an alternative treatment to the traditional treatment of CL with Meglumine antimonite. We find significant efficacy of Dapsone (200 mg) therapy in the study group as 66% (33/50) in contrast to meglumine antimoniate where 42% (21/50) reached 75–100% improvement in their lesions. Dogra *et al* documented clinical and pathological cure of cutaneous leishmaniais in 50 patients with successful use of Dapsone for 21 days.[11] Dogra J. in a double blinded study on efficacy of Dapsone in cutaneous leishmaniasis found 82% patients of CL were cured.[16] Al-Mutairi *et al*. documented Dapsone (100–150 mg daily) as monotherapy showed good to excellent response in 43.8% (7/16) of CL patients.[17] Oral Dapsone is better than other current forms of treatment as it is well tolerated, cost effective and easily available. Osorio LE *et al.* in an uncontrolled trial at Columbia on 11 patients of CL did not find dapsone as promising treatment for cutaneous leishmaniasis. However, limitation of trial was small number of patients so results were not conclusive.[18] Keeping in mind the above mentioned researches we have given higher dose of 2.5mg/kg body weight/day, with a maximum dose of 200 mg to our patients to study better response with higher doses. Five patients on Dapsone withdrew from the study, comparable to patients on meglumine antimoniate.

Aflatoonian *et al*. in their study in Iran found that systemic MA therapy is refractory in CL cases, so man-vector exposure should be reduced and new effective alternative drugs should be considered in cases of L. tropica.[19] Mohammadzadeh *et al*. in Iran prescribed 20mg/kg/day intramuscular meglumine antimoniate for 20 days, their failure rate of treatment was 22.6%. They found antimony exposure was the only factor associated with failure to treatment[20]. There are concerns about cost, drug resistance and toxicity of antimony compounds.

Meglumine antimoniate therapy in our study group displayed a comparatively fast-paced recovery in (21–40 days) whereas Dapsone group showed better recovery in (41–60 days) in their lesions. Dogra J *et al.* used Dapsone 2 mg/kg/day for 6 weeks and found no recurrence of the lesions.[21] Romero *et al*. in Brazil used 20 mg/kg/day of pentavalent antimonial for 20 days, it was concluded that Leishmania species predict the outcome of treatment with antimonials.[22]

The statistically insignificant p-values obtained for age, weight, number of lesions and the size of lesions for the participants of the two study groups confirm the absence of study bias for both groups. All participants in this study were characteristically and symptomatically equal. Limitations of the study were the absence of female's participants in the study. The identification of Leishmania species was not done. The study sample included patients from the department of dermatology of a tertiary care hospital, Rawalpindi, Pakistan where CL cases were mostly reported by males employed in sand-fly affected areas.

CONCLUSION

Dapsone is an economical, readily available, and effective alternative treatment for CL.

AUTHORS' CONTRIBUTION

NA: Conceptualization of study design, data collection, data interpretation. SM: Conceptualization of study design, data collection. data interpretation. MT: Literature search, data interpretation, write up, proof reading. AR: Literature search, proof reading. IF: Data analysis, Data Interpretation. NR: Conceptualization of study design. NI: Conceptualization of study design

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