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Original Article

Comparing intramuscular meglumine antimoniate with oral chloroquine in the treatment of cutaneous leishmaniasis: A randomized controlled trail

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Abstract

Background Cutaneous leishmaniasis (CL) is highly prevalent in developing countries, including Pakistan. The conventional treatment for CL, meglumine antimoniate (MA), is unfortunately associated with considerable toxicity. Studies of alternative treatment options have reported inconsistent results. This study aimed to quantitatively compare the effectiveness of intramuscular MA with oral chloroquine in the treatment of CL.

Methods Patients of both genders between the ages of 06-60 years, presenting with CL lesions of less than 03 months duration were enrolled in this randomized controlled trial (RCT), carried out from August 2021 to February 2022 at the Department of Dermatology, Lady Reading Hospital, Peshawar. CL patients with a history of prior treatment and/or those with comorbidities were excluded. Eligible patients were allocated randomly into two groups, where patients in Group I were given intramuscular MA (20 mg/Kg body weight once daily for 4 weeks) while patients in Group II were given oral chloroquine (250 mg, twice daily over 4 weeks). The treatment response was assessed at 4-week follow-up after completion of the treatment.

Results The enrolled CL patients (n=82) were equally divided in two groups. The age and gender was evenly distributed between the two groups. The mean patient's age in Group I and II was 36.49±13.22 years and 37.34±13.19 years, whilst the male to female ratio was 1.28 and 1.16, respectively. Results showed a significantly higher rate of complete treatment response in Group I compared to Group II (78% vs. 48.8%, p=0.006). Treatment responses in both groups were also stratified on the basis of gender and socioeconomic status.

Conclusion This study indicated significantly higher efficacy of intramuscular MA compared to oral chloroquine for CL treatment.

Key words
Cutaneous leishmaniasis; Efficacy; Meglumine antimoniate; Chloroquine; Intralesion.

Introduction

The World Health Organization (WHO) reports that leishmaniasis infect approximately 1.5 million individuals annually, establishing it as the sixth most life-threatening disease on a global scale.[1,2] Leishmaniasis is manifested in three major variants: cutaneous leishmaniasis (CL), which induces dermal lesions on exposed anatomical regions; visceral leishmaniasis (VL), characterized by recurrent febrile episodes, anemia, weight loss, and hepatosplenomegaly

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and mucocutaneous leishmaniasis (ML); predominantly affecting the mucous linings of the oral, nasal, and throat passages.[3-5] Among these, CL prevails as the most widespread variant. Subsequent to the bite of phlebotomine sandflies, individuals manifest cutaneous ulcers or nodules within few days.[6,7]

Meglumine antimoniate (MA) is the primary therapy for CL patients, typically administered intralesionally over extended periods.[8,9] Albeit MA offer satisfactory treatment outcomes (i.e., 72-100 %),[10,11] this treatment is not without adverse effects.[12] Alternative treatments for CL encompass amphotericin B, pentamidine, cryotherapy, low-level laser therapy, photodynamic therapy (PDT), excision, and curettage.[13-16] Each of these approaches carries its own set of advantages and disadvantages. There is a need to establish an effective CL treatment characterized by minimal or no toxicity, cost-efficiency, and superior cosmetic outcomes.

Chloroquine, an affordable antiprotozoal drug primarily employed for malaria treatment, has exhibited promise in managing CL cases. Various studies have investigated the comparative efficacy of MA and chloroquine, yielding diverse findings. For example, it was found that while MA demonstrated superior effectiveness, oral chloroquine presented itself as a viable alternative.[17] Another analogous study reported that intralesional chloroquine is endowed with superior efficacy than intralesional MA.[18] More importantly, the findings showed a greater number of MA injections were required to achieve the same level of efficacy as chloroquine treatment. Furthermore, a comparison between oral and intralesional chloroquine administration has demonstrated similar efficacy in CL treatment. Nevertheless, intralesional injection has the advantage of shorter treatment duration and lower total dosage requirements compared to oral administration.[19] Herein, the primary goal was to assess and compare the effectiveness of intramuscular MA and oral chloroquine in the treatment of CL patients.

Materials and Methods

This randomized controlled trial (RCT) was carried out at the Department of Dermatology, Lady Reading Hospital (LRH) Peshawar, from August 2021 to February 2022, spanning over seven months. Diagnoses of the lesions as CL was confirmed through the examination of slit skin smears to detect the presence of Leishmania Trophozoites (LT) bodies and histopathological analysis of biopsied lesion samples. The Ethical Committee of LRH, Peshawar granted approval to conduct this study (vide letter No. 201/LRH/MTI dated: 28/07/2021). Patients were provided with detailed information regarding the treatment procedures, followed by obtaining written consent from each patient.

Patients of both genders between the ages of 6-60 years, presenting with CL lesions of less than 03 months duration, confirmed through the presence of LT bodies, were considered eligible for participation in this study. Alternatively, patients with CL who had a history of prior treatment, either on-going or completed, and/or those with comorbidities such as hepatic disease and end-stage renal disease were not eligible for participation in this study.

Patients meeting the inclusion criteria were allocated randomly into either Group I or II using the blocked randomization technique. Group I received treatment with intramuscular MA (dosage: 20 mg/Kg body weight once daily for 4 weeks). Moreover, patients in Group II were administered oral chloroquine twice daily at a dosage of 250 mg over the same 4-week period.

Although the classical clinical criteria employed

for assessing individual treatment responses in CL cases have not been definitively established, evaluating the ultimate treatment response is further complicated by virtue of extended intervals between the response initiation and recurrence of the parasite. This necessitates prolonged follow-up periods.[20] Furthermore, the reported clinical parameters for evaluating treatment response encompass clinical variables such as the dimensions of CL lesions, and status of inflammatory indicators; these may include skin erythema, hardening, edema, epithelialization and scarring of the lesions.[20,21]

The baseline for evaluating treatment response in this study was established by assessing the initial clinical appearance of the disease. The treatment response in both study groups was then assessed after a 4-week follow-up following the completion of treatment. Complete response (CR) indicated the total disappearance of the disease, with no scar or symptoms remaining. Conversely, cases where there was an absence of reduction in the lesion's size (as compared to the baseline) after treatment were designated as "no response (NR)". Furthermore, a decrease in the lesion size, ulceration, and skin edema was classified as partial response (PR).

A comprehensive medical history was obtained, and a thorough clinical examination was conducted for all patients. Relevant patient data, including age, gender, socioeconomic status, treatment history, the number, and size (diameter) of lesions, were documented and high-resolution photographs were taken. The socioeconomic status was classified in three categories: upper class with monthly income over Rs. 50000/-, middle class with monthly income of Rs. 30000/- to 50000/-, and lower class with monthly income below Rs. 30000/-. The photograph of the lesion captured during the initial visit served as the baseline for evaluating the treatment response.

Data handling and statistical analyses were executed utilizing SPSS software (version 23). Descriptive statistics, including mean and standard deviation, were computed for age and disease duration. Categorical variables such as gender, treatment response, and socio-economic status were analysed in terms of frequencies and percentages. The efficacy of the two treatments was stratified based on age, gender, socio-economic status, and disease duration. Post-stratification chi-square tests were employed, with statistical significance set at $p < 0.05$.

Results

A total of 82 patients were enrolled, with 41 in group I (MA) and 41 in group II (chloroquine). Descriptive statistics for mean age, disease duration, and patient gender in both groups are summarized in **Table 1**. The statistical analysis showed no significant differences ($p > 0.05$) in mean age, disease duration, or patient gender between the two groups. **Table 2** provides

Table 1 Descriptive statistics of mean age, duration of disease and patient gender (n=82).

Patient group	*Age (yrs.) (mean±SD)*	*Duration of disease (mon.) (mean±SD)*	*Male patients n (percent)*	*Female patients n (percent)*
Group I	36.49±13.22	1.51±0.51	23 (56.1)	18 (43.9)
Group II	37.34±13.19	1.37±0.49	22 (53.7)	19 (46.3)

yrs: years, SD: standard deviation, mon: month,

Table 2 Frequency of patient's socioeconomic status in both groups (n=82).

Patient group	*Socioeconomic status*		
	Upper class† (percent)	*Middle class* (percent)*	*Lower class‡ (percent)*
Group I	5 (12.2)	23 (56.1)	13 (31.7)
Group II	5 (12.2)	21 (51.2)	15 (36.6)

†: monthly income > Rs. 50000/-, *: monthly income = Rs. 30000/- to 50000/-, ‡: monthly income < Rs. 30000/-

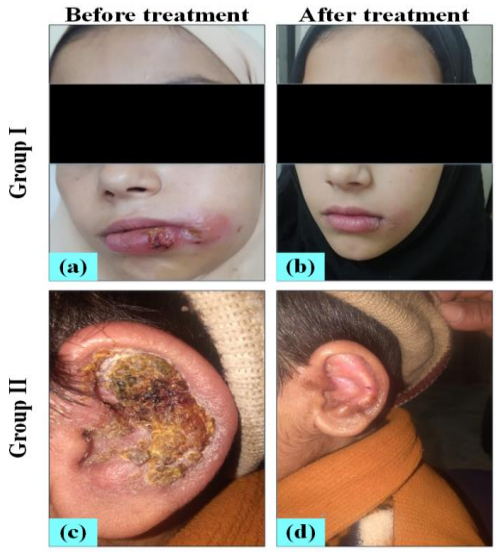

Figure 1 Illustrative white light photos of the CL lesions from Group I (a, b) and Group II, before (a, c) and after treatment (b, d). Complete response to the treatment has been demonstrated.

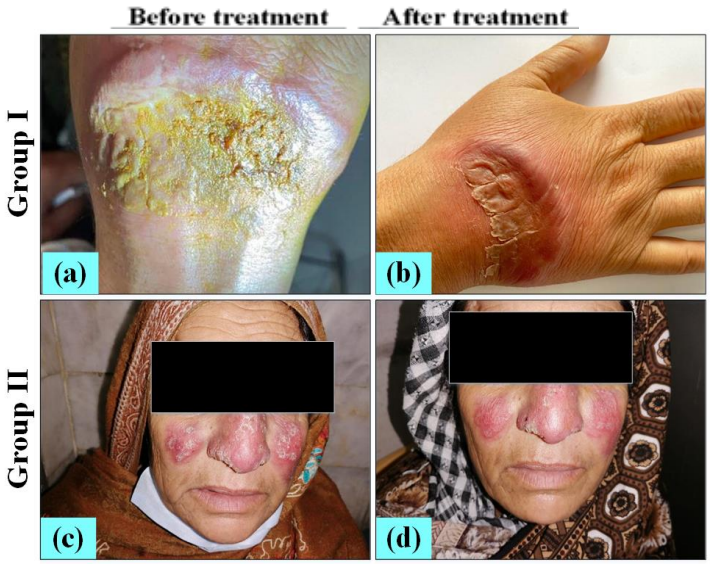

Figure 2 Illustrative white light photos of the CL lesions from Group I (a, b) and Group II, before (a, c) and after treatment (b, d). Partial response to the treatment has been demonstrated.

information on the distribution of patients' socio-economic status in both groups. It is evident that a relatively small number of patients (n=10; 12.2%) fell into the upper-class category, characterized by a monthly income exceeding Rs. 50,000/-.

Figure 1 presents white light photographs of CL patients from Group I (a, b) and Group II, both before treatment (a, c) and after treatment (b, d). In these images, it is evident that these patients exhibited a complete response to the treatment. Similarly, **Figure 2** displays white light images of CL patients from both groups, depicting cases with a partial response to the treatment.

The treatment responses exhibited by CL patients in the two groups are presented in **Table 3**. Evaluation of all patients after four weeks of completing the treatment revealed a significantly higher rate of complete responses in Group I compared to Group II (78% vs. 48.8%, p=0.006). There was no case of NR. **Tables 4** and **5** illustrate the stratification of treatment responses concerning gender and socioeconomic status in both groups, respectively.

Table 3 Treatment response in the two groups (n=82).

Patient group	*Treatment response*		*p value*
	CR; n (%)	*PR; n (%)*	
Group I	32 (78.0)	9 (22.0)	0.006
Group II	20 (48.8)	21 (51.2)	

CR: complete response, PR: partial response.

Discussion

The efficacy of intramuscular MA (Group I) was compared with oral chloroquine (Group II) for the treatment of patients presenting with CL. At four weeks follow-up, the treatment response of CL lesions was significantly higher in the intramuscular MA group than the oral chloroquine group (78% vs. 48.8%, p=0.006).

The observation that MA is endowed with an elevated treatment response is consistent with results from previous studies that conducted comparisons of this agent with alternative antiparasitic medications. For example, intralesional MA was found significantly more effective ($p<0.05$) compared to intralesional sodium stibogluconate, regardless of patient's demographic variables or clinical presentation.[22]

Table 4 Stratification of treatment response with respect to gender in both groups (n = 82).

Gender		*Treatment response*		*P value*
		CR; n (%)	*PR; n (%)*	
Male	Group I	17 (73.9)	6 (26.1)	0.17
	Group II	12 (54.5)	10 (45.5)	
Female	Group I	15 (83.3)	3 (16.7)	0.01
	Group II	8 (42.1)	11 (57.9)	

CR: complete response, PR: partial response.

Table 5 Stratification of treatment response with respect to socioeconomic status in both groups.

Socioeconomic status		*Treatment response*		*Total*	*p value*
		CR; n (%)	*PR; n (%)*		
Upper class†	Group I	4 (80.0)	1 (20.0)	5	0.05
	Group II	1 (20.0)	4 (80.0)	5	
Middle class*	Group I	17 (73.9)	6 (26.1)	23	0.13
	Group II	11 (52.4)	10 (47.6)	21	
Lower class‡	Group I	11 (84.6)	2 (15.4)	13	0.07
	Group II	8 (53.3)	7 (46.7)	15	

CR: complete response, PR: partial response.
†: monthly income > Rs. 50000/-, *: monthly income = Rs. 30000/- to 50000/-, ‡: monthly income < Rs. 30000/-

Comparison of intralesional and systemic administration of MA in a systematic review (with 40 studies and 5679 patients) showed identical efficacy for the treatment of CL.[23] Moreover, an RCT assessed the efficacy of combining oral itraconazole with intralesional MA compared to intralesional MA alone.[24]

This study found that the combination therapy did not significantly reduce the duration of therapy or provide any notable advantage over intralesional MA monotherapy in managing CL. Likewise, other studies have compared the effectiveness of MA with trichloroacetic acid,[25] topical trichloroacetic acid plus glucantime,[26] laser therapy plus glucantime,[26] and paromomycin sulfate.[27]

In this study, the CR rates in Group I and Group II were 78% (n=32/41) and 48.8% (n=20/41), respectively. The success rates of MA treatment documented by previous studies range from 97.2% to 41.7%.[28-30] The efficacy outcomes in our study align more closely with the findings reported by Vasconcellos *et al;*[31] who observed a CR rate of 83%.

Discrepancies between the results of this study and other investigations may be attributed to diverse host-related factors, including genetic variations and nutritional status, which can impact treatment response.[32,33] Additionally, differing Leishmania strains from various geographical regions may exhibit varying susceptibilities to MA.[34]

Conclusions

This study demonstrates a notable difference in efficacy between intramuscular MA and oral chloroquine for the management of cutaneous leishmaniasis, with intramuscular MA exhibiting a significantly higher cure rate (78% vs. 48.8%, p=0.006).

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

MP: Study design, data acquisition, manuscript write-up, final approval of the version to be published.

MW: Study design, analysis, data acquisition, final approval of the version to be published.

SMN: Data acquisition, manuscript write-up, final approval of the version to be published.

AQK: Concept and design of the work, manuscript write-up, final approval of the version to be published.

IA: Analysis, manuscript write-up, final approval of the version to be published.

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