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Comparison of Efficacy of Oral Azithromycin Versus Oral Chloroquine in the Treatment of Cutaneous Leishmaniasis

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ABSTRACT

Background: Cutaneous leishmaniasis is a parasitic disease-causing significant morbidity, particularly in endemic regions. Effective and accessible treatments are crucial, especially in resource-limited settings. While antimonials remain the standard, oral chloroquine and azithromycin have emerged as potential alternatives, though their comparative efficacy remains understudied. **Objective:** To compare the efficacy of oral azithromycin and oral chloroquine in the treatment of cutaneous Leishmaniasis. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** The study was conducted from December 2024 to February 2025 at the Dermatology Department of the Pakistan Institute of Medical Sciences (PIMS), Islamabad. **Methodology:** Sixty patients with confirmed CL were randomized into two groups: Group A received oral chloroquine (250 mg twice daily) and Group B received oral azithromycin (250 mg twice daily) for six weeks. Lesion characteristics, including size, induration and healing were assessed fortnightly. Efficacy was defined as complete lesion healing with or without scarring, confirmed by reduced lesion size and absence of amastigotes on rebiopsy. **Results:** The mean age of participants was 36.82 ± 10.54 years, with 63.3% males and 36.7% females. Lesions were predominantly on hands and arms (73.3% in Group A, 53.3% in Group B). Chloroquine demonstrated significantly higher efficacy (90%) compared to azithromycin (60%) (p=0.015). **Conclusion:** Our study confirms that oral chloroquine is highly effective for cutaneous leishmaniasis, outperforming azithromycin. Chloroquine showed consistent efficacy across age, gender and lesion locations, particularly for extremity lesions and shorter disease duration. Azithromycin had moderate overall efficacy but was significantly less effective in females and body lesions.

INTRODUCTION

Cutaneous leishmaniasis is a parasitic infection of the skin caused by protozoa of the genus *Leishmania* and transmitted by an infective bite from infected female phlebotomine sandflies.[1] The disease then manifests as ulcers, nodules, or papules on the skin that can result in scarring and disfigurement if not treated.[2] It is endemic in tropical and subtropical areas, foci of infection being described in Africa, Asia, the Middle East, and South America.[3] The severity and evolution of the disease depend on the *Leishmania* species and the host's immunological response.[4] Diagnosis is usually confirmed by microscopic identification or molecular techniques and thus requires treatment to avoid complications and reduce the reservoir.[5]

Treatment options for cutaneous leishmaniasis depend on the species of *Leishmania*, geographical region, and severity of infection.[6] First-line treatment generally includes antimonial compounds sodium stibogluconate and meglumine antimoniate, which can be given intramuscularly and intralesionally.[7] Nevertheless, because of toxicity ,cost or even availability of some of these treatments, other oral therapies have been used and continue to be studied. namely azithromycin and chloroquine, which are more available and easier to be administered particularly in resource-poor settings.[8]

Azithromycin is a macrolide antibiotic of potential interest in cutaneous leishmaniasis treatment for its antiparasitic and anti-inflammatory action.[9] It may interfere with the protein synthesis in the parasite, making it less viable.[9] In a few studies, azithromycin showed efficacy against different *Leishmania* species, especially when used in combination with other antileishmanial agents.[10] It is administered orally and has a very favorable safety profile, making it a very attractive option, especially for patients who cannot tolerate more toxic therapies. Its efficacy depends on the *Leishmania* species and further clinical trials are needed to establish standardized dosing regimens and confirm its role as a standalone or adjunctive treatment.[11]

Chloroquine represents another antimalarial drug that has been tried in cutaneous leishmaniasis.[12] Chloroquine is considered to act by accumulation of this drug within the parasite's acidic vacuoles, there by interfering with the cellular functions of the parasite and leading to parasitic death.[13] Clinical efficacies in humans are controversial, in contrast to the promising results observed in invitro and animal studies.[14] Other studies have suggested that it may be usefully tried in combination with other antileishmanials but because of inconsistent efficacy, it was not recommended as alone therapy.[15] Finally, chloroquine remains a candidate; research is warranted where access to care is limited due to poor availability of standard therapy where alternative therapies may be urgently needed.

Malik et al. [16] demonstrated a remarkable therapeutic efficacy with 100% cure rate observed in patients treated with oral chloroquine. In contrast, Shahzad et al. [17] documented a 67.86% cure rate among patients administered oral azithromycin, highlighting its potential as a viable treatment option. Farooq et al. [18] further contributed to the evidence base, reporting a 56% improvement rate in the oral chloroquine group, underscoring its variable but notable effectiveness. However, Paracha et al. [19] revealed more modest efficacy of 48.8% for oral chloroquine suggesting potential limitations in its application. Similarly, Seyyed et al. [20] observed a 46.4% cure rate in the oral azithromycin group, reinforcing the need for further research to optimize treatment protocols and enhance patient outcomes.

Cutaneous leishmaniasis should be taken as a serious public health problem in the rural and resource-limited areas of Pakistan. The need of the hour, in this context, is to identify safer, cost-effective, and accessible alternatives. This study will, therefore, compare the efficacy of oral azithromycin with oral chloroquine, as the two affordable and widely accessible drugs for the treatment of cutaneous leishmaniasis among the population in Pakistan. This study will provide evidence-based recommendations based on a comprehensive evaluation of their therapeutic outcomes, safety profiles, and feasibility of use in local healthcare settings to improve treatment accessibility, reduce the economic burden and enhance patient care in endemic regions of Pakistan.

METHODOLOGY

This randomized controlled trial was carried out between December 2024 and February 2025 at the Dermatology Department of the Pakistan Institute of Medical Sciences (PIMS) in Islamabad. The study included 60 participants diagnosed with cutaneous leishmaniasis, confirmed through clinical evaluation and Giemsa-stained smear biopsy. These participants were evenly distributed into two groups of 30 each, adhering to predefined inclusion and exclusion criteria. The sample size was determined using the WHO sample size calculator, with an 80% power of test and 5% significance level, based on assumed efficacy rates of 100%[16] for chloroquine and 67.86%[17] for azithromycin, as referenced from previous research. Inclusion criteria comprised individuals aged 18 to 60 years, of both genders presenting with cutaneous leishmaniasis lesions less than six months old, confirmed by clinical examination and Giemsa-stained smear biopsy. Exclusion criteria included patients with a history of allergy or intolerance to the study drugs, chronic debilitating diseases (e.g., end-stage hepatic, renal, or cardiac failure), recent treatment for CL within past three months, pregnant and lactating women.

After obtaining ethical approval and informed consent, participants were randomly allocated into two treatment groups using the lottery method. Group A received oral chloroquine at a dose of 250 mg (10 mg/kg/day) twice daily for six weeks, while Group B received oral azithromycin at a dose of 250 mg twice daily for six weeks. Patients were evaluated fortnightly for lesion characteristics including size, induration, erythema and secretion. Ophthalmic assessments were conducted before and after treatment to monitor potential adverse effects. Treatment efficacy defined as complete lesion healing with or without scarring was assessed by reduction in lesion size (measured via paper grid method), decreased induration (palpation) and absence of amastigotes on rebiopsy after six weeks of treatment. Data collection was performed by a single resident under the supervision of an experienced consultant dermatologist to minimize bias. Demographic details, clinical history and treatment outcomes were recorded in a structured proforma. Statistical analysis was performed using SPSS version 25. Continuous variables, such as age and disease duration was expressed as mean ± standard deviation, while categorical variables including gender, lesion site and treatment efficacy that were presented as frequencies and percentages. The chi-square test was used to compare efficacy between the two groups with p-value ≤ 0.05 considered statistically significant. Stratification was performed for age, gender, disease duration and lesion site to control for potential confounding variables, followed by post-stratification chi-square analysis.

RESULTS

Demographic characteristics showed that the mean age of patients in the Chloroquine group (Group A) was 35.7±10.89 years, while in the Azithromycin group (Group B), it was 37.93±10.19 years. The mean duration of the disease was similar in both groups, with Group A at 3.3±1.66 months and Group B at 3.37±1.69 months. Gender distribution was identical, with 63.3% males and 36.7% females in each group. Lesion sites varied, with 73.3% of Group A having lesion on hands and arms

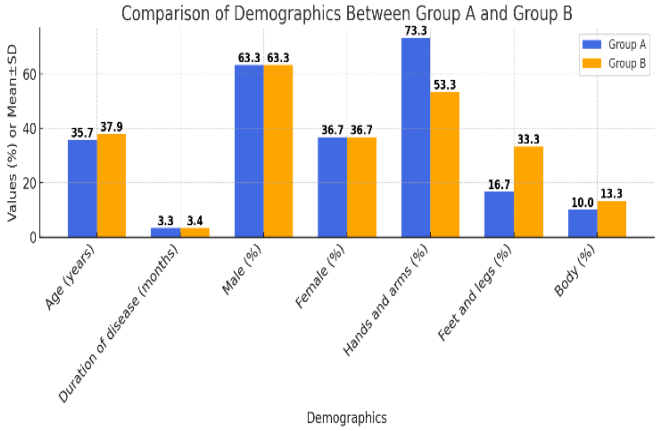
compared to 53.3% in Group B, while 16.7% of Group A and 33.3% of Group B had lesions on feet and legs. Body lesions were present in 10% of Group A and 13.3% of Group B as shown in Table-1.

Table 1

Demographics of the patients (n=60)

Demographics		Group A n=30 Mean±SD	Group B n=30 Mean±SD
Age (years)		35.700±10.89	37.933±10.19
Duration of disease (months)		3.300±1.66	3.366±1.69
Gender	Male n (%)	19 (63.3%)	19 (63.3%)
	Female n (%)	11 (36.7%)	11 (36.7%)
Lesion Site	Hands and arms n (%)	22 (73.3%)	16 (53.3%)
	Feet and legs n (%)	5 (16.7%)	10 (33.3%)
	Body n (%)	3 (10%)	4 (13.3%)

Figure 1



In terms of treatment efficacy (Table-2), oral Chloroquine (Group A) demonstrated a significantly higher efficacy rate (90%) compared to oral Azithromycin (Group B) (60%) with a p-value of 0.015.

Table 2

Comparison of efficacy between the two groups. (n=60)

Efficacy	Group A n=30 n (%)	Group B n=30 n (%)	P value
Yes	27 (90%)	18 (60%)	
No	3 (10%)	12 (40%)	0.015*
Total	30 (100%)	30 (100%)	

*Fischer Exact Test

Stratified analyses further revealed that efficacy varied based on demographic and clinical factors. For patients aged 18-40, 90% in the Chloroquine group reported efficacy compared to 58.8% in the Azithromycin group (p=0.052). In the 41-60 age group, efficacy was 90% in the Chloroquine group and 61.5% in the Azithromycin group (p=0.179). Male patients in the Chloroquine group had 94.7% efficacy rate versus 73.7% in the Azithromycin group (p=0.179), while female patients in the Chloroquine group had an 81.8% efficacy rate compared to 36.4% in the Azithromycin group (p=0.081). Patients with disease duration of 1-3 months in the Chloroquine group had a 100% efficacy rate, whereas the Azithromycin group showed 68.8% efficacy (p=0.018). For lesions on hands and arms, the Chloroquine group achieved 100% efficacy rate compared to 68.8% in the Azithromycin group (p=0.009). Lesions on feet and legs showed 100% efficacy in the Chloroquine group and 70% in the Azithromycin group (p=0.506), while body lesions had no efficacy in either group (p=1.000) as shown in Table-3.

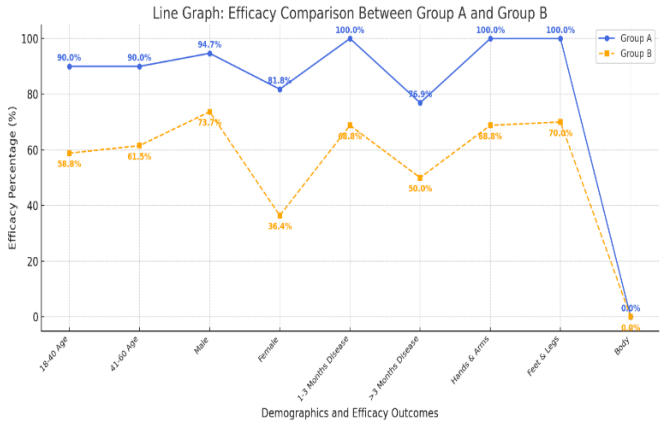
Table 3

Stratification of Efficacy Based on Demographic Variables Across Groups

Demographics variables		Group	Efficacy Yes (n %)	Efficacy No (n %)	P-value
Age (years)	18-40	A	18 (90%)	2 (10%)	0.052*
		B	10 (58.8%)	7 (41.2%)	
	41-60	A	9 (90%)	1 (10%)	0.179*
		B	8 (61.5%)	5 (38.5%)	
Gender	Male	A	18 (94.7%)	1 (5.3%)	0.179*
		B	14 (73.7%)	5 (26.3%)	
	Female	A	9 (81.8%)	2 (18.2%)	0.081*
		B	4 (36.4%)	7 (63.6%)	
Duration of	1-3	A	17 (100%)	0 (0%)	0.018*
		B	11 (68.8%)	5 (31.2%)	
	>3	A	10 (76.9%)	3 (23.1%)	0.237*
		B	7 (50%)	7 (50%)	
Lesion Site	Hands and arms	A	22 (100%)	0 (0%)	0.009*
		B	11 (68.8%)	5 (31.2%)	
	Feet and legs	A	5 (100%)	0 (0%)	0.506*
		B	7 (70%)	3 (30%)	
	Body	A	0 (0%)	3 (100%)	1.000*
		B	0 (0%)	4 (100%)	

*Fischer Exact Test

Figure: 2



DISCUSSION

Oral Chloroquine demonstrated a higher overall efficacy rate (90%) compared to Azithromycin (60%), suggesting that Chloroquine may be more effective in managing the disease. This may be so because of the well-documented antiparasitic role of Chloroquine, which acts against the parasite itself by disrupting its metabolic processes, particularly in the acidic environment of parasitophorous vacuoles. In addition, Azithromycin has effects primarily against intracellular organisms, with undoubtedly poorer direct action upon Leishmania species.

The stratified analysis further revealed that Chloroquine was highly effective in patients below 40 years of age and with a disease duration of 1 to 3 months. This is because, in most cases, younger patients and those in the early stages of infection are able to mount a robust immune response, which may synergize with Chloroquine's antiparasitic effects. Furthermore, the higher efficacy of Chloroquine in treating lesions of the hands and arms, compared with Azithromycin, may be related to better drug penetration in these more vascularized areas compared to other lesion sites, such as the body, where both treatments were ineffective. Suboptimal delivery of the drugs to these body regions or differences in the immune microenvironment at these sites may explain the reduced effectiveness of both treatments against body lesions.

Our findings are consistent with and further extend previous studies on the treatment of cutaneous leishmaniasis. Regarding efficacy, oral chloroquine in Group A had a significantly higher efficacy rate of 90% compared to oral azithromycin in Group B, which was 60%, with a p-value of 0.015. These observations are in complete agreement with findings by Malik et al.[16] who demonstrated oral chloroquine to be 100% effective, and Farooq et al.[18] who found chloroquine to be effective, though less so than meglumine antimoniate. In contrast, these results differ from the findings of Prata et al.[21] and Shahzad et al.[17] who reported efficacy rates for azithromycin of 85% and 67.86%, respectively. The relatively low efficacy of azithromycin in our study could be attributed to differences in Leishmania species, patient populations or treatment regimens. For example, Prata et al. [21] focused on Leishmania Viannia brasiliensis, while our study may have included other species with varying drug sensitivities.

The further stratified analysis in our study also revealed that demographic and clinical factors influenced efficacy. Patients aged between 18-40 years had an efficacy rate of 90% in the chloroquine group compared to 58.8% in the azithromycin group (p=0.052). For patients aged 41-60 years, the efficacy rates were 90% and 61.5% for chloroquine and azithromycin groups, respectively (p=0.179). Male patients in the chloroquine group had a 94.7% efficacy rate compared to 73.7% in the azithromycin group, while female patients in the chloroquine group had an 81.8% efficacy rate compared to 36.4% in the azithromycin group. These results demonstrate the consistent efficacy of chloroquine across different age groups and genders, particularly in males. This aligns with Malik et al. [16] who reported no significant differences in efficacy based on age or gender for chloroquine.

Patients with a disease duration of 1-3 months in the chloroquine group had a 100% efficacy rate, whereas the azithromycin group showed 68.8% efficacy (p=0.018). This suggests that early intervention with chloroquine may yield better outcomes, a finding supported by Farooq et al.[18] who noted that shorter disease duration correlated with improved treatment responses. For lesions on the hands and arms, the chloroquine group achieved a 100% efficacy rate compared to 68.8% in the azithromycin group (p=0.009). Lesions on the feet and legs showed 100% efficacy in the chloroquine group and 70% in the azithromycin group (p=0.506), while body lesions had no efficacy in either group (p=1.000). The superior efficacy of chloroquine for lesions on extremities may be due to its systemic distribution and anti-inflammatory properties, as suggested by Malik et al. [16] and Hanif et al. [22]

Azithromycin also demonstrated limited efficacy in treating body lesions, as no efficacy was observed in either group. This finding contrasts with those of Prata et al. [21] and Shahzad et al. [17] who reported high cure rates for azithromycin without specifying lesion locations. The discrepancy may be due to differences in lesion characteristics or the extent of disease involvement in our study population.

Our findings support the use of oral chloroquine as a highly effective treatment for cutaneous leishmaniasis, particularly for lesions on the extremities and in patients with shorter disease duration. While azithromycin showed moderate efficacy, its performance was inferior to chloroquine, especially in females and for body lesions. This study has several limitations that should be acknowledged. First, its single-center design may limit the generalizability of the findings to other geographical regions with different Leishmania species. Second, the study compared only two drug regimens without including other standard treatments, such as antimonials. Third, the Leishmania species were not identified, which could significantly influence treatment response. Finally, the lack of long-term follow-up precludes an assessment of the sustainability of treatment outcomes and relapse rates. Future studies should involve multiple centers, larger sample sizes, species identification and extended followup periods to address these limitations.

CONCLUSION

Our study has determined that oral chloroquine is a very effective treatment for cutaneous leishmaniasis, with higher efficacy as compared to oral azithromycin. Chloroquine was homogeneously effective across age, gender and lesion location subgroups, especially for lesions of the extremities and in patients with a shorter duration of the disease. Azithromycin demonstrated moderate efficacy overall but showed strikingly poorer efficacy in several subgroups, such as females and with body lesions.

Ethical Approval

The study protocol was approved by the Ethical Review Board of the PIMS HOSPITAL ISLAMABAD (Reference Number: F-5-2/2024(ERRC)/PIMS)

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