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Comparison of Efficacy of Intralesional Metronidazole Versus Intralesional Meglumine Antimoniate in Patients of Cutaneous Leishmaniasis

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ABSTRACT

Objective: To compare the effectiveness of intralesional Metronidazole versus intralesional Meglumine antimoniate in the treatment of cutaneous leishmaniasis.

Study Design: Quasi experimental study.

Place and Duration Of Study: Department of Dermatology, Combined Military Hospital, Peshawar Pakistan, from Dec 2019 to June 2020.

Methodology: After informed consent from study participants and approval from the hospital ethical committee, sixty patients with cutaneous leishmaniasis from the dermatology OPD who met the inclusion criteria were chosen. Patients were randomly assigned to one of two therapy groups using simple randomization. Group A was given intralesional Metronidazole 1-2 ml (5-10mg) per lesion twice a week and Group B received intralesional Meglumine antimoniate 1-2 ml (90-180mg) per lesion twice a week for 8 weeks. Lesions were measured using a ruler and palpation to determine their size and induration. Patients were followed up till their treatment was completed. The drug was considered efficacious if there was 75 percent reduction in size or induration of lesion.

Results: At the end of eight weeks, clinical effectiveness was observed in 16(53.33%) patients in Group A and 28(93.33%) patients in Group B. The results were found to be statistically significant with a *p*-value of 0.001.

Conclusion: Intralesional Meglumine antimoniate is more effective than intralesional Metronidazole in the treatment of cutaneous leishmaniasis.

Keywords: Cutaneous leishmaniasis, Metronidazole, Meglumine antimoniate, Intralesional therapy.

How to Cite This Article: *Gul RK, Kausar S, Naveed T, Saleem S, Riaz S, Said G. Comparison of Efficacy of Intralesional Metronidazole Versus Intralesional Meglumine Antimoniate in Patients of Cutaneous Leishmaniasis. Pak Armed Forces Med J 2025; 75(Suppl-1): S101-S104. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-1.7417*

INTRODUCTION

Leishmaniasis is a parasitic infection caused by the genus Leishmania, which spread through the bite of sandfly. It includes cutaneous, mucocutaneous and visceral manifestations of the disease. Humans are frequently infected by the parasite after being bitten by infected sandflies. The most common form of human leishmaniasis is cutaneous leishmaniasis.[1] In cutaneous leishmaniasis, single or multiple papules develop that eventually evolve into plaques, nodules and ulcers. Untreated cases may take several months to heal completely leaving behind disfiguring scars. Cutaneous leishmaniasis can causes substantial morbidity depending on the size and site of the lesion and the psychological effects of disfigurement can not be denied as well.

The disease burden of cutaneous leishmaniasis is considered to be the 9th highest among all infectious diseases.[2] A total of 12 million people are infected worldwide, with an additional 350 million people in over 100 countries at risk of infection.[2] In Pakistan, the annual incidence is estimated to be between 21700 and 35700 cases.[3] Baluchistan, Interior Sind, Multan, and KPK are the endemic areas for it with sporadic foci in especially those bordering Afghanistan due to the maximum influx of refugees and military personnel due to their deployment on border areas.[4,5]

Diagnosis is confirmed on visualization of the parasite on slit skin smear and histopathological examination of skin biopsy. The lesion of cutaneous leishmaniasis can heal spontaneously but at the cost of a disfiguring scar.[6] Therefore the treatment becomes necessary to avoid morbidity related to this disease. Treatment options for cutaneous leishmaniasis include both oral and parenteral medication. Pentavalent antimonials remain the treatment of choice.[7] However, the adverse effects of antimony compounds on the cardiovascular, hepatic and musculoskeletal systems are well established.[8] Other treatment options may

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Received: 22 Sep 2021; revision received: 13 Jul 2022; accepted: 15 Jul 2022

include liposomal Amphotericin B, Miltefosine, Rifampicin, Itraconazole, Allopurinol, and Metronidazole.[9] Metronidazole is an antibacterial drug and has been used orally as a second-line drug for the treatment of cutaneous leishmaniasis. Various studies have elaborated the beneficial role of intralesional Metronidazole in this disease and have documented the results comparable to the pentavalent antimonials.[10]

The objective of this study was to compare the effectiveness of intralesional Metronidazole versus intralesional Meglumine antimoniate in the treatment of cutanoeus leishmaniasis. As Meglumine antimoniate is expensive and health facilities frequently run out of it, whereas Metronidazole is readily available, inexpensive and would provide an alternate treatment option.

METHODOLOGY:

This Quasi experimental study was conducted in dermatolgy department of Combined Military Hospital Peshawar from Dec 2019 to June 2020. Approval from the hospital ethical and research committee was taken, and sixty patients were enrolled in this study after their informed written consent. The WHO sample size calculator for two proportions based on outcome variable was used to determine the sample size keeping the level of significance 5% and power of test 90%. Anticipated population proportion (P1) was 81%, (P2) was 16.6% and calculated sample size was 60 patients (30 patients in each group).[11] Consecutive non-probability sampling was used. The diagnosis was made clinically and based on the presence of LT bodies on smears. In case of a negative slit skin smear, a skin biopsy was taken to confirm the diagnosis. Inclusion criteria included patients from both genders and all age groups, duration of lesions between 06 weeks to 06 months, and patients who had not received any treatment so far. Pregnant or lactating females and patients with history of hepatic, renal, or cardiac illness were excluded from the study. The study excluded patients with mucosal lesions, lesions on the ear or nasal cartilage or with sporotrichoid spread, lesion more than 4 cm in size and secondarily infected lesions.

Patients were divided into two therapy groups using a simple lottery method of randomization. Intralesional Metronidazole 1- 2ml (5-10mg) per lesion was given twice a week to group A, while intralesional Meglumine antimoniate 1-2ml (90-180mg) per lesion was given twice a week to group B. The intralesional injection was administered enough to blanch the lesion. On a weekly basis, the size and indurations of each lesions were measured using a ruler, palpation and ulcer charting.

The response to treatment was graded as no response (less than 25% reduction in size with persistent induration), partial response (25 to 75% reduction in size with persisting induration) and complete response (more than 75% reduction in size without any induration) eight weeks after starting the therapy. Complete response was considered as efficacy. The data was analysed using SPSS version 23. Numeric variables such as age and duration of the disease were described using mean and standard deviations. Categorical factors including gender, efficacy, and responsiveness were described using frequencies and percentages. Chi-square test was used to compare the efficacy of the two groups keeping *p*-value ≤0.05 as significant.

RESULTS

The mean age of the patients in groups A and B was 33.47±9.22 and 32.17±8.38 years, respectively. In group A, there were 28(93.33%) males and 2(6.66%) females, while in group B, there were 26(86.66%) males and 4(13.33%) females. The majority of the patients 41(68.33%) had a disease duration of 2 to 3 months. The minimum number of lesions in any patient was 1, while the maximum number was 7. The majority of patients had two or more lesions, with 16 patients in Group-A (53.3%) and 18 patients in Group-B (60%) had two or more lesions.

In group A, 16(53.33%) patients showed complete response, 11(36.66%) patients showed partial response and 3(10%) patients showed no response. Whereas in group B complete and partial response was seen in 28(93.33%) and 2(6.66%) patients respectively. Overall, group B has a better response than group A and the results were found to be statistically significant with a p-value of 0.001 as shown in the Table.

Table: Comparison of Efficacy Between the Two Groups (n=60)

Efficacy	Group A (n=30)	Group B (n=30)	*p*-value
	Number of patients	Number of patients	
Yes (complete response)	16(53.33%)	28(93.33%)	<0.001
No (partial/no response)	14(46.67%)	2(6.67%)	

Group A: Patients treated with intralesional Metronidazole
Group B: Patients treated with intralesional Meglumine antimoniate

Group A: Patients treated with intralesional Metronidazole

Group B: Patients treated with intralesional Meglumine antimoniate(Figure).

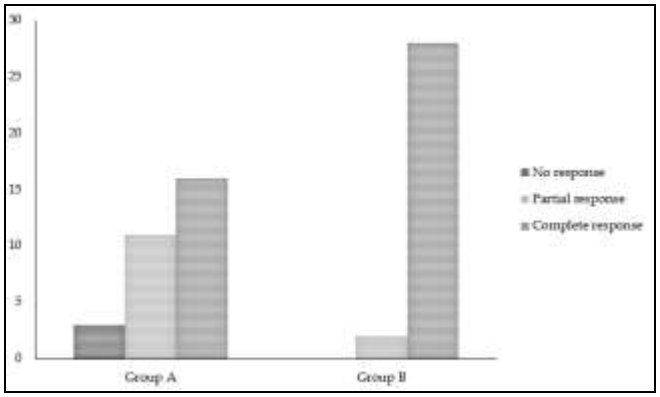

Figure: Response at 8 weeks of treatment (n=60)

DISCUSSION

Even though there is a high rate of spontaneous recovery in patients with lesions of cutaneous leishmaniasis, different treatment modalities are used for complete cure of the disease due to the reason that the lesions are mostly present on the exposed parts of the body and there is a high risk of leaving behind disfiguring scars.

The gold standard treatment for CL is Meglumine antimoniate. It works by interfering with the amastigote form of Leishmania's bioenergetic pathways and altering the oxidation and glycolysis processes thus lowering the cell's adenosine triphosphate levels.[12] In vivo and in vitro experiments, Hajjaran H and several other scientists have revealed diminishing efficacy and rising treatment failure using pentavalent antimony compounds.[13] Antimony can cause serious side effects like leucopenia, anaemia, liver enzyme elevations, pancreatitis and ECG abnormalities.[14] Alternative therapy options for cutaneous leishmaniasis have gained a lot of interest in recent research because of their possible toxicity, cost, and developing drug resistance.

Metronidazole is an antibacterial drug in the nitroimidazole class and it affects an anaerobic environment by forming free radicals and interfering with osmotic pressure locally which results in the death of the organism.[15] There are very few clinical trials on the efficacy of intralesional Metronidazole internationally and none in our population. Even among the few trials included, treatment response varies so we designed this study to compare its efficacy with Antimoniate.

In our study, we gave intralesional injections of both Meglumine antimoniate and Metronidazole twice weekly and patient tolerated it well without any side effects except the pain at the injection site. Majority of the patients in this study were male as compared to female because most of our patients were military personnel deployed in border areas where they were usually working and sleeping outdoors which increased the likelihood of acquiring the disease. Regarding response, Meglumine antimoniate was found clinically and statistically more effective than Metronidazole with a cure rate of 93.3% vs 53.33%.

The efficacy of intralesional Metronidazole in cutaneous leishmaniasis has been debated in the literature. Al Waiz investigated different strengths of intralesional Metronidazole (5% vs. 0.5%) with control and found that the stronger strength had a superior response than the weak strength (87% vs 81% efficacy).[15]

Mapar enrolled 36 patients of cutaneous leishmaniasis to evaluate the efficacy of intralesional Meglumine antimoniate against intralesional Metronidazole.Group A was treated with intralesional Meglumine antimoniate and group B with intralesional Metronidazole weekly. After 8 weeks, 13/16 patients recovered (81%) in group A and only 3/18 patients recovered in group B (16.6%).[11]

Kellapatha *et al*. undertook a randomised double-blind controlled trial to test the efficacy of intralesional Sodium Stibogluconate (SSG) versus Metronidazole. They found that patients treated with SSG had higher clinical responses than those treated with Metronidazol after 24 weeks (complete cure rate 66.03% vs.29.78% respectively).[16] These results are consistent with the results of our study which also showed a better efficacy of Meglumine Antimony than Metronidazole. However, we had a cure rate of 93.3% vs 53.3% respectively.

Somaratne conducted a study in patients with cutaneous leishmaniasis and recorded a higher response rate with intralesional Sodium stibogluconate in comparison with Metronidazole (77% vs. 63% respectively).[17] Bahnan conducted a study in Erbil city of Iraq on 50 patients with cutaneous leishmaniasis and recorded the reduction in size and induration of individual lesions. The difference between the two groups treated with intralesional Pentostam and Metronidazole (p=0.128)

was statistically insignificant18. In terms of Metronidazole response, our findings are superior than those of Mapar, Kellapatha, and Somaratne (16.6 %, 29.78% and 63% respectively). We gave twice weekly injection of Metronidazole as compared to weekly injection being given in most of the other studies and that might be the reason for better treatment response in our study .

Despite the fact that the two groups in our study had a significant difference in response, Metronidazole can still be considered an effective, inexpensive and safe alternative treatment option when Meglumine antimoniate is contraindicated, unavailable or the patient is non affording. However, due to better therapeutic response and low resistance Meglumine antimoniate will continue to be the treatment of choice.

The main limitation of our study was that majority of the patients were enrolled from military set up and a specific area has been taken into consideration which is the main obstacle in generalization of our results over vast population. So studies with larger sample size and conducted at various public care hospitals are required to validate our results.

CONCLUSION

Intralesional Meglumine antimoniate is found more effective than Intralesional Metronidazole in the treatment of cutaneous leishmaniasis.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Th following authors have made substantial contributions to the manuscript as under:

RKG & SK: Data acquisition, data analysis, critical review, approval of the final version to be published.

TN & SS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SR & GS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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