

Comparison of Oral Allopurinol with Intralesional Meglumine Antimoniate in Treatment of Cutaneous Leishmaniasis

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ABSTRACT

Objective: To establish efficacy of Allopurinol in Cutaneous Leishmaniasis.

Study Design: Quasi experimental study.

Place and Duration of study: Department of Dermatology, Combined Military Hospital, Rawalpindi Pakistan, from Apr to Sep 2024.

Methodology: After approval from hospital ethical committee 60 patients of age ranging from 20 – 50 years, who fulfilled the inclusion criteria were enrolled in this study. Duration of study was 6 months. Patients were randomly allocated to Group-1 and Group-2 and each group had 30 participants. Group-1 patients were given oral Allopurinol 10-15mg/kg in 2-3 divided doses for 8 weeks. Group-2 patients were given 1-2ml intralesional Meglumine Antimoniate according to lesion size for 8 weeks. Lesions were assessed at the end of treatment by palpation to measure the induration and by ruler to measure the size of lesion. The drug was considered efficacious if there was 75 percent reduction in size and induration of lesion.

Results: At the end of eight weeks, complete response (effectiveness) was observed in 22(73.3%) patients in Group-1 and 27(90%) patients in Group-2. When compared these results were found to be statistically significant with a *p*-value of 0.032.

Conclusion: Intralesional Meglumine Antimoniate is more effective than oral Allopurinol in the treatment of Cutaneous Leishmaniasis.

Keywords: Allopurinol, Cutaneous Leishmaniasis, Drug, Intralesional, Meglumine Antimoniate, Treatment.

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INTRODUCTION

Leishmaniasis is prevalent in many countries of the world.¹ It is endemic in many areas of Pakistan, from Northern areas of Khyber Pakhtunkhwa, Kashmir, Punjab reaching up to coastal areas and Balochistan.² This condition affects over 12 million people globally, with 900,000-1.3 million new cases annually.³ In Pakistan alone, 21000 to 35000 cases are reported every year.

Leishmaniasis is caused by an intracellular protozoon (genus *Leishmania*) that spreads through the bite of infectious female Sand fly. Clinical spectrum of the disease includes cutaneous, mucocutaneous and visceral forms.⁴ Cutaneous Leishmaniasis is characterized by the development of crusted papules, plaques, nodules and ulcers commonly on the exposed skin^{4,5} which can progress due to sporotrichoid spread. Leishmaniasis is diagnosed by detection of the parasite on slit skin smear or on histopathological examination of a skin biopsy. There is a high rate of spontaneous recovery in patients with Cutaneous Leishmaniasis. Since lesions

are mostly present on the exposed parts of body and there is a significant risk of leaving behind disfiguring scarring which necessitates its treatment.

Antimonials are the 1st line treatment till date. They can be administered both by intramuscular and intravenous route.⁶ Intramuscular route is associated with many local and systemic side effects. Local side effects are tenderness, cellulitis and abscess formation. Systemic adversities include hepatitis, myalgias, pancreatitis, cardiac rhythm irregularities, anorexia, and fever, it therefore necessitates intensive monitoring.⁷ Side effects observed with intralesional injection are pain, burning sensation, erythema, pruritus, secondary infection, nausea, urticaria, necrosis, sporotrichoid spread and anaphylactic shock.⁸ In quest of a treatment option with better side effects profile, ease of administration and less rigorous monitoring many new drugs have been tried. Other medications used to treat Cutaneous Leishmaniasis are Miltefosine, Rifampicin, Itraconazole, Metronidazole and Liposomal Amphotericin-B.⁹ The use of second line drugs is beneficial due to ease of administration and less toxicity and monitoring.¹⁰ The aim of this study was to compare the efficacy of oral Allopurinol with intralesional Meglumine antimoniate in treatment of Cutaneous Leishmaniasis. Its

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metabolites inhibit RNA and protein synthesis of parasites and heal the skin lesions. Allopurinol is a cost-effective and easily accessible medication and can be a potential alternative treatment.

METHODOLOGY

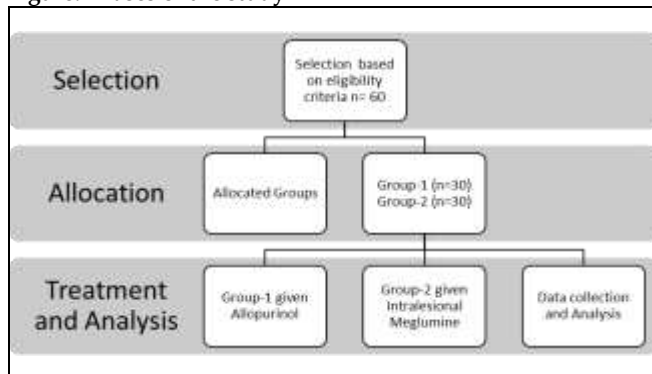
This Quasi experimental study of 6 months duration was conducted at Dermatology Department of Combined Military hospital Rawalpindi, Pakistan after approval from hospital ethical committee (Ser No. 588 dated 28th March 2024). The WHO sample size calculator for two proportions based on outcome variable was used to calculate the sample size keeping the level of significance 5% and power of test 90%. P1 was taken 34% (efficacy of Meglumine) and P2 - 80% (efficacy of Allopurinol).¹¹ Consecutive non-probability sampling was used. Written informed consent was taken from each patient. Confirmed cases of Leishmaniasis on slit skin smear or skin biopsy (where slit skin smear was negative) were recruited based on following inclusion and exclusion criteria.

Inclusion Criteria: Patients aged between 20–50 years, confirmed Cutaneous Leishmaniasis (via slit skin smear or biopsy), lesions between 1–4 in number and no history prior treatment for Cutaneous Leishmaniasis were included in the study.

Exclusion Criteria: Pregnant or lactating women, significant comorbidities (renal, hepatic, cardiac disease), mucosal, joint, ear, or nose involvement and lesions >4 cm or with superadded infection were excluded.

Recruited patients were divided into two groups. Each group included 30 patients. Group-1 was given Allopurinol 10-15mg/kg/day in divided doses for 8 weeks. Meglumine antimoniate intralesional was given in a dose of 1-2ml (90-180mg) per lesion till the lesion blanches twice a week to Group-2 (Figure). The size was measured with scale and induration was measured by palpation every week.

Figure: Phases of the study



Eight weeks after starting the treatment response was considered as “No” response (<25% reduction in size with persistent induration), “partial” response (25 to 75% reduction in size with persistent induration) and “complete” response (>75% reduction in size without any induration). Complete response was considered as efficacy.

The data was analyzed using Statistical Package for Social Sciences version 23. Quantitative variables like 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 study groups keeping p -value ≤ 0.05 as significant.

RESULTS

A total of two groups were compared based on various baseline and clinical characteristics each group has 30 patients. The mean age of participants in Group-1 (Allopurinol) was 35.20 ± 8.23 years, while in Group-2 (Meglumine antimoniate), the mean age was slightly lower at 33.4 ± 9.21 years. The majority of patients were male in both groups, with 27 males (90%) in the Allopurinol group and 29 males (96.67%) in the Meglumine group. The mean duration of disease was reported as 2.06 ± 0.52 months in Group-1 and 2.20 ± 0.55 months in Group-2. Group-1 had 23 patients (76.67%) presenting with multiple (≥ 2) lesions, compared to 20 patients (66.67%) in Group-2. Regarding recovery, complete recovery was observed in 22 patients (73.33%) in the Allopurinol group and in 27 patients (90%) in the Meglumine group (Table-I).

Table-I: Demographic Characteristics of Study Participants (n=60)

Characteristic(s)	Group-1 (Allopurinol) (n=30)	Group-2 (Meglumine) (n=30)
Age, years (Mean+SD)	35.20±8.23	33.4±9.21
Male, n (%)	27 (90.0%)	29 (96.8%)
Duration of disease (Months), (Mean+SD)	2.06±0.52	2.20±0.55
Patients with multiple (≥ 2) lesions, n (%)	23 (76.7%)	20 (66.7%)

Table-II: Association of efficacy between the Study groups (n=60)

Efficacy	Group-1 Allopurinol (n=30) n (%)	Group-2 Meglumine (n=30) n (%)	p-value
Yes	22 (73.3%)	27 (90.0%)	0.032
No	8 (26.7)	3 (10.0%)	

In Group-1, 22 patients (73.3%) showed a positive treatment response, whereas in Group-2, 27 patients (90.0%) experienced effective outcomes. Conversely,

treatment was not effective in 8 patients (26.7%) in Group-1 and in 3 patients (10.0%) in Group-2. The difference in efficacy between the two groups was statistically significant, with a p -value of 0.032 shown in Table-II.

DISCUSSION

The results of our study show that Intralesional Meglumine Antimoniate is more effective than oral Allopurinol in the treatment of Cutaneous Leishmaniasis. Pentavalent antimonials continue to be the treatment of choice, though toxic nature of antimony compounds is well known.¹² The mechanism of action of the antimonials is hypothesized as interference with the bioenergetic processes of the *Leishmania* amastigotes.¹³ The antimonials act by inhibiting various parasitic proteins mainly enzymes that take part in glycolysis and fatty acid oxidation.¹⁴ The impact on the cardiovascular, liver, and musculoskeletal systems is significant¹⁵ and requires extensive monitoring and therefore drug is only being used in tertiary care settings after admitting the patient. Despite of being the gold standard, the use of drug is limited due to the side effect profile and not being cost effective and readily available.

Different treatment modalities are used for complete cure of the disease. Allopurinol is a xanthine oxidase inhibitor that inhibits the conversion of hypoxanthine to xanthine to uric acid and decreases the production of uric acid without disrupting synthesis of vital purines.¹⁶ Its metabolites inhibit RNA and protein synthesis of parasites and heal the skin lesions. Allopurinol has been tried in past as an adjunct to Antimony compounds and is found to enhance their efficacy.

In this study, Group-1 patients were treated with Allopurinol, although it was well tolerated generally, one patient developed DRESS syndrome, and the drug had to be withdrawn. 3 patients reported GI symptoms including nausea and vomiting. Meglumine antimoniate was administered through intralesional route to 30 patients of Group-2. Local side effects observed were pain and burning sensation. 2 patients had superadded bacterial infection which was treated with antibiotics and injection was halted for 1 week. In our study there was a reasonable response to Allopurinol in Group-1 patients (22 patients had complete recovery) though less than Meglumine Group. (27 patients had complete recovery).

Study found Meglumine superior to Allopurinol in terms of cure. Allopurinol though found to be less effective yet was able to produce significant results. Majority of patients were males so study could not eliminate gender bias. Most of the patients came from same geographical area. In terms of outcome, Meglumine antimoniate was found clinically and statistically more effective than Allopurinol with a cure rate of 90% vs 73.3%. p -value 0.032 indicates that the the difference between two drugs is statistically significant.

Efficacy of intralesional meglumine has been proved in various studies. Intralesional administration of antimonial Meglumine was clinically effective, with a 77% healing proportion was achieved six months post-treatment in a study conducted in Bolivia by Rojas C *et al.*¹⁷

Allopurinol has been studied in past by multiple researchers. Henten S. *et al.*, studied Allopurinol as an adjunct to Sodium Stibogluconate.¹⁸ Treatment with SSG and low-dose Allopurinol (100mg/day) led to low cure rates after one cycle, with frequent treatment extensions. After 180 days, around 50% of patients were clinically cured and 30% showed partial improvement.

Haroon ur Rashid *et al.*, studied Sodium Stibogluconate with Allopurinol and compared with Sodium Stibogluconate¹⁹ alone in 164 patients. Study found better outcomes in terms of recovery and duration of treatment in group where Allopurinol was used as an adjunct. Vahid MG *et al.*, studied Allopurinol as an adjunct to Itraconazole in 27 patients and found good response in terms of cure in 85.7% patients.²⁰

There is a statistically significant difference in response between two groups. Meglumine antimoniate resulted superior to Allopurinol, but it should still be considered an effective, safe alternative treatment option when Antimony compounds are contraindicated or not feasible. However, due to better therapeutic response and low resistance Meglumine antimoniate will continue to be the treatment of choice.

The limitations of our study were limited sample size, patients from same set up and a specific geographical area were included, which does not allow the results to be generalized. Further studies with Allopurinol with larger sample size at various setups are required to further authenticate our findings.

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CONCLUSION

Intralesional Meglumine antimoniate is found more effective than oral Allopurinol in the treatment of Cutaneous Leishmaniasis.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MN NI: Data acquisition, data analysis, critical review, approval of the final version to be published.

TN: Study design, data interpretation, drafting the manuscript, critical review, 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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