ORIGINAL ARTICLE

Comparison of Intralesional Meglumine Antimoniate Plus Oral Allopurinol with Intralesional Meglumine Antimoniate Alone for the Treatment of Cutaneous Leishmaniasis- A Prospective Study

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ABSTRACT

Objective: To evaluate the efficacy of the combination of oral allopurinol plus intralesional meglumine for the treatment of Cutaneous Leishmaniasis.

Study Design: A prospective study.

Place and Duration of Study: The study was carried out at the Department of Dermatology, Combined Military Hospital, Multan, Pakistan from 18th September 2021 to 18th March 2022.

Methods: The study was conducted on a total of 60 patients (30 in each group) who fulfilled the inclusion criteria. Patients in group A were given oral allopurinol (15mg/kg/day) and intralesional meglumine antimoniate (2-5 ml). Patients in group B were given intralesional meglumine antimoniate (2-5 ml). All patients were given 2 injections each week and were followed up for 8 weeks. The efficacy of the treatment was noted by the disappearance of induration of the lesion and complete reepithelization of the ulcer. Healing was characterized by scar formation and was recorded.

Results: Results showed that the cure rate in Group B was 16.6% (5), while in Group A it was 56.6% (17) (P<0.03). There was no significant difference in efficacy between both groups when stratified based on age, number of lesions per patient, and lesion location. However, the cure rate of ulcers and papules was significantly higher in group A compared to group B.

Conclusion: It was concluded that the combination of intralesional meglumine antimoniate and oral allopurinol has higher efficacy than intralesional meglumine antimoniate alone in the treatment of patients with cutaneous leishmaniasis.

Keywords: *Allopurinol, Cutaneous Leishmaniasis, Meglumine Antimoniate.*

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Introduction

Leishmaniasis is an infectious disease caused by protozoa Leishmania. It is transmitted by sandflies infected by Leishmani. It is rarely transmitted by needle sharing, blood transfusion, and from infected mother to child during pregnancy. It may be present as a cutaneous ulcer or serious mucocutaneous or systemic disease. The most common form of Leishmaniasis is cutaneous leishmaniasis (CL), which is harmful to humans. The World Health Organization (WHO) termed it a major tropical disease.[1] CL is an epidemic in Pakistan.[2] CL causes lesions on the skin that appear after weeks of exposure. These lesions appear initially as papules which progress to nodular plaques and ulcerative lesions covered by crust or scab. These may be painful, particularly in later ulcerative stages. CL is diagnosed through histopathology, culture, smear, and PCR. Quantitative PCR has high sensitivity and

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specificity and can diagnose CL in humans and other forms like feline and canine Leishmaniasis. It also provides useful information about the course of disease and treatment strategies.[3]

CL has diverse presentations due to which no single treatment is effective for all forms. However, antimonials remain the first-line treatment in various regions like Pakistan, India, Bangladesh, and African countries.[4] Nevertheless, there has been increasing drug resistance due to which alternative drugs are being considered.4 Localized CL is mainly treated directly by thermotherapy, cryotherapy, topical paromomycin, and intralesional antimony. For improving efficacy and reducing treatment time different drugs, like allopurinol, are used along with antimonials. There is evidence that it controls the growth of lesions in vitro and inhibits its spread in tissues.[5] Recent clinical studies have reported the efficacy of allopurinol combined with pentavalent antimony for the treatment of visceral leishmaniasis, where allopurinol was also effective in treatment-resistant patients.[6] Another case-control study compared its efficacy with Glucantime which is an effective drug for treating CL, the results showed comparable effectiveness.[7]

We plan to explore the effectiveness of combination therapies with antimonial to improve disease outcomes. This study aims to gather local data for evaluating the efficacy of a combination of oral allopurinol plus intralesional meglumine for the treatment of CL.

Methods

The prospective study was conducted at the Department of Dermatology, Combined Military Hospital, Multan, Pakistan from 18th September 2021 to 18th March 2022. The study included patients aged between 20 to 40 years who had ≥1 CL for 12 weeks by using consecutive sampling. Patients with allergy to topical agents and a history of use of psychotropic drugs, liver impairment, or any comorbidity were excluded. Informed consent of the participants was taken. The Ethical Review Board of the hospital approved the study vide letter no: 12/148 held on 15th August 2021.

The study was conducted on a total of 60 patients (30 in each group) who fulfilled the inclusion criteria. A proforma including questions about baseline data, detailed history, duration and type of cutaneous lesion, and ulcer size was used to collect data. All patients underwent clinical examinations and were consecutively divided into two groups. Patients in group A were given oral allopurinol (15mg/kg/day) and intralesional meglumine antimoniate (2-5 ml) in each lesion size for 8 weeks. Patients in group B were given intralesional meglumine antimoniate (2-5 ml) in each lesion size for 8 weeks. All patients were given 2 injections for lesions >1 each week and were followed up for 8 weeks in each lesion. The efficacy of the treatment was noted by the disappearance of induration of the lesion and complete reepithelization of the ulcer. Healing was characterized by scar formation and was recorded.

SPSS 23.0 was used for data analysis. Quantitative data was presented as mean ± standard deviation and categorical data as frequencies and percentages. The chi-square test was used for intergroup comparison. The data was stratified based on age, gender, and duration of lesions. *P* value < 0.05 was considered statistically significant.

Results

A total of 60 patients were included for analysis (Figure.1). Group A included 30 subjects, all male, with a mean age of 29.93+5.092 years. Group B also included 30 patients, all male, with a mean age of 31.30+5.590 years (Figure.2). In Group-A. The mean lesion size was 1.96+0.85 cm, while in Group 'B' the mean lesion size was 1.93+0.907 cm. In Group-A. the mean number of lesions per patient was 3.33+1.268, while in Group B the mean number of lesions per patient was 3.16+1.315.

Location of lesions in group A was as follows: face in 3 patients (5%), arms in 5(8.5%), legs in 17(28.3%) & trunk in 5(8.3%), while in group B location was: face in 1(1.7%), arms in 4(6.7%), legs in 18(30%) & trunk in 7(11.7%) patients (*P*<.267).

Lesion type in Group A was an ulcer in 22(36.7%), papule in 5(8.5%), and plate in 3(5%), while in Group B the Lesion type was an ulcer in 23(38.3%), papule in 5(8.5%) and plate in 2(3.3%) patients (*P*<0.143).

In our study cure rate in Group B was 16.6% (n=5), while in Group A it was 56.6% (n=17) (*P*<0.03). The frequencies of age, gender, no of lesions per patient, lesion location, and lesion type groups were calculated according to efficacy. There was no

significant difference in efficacy between both groups when stratified on the basis of age, number of lesions per patient, and lesion location. However, the cure rate of ulcers and papules was significantly higher in group A compared to group B. (Table-1).

Table 1: Comparison of treatment outcomes in both groups

Variable	Group A		Group B		*P*-value
	Patients responding to therapy n (%)	Patients not responding to therapy n (%)	Patients responding to therapy n (%)	Patient not responding to therapy n (%)	
Age					
21-30	13(21.5%)	4(6.8%)	5(8.5%)	7(11.9%)	0.97
31-40	10(16%)	3(5%)	5(8.5%)	13(21.5%)	0.42
Gender					
Male	23(18.7%)	7(6.8%)	10(8.5%)	20(15%)	0.29
Female	0	0	0	0	
No of lesions per patient group					
21-30	19(32%)	7(11.9%)	7(11.9%)	19(32%)	0.23
31-40	4(6.8%)	0(%)	3(5%)	1(1.7%)	0.05
Lesion location					
Face	3(5%)	0(%)	0(%)	1(1.7%)	0.28
Arms	4(6.8%)	1(1.7%)	2(3.3%)	2(3.3%)	0.27
Legs	11(18.7%)	6(10.2%)	5(8.5%)	13(22%)	0.67
Trunk	5(8.5%)	0(%)	3(5%)	4(6.8%)	0.67
Lesion type					
Ulcer	19(32.3%)	3(5%)	9(15.3%)	14(23.6%)	0.00
Papule	4(6.8%)	1(1.7%)	1(1.7%)	4(6.8%)	0.00
Plaque	0(%)	3(5%)	0	2(3.3%)	0.41

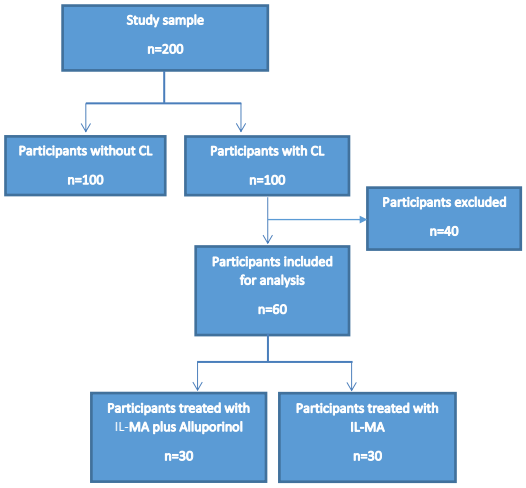

Fig.1: Flow Chart showing study sample

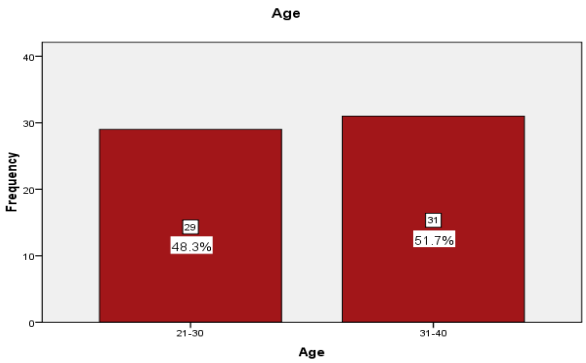

Fig.2: Age distribution of participants

Discussion

Leishmaniasis is a major health concern in developing countries. It is majorly treated by pre-natal antimony. Treatment with drugs has induced resistance, may cause toxicity, and is expensive. Though newer regimens have reduced toxicity but have reduced efficacy.[8] In this study we compared the efficacy of the combination of oral allopurinol plus intralesional meglumine with intralesional meglumine alone for the treatment of CL. The results showed that 16.6 % of patients in Group-B and 56.5% in Group-A recovered from the disease. This was comparable to the findings of a previous study conducted on 180 CL patients in Iran which reported that the cure increased from 36% to 74% with the addition of allopurinol along with 01-1.5 ml of meglumine antimoniate.[9] Due to increased resistance to antimonials other drugs like allopurinol are being effectively used to treat CL. Allopurinol is more cost-effective and safer than antimonials. Previous studies have reported satisfactory results of allopurinol in patients with leishmaniasis.[5,10-12] According to previous studies is dose may range from 10.8 to 39 mg/kg/day for 2 to 16 weeks.[13,14] Parenteral antimonials, mainly meglumine antimoniate, are treatment of choice. However, studies show that MA is not well tolerated by many patients because of pain, arthralgias, and fever. Thus there is a need of a more effective and better-tolerated treatment modality.[15] Studies have been conducted to evaluate various alternatives but there are conflicting results. A study reported that both intramuscular and intralesional injections of meglumine antimoniate are equally effective, while intralesional meglumine antimoniate is significantly more effective compared to Sodium stibogluconate.[16] Thermotherapy, carbon dioxide laser, cryotherapy, zinc sulfate and paromomycin cream have a variable success rate.[17]

Purine metabolism in humans and Leishmania is different, to exploit this difference purine analog are used for treat of leishmaniasis. Recently, pyrazolopyrimidines have been considered as the most effective therapeutic agent in addition to allopurinol in our study. A study reported that pentostam (sodium stibogluconate) and allopurinol have synergistic effects against Leishmania.[7] Another study reported that the addition of allopurinol to the meglumine antimoniate resulted in excellent treatment response in 46% of cases as compared to 24% in whom the meglumine antimoniate was used alone.[18] The results of the current study clearly show better efficacy of the combination of allopurinol and meglumine antimoniate and provide supportive evidence for better results with allopurinol alone than with meglumine antimoniate alone. Treatment methods for CL are varied and their efficacy depends upon the Leishmania species and possibly with the region of origin. A study reported that despite treatment failures in a few cases antimonial drugs are largely effective all over the world.[7] Studies demonstrate that combination therapy with allopurinol, miltefosine, and cryotherapy is more effective compared to monotherapy with antimonial alone as cumulative effect increases the efficacy of antimonial. Combination therapy has been shown to produce favorable outcomes in cases where respective monotherapies have failed.[19] Unresponsiveness to drugs or treatment failures limit the effectiveness of most drugs against CL. The discovery of non-chemotherapeutic methods or new drugs and the use of combination therapy with specie specific response can improves treatment outcomes. The limitation of this study is the small sample size, a larger study is recommended for further analysis. Moreover, Leishmania specie was not identified which can have an impact on treatment response.

Conclusion

A combination of intralesional meglumine antimoniate and oral allopurinol has higher efficacy than intralesional meglumine antimoniate alone in the treatment of patients with cutaneous leishmaniasis.

REFERENCES

1. Torres-Guerrero E, Quintanilla-Cedillo M, Ruiz-Esmenjaud JandArenas R. Leishmaniasis: A review. F1000 Ressearch. 2017; 6: 750. doi: 10.12688/f1000research.11120.1
2. Bari AU. Clinical spectrum of cutaneous leishmaniasis: an overview from Pakistan. Dermatology online journal. 2012; 18: 4.

3. Castelli G, Bruno F, Reale S, Catanzaro S, Valenza VandVitale F. Molecular diagnosis of leishmaniasis: quantification of parasite load by a real-time PCR assay with high sensitivity. Pathogens. 2021; 10: 865. doi: 10.3390/pathogens 10070865
4. Wijnant GJ, Dumetz F, Dirkx L, Bulté D, Cuypers B, Van Bocxlaer K, et al. Tackling drug resistance and other causes of treatment failure in leishmaniasis. Frontiers in Tropical Diseases. 2022; 3: 837460. doi: 10.3389/fitd.2022.837460
5. Khodabandeh M, Rostami A, Borhani K, Gamble HR, Mohammadi M. Treatment of resistant visceral leishmaniasis with interferon gamma in combination with liposomal amphotericin B and allopurinol. Parasitology international. 2019; 72: 101934. doi: 10.1016/j.parint. 2019.101934
6. Husein-ElAhmed H, Gieler U, Steinhoff M. Evidence supporting the enhanced efficacy of pentavalent antimonials with adjuvant therapy for cutaneous leishmaniasis: A systematic review and meta-analysis. Journal of the European Academy of Dermatology and Venereology. 2020; 34: 2216-28. doi: 10.1111/jdv.16333
7. Khattak JI, Ullah G, uddin Khan CQ. Efficacy of combined parenteral meglumine antimoniate and oral allopurinol with meglumine antimoniate alone in treatment of cutaneous leishmaniasis. Journal of Pakistan Association of Dermatologists. 2020; 30: 644-9.
8. Organization WH. Manual of procedures for leishmaniases surveillance and control in the Americas. Pan American Health Organization. 2019. Available at https://iris.paho.org/handle/10665.2/51838
9. Javadi A, Khamesipour A, Ghoorchi M, Bahrami M, Khatami A, Sharifi I, et al. Efficacy of intra-lesional injections of meglumine antimoniate once a week vs. twice a week in the treatment of cutaneous leishmaniasis caused by L. tropica in Iran: A randomized controlled clinical trial. PLoS Neglected Tropical Diseases. 2022; 16: e0010569. doi: 10.1371/journal.pntd.0010569
10. Dornbusch HJ, Perwein T, Ritter-Sovinz P, Urban C. Visceral leishmaniasis in a 10-month-old Austrian Girl Epidemiological Aspects and Treatment Strategies with review of the literature. Archives of Clinical and Medical Case Reports. 2023; 7: 345-9. doi: 10.26502/ acmcr.96550627
11. Ur Rashid H, Ullah I, Adeeb H, Zeb M, Mohammad A, Rehman N. Synergistic effect of oral allopurinol and intralesional sodium stibogluconate in the treatment of cutaneous leishmaniasis. Journal of Ayub Medical College Abbottabad. 2020; 32: 558-61.
12. Goyonlo VM, Derakhshan Z, Darchini-Maragheh E. Treatment of Cutaneous Leishmaniasis with Allopurinol Plus Itraconazole in Iran. The American Journal of Tropical Medicine and Hygiene. 2023; 108: 1164-6. doi: 10.4269/ ajtmh.22-0733
13. Sampaio RN, Ferreira MF, Martins SS, Motta JD. Successful treatment of diffuse cutaneous leishmaniasis caused by Leishmania amazonensis. Anais Brasileiros de Dermatologia. 2021; 96: 602-4. doi: 10.1016/ j.abd.2021.03.003
14. Arboleda M, Barrantes S, Úsuga LY, Robledo SM. Successful treatment of cutaneous leishmaniasis with intralesional meglumine antimoniate: A case series. Revista da Sociedade Brasileira de Medicina Tropical. 2019; 52: e20180211. doi: 10.1590/0037-8682-0211-2018.
15. Ullah N, Uzair M, Khan NU, Butt G. Comparative cost-effectiveness of intralesional meglumine antimoniate alone versus cryotherapy plus intralesional meglumine antimoniate in cutaneous leishmaniasis: Experience from a high capacity dermatology centre. Journal of Pakistan Association of Dermatologists. 2022; 32: 353-9.
16. Sridharan K, Sivaramakrishnan G. Comparative assessment of interventions for treating cutaneous leishmaniasis: A network meta-analysis of randomized clinical trials. Acta Tropica. 2021; 220: 105944. doi: 10.1016/j.actatropica. 2021.105944
17. Yesilova Y, Surucu HA, Ardic N, Aksoy M, Yesilova A, Oghumu S, et al. Meglumine antimoniate is more effective than sodium stibogluconate in the treatment of cutaneous leishmaniasis. Journal of Dermatological Treatment. 2016; 27: 83-7. doi: 10.3109/09546634.2015.1054778
18. Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. International journal of dermatology. 2002; 41: 521-4. doi: 10.1046/ j.1365-4362.2002.01526.x
19. Sivayogana R, Krishnakumar A, Kumaravel S, Rajagopal RandRavikanth P. Treatment of Leishmaniasis. Leishmaniasis-General Aspects of a Stigmatized Disease: IntechOpen; 2022. doi: 10.5772/intechopen.95200. Available at https://www.intechopen.com/books/10891

Authors Contribution

NQ: Study designing, manuscript writing, and proofreading
PG: Data collection, data analysis, results and interpretation
AZ: Idea conception, study designing
MJ: Idea conception, data collection
MA: Study designing, data analysis
SS: Data collection