

Efficacy of combined parenteral meglumine antimoniate and oral allopurinol with meglumine antimoniate alone in treatment of cutaneous leishmaniasis

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Abstract

Objective To compare the efficacy of combined parenteral Meglumine Antimoniate and oral Allopurinol with Meglumine Antimoniate alone in the treatment of Cutaneous Leishmaniasis.

Study Design Randomized controlled trial.

Place and duration of study Department of Dermatology, Combined Military Hospital, Peshawar from May 2016- Oct 2016.

Methods A total of 112 patients presenting with Cutaneous leishmaniasis were included in the study and randomly allocated in two groups. In group I participants received combined therapy with oral allopurinol 15mg/kg/day and parenteral meglumine antimoniate 15mg/kg/day while group II participants received only meglumine antimoniate 15mg/kg/day. Follow up was done at 8th week and results were recorded.

Results The mean age of the whole study sample was 27.4±4.6 years. In group I the efficacy was observed in 83.9% of patients compared to 73.2% in group II (p 0.167).

Conclusion Our study concluded that the combination therapy (MA plus CL) is more effective in treating CL than isolation therapy with MA alone. More randomized controlled trials with larger sample sizes are highly recommended to draw more conclusive results and generate further evidence for uniform decision making in the treatment of CL.

Key words

Cutaneous leishmaniasis, maglumine antimoniate, allopurinol.

Introduction

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis affecting humans. It is a cutaneous infection caused by a parasite that is transmitted by the bite of a

sandfly. There are about twenty species of Leishmania that may cause CL.¹ CL is an important cause of disability in 98 endemic countries. It is estimated that there are between 0.7 to 1.2 million new cases of CL per year worldwide.² Pakistan is one of the countries where CL is epidemic.³ The prevalence in Pakistan has been estimated at 2.7% in the North-Western part of the country with incidence at 4.6 cases/1000 persons/year over the last ten years.⁴

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Cutaneous leishmaniasis results from the parasitization of skin macrophages and is clinically manifested as a papule that enlarges to a nodule that often ulcerates during a period of 1 to 3 months. CL resolves without treatment in a few months to several years. CL can cause substantial morbidity depending on the site and size of lesion and the psychological effects of disfigurement⁵. Diagnosis of CL is made by use of smear, culture, histopathology and serological tests like PCR.⁶

Several treatment options for CL are available. Pentavalent antimonials (Sodium Stibogluconate, meglumine antimoniate) remain the first choice treatment for CL. Alternative treatment regimens include miltefosine, amphotericin B, antifungal agents, allopurinol and cryotherapy.⁷

In order to increase the efficacy and reduce treatment time several drugs have been used in combination with parenteral antimonials. Allopurinol is one of them. Cure rate of antimoniate ranges from 41% to 98% depending upon dose of drug and species of *Leishmania*. In one study cure rate of meglumine was 55%.⁸ Combination of parenteral antimonials (30mg/kg/day) and oral allopurinol (20mg/kg/day) for 20 days showed a cure rate of 80.6%.⁹ Combination of allopurinol with antimoniate has been found to be effective.¹⁰ Another study compared allopurinol 20 mg/kg plus meglumine antimoniate 30 mg/kg/day with meglumine antimoniate 60mg/kg/day for 20 days. After 51 days of treatment cure rate was 69% and 72% respectively.¹¹

Our research was to determine the efficacy of combination of parenteral meglumine plus oral allopurinol in the treatment of cutaneous leishmaniasis. We can hypothesize that the combination of these drugs is more superior in efficacy than traditional meglumine alone. We

did not find any similar research in KPK. If the hypothesis is found correct, then a better option for the treatment of CL will be made available to our population.

Methodology

This study was conducted through a randomized controlled trial in the Department of Dermatology, Combined Military Hospital, Peshawar from May 2016 – Oct. 2016. A total of 112 patients presenting with Cutaneous leishmaniasis were included in the study and randomly allocated in two groups. Approval was obtained from institutional research and ethical committee/ board before starting the study. The purpose and benefit of the study were explained to the patient and the patient was assured that the study is purely done for data publication and research and a written informed consent was obtained. Patients of CL reporting to Dermatology unit Combined Military Hospital Peshawar and fulfilling the inclusion criteria were included in the study. Diagnosis was made on clinical grounds as well as positive smear for LT bodies. Those patients with typical lesions but having negative smear for LT bodies underwent skin biopsy for histopathology. After taking complete history, a thorough general physical and systemic examination was done. 112 (56 in each group) patients were randomly allocated in two groups by lottery method.

In group I participants received combined therapy with oral allopurinol 15 mg/kg/day and parenteral meglumine antimoniate 15 mg/kg/day while group II participants received only meglumine antimoniate 15 mg/kg/day. Participants with weight <50 were given 2 tablets/day. Participants with weight 51-60kg were given 3 tablets/day. Participants weight 61-80kg was given 4 tablets/day.

Efficacy was measured in the form of clinical improvement of lesion (in case of nodular lesion, disappearance, in case of ulceration disappearance and in case of crusting absence and decrease in size of the lesions) at 8th week post treatment.

Patient having any major hepatic, renal and cardiac illness, taking or have received any form of treatment previously for CL, known hypersensitivity to meglumine antimoniate and/or Allopurinol and having weight <35kg or >80kg were excluded from the study.

Statistical analysis was performed using statistical program for social sciences (SPSS 21.0 for windows). Student-T test was applied to test the significance of the difference among the quantitative variables of both groups. P-value ≤ 0.05 (5%) was considered as significant.

Results

112 patients presenting with cutaneous leishmaniasis were included in the study. Of the sample size, 56 patients randomly allocated in two groups by lottery methods. One group was subjected to allopurinol plus meglumine (group I) while the other was subjected to meglumine alone (group II).

The mean age of the whole study sample was 27.4±4.6 years. The mean age of patients in group I was 27.2±4.4 years while mean age of patients in group II was 27.7±4.7 years. The difference was statistically insignificant with a p value 0.542 after applying independent sample T test. All the presented patients (100%) were of male gender.

The mean weight of the whole study sample was 64.03±7.9 kg. The mean weight of patients in group I was 63.7±9.2 while that of group II was 64.2±6.5. The difference was statistically

insignificant after applying independent sample T test with a p value of 0.706.

The difference in distribution of the lesions at presentation between both treatment groups was statistically insignificant (p=0.917).

Both the treatment groups were subjected to standard medication as per individual group protocols and followed over for the improvement in the lesions. In group I the efficacy was observed in 83.9% of patients compared to 73.2% in group II. The difference was statistically insignificant after applying chi square test with a P value of 0.167 (**Figure 1**).

Various types of lesion shows significant difference in efficacy with p-value=0.038 (**Table 1**).

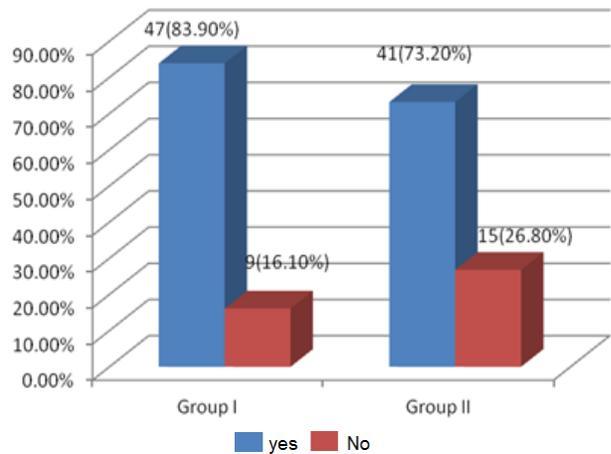


Figure 1 Comparison of efficacy between both groups (n = 56 in each group), p-value=0.167.

Table 1 Type of lesion wise stratification of efficacy.

Lesion	Efficacy		Total	P value
	Yes	No		
Ulcer	8 (57.1%)	6 (42.9%)	14 (100.0%)	0.038
Nodule	3 (100.0%)	0 (0.0%)	3 (100.0%)	
Crust	53 (86.9%)	8 (13.1%)	61 (100.0%)	
Multiple	24 (70.6%)	10 (29.4%)	34 (100.0%)	
Total	88 (78.6%)	24 (21.4%)	112 (100.0%)	

Discussion

Cutaneous leishmaniasis may be limited to a single part of the skin (localized cutaneous leishmaniasis) or may produce a large number of lesions (diffuse cutaneous leishmaniasis). Mucocutaneous leishmaniasis can lead to the destruction of mucous membranes of the nose, mouth and throat. In immunocompetent patients, clinical features of cutaneous leishmaniasis depend mainly on the causative *Leishmania* species.¹²⁻¹⁴

In the Old World, localized cutaneous leishmaniasis is due frequently to *L. major* (zoonotic cutaneous leishmaniasis), and this leishmaniasis tends to resolve within 2–4 months. *L. tropica* is restricted strictly to human beings (anthroponotic cutaneous leishmaniasis) and the lesions due to this species may persist for a longer time (6–15 months).¹⁵

The World Health Organization (WHO)^{16,17} recommendations for the treatment of cutaneous leishmaniasis are intralesional or systemic antimonials, according to the species and the clinical features. Local infiltration with pentavalent antimony has been used in localized cutaneous leishmaniasis. WHO recommends an injection of 1–3ml under the edges of the lesion and the entire lesion until the surface has blanched. The infiltration could be given every 5–7 days, for a total of 2–5 times. In 1999, a systematic review of the reported series showed that intra-lesional antimonials partially or completely cured 72–97% of the lesions caused by *L. Major*.¹⁸

The mean age of our sample was 27.4±4.6 years. The mean age of patients in group I was 27.2±4.4 years while mean age of patients in group II was 27.7±4.7 years. The difference was statistically insignificant with a p value 0.542 and all the patients (100%) were male.

The mean weight of our patient was 64.03±7.9 kg. The mean weight of patients in group I was 63.7±9.2 while that of group II was 64.2±6.5. Both the treatment groups were subjected to standard medication as per individual group protocols and followed over for the improvement in the lesion. In group I the efficacy was observed in 83.9% of patients compared to 73.2% in group II. The difference was statistically significant.

Allopurinol (AL) has already been suggested for treatment of CL. The efficacy of combination of AL and meglumine antimoniate (MA) in treatment of non-healing cases of CL has been evaluated. A combination of AL and MA increase the antileishmanial effects of antimoniate.¹⁹

The efficacy of antimonials has been reported to be more than 90% in the majority of studies, although cure rates range from 34% to 100% depending on the parasite species and the dose and duration of treatment²⁰. Increasing resistance of CL to antimonials has been reported in many countries.^{21,22} There is evidence that AL can inhibit the growth of *Leishmania* in vitro and in tissue culture.²³⁻²⁶ AL and sodium stibogluconate have a synergistic action against *Leishmania* in tissue culture.²⁷

If two drugs with different modes of actions are used, then they could helpfully prevent emergence of the resistant mutant.²⁸ Application of two drugs with different modes of action may synergistically reduce the number of burden of the disease.²⁹

In another study, it was concluded that a combination of allopurinol plus meglumine antimoniate may be considered as a highly effective treatment for CL. All patients, except two (87.5%), responded well to treatment within 30 days. No significant side-effects were

observed. Histologic examination of nine cases during and at the end of therapy showed a progression to atrophied granulomata, more lymphocytic than histiocytic infiltration, and, finally, fibrosis replacing the granulomata.³⁰

Study conducted in Iran examining the combination of oral allopurinol at doses of 15–20 mg/kg/ day for 20 days (*L. tropica*) proved to be more effective than monotherapy but only achieved a CR of 46 %. However, in another study, the combined therapy treatment of parenteral antimonials (30 mg /kg/day) and oral allopurinol (20 mg/kg/day) for 20 days reached higher CRs (80.6 %).⁹

In another study, a total of 324 patients were included in the study. Group A patients were given meglumine antimoniate 20 mg/kg/day/intramuscular till clinical resolution or for 28 days maximum. Group B patients were given intramuscular meglumine antimoniate 10mg/kg/day along with allopurinol 20 mg/kg/day/per oral till clinical resolution or for a maximum of 28 days. MA Group had 151 (46.6%) patients while 173 (53.4%) were in MA plus AL group. Lesion size at baseline in MA group was 29.7+16.4 mm, while in MA plus AL group it was 28+15.8 mm (p=0.35). Lesion size at the end of treatment period was 1.5+3.4 mm in MA group and 0.9+2.6 mm in MA plus AL group (p=0.07). Lesion size at the end of follow-up period was 0.1+0.9 mm in MA group and 0.03+0.4 mm in MA plus AL group (p=0.40). A total of 109 adverse effects were seen, 60 in MA group and 49 in MA plus AL group (p=0.05).¹⁰

Our study is unique in that we have done a randomized, controlled trial on 112 patients which, as far as we have searched, is the largest randomized controlled trial testing the combination in old world disease locally. Secondly, we have used 15 mg/kg of meglumine in combination with 15 mg/kg of allopurinol,

while other trials have mostly used a higher dose of meglumine antimoniate. We can say that our study is exploring the efficacy of meglumine antimoniate/ allopurinol combination in low doses.

Conclusion

Cutaneous leishmaniasis is emerging as an important disease in KPK. Accurate diagnosis and timely initiation of treatment are critical to the management of disease.

Our study concluded that the combination therapy (Meglumine Antimoniate plus allopurinol) is more effective in treating CL than isolation therapy with MA alone. More randomized controlled trials with larger sample sizes are highly recommended to draw more conclusive results and generate further evidence for uniform decision making in the treatment of CL.

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