ORIGINAL ARTICLE

SYNERGISTIC EFFECT OF ORAL ALLOPURINOL AND INTRALESIONAL SODIUM STIBOGLUCONATE IN THE TREATMENT OF CUTANEOUS LEISHMANIASIS

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Background: Leishmaniasis is an endemic disease and a major public health problem throughout the world. Its geographic distribution has been extended over the past few years in Pakistan. The available treatment options of Leishmaniasis are limited and mostly parenteral, and hence a non-toxic oral alternative therapy is urgently needed to overcome the problem. The objective of this study was to evaluate the synergistic effect of Allopurinol as an adjunct therapy along with conventional intra-lesional sodium Stibogluconate in the treatment of cutaneous Leishmaniasis. **Methods:** This single blinded randomized controlled trial was carried out at the tertiary care hospitals of district Peshawar, Pakistan. A total of one hundred and sixty-four (164) patients of age range from 19–56 years, consisting of both genders were included in this study. All subjects were randomly allocated to Group-1 and Group-2 where each group had 82 patients of comparable age and genders. Group-1 patients were given an intra-lesional injection of sodium Stibogluconate at a dose of 1–5 ml depending on the lesion size, where one ml injection contained 100 mg of the drug. Group-2 patients were given combination therapy of oral Allopurinol (20 mg/kg/day in divided doses) along with the same intra-lesional sodium Stibogluconate dose as group-1 until complete cure of the lesion. **Results:** Combination therapy of sodium Stibogluconate along with Allopurinol was found superior to sodium Stibogluconate alone in terms of duration of treatment. Group-1, patients who received only sodium Stibogluconate required prolonged treatment duration of 6–9 weeks depending upon the lesion size, while group-2 patients who received combination therapy of sodium Stibogluconate and Allopurinol responded more quickly and their lesions cured in 3–6 weeks depending upon the lesion size. **Conclusion:** Oral Allopurinol has a synergistic effect when used with intra-lesional sodium Stibogluconate and effectively reduces the treatment duration required for complete cure of cutaneous Leishmaniasis. Treatment duration was reduced by 3 weeks in the present study when combination therapy was given to the patients of cutaneous Leishmaniasis.

Keywords: Allopurinol; Cutaneous leishmaniasis; Sodium Stibogluconate; Leishmania

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INTRODUCTION

Leishmaniasis is endemic in more than 90 countries worldwide[1]. In Pakistan, the geographic distribution of cutaneous Leishmaniasis (CL) has extended over the past few years and emerged as one of the major public health problems. For more than half century, pentavalent antimony has been used as first line systemic therapy for Leishmaniasis, but due to its difficulty in administration, less patient compliance and high cost, treatment failure has been reported from around the world.[2,3] The study aims to compare alone therapy with combination therapy which increases efficacy and reduces the cost and dose dependent toxicity level.

There are three forms of Leishmaniasis; cutaneous, muco-cutaneous and visceral Leishmaniasis.[4] According to the WHO, 0.7 to 1.2 million fresh cases of Leishmaniasis are reported around the world annually.[1] In Pakistan, Leishmaniasis is present in Lasbella, Makran coastal areas, Northern hilly areas of Kashmir and in Punjab. In the recent years, Leishmaniasis has affected almost all areas of Pakistan, but is more prevalent some areas of Khyber Pakhtunkhwa. Endemic foci of the disease are reported from district Peshawar, Kohat, Karak, Swat, Timargara on regular basis.[5,6]

The Leishmaniasis parasite is an intracellular protozoan transmitted to its human host through the bite of a vector female sandfly.[7] On getting the disease, the human host may develop a superficial self-limiting ulcer, muco-cutaneous disease or systemic illness. Cutaneous Leishmaniasis mainly affects the exposed parts of

the human body and can lead to disfiguring scars.[8]

Allopurinol has been studied in Leishmaniasis in vitro. In Leishmania *braziliensis panamensis*, allopurinol was first used and found to be effective.[9] The invitro studies of Allopurinol have demonstrated its anti-parasitic action, and led to its development as a chemotherapeutic agent for the diseases caused by these organisms.[10]

The major metabolic derivative of Allopurinol in humans, oxipurinol, is also anti-leishmanial for the *Leishmania donovani*. It is proposed that adenyl-succinate-synthetase or the adenine phosphoryl-transferase may be sites of action for these agents.[11] The antileishmanial effects of Allopurinol make it a suitable candidate for the treatment of Leishmaniasis and are safe without adverse effects and its availability as oral therapy.[12] In the present study, we looked at the synergistic effects of Allopurinol and sodium Stibogluconate in human subjects but could not test the drug alone because of ethical issues.

MATERIAL AND METHODS

This single blinded randomized controlled trial was conducted on out patients and admitted patients of Hayatabad Medical Complex Peshawar, Kuwait teaching hospital Peshawar and Afghan refugee camp Baghbanan Peshawar, Khyber Pakhtunkhwa from January 4, to June 8, 2015.

During this 6-months study, a total of 164 patients including of both genders, same number of males and females and age ranging from 19–56 years were enrolled through convenient sampling technique. Sample size was calculated based on the prevalence from a study conducted by Ejaz A *et al.* 2014 using the G-power software for sample size calculation.[13] All patients of any age and gender having the disease diagnosed clinically and lab examination of the smear, culture or skin biopsy, and those having not received previous therapy with lesion size ≤4 cm and number of lesions ≤4 where site was accessible for local treatment were included in the study. Patients having known or suspected allergy to Allopurinol or sodium Stibogluconate, pregnant and nursing women, who were immune-compromised, had uncontrolled Diabetes Mellitus, heart disease, liver or kidney diseases and those not consenting for the study were all excluded from the study.

Patients were allocated into two groups; Group-1 and Group-2 having eighty-two patients of nearly similar age and equal number of both genders. For each group one of the therapeutic modality was applied; Group-1 patients were given an intra-lesional injection of sodium Stibogluconate 1–5 ml, depending on lesion size where 1ml injection contains 100 mg of the drug, and the dose was given as 50 mg/cm of the lesion size twice weekly not exceeding 20 mg/kg until complete cure.[2] Group-2 patients were given combination therapy of oral Allopurinol in a dose of 20mg/kg/day in divided doses along with the above dose of sodium Stibogluconate until complete cure.

All routine investigations like complete blood count, liver function tests, blood urea nitrogen, serum creatinine, ECG and Leishmania smears were performed on the first day and after the treatment. At each visit, patients were examined for any possible drug complication like ulceration, induration, erythema and size of the lesion and the results were recorded. Data were recorded and analyzed using SPSS-20, and the response time of combination therapy was recorded and presented in tabulated form in comparison to only sodium Stibogluconate.

RESULTS

Data were collected and analyzed for any significant difference in the treatment modalities used for both Group 1 and 2 of the study population.

Descriptive statistics based on the age distribution of patient in both groups was done. Mean age of patients in Group-1 and in Group-2 was 39.92±7.69 and 39.32±7.73 years respectively. Minimum and maximum age of patients in both groups was 19 and 56 years respectively as shown in table-1.

Gender distribution was analyzed and both Group-1 and Group-2 had 45 males 37 female patients respectively as shown in table 2.

Treatment response with sodium Stibogluconate alone was observed in weeks based on the lesion size, and the average response time was found to be 6-9 weeks as shown in table 3.

Treatment response with sodium Stibogluconate along with Allopurinol was observed in weeks based on the lesion size, and the average response time was found to be 3–6 weeks as shown in table-4.

Table-1: Descriptive statistics for age of the patients (n=164)

Patients	Group-1	Group-2
Number	82	82
Mean age	39.92	39.32
SD	7.69	7.73
Minimum age (in year)	19.00	18.00
Maximum age (in years)	56.00	55.00

Group-1 =Sodium Stibogluconate
Group-2 = Sodium Stibogluconate plus Allopurinol

Table-2: Gender distribution of patients in Group-1& 2 (n=164)

Patients	Group-1	Group-2	Total
Male	45	45	90
Female	37	37	74
Total	82	82	164

Table-3: Treatment response time in group-1 patients (sodium Stibogluconate alone) in weeks

Lesion size	Number of patients	Response (ulcer healed)
1 cm	6	6-8 Weeks
1.5 cm	13	6-8 Weeks
2 cm	31	6-9 Weeks
2.5 cm	12	6-9 Weeks
3 cm	08	6-9 Weeks
3.5 cm	07	7-9 Weeks
4 cm	05	8-9 Weeks

Table-4: Treatment response time in group-2 patients (sodium Stibogluconate + Allopurinol) in weeks

Size of lesion	Number of patients	Response (ulcer healed)
1 cm	10	3-5 Weeks
1.5 cm	11	3-5 Weeks
2 cm	25	3-5 Weeks
2.5 cm	19	3-5 Weeks
3 cm	06	3-5 Weeks
3.5 cm	10	4-5 Weeks
4 cm	01	9 Weeks

DISCUSSION

Leishmaniasis is a highly prevalent third world disease and exists in three different clinical forms in these countries. Leishmaniasis has been treated by parenteral administration of penta-valent antimony for the past 50 years. These drugs have high risk of toxicity. They are expensive and non-availability in the developing world is an issue. Some new treatment options with oral administration and lower toxicity level are the need of the day to be developed to overcome this problem.[14,15]

In the present project, we used Allopurinol as an adjunct therapy because of several reasons. Allopurinol has shown efficacy as anti-Leishmanial drug in-vitro and has been used for more than three decades with minimum side effects.[13] It is not expensive and easily available all over the world. Response of Allopurinol was studied in terms of reduction in treatment duration in weeks and was administered along with sodium Stibogluconate.

Two groups were observed at different intervals during treatment and baseline investigations were performed to look for any toxicity. There was no toxicity reported except mild rise in the liver function tests and rare skin rash in few cases who received Allopurinol. The total cost of Allopurinol per patient was around PKR 140/- which shows a low-cost treatment.

When we looked at the duration required for curing the lesion, it was superior with the addition of Allopurinol to sodium Stibogluconate alone. The lesion cure duration reduced to 3 to 5 weeks from 6 to 9 weeks with the addition of Allopurinol to sodium Stibogluconate therapy. A similar study conducted in Southern Colombia by Martnez S, *et al.*[16] in 1997 where the cure rate was increased from 39 to 71% by the addition of Allopurinol with sodium Stibogluconate. Similarly, another study conducted by Momeni AZ *et al.*[17] in 2002 shows that complete cure rate of the lesion increased from 74.2 to 80.6% cases with the addition of Allopurinol to the conventional therapy which supports our finding in the present study.

Patients who received only sodium Stibogluconate required prolonged treatment duration of 6 to 9 weeks depending upon the lesion size, while those who received combination therapy of sodium Stibogluconate and Allopurinol responded more quickly and their lesions completely cured in 3 to 5 weeks duration depending upon the size of lesion. There was only a single patient who responded slow and his lesion cured in 9 weeks which was probably due to compliance problem. A study conducted by Ejaz A *et al.*[13] in 2014 in military hospitals of Pakistan showed that the decrease in lesion size of cutaneous leishmaniasis was quicker with the addition of Allopurinol to the conventional therapy and their findings support the results of the present study.

CONCLUSION

The addition of oral Allopurinol to the conventional therapy sodium Stibogluconate reduces time required for cure of cutaneous leishmaniasis. The addition of Allopurinol, a uric acid lowering drug to the sodium Stibogluconate therapy have no additional side effects. The lesion size decreases quicker with the addition of Allopurinol and complete cure is faster than sodium Stibogluconate alone therapy.

AUTHORS' CONTRIBUTION

1-HUR: Data collection, and Manuscript writing. IU: Data analysis, manuscript writing and tables, figures. HA: Data analysis, manuscript writing and correspondence with journal. MZ: Manusript writing, expert opinion and final proof reading. AM: Main idea, corrections in the typhography and final approval. NR: Writing manuscript, referencing and final correction.

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