EFFICACY OF COMBINED INTRALESIONAL MEGLUMINE ANTIMONIATE AND CRYOTHERAPY VERSUS CRYOTHERAPY ALONE FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

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ABSTRACT

Objective: To compare the efficacy of combined intra-lesional meglumine antimoniate and cryotherapy versus cryotherapy alone for the treatment of cutaneous leishmaniasis in our population.

Methodology: A total of 76 patients were randomly divided into two equal groups A and B. Patients in group A were given combined intra-lesional meglumine antimoniate and cryotherapy weekly for 06 weeks and patients in group B were given cryotherapy alone weekly for 06 weeks. At the end of 06 weeks of the treatment, direct skin smear test for Leishmania donovani bodies was performed to determine intervention efficacy.

Results: Male to female ratio in A and B groups was 2.4:1. Average age was 29.16 ±10.636 years and 24.39 ±12.262 years respectively. In group A, an efficacy of 100% was noted in all patients while in group B, an efficacy of 18.4% was noted and no response was observed in 81.6% patients. The efficacy as a whole was statistically significant with p value =0.000.

Conclusion: Combined intra-lesional meglumine antimoniate and cryotherapy is a better option for the treatment of cutaneous leishmaniasis as compared to cryotherapy alone.

Key Words: Cryotherapy, Meglumine antimoniate, Leishmaniasis

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INTRODUCTION

Cutaneous leishmaniasis (CL) is a chronic parasitic disease that is endemic in many regions of the world[1]. Leishmaniasis is prevalent in 88 countries, affecting an estimated 12 million people with approximately 2 million new cases per year. Among these, 5,00,000 are visceral leishmaniasis and 15,00,000 are cutaneous leishminiasis[2]. Khyber Pakhtunkhawa province in Pakistan is one of the most endemic areas in the country. Leishmania tropica and also leishmania major is endemic in this region and its prevalence is not age dependent[2,3]. Cutaneous leishminiasis mainly affects the poorest populations, being associated with poor housing conditions and a lack of economic resources[4,5].

Treatment for CL aims to hasten the recovery and prevent further transmission and secondary bacterial infection. However, response to treatment is often unpredictable and unsatisfactory[6]. Different treatments for leishmaniasis include local and systemic methods, in which cryotherapy with liquid nitrogen and intra-lesional glucantime are more commonly used[7-9]. Cryotherapy is an effective treatment for leishmaniasis. All leishmania species are markedly thermo-sensitive and cryosurgery has several advantages in the treatment of CL. Cryotherapy is a controlled and targeted destruction of diseased tissue by the application of liquid nitrogen, which result into rapid heat transfer from the tissue causing tissue injury, vascular stasis & occlusion and inflammation[10].

Antimonial compounds are associated with significant side effects but have lower failure rates. However, resistance has been reported against glucantime[11]. The precise mechanism of action of intra-lesional glucantime, is not known; the antimony is known to inhibit glycolytic enzymes and fatty acid oxidation in leishmania amastigotes. There is dose dependent inhibition in net formation of adenosine triphosphate [ATP] and guanine triphosphate [GTP][12]. Several studies have compared intra-lesional glucantime with cryotherapy either alone or

as a combined therapy[9,10,12]. Leibovici et al[13] reported response rates of 90% for combined therapy (glucantime plus cryotherapy) and of 58% for cryotherapy alone.

Variation has been observed in cure rates for leishmaniasis in response to cryotherapy and intra-lesional meglumine antimoniate, either combined or alone in different studies. The objective of doing this study was to compare the efficacy of cryotherapy and intra-lesional meglumine antimoniate versus cryotherapy alone. If the combined treatment is found to be either equally or more effective, then it will be recommended for the treatment of local lesions due to low cost and high efficacy. Since no local study has been done to compare the efficacy of cryotherapy vs. intra-lesional meglumine antimoniate alone or in combination, therefore it seems worth to get a recent study done in this regard.

METHODOLOGY

This randomized controlled study was conducted in the Department of Dermatology, Lady Reading Hospital, Peshawar, from June 2014 to December 2014. Sample size of 38 in each group was calculated by WHO sample calculator with 95% confidence interval and 5% margin of error, using 90% improvement in combined intra-lesional meglumine group and 58% in cryotherapy alone group. The inclusion criteria of the study were male and female patients of cutaneous leishmaniasis of any age, who had lesions of more than 12 weeks' duration. Cutaneous leishmaniasis was operationally defined as all patients presenting with characteristic brownish skin nodule with plaque or ulcer formation having positive direct skin smears for Leishmania donovani (LD) bodies. Patients with size of lesion greater than 5 centimeters, more than three lesions and sites of involvement including joints, tip of the nose and fingers were excluded from the study. Patients on systemic medications for the treatment of cutaneous leishmanisais were also excluded from the study. Patients were administered 1 to 3 ml of intra-lesional glucantime till complete blanching of lesion was achieved. Two cycles of freeze thaw for 30 seconds were done to treat each lesion with liquid nitrogen

The statistical analysis was performed using statistical program for social sciences (SPSS 24 for windows). Frequencies and percentage was calculated for gender and intervention effectiveness. Means + standard deviation were computed for age of the patients. Chi-square test was used to check the efficacy by comparing the intervention effectiveness in both the groups. Also intervention effective was stratified among the age and gender to see the effect modifiers. P value <0.05 was considered as significant.

RESULTS

Total number of male and female patients were 54 and 22 respectively. The age of the patients ranged from 02-56 years. Maximum numbers of patients were in the 2nd and 3rd decade of their lives as shown in Table 1. In group A, male and female patients were 27 (71.1%) and 11 (29.9%) respectively, while in group B male patients were 27 (71.1%) while 11(29.9%) patients were females, as shown in Table 2.

Mean age in group A was 29.16 ±10.638 years while in group B it was 24.39 ±12.262 years.

The Efficacy of both groups was better in age (16-45 years) as compared to older age (>45 years) or younger age (<15 years). However statistically this difference was not significant with p value of 0.923.

The Efficacy of both groups was better in male patients as compared to female patients with p value of 0.616 which was not significant. In combined intra-lesional meglumine antimoniate and cryotherapy group, an efficacy of 100% was noted in all patients while in

Table 1: Age of patients

Age	Group A	Group B	Total
<15	4	11	15 (19.7%)
16-30	16	13	29 (38.2%)
31-45	16	12	28 (36.8%)
≥46	2	2	4 (5.3%)
Total	38	38	76 (100%)

Table 2: Age wise efficacy

Age	Efficacy	P value
<15	8 (17.8%)	0.923
16-30	18 (40%)	
31-45	17 (37.8%)	
≥46	2 (4.4)	

Table 3: Efficacy in groups (n =76)

Number of Patients	Group A (n=38)	Group B (n=38)	P value
Efficacy Yes	38 (100%)	7 (18.4%)	0.000
Efficacy No	0 (0%)	31 (81.6%)	
Total	38 (100%)	38 (100%)	

cryotherapy alone group an efficacy of 18.4% was noted and no response was observed in 81.6% patients as shown in Table 3. The Efficacy as a whole was statistically significant with p value=0.000.

DISCUSSION

The province of Khyber pakhtunkhawa in Pakistan is one of the most endemic area in the country. In our study, majority of patients were in the 2nd and 3rd decade. It is in accordance with study conducted by Ayaz et al[14]. Number of male patients was greater in our study which may be due to the fact that males are more exposed to bites of vector due to their activities outdoor. Being engaged in farm activities and outdoor work is considered as a risk factor for exposure to CL infection[15].

Talari and others[16] in a systematic review evaluated randomized controlled trials in which cryotherapy alone or in combination with other therapeutic modalities was used in the treatment of Old World CL. They concluded that these treatment modalities had good efficacies and negligible side effects. In a recent report by Mosleh et al[17] evaluated the efficacy of a weekly cryotherapy regimen in patients infected with L. major, all patients were cured, no relapses occurred and cosmetic results were good.

Leibovici et al[13] reported response rates of 55.63% for glucantime, 57.15% for cryotherapy and 41.4% for combined therapy (glucantime plus cryotherapy). Gurei et al[18] in a clinical trial compared the efficacy of intra-lesional sodium stibogluconate (pentostam) with cryotherapy in the treatment of CL. A total of 92% of cases who received pentostam and 78% of those who received cryotherapy were clinically cured at the end of three-month follow-up period. In another study, 14 patients with acute CL who were treated with cryotherapy were clinically and parasitologically cured within 3–8 weeks, with no noticeable scars at lesion sites[19].

Several factors may be responsible for variation in cure rates of cutaneous leishmaniasis in response to cryotherapy in different studies such as diagnosis; type of CL; causative species; size, duration and location of lesions; population variations; cryotherapy regimen; and accuracy and consistency in performance should be taken into consideration. However, most of the reported results showed a high efficacy for this therapeutic method. In the current study, the complete response rate was significantly higher in the combined intra-lesional meglumine antimoniate and cryotherapy than in the cryotherapy alone group (38 of 38 patients versus 07 of 38 patients; P =0.000). We found that the size of the lesion, but not its duration, significantly affected the response to therapy while other studies showed the lesion size, duration and location were important factors[9].

No serious post-treatment side effects were observed in either group. During cryotherapy, the most common adverse reactions were erythema and edema of the treated site, which appeared during the initial hours of treatment and blistering of the treatment site, which became evident 1–2 days after treatment and responded well to topical treatment. Slight changes in pigmentation also occurred post-inflammation as either hypopigmentation or hyperpigmentation. However during the therapy and at 1 month follow up, the skin color at affected areas started to improve. Previous investigators have also found that color change due to cryotherapy was a transient side effect that resolves within months[7].

All our CL patients treated with combined intralesional meglumine antimoniate and cryotherapy were cured as compare to cryotherapy alone group. So our findings suggested that combined intralesional meglumine antimoniate and cryotherapy were significantly better than cryotherapy alone. At six months of follow-up, no recurrence of the disease was noted in cured patients in both groups.

CONCLUSION

In all age groups combined intra-lesional meglumine antimoniate and cryotherapy is more effective than cryotherapy alone for the treatment of cutaneous leishmaniasis.

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CONTRIBUTORS

MZB conceived the idea, planned the study and drafted the manuscript. SMN, MMP and GU helped acquisition of data, did statistical analysis and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.