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Original Article

Comparative cost-effectiveness of intralesional meglumine antimoniate alone versus cryotherapy plus intralesional meglumine antimoniate in cutaneous leishmaniasis: Experience from a high capacity dermatology centre

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Abstract

Background There is a high prevalence of cutaneous leishmaniosis (CL) in southern Khyber Pakhtunkhwa and most patients present late. Conventional treatment takes longer and hence patients loose adherence to their treatment. Recently cryotherapy has been shown to speed up lesion healing with lower chemotherapeutic drug requirements.

Objective To compare the cost-effectiveness of intralesional meglumine antimoniate (MA) alone and cryotherapy plus intralesional MA for CL in terms of overall effectiveness, time to healing and its impact on patient adherence from a poor Pakistani community.

Methods Prospective randomised study with two treatment arms. Group A included patients treated with standard intralesional MA alone and group B included patients treated with cryotherapy plus intralesional MA. Data was collected for time to healing of the lesions; total direct treatment cost and overall effectiveness. Both treatment arms were also compared in the failure and success rates.

Results The overall mean age was 15.06±14.23 years with a mean duration of the lesion appearance of 4.5±2.1 weeks (range: 1-9 weeks). The mean surface area of the lesions was 2.6±0.7 cm^2. There were 84 (62.7%) males and 50 (37.3%) females in a ratio of 1.6 to 1. The overall mean time to healing was 19.7±9.1 days with a mean treatment sessions of 2.8±1.07. The mean overall direct cost of treatment was 4364.2±2180.31 rupees. At the end of the study, there were 44 (32.8%) cases of treatment failures. Of these, 29 (21.6%) were from group A and 15 (11.2%) were from group B ($p=0.005$). An independent samples t-test showed that there were significant mean differences for time to healing, number of treatment sessions required until healing and the direct total cost of treatment ($p<0.0001$).

Conclusion Cryotherapy in combination with intralesional antimonials is highly effective. The effectiveness of cryotherapy is more pronounced when the cost of the treatment is considered for the poor population that is afflicted with this condition. Lower treatment costs enhance higher follow-up rate and shorter treatment duration.

Key words
Cutaneous leishmaniasis, intralesional antimonials, cryotherapy, cost-effectiveness.

Introduction

Cutaneous leishmaniasis (CL) is a dermatologic infestation by the morphologically similar parasite leishmania. The vector for its

transmission is Phlebotomine sand-flies.[1] This organism is endemic in the southern districts of Khyber Pakhtunkhwa and has a high prevalence in all age groups but it is particularly common in young children.[2] Cutaneous leishmaniasis has a toll on the overall health of the patients and in this region where poverty is widespread, it adds to the increased suffering of the affected as well as their families and caretakers. The disease is equally dreaded by patients and physicians, not only due to its protracted course, but also due to the nature of the treatment and the unsightly scars that it leaves behind.[3]

The current management strategies include pentavalent antimony compounds provided in the form of meglumine antimoniate, or sodium stibogluconate.[4,5] None of the treatment method is fully effective and research is still on to identify rapid healing and safe antiparasitic agents. The drawbacks of the current therapeutic regimes is its slower action requiring multiple and prolong therapies and more invasive intralesional nature.[6,7] Topical cryotherapy is one of the recently introduced modality to directly treat the leishmaniasis lesions. Asilian and co-workers[8] undertook a randomised study and looked in to the efficacy of the three available modalities, i.e. cryotherapy alone, intralesional meglumine antimoniate (MA) alone and a combination of intralesional MA plus cryotherapy. They reported a cure rate of more than 90% with the combined therapy (intralesional MA plus cryotherapy).

Since poverty is highly prevalent in our region, it is one of the main hurdle in adherence to prolonged treatment regimens and multiple follow-up visits for an invasive treatment.[9-11] Patients usually stop pursuing their treatment sessions due to inability of paying for the intralesional injections. Cryotherapy hasten the healing of the lesions when combined with intralesional MA.[12,13] Our hypothesis was that if the number of treatment sessions can be reduced by the combination therapy, it will lead to effective follow-up due to reduction of the overall cost. Moreover, cryotherapy is available free of cost at our department and is non-invasive; we undertook this study to see the cost-effectiveness, patient adherence and overall clinical efficacy of the combination therapy (intralesional MA plus cryotherapy) as compared to intralesional MA. If proven effective, it will be a major step forward in leishmaniasis treatment.

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Methods

This is a prospective randomised study conducted at the department of dermatology Khalifa Gul Nawaz Hospital, Bannu between April 2015 and September 2020 (65 months) after obtaining approval from the hospital ethical committee. Patients were randomised using the random allocation table generated using the 'Random Allocation Software' version 1.0.

An informed consent was obtained from all the patients regarding the type of treatment and follow-up requirements. All patients with confirmed clinical and laboratory diagnosis of cutaneous leishmaniasis between the ages of 1 year and 65 year irrespective of their gender. Only clinically active lesions, i.e. enlarging indurated lesions were selected for the therapy. Cases of visceral leishmaniasis, lesions larger than 5 cm^2 (single or multiple), lesion location excluding administration of intralesional MA such as those affecting eyelids, tip of the nose, genitalia etc. were excluded. Similarly, patients allergic of MA, refusing any of the modality offered, pregnant or lactating women were also

excluded. The diagnosis as suspected from clinical examination was confirmed using slides prepared from scrapings of the lesions under light microscopy using Giemsa stain.

We defined treatment success as the appearance of lesion healing with flattening of lesions and loss of induration oedema and redness. This was initially established on clinical examination and a negative Giemsa stain was used as confirmatory evidence for lesion healing. Lesions requiring more than five treatment sessions or those taking more than thirty days to show signs of recovery (loss of induration, flattening of lesion) were labeled as treatment failures. Treatment failures were either switched to systemic antimonial treatment or started with oral therapy of miltefosine.

We divided the patients in two intervention groups, Group A constituted patients who received standard intralesional MA while Group B comprised of patients who received cryotherapy plus intralesional MA. All patients were followed-up for at least 30 days or until the lesion showed signs of healing, whichever was reached earlier.

Meglumine antimoniate (Glucantime®) is available in 85 mg/mL. It was used as 1 mL/cm^2. A direct intralesional injection was performed intradermally, using a 22 G needle until the lesion was blanked along with 2 mm margin of normal skin. After marking the lesion margins, it was approached at right angle and the drug was injected under pressure until the lesion was blanched. Each intralesional injection was performed once weekly and the lesion was assessed for signs of resolution on each follow-up visit.

Brymill Cryogun (SSS Australia) was used for cryotherapy. It creates a surface temperature of -196 ºC. Cryotherapy session was repeated every week until the lesion showed signs of regression. Each intralesional injection in Group B was preceded by cryotherapy.

Data was collected about patient age, gender, duration of the appearance of lesion, number of lesions, cumulative size of the lesions in cm^2, body region involved, duration till lesion healing, total number of treatment sessions required, number of treatment failures and total cost of the treatment.

SPSS version 22.0 was used for data entry and analysis. Continuous variables were presented as mean±standard deviations and categorical variables as frequencies and percentages. An independent t-test was used for testing the hypothesis that lower costs in cryo+intralesional MA lead to better patient adherence with lower loss to follow-up. A p value ≤ 0.05 was considered significant.

Results

A total of 146 patients were included in the study, 77 in Group A and 69 in group B. During the study duration, 12 patients were lost to follow-up (Fisher's exact test: group A; 12 versus 0 for group B; $p<0.0001$), therefore, we included a total of 134 patients (65 in group A and 69 in group B) and 218 lesions (103 in group A and 115 in group B) in the final data analysis.

The overall mean age was 15.06±14.23 years with a mean duration of the lesion appearance of 4.5±2.1 weeks (range: 1-9 weeks). The mean surface area of the lesions was 2.6±0.7 cm^2. There were 84 (62.7%) males and 50 (37.3%) females in a ratio of 1.6 to 1.

The overall mean time to healing was 19.7±9.1 days with a mean treatment sessions of 2.8±1.07. The mean overall direct cost of

treatment was 4364.2±2180.31 rupees. At the end of the study, there were 44 (32.8%) cases of treatment failures. Of these, 29 (21.6%) were from group A and 15 (11.2%) were from group B (p=0.005).

An independent samples t-test was run to ascertain a mean difference between the two treatment groups for age, duration of the disease, number of lesions, time to healing and direct cost of the treatment. As shown in **Table 1**, there were no significant differences for age, duration of the disease and number and size of lesions. However, it is notable that there were significant mean differences for time to healing, number of treatment sessions required until healing and the direct total cost of treatment (p<0.0001) **Table 1**.

Kaplan-Meier analysis was performed to analyse the two different interventions for their effectiveness in time taken to lesion healing. Participants that underwent the intralesional MA only treatment had a median time to healing of the lesion of 22.0 (95% CI, 15.2 to 28.8) days. This was longer than the cryo+intralesional MA group, which had median time to healing of 12.0 (95% CI, 11.04 to 12.95) days. A log rank test was conducted to determine if there were differences in the survival distributions for the two different types of intervention. The survival distributions for the two interventions were statistically significantly different, $\chi^2(1)=17.5$, p<0 .0001 **Figure 1**.

Discussion

The aim of the old world cutaneous leishmaniasis (CL) therapy is to shorten the length of the disease and to prevent disfiguring scars.[14,15] Over the course of the recent two decades, intralesional antimonial compounds have become one of the most common way to treat these lesions. However, the wide prevalence in our country, especially in the poverty-stricken peripheries of our province warrant considerations for new regimens.[2,16] A successful regimen should have two inherent qualities; it should be available with low cost and highest efficacy. Unfortunately, no agent for chemotherapy of CL is cheap or 100% effective. From the perspective of our society, where poverty is high, cost of the treatment also determines other important attributes of the therapy, namely, adherence and compliance.

Table 1 The independent samples t-test for mean difference between the 2 groups, 95% Confidence interval (CI) and their statistical significance.

Variables	*Tx group*	*N*	*Mean*	*SD*	*MD*	*95% CI*		*P value*
Patient Age	Group A	65	16.68	16.3	1.9	-2.89	6.9	0.423
	Group B	69	14.70	12.0				
Lesion duration (weeks)	Group A	65	5.63	5.1	-1.3	-3.0	0.49	0.158
	Group B	69	6.88	5.08				
No. of lesions	Group A	65	1.58	0.88	-0.08	-.39	0.23	0.599
	Group B	69	1.67	0.91				
Size of lesions (cm^2)	Group A	65	2.623	0.75	-0.042	-.311	0.23	0.757
	Group B	69	2.665	0.81				
Time to healing (days)	Group A	65	23.40	8.7	7.1	4.1	9.9	<0.0001
	Group B	69	16.35	8.1				
No of tx sessions	Group A	65	3.48	0.83	1.3	1.03	1.6	<0.0001
	Group B	69	2.16	0.85				
Total tx Cost (rupees)	Group A	65	6281.54	1183.7	3723.6	3337.6	4109.5	<0.0001
	Group B	69	2557.97	1074.4				

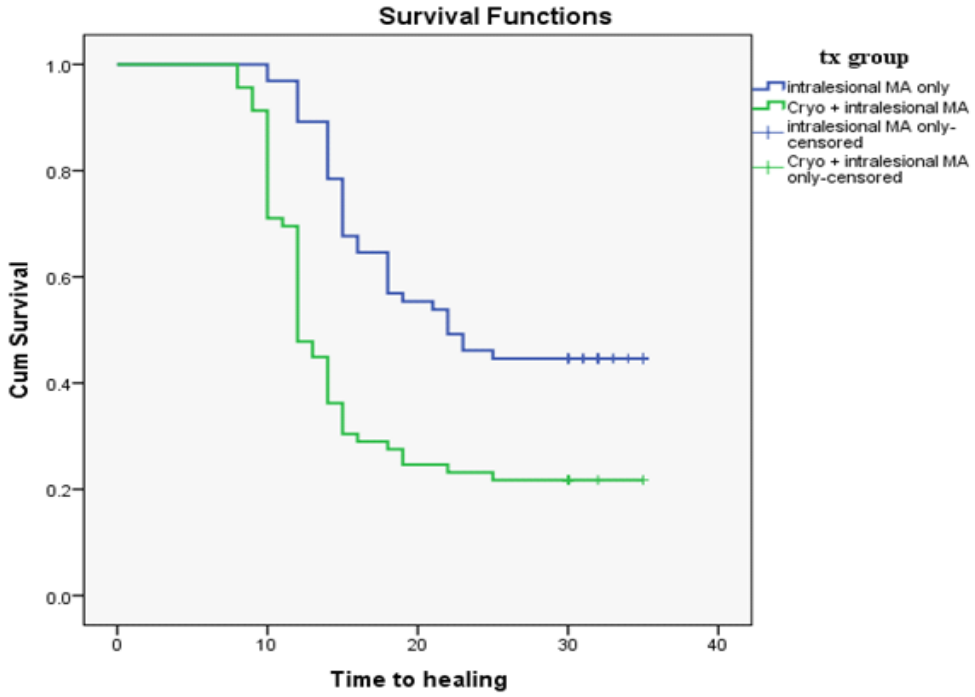

Figure 1 Kaplan Meier survival curve for the two treatment groups and the total time to healing.

Majority of patients seldom follow expensive therapies.[17-19] They would prefer spiritual healing (which is comparatively cheap) if presented as an alternative for an expensive medical treatment. In case of CL, though, the effectiveness is variable, but patients do accept it if offered as a form of therapy. However, the dropout rate for patients in follow-up is high, mainly due to the prolonged course of painful intralesional injections and its cost.[20]

Recently, Asilian and associates[21] conducted a randomised study to compare the effectiveness of intralesional MA plus cryotherapy, cryotherapy alone and intralesional MA alone. They showed a cure rate of 90.9% for the combined chemotherapy plus cryotherapy while cure rates of 57% and 55% for the other groups respectively. In our study the success rate for intralesional MA alone was 55.4% while for cryotherapy plus intralesional MA, it was 78.3%. These results are in agreement with the findings of Asilian *et al.*[21] and Faris *et al*.[22] In Faris *et al.* series, the total number of injections ranged between 8 and 24. In our series, the number of treatment sessions for intralesional MA alone ranged from one to four. Majority of lesions healed after the 4th intralesional injection (52.3%, n=34) in group A while in group B, majority of cases showed signs of healing after 2nd treatment session (52.2%, n=36) (Mann Whitney U=673.5, Z=-7.3, p<0.0001). In another series by Solomon *et al.*,[6] the healing rate of 91% was achieved with intralesional MA alone with an average of three treatment sessions. One randomised study from Kabul by Reithinger *et al.*,[23] compared the efficacy of thermotherapy, intralesional MA and intramuscular MA. They concluded that thermotherapy rapidly lead to healing of the lesion as compared to intralesional MA or intramuscular MA, though they did not find any difference between the efficacies of intralesional MA or thermotherapy alone.

It is a very unfortunate fact that leishmaniasis primarily affect the extremely poor communities for whom seeking complete treatment is near to

impossible.[3,20,24] The government of Pakistan, the provincial government and numerous non-governmental aid agencies provide various anti-leishmanial agents on a subsidized price. In our district, a limited supply of Glucantime® is provided with a minimum cost of rupees 500 each 5 mL vial (85 mg/mL meglumine antimonite). Other pharmacologic agents, such as miltefosine are rarely available in the local medical stores and are highly expensive (rupees 16000 per course). Poverty combined with chronic disfiguring disease, prolonged sickness and prolonged, expensive with limited available drugs discourages many patients to pursue complete treatment. Many patients seldom pursue their treatment course for more than a month, and the most common reason is financial overburden.[14,18] With the availability of Cryogun by the provincial government, we felt the need to see if cryotherapy may reduce the treatment duration and hence direct medication cost. The results of our study were very encouraging with regard to the total direct cost on the part of the patient, which resulted in a 100% follow-up rate for group B, whereas for group A of our study population, there were 12 patients who lost to follow-up.

We feel the need to elucidate further the cost-effectiveness by determining patient satisfaction as well as time to complete healing and recurrence rates. Since this study only took into account the initial signs of healing of the lesions, it is imperative to look into the long-term benefits of the combination of cryotherapy plus intralesional MA therapy.

Conclusion

Cutaneous leishmaniasis is a very common parasitic disease mostly affecting the very poor. Pentavalent antimonials are the first line drugs, with intralesional injection of meglumine antimoniate as more successful and with less adverse effects than the systemic drug. Cryotherapy in combination with intralesional antimonials is highly effective. The effectiveness of cryotherapy is more pronounced when the cost of the treatment is considered for the poor population that is afflicted with this condition. Lower treatment costs enhance higher follow-up rate and shorter treatment duration.

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