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Original Article

Comparison of the efficacy of intralesional versus intramuscular injection Meglumine Antimoniate in the treatment of sores of Cutaneous Leishmaniasis

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Objectives: To compare the efficacy of intralesional with intramuscular injection meglumine antimoniate in the treatment of Cutaneous Leishmaniasis.

Design: Prospective, comparative, interventional study.

Setting: Pakistan Institute of Medical Sciences, [PIMS] Islamabad.

Material and Methods: Seventy six (40 males, 36 females) consecutive patients with sores of Cutaneous Leishmaniasis presenting to the Dermatology department, underwent treatment with Intralesional (1 ml/cm2 of Sb) or Intramuscular injection Meglumine antimoniate ((20 mg Sb/kg/day for 21 to 28 days) according to the selection criteria for each group from April 2004 to March 2005. On the basis of demonstration of Leishmania tropica (LT) bodies in the skin slit smears/skin biopsies, 76 patients were included in the study and were followed-up for therapeutic safety and efficacy at different intervals. After completing local or systemic treatment, cure rate was calculated by observing the improvement criteria i.e. flattening, softening, decrease in size of lesion and absence of erythema, induration, . According to the sample selection procedure for the two modalities of treatment 46 (60.5%) patients were found suitable for Intralesional therapy and 30(39.5%) were found suitable for Intramuscular therapy.

Results: Males 40(52.6%) constituted a slightly greater number than females 36(47%) The final outcome of intralesional injection meglumine antimoniate at weekly intervals in 46 patients was that 44 (95.65%) got completely cured, whereas among those receiving I/M therapy 25(83.3%) got cured with their lesions getting almost flattened and itch/pain subsided. Z test for proportion was used for comparison which was Z=1.75 showing that proportion of cured patients with IL treatment was greater than IM treatment (P= 0.027 =<0.05) which confirms that there is a significant relationship between route of administration and outcome of lesion .The average number of injections required for 1/L was found to be 6 at weekly intervals and 18 for 1/M treatment. Both the treatments were given according to the recommended guidelines of WHO.

Design: Prospective, comparative, interventional study.

Conclusion: Intralesional therapy is superior to Intramuscular therapy with meglumine antimoniate in terms of efficacy, safety, outcome.

Key Words: Cutaneous Leishmaniasis CL, Meglumine antimoniate, Intramuscular [I/M], Intralesional [I/L].

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Introduction

Cutaneous Leishmaniasis is caused by different species of intracellular protozoan parasites belonging to the genus Leishmania and transmitted through the bite of sandflies[1].

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Different Leishmania species occur in different geographical zones. Depending on the extent and severity of disease, infection can be classified into four clinical syndromes of Cutaneous Leishmaniasis CL, diffused Cutaneous Leishmaniasis DCL, Mucocutaneous Leishmaniasis MCL and Visceral Leishmaniasis VL [1].

Prevalence of all forms is in excess of 12 million cases while 1.5 million new cases of CL are being reported

every year[2]. Approximately 90% of all cases of cutaneous leishmaniasis occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria. Cutaneous leishmaniasis is endemic along the northern areas of Baluchistan, Sindh, tribal area (refugees from Afghanistan), and western border of Pakistan. Sporadic cases have been reported from southern Punjab, Azad Kashmir, northern areas and Islamabad.[3,4] Incidence is highest in rural areas and where conditions are favorable for sand files i.e. a wide variety of niches, in rodent burrows, crevices and holes in banks, trees(barks) and houses in old world and in tree canopies and forest litter in New world.[5].

Migration pattern of Afghan refugees and people from endemic areas within Pakistan, besides poverty, poor hygiene and overcrowded living conditions led to sharp rise in the incidence of CL. High cost of antimonials compounded their misery which led to this hospital based study to compare the efficacy of I/L modality versus I/M Inj meglumine antimoniate in terms of dose, cost effectiveness, side effects so that problem of short supply and increase demand can be easily met with.

The pentavalent antimony compounds sodium stibogluconate and meglumine antimoniate have been the mainstays of anti-leishmanial therapy for both visceral and cutaneous leishmaniasis[6,7] Amphotericin B and pentamidine are traditional parenteral alternatives to antimony but are more toxic and costly, had availability issues and usually considered for treatment failures. Rifampicin, ketoconazole, allopurinol, itraconazole, topical paromomycin, dapsone and miltefosine were used in various studies, however, with conflicting results[8-12]. The species causing CL in New world are mostly unresponsive to traditional antimonials and clinical trials on I/L meglumine antimoniate are negligible as they prefer other modes of treatment to I/L therapy. In most of the published regimens adequate data is lacking regarding practicability of I/L and I/M therapy depending upon number and characteristics of lesions. They also vary widely in total number and interval between injections. The aim of the study was to monitor and compare clinical response of I/M with I/L injection meglumine antimoniate (I/L) in old world CL.

Materials & Methods

This prospective, comparative, interventional study was conducted in the Department of Dermatology, Pakistan Institute of Medical Sciences, Islamabad from April 2004 to May 2005 .Seventy six consecutive patients affected by CL who had not received any treatment and qualified for the selection criteria (46(60.5%) found to be suitable for I/L therapy while 30(39.5%) for I/M therapy) were included in the study, once they had given the informed consent.

The patients were thoroughly evaluated clinically and all information i.e. patient profile, the demographic variables, distribution, type, size and number of lesions etc, were recorded in the data collection form. Pretreatment investigations included complete blood counts, renal and liver function tests, fasting blood glucose and fasting lipid profile. Urine samples were examined for proteins, glucose/deposits and electrocardiographs and chest radiographs were also obtained.

Skin biopsy and slit skin smear from the active, infiltrated edge of lesions were taken on the day of enrollment. The inclusion criteria was demonstration of Leishmania tropica (LT) bodies in skin slit smears/skin biopsies or epitheloid cell granulomas in dermis in the presence of plasma cells and neutrophils on histopathology. Patients enrolled in I/L treatment group were the ones who had small active lesions of less than 5 cm diameter, and patients with chronic/lupoid lesions. Inclusion criteria for I/M treatment was presence of large (>5cm) diameter active lesions (with a raised edge), multiple lesions at sites that are difficult to inject (ears, eyelid, nose), large number of lesions on the same or different sites on the body, where there was evidence of lymphatic spread and in children who could not be restrained for I/L treatment. The patients who had already been treated, patients with known hypersensitivity to antimonial compounds, those with cardiovascular, renal, hepatic or hematologic disorders were excluded from the study. Both the treatments were given according to the recommended guidelines of WHO[13] i.e. patients in I/M group received 20 mg of Sb/kg of meglumine antimoniate daily for 21 to 28 days; while those in I/L group received 1 ml/cm^2 of same into upper and mid-dermis of each lesion on weekly basis. The absence of crusts up to 1 month, erythema and induration up to 3 to 5 months and flattening/softening of lesions was considered as a parameter for cure[14]. Adverse effects were recorded during treatment. Descriptive statistics were used to calculate mean, standard deviation for age and regression in lesion size. Frequencies and percentages were calculated for categorical variables e.g. response to treatment. Chi-square test was used to compare response (categorical variables) while t-test was used to compare numerical variables.

Results

The results are based on the analysis of 76 patients with a total of 136 lesions and a mean age of 24.1 years. Males 40(52.6%) constituted a slightly greater number than females 36(47%). Out of 76 patients, 64 (84.2%) had dry type whereas 12(14.3%) had wet type of lesions in the form of ulcers or erosions.

The patients on intralesional meglumine antimoniate showed better response (Table 1). At the end of follow up, complete cure was achieved in 44(95.65%) patients in I/L group (P-0.027) and 2(4.35%) were lost in the follow up and none was left uncured. Among those receiving I/M therapy 25(83.3%) got cured with their lesions getting almost flattened and itch/pain subsided. Three developed systemic side effects in the form of deranged liver function tests, 3 had gastrointestinal upset, 2 had a fall in hemoglobin, and 1 developed prolonged QT interval in ECG at the beginning of 2nd week of treatment which normalized upon treatment discontinuation. After 14 days gap the tests were repeated which were found normal and symptoms relieved and then were resumed with I/L meglumine antimoniate instead of I/M, to which they responded very well. Side effects common in both groups were mylagias, arthralgias, headache, urticaria, cellulitis and pain at injection sites. These were transient and disappeared upon treatment discontinuation.

The mean number of injections required for I/L treatment and for I/M treatment was 6 and 18 respectively.

Z test for proportion was used to compare the proportion of cure rate for intramuscular and I/L injections which was Z=1.75 showing that proportion of cured patients with IL treatment was greater than IM treatment. P= 0.027 (<0.05) confirmed that there is a significant relationship between route of administration and outcome of lesion (Table 2) as 44(95.65%) got cured with I/L treatment as compared to 25 (83.33%) with I/M meglumine antimoniate.

Majority of the patients presented early in disease course i.e with lesions of upto 3 months duration Table 2

Itching was reported in 71 patients while only 5 complained of pain in the lesions. Clinical examination revealed different morphological patterns of lesions showing that 57 had plaques (Fig 2) 5 had papules and nodules (Fig1) respectively and 9 had ulcers.

Discussion

Pentavalent antimonials, sodium stibogluconate and meglumine antimoniate, are still the drugs of first choice, despite the fact that a wide variety of oral, parenteral, topical, surgical, combination and cryotherapy had been tried in the past with conflicting results. Although the two compounds have almost similar efficacy and toxicity, parenteral administration of meglumine antimoniate showed variable efficacy from 65% to 95% in various studies[15-17].

This was a prospective, interventional study carried out in Dermatology outpatient of Pakistan Institute of Medical Sciences (PIMS). In our study, patients administered intramuscular therapy showed 83.3% cure rate which increased to 95.65% with intralesional therapy which was in conformity to previous studies [22-24]. A minor difference may have been due to different or resistant parasite strain or technique of intralesional treatment; however, in I/L group the efficacy was enhanced at the cost of few side effects as compared with I/M group. Therapeutic decision depends on the site of lesion, e.g., lesions on face, tip of nose, lesions overlying joints, ear and eye are too sensitive to be treated by intralesional route. Single lesions, especially on the extremities, may be treated exclusively by Intralesional therapy, whereas for multiple and extensive lesions intramuscular therapy combined with intralesional therapy is much more effective.

The mean age of 24 years shows that the disease is more prevalent in children and young adults, this being consistent with previous studies where retrospective analysis showed that the disease was more common in the children and young adults[18]. Maximum number of our patients presented with lesions of 3 or less than 3 months duration and simultaneously most of the women seeking consultation had lesions on the face and hands. Both these findings clearly indicate the concern of affected individuals for cosmetic disfigurement and the need to adopt preventive measures in endemic areas[19]. The maximum number of lesions previously reported was on the lower legs and in southern belt of country[20]. As the desire to prevent mucosal disease is a prime motivator for adequate treatment of New World CL, our Old World desire is to prevent development of disfiguring scars on exposed areas of body especially face.

Morphology showed that 64 had dry crusted plaque (Fig 2) urban type of lesions 5 had papules,4 had nodules (Fig 1) and 9 had ulcers. This is in contrast to

the morphological patterns described earlier, where the predominat clinical from of disease seen was wet (rural) type[21].

The results of the present study confirm the observation of previous investigators (with some differences in the regimens used), that I/L antimonials are safe and cost effective [22-24]. Faris et al showed complete healing of 756/1050 (72%) lesions by I/L sodium stibogluconate on alternate days and on average 8 injections were required.[22] Sharique et al reported good clinical response in 123/130 (95%) lesions with 1-3 weekly I/L sodium stibogluconate.[23] National Institute of Health conducted a study in 3 Afghan refugee camps on efficacy of I/L meglumine that showed 99% efficacy of I/L treatment and only 10 ml meglumine antimoniate was required for a single patient in total which they claim is cost effective with minimal side effects, and is suitable for endemic areas in developing countries, including Pakistan. However, Intralesional treatment is sophisticated technique, which requires patience and skill. In contrast our study has specified interval of 6-7 days between two doses of IL meglumine antimoniate and a dose of 1ml/cm^2 of lesion. The mean number of injections required for I/L treatment and for I/M treatment was 6 and 18 respectively i.e lesser the number of injections lesser the side effects.

The results seem to be better than previous trials with just meglumine antimoniate, where Ghulam Mujtaba et al showed that 418(84.4%) lesions healed completely, 59(12%) showed fifty percent improvemnet and 8(4.6%) developed hypersensitivity reactions to antimony compound.[24]

Conclusion

Intralesional therapy is superior to Intramuscular therapy with meglumine antimoniate in terms of efficacy, safety, outcome with fewer side effects and more cost effective .Dosage specified is 1ml/cm^2 at interval of 6-7 days over the average duration of 6 weeks.

References

1. Fitzpatric TB, Elisen AZ,Wolf K, Freedberg 1M Eds. Dermatology in general medicine 4th ed. Boston. Mc Graw Hill; 1993: 2772-77
2. Alkhawajah, M., Jain, s., Larbi, e. M., aA-gindan, y. & Abahussien, a. (1995). The efficacy of different dosage regimens of pentavalent antimony compounds on cutaneous leishmaniasis in mice. Saudi Pharmaceutical Journal, 3, 36 – 40.
3. Rab MA, Azmi FA, Iqbal J, Hamid J, Ghafoor A, Burney MI, et al. Cutaneous leishmaniasis in Baluchistan: reservoir host and sandfly vector in Uthal, Lasbella. J Pak Med Assoc 1986; 36: 134-8.
4. Mujtaba G, Khalid M. Cutaneous leishmaniasis in Multan, Pakistan. Int J Dermatol 1998:37; 843-6
5. John Haper, N Ewan Wang. Leishmaniasis. E Medicine Journal Sep 2001;2(9):{cited 2002 Feb 6} Available from http://www.emedicine.com/emerg/topic
6. Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. J Am Acad Dermatol 2007 Mar 6; [Epub ahead of print].
7. Bari AU, Rahman SB. A therapeutic update on cutaneous leishmaniasis. J Coll Physicians Surg Pak 2003; 13: 471-6.
8. Urcuyo FG, Zaias N. Oral ketoconazole in the treatment of leishmaniasis. Int J Dermatol 1982; 21:414-6.
9. Moosavi Z, Nakhli A, Rassaii S. Comparing the efficacy of topical paromomycin with intralesional meglumine antimoniate for cutaneous leishmaniasis. Int J Dermatol 2005; 44:1064-5.
10. Dogra J. A double-blind study on the efficacy of oral dapsone in cutaneous leishmaniasis. Trans R Soc Trop Med Hyg 1991;85: 212-3.
11. Berman JD. Editorial response: U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis 1999; 28: 49-51.
12. Bhutto AM, Soomro RA, Nonaka S, Hashiguchi Y. Detection of new endemic areas of cutaneous leishmaniasis in Pakistan: a 6-year study. Int J Dermatol. 2003; 42:543-8.
13. WHO Guidelines for treatment of cutaneous Leishmaniasis in Pakistan. March 2002.
14. Bogenreider T, Lehn N, Landthaler M, Stolz W. Treatment of Old World cutaneous leishmaniasis with intralesionally injected meglumine antimoniate using a Dermojet device. Dermatology 2003;206: 269-72.
15. Salman Pour R, Razmavar MR, Abtahi N. Comparison of intralesional meglumine antimoniate, cryotherapy and their combination in treatment of cutaneous leishmaniasis. *Int J Dermatol* 2006; 45:1115-6.
16. Alkhawajah AM, Larbi E, el-Gindan Y, Abahussein A, Jain S. Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. *Ann Trop Med Parasitol* 1997; 91: 899-905.
17. Bogenreider T, Lehn N, Landthaler M, Stolz W. Treatment of Old World cutaneous leishmaniasis with intralesionally injected meglumine antimoniate using a Dermojet device. *Dermatology* 2003;206 :269-72.
18. Ayub S, Khalid M, Mujtaba G, Bhutta R A. Profile of patients of cutaneous leishmaniasis form Multan. J Pak Med Assoc Aug 2001; 51(8): 279-8.
19. Clive R Davies, Paul Kaye, Simon L Croft, Shyam Sundar Leishmaniasis: new approaches to disease control. Br Med J Feb 2003; 326: 377-8.

20. Ghulam Murtaza Pathan, Farooq Rahman Soomro. Cutaneous Leishmaniasis in a village of mountainous belt of Larkana District. *J Pak Asso Derma* Jun 2001;11: 16-9.
21. Simeen Ber Rahman, Arfan Ul Bari. Morphological patterns of Cutaneous Leishmaniasis seen in Pakistan. *J Pak Assoc Derma* Sep, 2002; 12: 122-9.
22. Faris RM Jarallah JS, Khoja TA al-Yamani MJ Intralesional treatment of cutaneous leishamniasis with sodium stibogluconate. Antimony *Int J Dermatol* 1993;32:610-612.
23. Sharique et al interlesional therapy of cutaneous leishmaniasis with sodium stibogluconate antimony. Br. J Dermatol 1998;119: 53-57.
24. Ghulam Mujtaba, Muhammad Khalid. Weekly vs. fortnightly intralesional meglumine antimoniate in cutaneous leishmaniasis. *Int Jour Dermatol*; 1999; 38(8): 607–609.