TREATMENT OF EARLY LESIONS OF OLD WORLD CUTANEOUS LEISHMANIASIS WITH PENTAVALENT ANTIMONIALS

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ABSTRACT

Objectives: This study highlights the importance of early diagnosis and efficacy of intralesional antimonials in the treatment of cutaneous leishmaniasis (CL) to achieve better cure and prevent disfiguring scar.

Methodology: The study was conducted in Hayatabad Medical Complex, Peshawar. Giemsa stained smears examination was used for diagnosis. Treatment was initiated with intralesional pentavalent antimonials (sodium stibogluconate or meglumine antimoniate), administered weekly for 3--7 weeks and cure rate was monitored for 6 months.

Results: The study population had a single or 2--4 lesions of CL. A total 123 patients were included in the study. Pentavalent antimonials achieved a cure rate of 78.9% (N = 97). Sixty nine (56.1%) patients needed 2--5 injections and 28 (22.8%) needed 6-7 injections. Better results (82.3%) were observed in papule. The cumulative frequency of healing was maximum i.e. 78.9% (N = 97) by Week 12 of start of treatment. Compliance and tolerance was good. No side effects or signs of recurrence were noted in follow up for 6 months. Patients remained outpatients during treatment and during follow up visits.

Conclusions: Early diagnosis and appropriate treatment shorten the healing period and prevent disfiguring scar in the lesions of CL.

Key Words: Cutaneous leishmaniasis, tropical regions, intralesional antimonials, better results, good tolerance.

INTRODUCTION

Leishmaniasis spreads by the bite of infected female sand fly[1]. Sand-flies are silent weak flyers that live in dark and damp places[2]. They are more active during dusk and dawn. Clinically leishmaniasis is present in three forms; cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML) and visceral leishmaniasis (VL). It is endemic in 98 countries and there are 350 million people at risk[3]. The common forms present in Asia are old-world cutaneous leishmaniasis (OWCL) and visceral leishmaniasis (VL). Cutaneous leishmaniasis causes skin lesions[4]. World Health Organization (WHO) has declared OWCL a category one emerging disease and a rapidly spreading public health challenge[5]. Cutaneous leishmaniasis is linked to tropical and subtropical climate, rural atmosphere and socioeconomic conditions like poverty, poor housing and lack of hygiene[6]. OWCL is endemic in Arabian Peninsula, Middle East, East Africa, Afghanistan, Iran, India, Bangladesh, South and Central America, Algeria, Syria, Egypt, Kuwait, Jordan, Iraq, Yemen, and Sudan[5,7]. The disease has spread to many rural and urban areas of Pakistan after the Afghan war due to displacement and massive migration of afghan refugees[8,9]. The risk factors for acquiring cutaneous leishmaniasis (CL) include a stay in endemic area. Travelers can acquire the infection even within 12 hours in an endemic area[10]. Three major species are responsible for OWCL. Leishmania tropica causes dry urban ulcer, Leishmania major causes inflamed ulcers, and Leishmania infantum causes single nodular lesion usually on face[5]. There is multiplicity in the clinical presentation of OWCL[11]. The lesion usually starts as a small painless, red papule at the site of sand-fly bite. There is granulomatous inflammatory response that leads to nodule or necrotic shallow ulcer[12]. Clinically the lesions may be solitary or multiple, red scabby papule, warty or tumor-like, or ulcerating lesion or plaque. Ulcer can be dry or moist; size can be variable from small ulcer to large mutilating lesion[13,14]. OWCL can be a single sore or multiple lesions infrequently on exposed parts of the body like face, neck, and extremities. The infection can disseminate easily in immune-compromised patients due to deficient cell-mediated immunity[15]. Localized spread with satellite papules can also occur[5]. Frequently it can be a non-healing lesion[13]. There can be superimposed bacterial or yeast infection. Often recurrence occur, months to years after clinical healing of the primary lesion (lupoid or tuberculoid leishmaniasis)[16]. Incorrect diagnosis or delay in proper treatment can lead to serious consequences, disfiguring scar, and

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social isolation[17].

Several methods are used to diagnose cutaneous leishmaniasis i.e. identification and culture-isolation of organism from the tissue extract, wound scrap, or tissue biopsy from the active margins of the lesion (sensitivity 19%-77%). PCR is rapid and definitive diagnostic technique and identifies also species of the parasite (sensitivity 97%-100%)[18]. Cutaneous leishmaniasis can heal up spontaneously in about 1-2 years, but prompt, suitable therapeutic interventions are essential to minimize dissemination and avoid disfiguring scar, morbidity, persistence of a disease focus in community, and potential anthroponotic spread[3,19]. Treatment options include local and systemic chemotherapy, and physical treatments (cryotherapy with liquid nitrogen, and localized application of heat at 50°C) depending upon location, size, and number of sores. The geographic location, species of the parasite, age, health, drug-allergies (especially pentavalent antimonials) and immune status of the patient are important for the selection of treatment[5]. Pentavalent antimonial compounds (cure rate 94%) are considered first line drugs for leishmaniasis and can be used safely in children[16,20]. It inhibits adenosine triphosphate synthesis. Other effective treatment include amphotericin B (Fungizone) if antimonials fail, pentamidine isethionate and topical paromomycin. Surgical excision is not recommended[16].

Local treatment is preferred for OWCL[21]. However systemic treatment is required where cartilage is involved or there is lymphangitis or the ulcer is bigger and extensive[22]. Intralesional (IL) pentavalent antimonial is suitable for early lesions, a solitary single lesion or few discrete lesions of OWCL. This local treatment has fewer side effects[16,23]. Cutaneous lesions demonstrate partial response during initial 3 weeks but the wound should be minimized by 75% after 6 weeks of cessation of treatment. Reassessment is required at 3 months, 6 months, and then after one year[19].

MATERIAL AND METHODS

This is a clinical study. The data of last 5 years was collected from Hayatabad Medical Complex (HMC), Peshawar, Pakistan. Diagnosis of cutaneous leishmaniasis (CL) was made by direct microscopic examination of Giemsa stained smears. Patients of all ages and both genders were included in the study. Patients had single or up to 4 lesions or ulcers (<0.5 cm across) of CL. Age of the wound was 6 weeks to 6 months. There was no history of CL in the past and the patients did not get systemic or local pentavalent antimonials for the sore.

Exclusion criteria included ulcers with age more than 6 months, the diameter of lesion more than 0.5 cm, ulcers with satellite lesions, multiple ulcers (more than 4); peri-cartilaginous (lesion on ear or nose), peri-articular or peri-orificial lesions, pregnancy, nursing mothers, kidney or liver diseases, immune-compromised, and allergy to antimony compounds. Patient's data included history of wound, systemic disease, tourism or visit to en-demic area of CL in the last couple of months, antibacterial and antimonials (systemic or local) and lymphadenopathy. Clinical laboratory tests like complete blood picture, blood sugar, serum urea, creatinine, LFTs, SGOT, alkaline phosphatase, urine examination, ECG and chest X-ray were performed.

Treatment with intralesional (IL) injections of pentavalent antimony compounds i.e. sodium stibo-

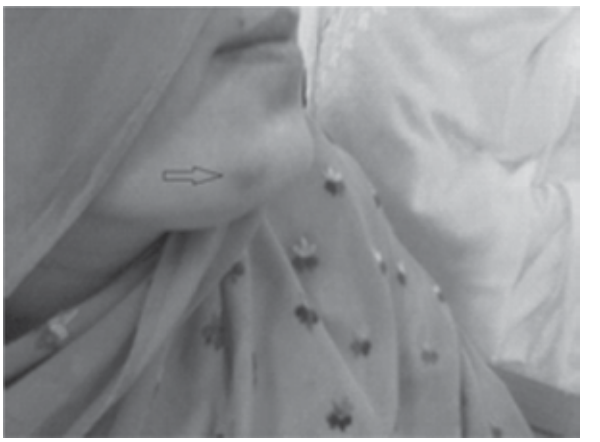

Fig 1: Afghan female from refugee camp with a CL lesion on chin. The lesion was cured with 4 intralesional injections of antimonial.

Fig 2: A child from Hayatabad (Phase 3), Peshawar had a papule of CL on face. The lesion cured with 3 intralesional injections of antimonial.

Table 1: Cure rate of OWCL with intralesional pentavalent antimonials

	Frequency	Percent
Cured	97	78.9%
Non-responders	26	21.1%
Total	123	100%

OWCL = Old-World cutaneous leishmaniasis.

Table 2: The efficacy of IL pentavalent antimonials in OWCL with variable clinical pictures

Picture of the lesion	Number of injections required		Non-responders	Total	P value
	2-5 IL Injections	6-7 IL Injections			
Papule	31 (75.6%)	5 (12.2%)	5 (12.2%)	41 (100%)	< 0.020
Wart or tumor like lesion	12 (57.1%)	6 (28.6%)	3 (14.3%)	21 (100%)	
Ulcer <0.5 cm	26 (42.6%)	17 (27.9%)	18 (29.5%)	61 (100%)	
Total	69 (56.1%)	28 (22.8%)	26 (21.1%)	123 (100%)	

IL = intralesional injection of Pentavalent antimony compound, OWCL = Old-World cu-taneous leishmaniasis.

Table 3: Prognosis and span of healing of OWCL

Span of healing	Frequency	Cumulative Percent
Week4	12	9.8 %
Week 5	24	29.3 %
Week 6	20	45.5 %
Week 7	15	57.7 %
Week 8	10	65.9 %
Week 9	8	72.4 %
Week 10	6	77.2 %
Week 12	2	78.9 %
Non-responders	26	21.1%
Total	123	100.0%

OWCL = Old-World cutaneous leishmaniasis.

gluconate (Pentostam) or meglumine antimoniate (Glucantim) was given at weekly intervals. Injections were given under strict aseptic precautions by cleaning the injection site with ethyl alcohol for 3-4 minutes and then carefully infiltrated 0.5 mL pentavalent antimonials (50 mg/cm2 of ulcer) with BCG syringe beneath the base of lesion to produce complete blanching and swelling. It filled the dermis of lesion with drug. The lesions were covered with sterile swab and dressed properly. Intralesional therapy was repeated weekly for a maximum of 7 doses[5,10,24].

Cure is defined as the complete resolution and re-epithelization of lesion, with no evidence of inflammation, induration or papule[25,26]. Indicators of improvements included disappearance of lesion, partial or complete fading of sore, reduction of in duration and size of lesion, flattening of wound; but the wound should be minimized by 75%, 6 weeks after cessation of treatment[19]. If the decrease in size of lesion was < 25% with persistent induration or the lesion was increasing in size, patients were labeled as non-responders[27]. Follow up visits were made biweekly till Week 24 of the start of treatment for clinical improvement and assessment of lesion, side effects of drugs and possible recurrence. Data was analyzed by SPSS (IBM).

RESULTS

A total 123 patients of cutaneous leishmaniasis (CL) were enrolled in this study. Lesions were mostly on exposed parts of the body and presented as a single sore in 112 patients while 11 patients had 2 discrete lesions. There were total 134 lesions (45 papule, 21 nodule, and 68 small ulcers <0.5 cm). The ages of 63 patients were <5 years, 30 patients were 5-15 years, and 30 patients were > 15 years (Median age was 4.5 years). Forty one patients (33.3%) had a papule (abortive type), 21 (17.1%) had warty or small tumor like lesion, while 61 (49.6%) had small crusted or weeping lesions. The ulcers were mostly painless except in 15 (12.2%) patients. The regional lymph nodes were palpable in 2 patients (1.6%) where the ulcers were infected with Staph aureus. Geographically 35 patients (28.46%) belonged to non-endemic zone of OWCL and 88 patients (71.54%) were residents of endemic areas for CL. Two of the non-endemic zone residents (5.7%) travelled to the endemic area of OWCL in the last 4-6 weeks. There was a history of insect bite in 17 patients (13.8%). One patient had a presumption of thorn prick on the lesion site, while 105 patients (85.4%) had no particulate relevant history. The time period(age) of the lesion was less than 6 weeks in 62 (50.4%) patients, 8-16 weeks in 34 (27.6%) patients, and 16-24 weeks in 27 (22%) patients. (Median duration of lesion was5 weeks). Intralesional pentavalent antimonials (0.5 ml) injected weekly for maximum 7 injections, showed the cure rate of 78.9% (N = 97), while 21.1% (N = 26) did not respond and were reflected as non-responders (Table 1).

The clinical efficacy of IL injection of pentavalent antimony compounds in papule was 75.6% (N=31) with 3-5 injections, 12.2% (N = 5) with 6-7 injections, while 12.2% (N = 5) were non-responders. Wart or tumor like lesions showed a cure rate of 57.1% with 3-5 injections, 28.6% (N = 6) with 6--7 injections, while 14.3% (N = 3) were non-responders. The ulcers (<0.5 cm) showed a cure rate of 42.6% (N = 26) with 3-5 injections, 27.9% (N = 17) with 6--7 injections, while 29.5% (N = 18) were non-responders (Table 2).

Follow-up weekly visits were arranged for 6 months. The span of healing and signs of recurrence were closely monitored during follow-up. The cumula-

tive cure rate of OWCL with IL treatment of pentavalent antimony compounds was 9.8% at Week four, 29.3% at Week five, 45.5% at Week six, 65.9% at Week eight, 72.4% at Week nine, 77.2% at Week ten, and 78.9% at Week twelve (Table 3). There were no side effects reported by the patients. There was no relapse or recurrence up to Week 24 in healed up sores.

DISCUSSION

Cutaneous leishmaniasis is a preventable, vector borne infection related to tropical climate and ecological factors. It is potentially a global problem. It is endemic in many parts of Pakistan and has different local names[1,6,9]. Lesions of OWCL can erode locally. An early diagnosis and commencement of appropriate treatment is essential for better results. Solitary early lesions can easily be treated, cure rates are better, and chances of disfiguring scar on the cosmetic parts of the body are less. Effective treatment in early phases of disease can easily eradicate the human foci of Leishmania tropica and its possible anthroponotic spread in the community[5]. A non-healing ulcer appeared after travel to leishmaniasis endemic area should be screened for LD bodies[18].

The patients in this study had lesions of CL on the exposed parts of the body in the form of papule, wart, tumor, or small ulcer. Diagnosis was made by detecting LD bodies (amastigotes) in the tissue smears or wound scrap. The microscopic examination of Giemsa stained smears reflected a rapid, out-patient, cost effective diagnostic tool for diagnosis of OWCL in developing countries. It lessens a need for costly procedures or hospitalization. It can easily be performed by skilled persons in clinical laboratories in the hard areas. Kevric et al cited a variable sensitivity of this diagnostic procedure i.e. 19% to 77% depending upon the expertise for collection of specimens[10]. Dar et al found 89.7% sensitivity of this procedure[28]. De Vries et al described it a good standard diagnostic tool because of its high specificity. He cited a sensitivity of this procedure to be 85.3%[3]. The sensitivity of this procedure is affected by superimposed microbial infection that requires appropriate treatment with antibiotics before excluding OWCL.

Intralesional therapy of antimonials showed a cure rate of 78.9%-87.8% in papule, wart or small ulcer of OWCL. The cure rate achieved with 3-5 IL injection was better i.e. 75.6% (N = 31) in papule as against 57.1% (N = 12) in warty lesions and 42.6% (N = 26) in ulcerative lesions. A small number of patients with papule i.e. 12.2% (N = 5) required 6-7 injections as against ulcerative lesions i.e. 29.5% (N = 18). The difference is significant (P value < 0.020). The cumulative efficacy of intralesional pentavalent antimony compounds to achieve recovery was 56.1% (N = 69) with 1-5 intralesional injection, and 78.9% (N = 97) with 7 injection. It demonstrated that earlier the OWCL is diagnosed and prompt commencement of treatment, better results are achievable. The efficacy of weekly IL therapy of pentavalent antimonials and its cure rate in OWCL in clinical studies reflected almost the same results like this study. In Asia and Mediterranean regions, the cure rate of OWCL was > 90% with 5-7IL injections; in Tunisia 93%, in Saudi Arabia 88% and 91%, in Sri Lanka almost 100%, in India 92%, and in Iran41.7%[23]. Safi et al found 74% cure rate of cutaneous leishmaniasis with 5 intralesional pentavalent antimony derivatives in a study in Afghanistan, follow up was done for 6 months[29]. Masmoudiet al cited a cure rate of 75% (1999-2006) in Tunisia[30]. A study in Saudi Arabia demonstrated a cure rate of 72% (N = 710) with complete healing of OWCL[31]. The healing rate of 91% (N = 33) was observed by Solomon et al in a study in Tel Avive[32]. In a recent study by Malik et al (2016) in Pakistan showed 68.4% complete cure and 23.7% partial cure with intramuscular (IM) pentavalent antimoniate when comparing oral zinc sulphate with IM pentavalent antimoniate for the treatment of cutaneous leishmaniasis[27]. In another study by Afghani et al (2016) showed successful results for intralesional antimoniate for the treatment of CL on eyelid[33].

The therapeutic efficacy of intralesional injection of pentavalent antimoniate in OWCL monitored weekly or bi-weekly revealed a minimum cumulative cure rate of 9.8% at Week 4, optimum in Week 8-9 (65.9%-72.4%), and maximum at week 12 (78.9%). Follow up carried out for 6 months showed no relapse in healed up sores. Gonzalez et al demonstrated a median healing period of 75 days with intralesional pentavalent antimonials[34]. Patients reported no side effects during treatment or follow-up in this study, except pain during injection. The compliance of intralesional therapy was found good in both adults and children. Patients were advised protein-rich diet and vitamin supplements when needed. Iron and nutrients deficiencies in children were looked for and corrected. Patients remained out-patients during treatment sessions and follow-up visits. Papules and small ulcers were treated without any remarkable disfiguring scar. This study also supported the study of Herwaldt et al who demonstrated partial response of OWCL in initial 3 weeks, and the wound reduced by 75% at Week 619. Good diet rich in protein, iron supplements and supportive correction of deficiencies are recommended by WHO during treatment and follow up[22].

RECOMMENDATIONS

This study emphasizes the following recommendations:

1. Physicians working in endemic areas must be vigilant, can make a diagnosis of CL and must know the local disease pattern16.
2. Suspected sores of CL in tropical and subtropical regions should be promptly screened for LD bodies.

3. Sand-fly bites are commonly imperceptible. The lesions of OWCL may have a typical or atypical history or presentation like thorn prick.

4. Lesions of OWCL can be diagnosed easily in Giemsa stained smears and mostly responded well to intralesional pentavalent antimonials in early stages. It may prevent disfiguring scar and morbidity.

5. The key control measures to prevent spread of cutaneous leishmaniasis in the community include identification of patients, the risk groups and prevention of risk factors for sand fly bites3.

6. People in endemic belt for OWCL should be educated about the significance of prevention and better-quality living conditions, use of personal protective clothing, use of insect repellent on exposed parts of the body, and window screen or net.

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