

Sodium Stibogluconate treatment for cutaneous leishmaniasis: A clinical study of 43 cases from the north of Jordan

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Abstract

Objective: to study the efficacy of Sodium Stibogluconate intramuscular injections in the treatment of cutaneous leishmaniasis, safety and side effects.

Method: A total 43 patients were seen over a period of 12 months, from January 2009 to December 2010. All cases were seen at Prince Rashed Military Hospital in the north of Jordan. The diagnosis of localized cutaneous leishmaniasis was made on clinical grounds proved by leishmania smear or skin biopsy. The distribution of patients according to gender, age groups, time of the year, was made. The criteria for sodium stibogluconate injection were: the severity of symptoms, site of lesion on face (ear, nose and cheek), and multiplicity of lesions. The dose of sodium stibogluconate given was 10 mg/kg given as intramuscular injections daily for total two weeks followed by complete blood count, liver function test, electrocardiogram as base line.

Results: 23 patients were males and 20 were females (16 of them were 14 years and below). The age group ranged from 2-72 years. One patient (2.3%) had resistant infection to sodium stibogluconate; and an admission was for one patient (2, 3%) for a few days because of a picture of Hepatotoxicity. 42 patients showed improvement of the lesion (98%); improvement is defined when the lesion flattens and ulceration disappears.

One patient (2.3%) demonstrated increase in liver enzymes after one week of treatment' upon stopping treatment for one week the patient then resumes treatment with no complications and with complete remission.

Conclusion: Many cases of cutaneous leishmaniasis are seen in Jordan causing cosmetic problems. Early introduction of systemic anti-leishmania agent is recommended. Sodium stibogluconate is an effective way to decrease scarring and depigmentation, with minimum side effects.

Key words: cutaneous leishmania, sodium stibogluconate, scar

Introduction

Leishmaniasis is a widely distributed disease with both visceral and cutaneous manifestations. Cutaneous leishmaniasis is the most common form of this disease. It has an annual incidence of 1 to 1.5 million cases. 90% of cases are reported in just six countries, Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria (1). Cutaneous leishmaniasis causes three distinct clinical entities: localized cutaneous leishmaniasis (a few lesions), diffuse cutaneous leishmaniasis (large number of lesions), mucocutaneous leishmaniasis (involving mucus membrane like nose, mouth, larynx). Other leishmania species may attack viscera causing visceral leishmaniasis or kala-azar (1,2).

Cutaneous leishmaniasis is divided into: the Old World and new world leishmaniasis (3). Old world leishmaniasis is due to *L. major* (zoonotic cutaneous leishmaniasis which tends to heal within 2-4 months), *L. tropica* (anthroponotic tends to heal 6-15 months), *L. aethiopica* and to *L. infantum*, which is responsible for all the cutaneous disease in the northern Mediterranean region and for some of the disease in North Africa.

In the New World, localized cutaneous leishmaniasis is caused mainly by *L. peruviana*, *L. guyanensis*, *L. braziliensis* or *L. mexicana* species. Diffuse cutaneous leishmaniasis is an infection caused by *L. aethiopica* in Africa, and *L. amazonensis* in South America. However, diffuse cutaneous leishmaniasis is also observed in immunosuppressed patients infected with species isolated commonly in localized forms. Mucosal dissemination is described in South America. It is caused by *L. braziliensis*, and, less frequently by *L. panamensis* or *L. guyanensis*(4).

Leishmania is highly contagious with at least ninety percent attack rate among susceptible individuals (5). Affecting children mainly, usually lesions are at site of sandfly bites on exposed areas like face (7).

Cutaneous leishmaniasis is a disfiguring disease that normally resolves within 3 to 18 months of initial infection. Treatment aims to cure as well as prevent the development of more complex manifestations like Mucocutaneous leishmaniasis and disseminated cutaneous leishmaniasis (10).

This study was conducted to examine cutaneous leishmania cases seen over a 12-month period, taking into consideration patients' ages, the time of occurrence during the year, the symptoms and signs at presentation, the treatments given and the complications encountered in affected patients.

Methods

Forty three patients clinically diagnosed to have cutaneous leishmaniasis were seen at Prince Rashid Hospital over a period of 12 months (between January 2009 to December 2010). The distribution of patients as regards the time of disease occurrence during the year, sex and age group, were documented. The diagnosis of cutaneous leishmania was established on clinical grounds. Nodulo-

ulcerative skin lesion, with erythematous, violaceous, edematous edge were the most common presenting features. Laboratory investigations were carried out for all patients and included leishmania smear to demonstrate Donovan bodies, skin biopsy was done only if the lesion was clinically suggestive but smear negative, followed by routine and biochemical blood tests including liver function test, ECG as base line.

All patients were given systemic sodium stibogluconate intramuscular injections, 10 mg/kg per dose daily for two weeks. The 1st injection was given in the clinic with the availability of resuscitation facilities to observe and interfere if anaphylactic reaction developed, then patient completed the course of injections at the nearest clinic. Patients received instructions in regard to the nature of disease and treatment options and to apply topical antibiotics. All patients were re-examined at follow up visit after two weeks to ensure complete cure of the lesion.

Simple non-parametric statistical analysis was made when necessary.

Results

Twenty three patients (53.5%) were males and 20 patients were females (46.5%). The age ranged from 2-72 years. The site of involvement in our patients is shown in Table 1. The distribution of patients according to age groups is shown in Table 2. The patients were from four districts, Table 3. The face was commonly involved (49%) : cheeks (39.2%), nose (18%), forehead (14.3%), pinna (14.3%), lip (10.7%), eyelid (3.5%).

One patient (2.3%) who was hospitalized, was 6 years old with three skin lesions on hand, neck and ear and received 2 ml sodium stibogluconate IM injections for one week and came to hospital with nausea, vomiting, abdominal pain. Liver function test showed raised liver enzyme SGOT 1838, SGPT 1306 Alkaline phosphatase 316, the 2nd day after cessation of therapy SGOT and SGPT dropped to 1314,741 respectively. WBC, PCV, PLATELET were normal. PT, PTT, INR normal, abdominal U/S normal, HBSAG, HC antibodies were negative. After 6 days SGOT and SGPT dropped to 180 and 175 respectively; lesions at these time showed 70% improvement.

One patient (2.3%) who had ulcerative nodule at the lower lip, clinically consistent with Cutaneous leishmania. Leishmania smear was negative but biopsy confirmative, and patient received sodium stibogluconate injection for one week and developed a slight rise in liver enzyme, Patient was stopped for one week and returned to normal resumption of injections with no complications with complete healing but with atrophic scar.

One patient (2.3%) received sodium stibogluconate injections for two weeks but did not show clinical improvement after completion of the course of injections, and was given alternative treatment.

Table 1: Site of involvements and their percentages

Site	Number of patients	Percentage
Face	21	49
Hand , forearm	8	18.6
Foot, leg	7	16.2
Neck	2	4.6
Multiple sites	5	11.6

Table 2: The distribution of patients according to age group

Age group	Number of patients	Percentage
2-19	21	49
20-29	6	14
30-39	6	14
Above 40	10	23

Table 3. The demographic distribution

District	Number of patients	Percentage
Irbid	15	35
Jarash	2	4.5
Ajloun	21	49
Al-Ghour	5	11.5

Discussion

Leishmaniasis are a group of chronic infections affecting human and other animal species, belonging to flagellated protozoans of the order kinetoplastidae, and transmitted by the bite of sandflies of the genera phlebotomus and lutzomyia (5). It is an obligate intracellular parasite that presents in two forms: promastigote in the gut of sandflies where it multiplies and migrates to the proboscis and is introduced to the host whether human, rodent, or other animal species and immediately phagocytosed by host phagocytes where it changed into amastigote(7). It is considered to be a self- limiting disease when localized to skin but always heals with retracted scar and depigmentation but some may become chronic or disseminated(2).

In endemic areas like Jordan where transmission is stable, children are especially affected. In our study children were affected in 37% of the cases, as shown in Table 7, and the cumulative rate of infection as determined by the presence of scars and positive leishmanin tests may approach 100%.

The treatment of cutaneous leishmaniasis depends on the species of leishmania but identification of the species by culture and isoenzyme is time consuming. Also new techniques of DNA amplification by polymerase chain reaction are not widely available which makes treatment depend on the geographical area and the epidemiology of the disease; the main cause of cutaneous leishmania in our area is leishmania tropica (5).

Cutaneous leishmaniasis is the primary infection with one of the leishmania species starting as a papule then increasing in size resulting in a nodulo-ulcerative lesion, usually on exposed areas at the site of sandfly bite (5). In our study, there are 21 cases (49%) involving the face, 8 cases (18.6%) involving the hand and forearm, 7 cases (16.2%) involving the foot and leg, 2 cases (4.6%) involving the neck, 5 cases (11.6%) involving multiple sites of those mentioned above with no single case involving a non-exposed area.

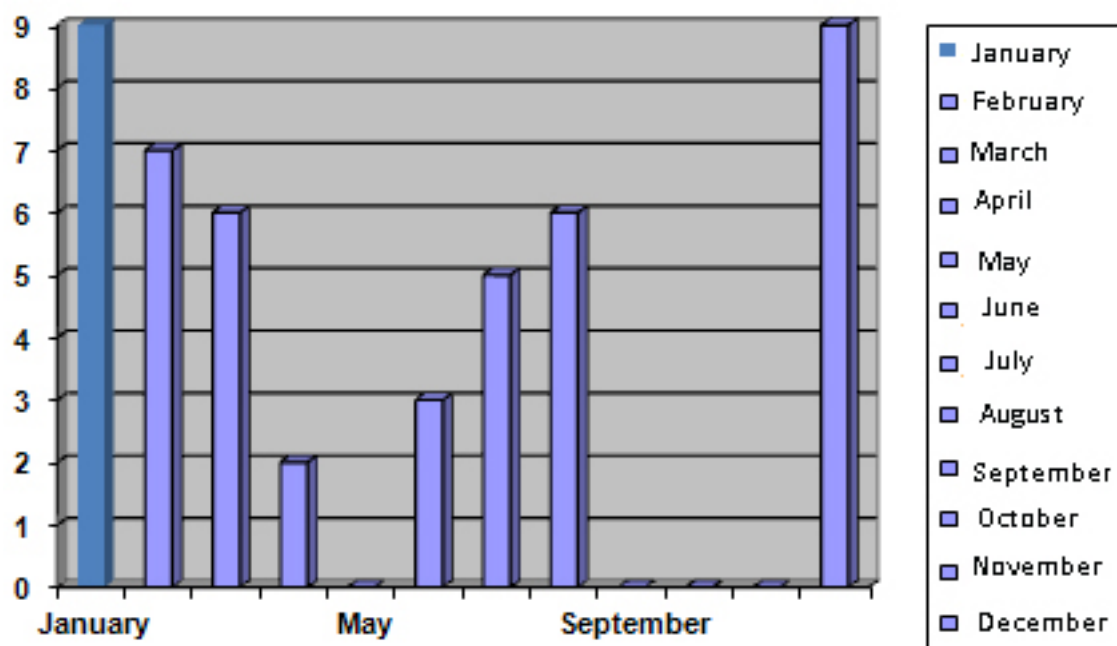
Ajloun district had the highest number of patients simply because towns of Ajloun are geographically appropriate for sandflies living and reproduction regarding temperature and humidity.

Our study shows the highest number of patients in January and December then March (Figure 1, next page), and this may be due to rainy season in winter with the formation of swamps which allow reproduction and growth of sand flies which facilitate vector transmission.

Pentavalent antimonials are the mainstay treatment for both visceral and cutaneous leishmaniasis (8). Two forms are currently available: meglumine antimoniate and sodium stibogluconate. The mechanism for their effectiveness is not well understood, but may involve inhibition of adenosine triphosphate synthesis(9).

The face is affected in 49% of the cases; it results in scarring and depigmentation which is disfiguring on the face.

It is generally recommended that anyone with cutaneous leishmaniasis is to be treated with systemic sodium stibogluconate (especially children and when face is involved) because scar and depigmentation will be inevitable and disastrous. Systemic antimonial decrease the size of the lesion, there is no progression to ulceration

Figure 1: The distribution of patients according to the time of year

and results in less scarring, and rapid healing. Therefore, we started all patients on sodium stibogluconate injection for two weeks; 98% showed complete cure of the lesion upon follow up 2-3 months after completion of the course.

One of the most important side effects of sodium stibogluconate is prolongation of QT interval predisposing to arrhythmias, which are uncommon when used in doses less than 20mg/kg and within a period of less than 2 weeks (6). In our study base line ECG was done excluding patients with abnormal Electrocardiogram from the study; follow up Electrocardiogram was done with no change.

Hepatotoxicity is another side effect of sodium stibogluconate injection which is reversible within 6 weeks of cessation of treatment (6). Base line liver function tests were done to exclude any patient with liver disease from the study; two patients developed increases in liver enzyme which returned to normal within two weeks of cessation of treatment.

Wide use of sodium stibogluconate in the treatment of cutaneous leishmaniasis can result in the emergence of a resistant strain(9). In our study one patient did not show improvement clinically after completion of the course of injections (still the lesion was wet and increasing in size). The mechanism for the development of resistance is not well understood. It could be an intrinsic difference in the species sensitivity to these medications; another mechanism is the efflux of a drug or its active derivative(9).

Studies showed that the addition of allopurinol to the treatment regimen gave better results regarding decrease of the size of the lesion and clearance (4). In our resistant case just when it showed no healing, a change to

rifampicin 300mg daily for 2 weeks allowed healing of the lesion.

In addition, there are several alternative treatment options available; local infiltration with sodium stibogluconate of the whole lesion intradermally with 2-3ml every week until 4 weeks (4). Also Oral zinc sulphate (5 mg/kg/day for 4 weeks) showed promising results in a recent Indian trial (8).

Cryotherapy using liquid nitrogen is a well known option for treatment in the middle east including Jordan where 2-3 sessions for 20-30 seconds freezing (one month interval) resulted in healing of most of the lesion but with a different degree of atrophic scar and depigmentation. But when multiple lesions, large lesions, over the joint, are on the face, the cosmetic unit usually tries to avoid cryotherapy.

Conclusion

Cutaneous Leishmaniasis is cosmetically disfiguring and slowly growing skin lesions are not fatal but occasionally can result in significant morbidity especially when present on the face.

Early treatment with systemic antimonial agent is essential in the adults and children to prevent or decrease the risks of complication like: scarring and depigmentation.

We believe that it is highly recommended to give systemic sodium stibogluconate injection to all patients with Cutaneous leishmaniasis, especially when certain areas like ear, eyelid, lip, cheek, nose, and multiple lesions are present.

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