EVALUATION OF THE CUTANEOUES LEISHMANIASIS TREATMENT IN AL-MERGHEB, LIBYA

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Abstract: Cutaneous leishmaniasis (CL) is a parasitic disease which endemic in the Mediterranean region, including Libya, and it is considered as main public health problem. Treatment of CL now a day's become a challenge to the scientists over the world. Pentostam has clinical efficacy against CL. Because of the limited data on the treatments used for CL in addition to undesirable side effects, there has been a demand for alternative therapies for CL. The objective of this study to evaluate the efficacy of the used remedy regime to treat the CL patients in Libya. We found that local and systemic pentostam for CL are useful and well tolerated. Combination of local pentostam and cryotherapy improve the chances that lesions will heal more rapidly. Because some of CL lesions heal spontaneously without treatment, decisions regarding additional therapy that heal lesions faster and prevent relapse must take into account. Therefore, we believe that further clinical studies should be conducted with cryotherapy in combination with other local medication.
Key words: Adverse effects ,Al-Mergheb, cutaneoues leishmaniasis, Cryotherapy, Leishmania major, Libya, Pentostam.
Introduction:

Leishmania is a major cause of illness and death and is considered as a main concern for the tropical disease program of the World Health Organization (WHO) (Alrajhi et al., 2002). The worldwide incidence of leishmaniasis is about 1.8 million new cases annually (WHO, 1996). The Leishmania protozoan was first described in 1903 by leishman and Donovan, working separately (Herwaldt, 1999).

Cutaneous leishmaniasis (CL) is a parasitic disease occurring in the New World and Old World, particularly the middle east and North Africa (Markle and Makhoul, 2004). CL is a major public health problem in the WHO Eastern Mediterranean Region. New cases are emerging in areas previously free of the disease. Over 100 000 new cases of CL are reported annually to WHO by countries in the Region, but the actual incidence is estimated to be three to five times higher since many patients never seek medical attention and not all patients with a diagnosis of CL are reported to health authorities (WHO, 2014). Many studies showed that certain medications are well documented to have activity against leishmania. Oral fluconazole is useful treatment for CL caused for Leishmania major (Alrajhi et al., 2002). However, response to treatment is often unpredictable and unsatisfactory (Hepburn, 2000). Different treatments for leishmaniasis include local and systemic methods, in which cryotherapy with liquid nitrogen and intralesional glucantime are more commonly used (Khatami et al., 2007; Layegh et al., 2009). Because of limited data on the clinical efficacy of fluconazole, a triazole antifungal agent is used as alternative therapy (Sundar et al., 1996; Torrus et al., 1996). Triazole has excellent safety profile and pharmacokinetic properties make it a proper alternative therapy for CL (Alrajhi et al., 2002). Amphotericin-B is another drug used as a second line treatment for CL especially with pentavalent antimony treatment failure, it has been used in the New World since the early 1960s (Wortmann et al., 2010). Previous studies have reported that pentostam has clinical efficacy against CL (Wortmann et al., 2010). Because of the limited data on the treatments used for CL, in addition to undesirable side effects, there has been a demand for

alternative therapies for CL. We report our experience with the use of treatment protocol of CL in Libya that is carried out by retrospective review of patients receiving different regimes of remedies using systemic antibiotics, local and systemic pentostam and cryotherapy, as shown in table 1. The objective of this study was to evaluate the efficacy of the used remedy regime to treat the CL patients in Al-Mergheb province - Libya.

Table 1: The used remedy regime at Al-khoms polyclinic to treat CL lesions.

Treatment
Cryotherapy + interalesional pentostam 1ml/lesion/week/ 3 sessions.
Systemic pentostam 20mg/kg/day for 21 days
Intralesional pentostam (alone) 1ml/lesion/week/ 3 sessions.
Cryotherapy (alone) 1ml/ lesion/each week/ 3 sessions.
Self healing

Materials and Methods:

Place of study and Subjects: The study was conducted in Al-khoms (32°38'59"N, 14°15'52"E), a city on the Mediterranean coast of Libya in the north-west about 97 km South-east of the capital city Tripoli. It is tourist destination. Al-Mergheb province is divided into 36 sub-provinces with a total population of 428,000 individuals. Al-khoms sub- province is the administrative city of the Al-Mergheb province, which is one of the most prominent sites of CL in Libya.

327 patient with CL attending at Al-khoms polyclinic (as outpatient), Al-khoms, Al-mergeb- Libya during the period from 1-11-2014 till 1-12-2015 were included in this study. Al-khoms polyclinic is the only leishmanasis clinic in Al-Mergheb province, to which all the cases are referred by the other clinics to seek medical diagnosis, treatment, and consultation. All CL cases were clinically diagnosed and confirmed by laboratory investigations at Al-khoms polyclinic.

Clinical presentation: The clinical presentation of the reported patients confirmed that it was CL lesions. The three clinical forms of CL lesions were 1) papulo-ulcerated, 2) nodular ulcerated and 3) indurated ulcerated

scaly plaque forms. Most of the CL cases included in this study were diagnosed by the formation of nodular ulcer. They start as papules and slowly changed to nodular ulcer and they mostly appeared on face, upper and/or lower limbs and feet. The number of lesions in the patients varied from 1 to 17 and the size varied from 3-5 cm.

Diagnosis: The broad clinical spectrum of CL makes diagnosis of present and past cases difficult. Differential diagnosis is important because diseases of other un-leishmanial causes with a similar clinical spectrum to leishmaniasis (e.g., leprosy, skin cancers, tuberculosis and cutaneous mycoses) are common in leishmaniasis- endemic areas (Escobar, et al, 1992). Parasitological diagnosis remains the gold standard in CL diagnosis, because of it is high specificity. Microscopic examination is probably the most common used diagnostic approach, because more sophisticated techniques are expensive and rarely available at primary, secondary and tertiary health-care levels in endemic areas. CL lesions were confirmed in the all patients included in this study. Skin smears for microscopic testing and photographs have been taken for the CL lesions. And the Giemsa stained smears confirmed our preliminary clinical diagnosis under light microscope as they revealed the presence of amastigotes stage of Leishmania parasite. Amastigote form are ovoid or round and 1.3 to 3.5 μm in diameter. They have thin cell membrane, a relating large nucleas, and a rod-shaped kinetoplast (Abdellatife et al., 2013).

Treatment method: As the treatment for CL should aim to hasten recovery and prevent further transmission and bacterial superinfection. Therefore, the non-fetal, CL has been treated to accelerate cure to reduce scarring, especially in cosmetic sites, and to prevent parasite dissemination or relapse. Overall, in all patients lesions have been washed with clean water and soap, and then covered by gauze. Each group of CL patients had received different treatment regime for three weeks as shown in (table 2).

Table 2: The used remedy regime at Al-khoms polyclinic to treat cutaneous leishmaniasis lesions.

The lesion location	The used treatment
Single lesion	intralesional K-permanganate 100 mg (1ml/lesion)
Ulcerative nodule/scare	intralesional K-permanganate 100 mg (1ml/ lesion) + cryotherapy (3 sets maximum)
Facial lesion Multiple lesion Single lesion+ lymphangitis or lymphe nodes	Hospitalisation+investigation+ systemic pentostam 20 mg sb5+/kg/day/21 days
Some of cases	Spontaneous healing

All the cases were treated firstly by systemic antibiotics to prevent secondary bacterial infection. Cases presented with single lesion were treated by intralesional K-permanganate 100 mg (1ml/ lesion), while cases that have ulcerative nodule or scare were treated by a combination of intralesional K-permanganate and cryotherapy (with either single set or not more than three sets) to reduce scare. Cases that are presented by facial lesion, multiple lesions or big lesion with lymphangitis or lymph nodes were the indicated for hospitalization with complete investigations (CBC, LFT, RFT, chest X-ray, ECG and serological investigations) and systemic pentostam 20 mg/kg for three weeks. Some cases got spontaneous healing without any treatment.

Statistical analysis: All data were subjected and statistically analyzed by using the statistical Minitab program, version 16. The results were expressed as percentages, and statistical analysis was carried out by using chi square test. A probability p-value of ≤ 0.05 was considered as significant whenever appropriate.

Results and Discussion:

Leishmaniasis is an important public health issue affecting billions of people around the world (Uzun, 2008). CL due to Leishmania tropica and L. Major is endemic in 18 countries: Afganistan, Egypt, Iraq, Islamic Republic of Iran, Jorden, Kuwait, Libya, Morocco, Oman, Pakistan, Saudi Arabia, Sudan, Syrian Arab Republic, Tunisia, West Bank and Gaza Strip, and Yemen (WHO, 2014). Currently there are no vaccines available against CL and the pursuit of an effective vaccine against all types of

leishmaniasis is under study. Moreover, treatment of CL now a day's become a challenge to the scientists all over the world. Several drugs were used by many published studies to treat CL caused by leishmania major. However, the infecting species, geographical region and the immune status of the patient affect the efficacy of treatment (WHO, 2014). Choosing the best therapeutic method for treatment of CL has always been one of the greatest health problems in leishmaniasis-endemic areas. Despite many therapeutic modalities available, there is still no consistency regarding treatment of choice (Layegh et al., 2009). Therefore, choosing a treatment method that is painless, effective, and has fewer side effects in children, who represent 7–10% of patients in disease-endemic areas, has always been an issue of great importance (Talari et al., 2006 & Sharifi et al., 1998). However, the current study is a retrospective study which have been done in the endemic area within the years 2014-2015. A total of 327 patients were assigned to receive the treatment protocol which have been used in Al-khoms polyclinic - Libya (the included cases have no other medical problems and their investigations were normal). This study has showed that a three weeks course of our protocol is safe and useful treatment for CL in Al-khoms polyclinic - Libya (table 3 shows the used treatment and the number of treated case). Failure treatment in two cases treated with systemic pentostam, which present (2.82%) of the treated cases as shown in table 3. This failure treatment has no significant differences if compared with 100% treatment success (P-Value = 0.579). According to some authors, one of the most important and common causes of treatment failure with Intralesional antimonials are inadequate infiltration of the lesions (González et al., 2008 & Faghihi and Tavakoli-kia, 2003).

Table 3: The used treatment and the No. of treated cases.

Treatment	No. of treated cases	Treatment efficacy	Treatment failure
Cryotherapy + interalesional pentostam 1ml/lesion/week/ 3 sessions.	161	100%	00%
Systemic pentostam 20mg/kg/day for 21 days *	71	97.18%	2.82%
Intralesional pentostam (alone)	42	100%	00%
Cryotherapy (alone) 1ml/ lesion/each week/ 3 sessions.	27	100%	00%
Self healing	26		
Total	327		

* Failure treatment in two cases treated with systemic pentostam.

As for the most common sites of CL (shown in table 4) are appeared in the upper and lower limbs (41.3% & 37.6% respectively) with no statistical differences. The other common CL sites are presented in face & trunk (15.9% & 5.2% respectively), with significant differences (P-Value < 0.005) when compare the lesions distribution in upper limb verses the face as well verses the trunk. The same P-Value (< 0.005) was the result between the lesions distribution in the face verses trunk. In disagreement with this result, Sharma et al., 2005 reported that lesions most commonly appeared on the face and then the upper limbs. In addition, Reports of CL from other countries and caused by different species have indicated similar findings (Mengistu et al., 1992).

Table 4: Distribution of cutaneous leishmaniasis lesions on infected patients.

Site of the lesion	No. of cases* (%)
Upper limb	135 (41.3%)
Lower limb	123 (37.60%)
Face	52 (15.9%)
Trunk	17 (5.2%)
Total	327

* Some had multiple lesions at different sites.

There are several risk factors such as, sex, age, residence in rural areas, occupation. However, we found that, the male: female ratio indicated that the infection rate among males (61.16%) was higher than females (38.84%) with significant differences P-Value < 0.005 (table 5 shows the infected rate in male and female patients). The possible explanation for that is the men have a habit of sleeping outside their homes during hot nights and busier in outdoor activities so they may be more prone to get bitten by infected sand flies compared to women who tend to have fewer activities outside their homes. As for the age groups, both male and female patients were infected (ages ranged <5–70 years). In addition, 207 (63.3%) of the patients they were suffering from multiple lesions, were as 127 (38.84%) of them they had single lesion (P-Value < 0.005) as shown in table 5.

Table 5: The infected rate in male and female patients.

Gender	Male (%)		Female (%)		Total (%)	
No. of lesions	Single Lesion	Multiple Lesion	Single Lesion	Multiple Lesion	Single Lesion	Multiple Lesion
Children	21 (6.42%)	12 (3.67%)	9 (2.75%)	22 (6.73%)	30 (9.17%)	34 (10.4%)
Adult	65 (19.88%)	102 (31.19%)	25 (7.65%)	71 (21.71%)	90 (27.52%)	173 (52.9%)
Total	86 (26.3%)	114 (34.86%)	34 (10.4%)	93 (28.44%)	120 (36.7%)	207 (63.3%)
	200 (61.16%)		127 (38.84%)		327	

-No. of cases= 327.

-26: self healing 9 male (1 child) - 17 female (5 children).

-301: cases received treatment.

These results are in consistence with a previous studies conducted in Gharyan – Libya (Ahmed and Abou faddan, 2013), Yafren region, Aljabal, Al-Gharbi (Libya) (El-Buni et al., 2000, Abdellatif et al., 2013 and Amro, et al., 2012). However, identifications of risk factors would help to guide the design of prevention strategies (Reithinger et al., 2007). In 2002, Alrajhi and his group found that oral fluconazole was very effective and well tolerated in Saudia Arabia patient of CL. Perhaps there

is a similarity in the weather between Saudia Arabia and Libya. Therefore, fluconazole could be used as an alternative systemic therapy instead of systemic antibiotic used in our study, with one defect, which is the cost of fluconazole. In United states pentostam is not an approved drug, therefore, amphotericine B was used as a treatment option for cutaneous leishmaniasis (Wortmann et al., 2010). It was very effective against the disease with high incidence of adverse effect especially nephrotoxicity. Unfortunately, the expense (pharmacy cost of $821 per 218-mg dose) and the potential toxicity of amphotericine B argue that an improved therapy for CL is still needed with perhaps an inexpensive, well tolerated oral regimen as the goal (Wortmann et al., 2010). In Colombia, cryotherapy was similar to single dose of oral miltefosine for 28 days and both were found to be very effective in treatment of CL with low toxicity (Lopez et al., 2013). Furthermore, combination of topical therapy offers few adverse effects, better compliance and reduced cost with oral fluconazole might be effective in Libyan populations and another studies are needed to be conducted.

In brief, the results of treatment regime used in this study in Al-khoms polyclinic-Libya was very effective in both sexes and ages. The treatment regime is the only model of the remedies used in Libya for CL with successful outcomes.

Conclusions:

In Al-khoms polyclinic pentostam have been used as the main treatment for CL which gives a good result in a short time. Local and systemic pentostam for CL are useful and well tolerated. Combination of local pentostam and cryotherapy improve the chances that lesions will heal more rapidly. However, a three weeks course of our protocol is safe and useful treatment for CL in Al-khoms polyclinic-Libya. Because some lesions of the CL heal spontaneously without treatment, decisions regarding additional therapy that heal lesions faster and prevent relapse must be taken into account. However, we believe that further clinical studies should be conducted with cryotherapy in combination with other local medication. It seems that new foci in Al-Mergheb province appear in addition to well-known zones of transmission. The Rodents and the sand fly should be controlled for the most prober control programs against CL infection.

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