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Treatment of Old World Cutaneous Leishmaniasis with Oral Dapsone & Radiofrequency Machine Alone and in Combination in Algalab Algarby Libya

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Abstract

Background: Cutaneous Leishmaniasis (CL) is a disease transmitted by infected sandflies in tropical and subtropical areas of the world. Over 12 million people are infected with CL, with 90% of cases occurring in Afghanistan, Iran, Algeria, Brazil, Peru, Saudi Arabia, Syria, and Libya. CL causes localized skin lesions that may disappear without treatment or persist, causing severe tissue damage, permanent disfigurement, and serious disability. Physical methods such as cryotherapy, heat therapy, photodynamic therapy, laser, and radiofrequency have shown promising results in treating CL. However, none of the suggested treatments are universally effective, and many of them are associated with serious local and systemic side effects. Early diagnosis and treatment can cure the disease, prevent psychological impact, and help in the prevention of transmission. Different therapeutic modalities (monotherapy or combined therapy) were used in patient treatment, with different approaches planned according to the severity and duration of the condition.

Patients and methods: The study was conducted on 60 Patients who were divided into three groups: 20 patients treated with dapsone tab 100mg once daily for one month and 20 with radiofrequency, the third group, 20 Patients were treated with a combination of dapsone tab 100mg and radiofrequency. Treatment sessions were scheduled 1 session every 2 weeks. Statistical analysis was carried out using SPSS software version 18 (USA). Results and

Discussion: Patients underwent weekly physical exams to evaluate clinical response and adverse effects. Clinical response was classified as complete, good, or poor. Data were analyzed using one-way NOVA, Turkey's test, chi-square test, ANOVA, and Fischer's exact test. There was no significant difference among studied groups regarding demographic data. Patients treated with dapsone and radiofrequency were significantly more cleared in 1-2 months than those treated with radiofrequency alone.

Conclusion: Patients had weekly physical exams to evaluate the clinical response and adverse effects. Clinical response was classified as complete, good, or poor. Data was analyzed using various tests. Dapsone and radiofrequency-treated patients cleared more in 1-2 months.

Keywords: Cutaneous leishmaniasis; Dapsone; Radiofrequency; Aalgabal algarby; Libya

Introduction

Cutaneous Leishmaniasis (CL) is an endemic disease of the tropical and subtropical areas of the world that is transmitted by the bite of an infected sandfly. It has an estimated incidence of 1.5 million cases [1].

Leishmaniasis is a set of infectious diseases caused by intracellular protozoan parasites of the genus *Leishmania*. Over 12 million people are infected with leishmaniasis and about 1.2 million new cases appear annually. Around 90% of CL cases occur in Afghanistan, Iran, Algeria, Brazil, Peru, Saudi Arabia, Syria, and Libya. *L. major*, *L. tropica*, and *L. aethiopica* are causative agents of OWCL. In Iran most cases of CL are caused by *L. major*, and then *L. tropica*, and rarely by *L. infantum* [2,3].

There are three main clinical manifestations depending on the tissues and organs affected by the parasite: cutaneous, mucosal, or visceral leishmaniasis. Focusing on Cutaneous Leishmaniasis (CL)

causes localized skin lesions that may disappear without treatment or persist, causing severe tissue damage, permanent disfigurement, and serious disability. In general, species that are prevalent in the "old world" (i.e., *Leishmania major* and *Leishmania tropica*) produce limited clinical manifestations compared with "new world" species (i.e., *Leishmania braziliensis*, *Leishmania amazonensis*, and *Leishmania mexicana*) [4].

Leishmaniasis are a group of vector-borne chronic infectious diseases caused by 21 different species of flagellate protozoa belonging to the genus *Leishmania*. These diseases are transmitted by blood-feeding female phlebotomine sandflies, 500 species of which have been recognized [5].

Although the condition is self-limited, its natural course is unpredictable. Cure rates vary and it may take months to years to heal. Spontaneous resolution can leave significant disfiguring scars and psychological trauma. Early diagnosis and treatment can cure the

disease, prevent psychological impact, and help in the prevention of transmission. A number of chemotherapeutic, surgical, and physical modes of therapy have been employed to treat CL, but none has been found to be consistently safe, simple, and effective; moreover, there are no uniform guidelines [6].

In spite of the efforts to find definite therapy for CL, none of the suggested treatments are universally effective, and many of them are associated with serious local and systemic side effects [7].

The use of physical methods for the treatment of CL, besides their efficacy, has the possible advantage of not having systemic side effects. Both cold and heat have been used for this purpose. Cryotherapy, heat therapy, photodynamic therapy, laser, and radiofrequency are among the physical methods that have shown promising results for the treatment of leishmaniasis [8].

To date, different sources of heat have been applied in trials for the treatment of leishmaniasis including hot water soaks, circulating hot water in heating pads, Infrared (IR) heat, and ultrasonically induced hyperthermia of the skin [9]. Of note, a trial for CL in Afghanistan compared the efficacy of one session of thermotherapy by radiofrequency with five sessions of intralesional Glucantime injection and found that the former was more effective, shorter in duration, had fewer side effects, and had better patient compliance [10].

Different therapeutic modalities (monotherapy or combined therapy) were used in patient treatment. The therapeutic approach for each patient was planned according to the severity and duration of the condition. All patients selected for monotherapy had almost the same level of disease severity (single small lesions of less than 1 year in duration). Systemic monotherapy (dapsone/itraconazole) was chosen for multiple, large (>3 cm), atypical, and disseminated lesions. Combination therapy was used for those not responding to monotherapy, and sometimes also according to the severity of the disease [11].

Methodology

This study was conducted on 60 patients with Old World cutaneous leishmaniasis at Algalab Aljarby Libya during the period from April 2022 to April 2023.

All patients were subjected to informed written consent, history taking, general and local examination. The number, location, shape, size (surface diameter was obtained by multiplying the longest and shortest diameters by one another), and duration of skin lesions were recorded. Inclusion in the study required the diagnosis of CL infection and the evidence of leishmania from skin lesions using the slit-smear technique. All patients had pertinent baseline tests, including Complete Blood Count (CBC), urinalysis, clinical chemistry, and Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) serology. Patients were divided into three groups:

Group (A): 20 Patients were treated with dapsone tab 100mg once daily for one month and in some cases for 2 months.

Group (B): 20 Patients were treated with radiofrequency. The equipment that was used for the treatment of leishmaniasis was ultrasound machine with a handheld applicator (2 cm), intensities range 1-3 p/s, and from 1-50 Hz, Temperature was monitored using Thermo Probe [12]. Thermotherapy was offered as an alternative treatment to patients with a limited number of lesions (less than 4) who will resistant or hypersensitive to antimonial compounds. After

fully discussing the treatment protocol and other alternatives, in the case of obtaining informed consent, the patients were enrolled in this study. Treatment sessions were scheduled 1 session every 2 weeks. In each session, the lesions were warmed to 50°C, five to ten cycles for each lesion. There is no distance between the device and the skin lesion. The full duration of the treatment was considered from 4 to 6 sessions, but if complete remission was achieved earlier, or when there was no more improvement after 6 consecutive sessions, the treatment was discontinued.

Group (C): 20 Patients were treated with dapsone tab 100 mg and radiofrequency.

Patients were followed up by weekly physical examinations to evaluate the clinical response and any possible local or systemic adverse effects during the treatment course and at the third month after treatment.

Clinical response was assessed according to the reduction in size and induration of the lesions and classified as: Complete response: 90-100% reduction, good response: 50-89% reduction or poor or no response: <50% reduction.

Statistical analysis

Data were analyzed using SPSS software version 18 (USA). The parametric data expressed as mean ± SD or number (%). The statistical comparisons between different groups were carried out using one way ANOVA followed by turkey's test for parametric data & Chi square test or Fischer exact for categorical data. The level of significance will be identified at P<0.05.

Results

Patients were followed up by weekly physical examinations to evaluate the clinical response and any possible local or systemic adverse effects during the treatment course and in the third month after treatment. Clinical response was assessed according to the reduction in size and induration of the lesions and classified as complete response, good response, or poor response. Data are represented as mean ± SD (Range) or number (%). Data are analyzed using one-way NOVA followed by Turkey's test and chi-square test. P1 significance between groups 1 &2, P2 significance between groups 1&3, and P3 significance between groups 2&3, as shown in Table 1. This table showed that there was no significant difference among studied groups regarding demographic data.

| Variable | Dapsone treated group (n=20) | Radiofrequency treated group (n=20) | Dapsone & Radiofrequency treated group (n=20) | F/X2 | P |
|--------------------------|------------------------------|-------------------------------------|---|----------------------|--------|
| Age | | | | | |
| Mean ±SD (Range) | 30 ± 9.9(20-54) | 31.3 ± 8.6(20-46) | 36 ± 10.9(23-52) | F=2.03 | P=0.14 |
| Gender Number (%) | | | | | |
| Male | 14 (70%) | 12 (60%) | 10 (50%) | X ² =1.66 | 0.43 |
| Female | 6 (30%) | 8 (40%) | 10 (50%) | | |

Table 1: Age and sex distribution of the three treated groups.

Data are represented as mean ± SD (Range) or number (%). Data are analyzed using one-way ANOVA followed by Turkey's test and Fischer's exact test. P1 significance between groups 1&2, P2 significance between groups 1&3, and P3 significance between groups 2&3 Table 2. This table showed that there was no significant difference among studied groups regarding characteristic lesions, as shown in Table 2.

| Character | Dapsone treated group (n=20) | Radiofrequency treated group (n=20) | Dapsone & Radiofrequency treated group (n=20) | F/X2 | P |
|---------------------------------|------------------------------|-------------------------------------|---|---------|--------|
| Number of lesion | | | | | |
| Mean ±SD (Range) | 2.7 ± 0.32(1-5) | 2.4 ± 0.34(1-5) | 2.7 ± 0.35(1-6) | F=0.25 | P=0.77 |
| Type of lesion(%) | | | | | |
| Nodular | 10(50%) | 16(80%) | 14(70%) | X2= 4.2 | 0.12 |
| Nodular & ulcerative | 10(50%) | 4(20%) | 6(30%) | | |
| Site of lesion (%) | | | | | |
| Face | 0(0%) | 4(20%) | 4(20%) | Fischer | 0.27 |
| Upper extremity | 12(60%) | 10(50%) | 8(40%) | | |
| Lower extremity | 8(40%) | 6(30%) | 8(40%) | | |
| Months since insect bite | | | | | |
| Mean ± SD (Range) | 2.3 ± 1.21(1-5) | 1.7 ± 0.68(1-3) | 2.2 ± 1.1(1-4) | F= 1.97 | P=0.14 |

Table 2: Characters of lesion of the three treated groups.

Data are represented as numbers (%). Data are analyzed using the Fischer exact test. P1 significance between groups 1&2, P2 significance between groups 1&3, and P3 significance between groups 2&3 as shown in Table 3. This table showed that patients treated with dapsone and radiofrequency (90%) cleared in 1-2 months were significantly more than patients treated with radiofrequency (70%) or dapsone (60%) alone (Table 3).

| Outcome | Dapsone treated group (n=20) | Radiofrequency treated group (n=20) | Dapsone & Radiofrequency treated group (n=20) | X2 | P |
|-----------------------|------------------------------|-------------------------------------|---|---------|------|
| Cleared in 1-2 months | 8(40%) | 7(35%) | 15(75%) | X2=7.6 | 0.02 |
| Cleared in 3-4 months | 6(30%) | 5(25%) | 2(10%) | X2=2.5 | 0.27 |
| Not improved | 6(30%) | 8(40%) | 3(15%) | X2=3.11 | 0.21 |

Table 3: Outcome of the three treated groups.

Discussion

Cutaneous Leishmaniasis (CL) is a significant public health problem with an incidence of around 1500,000 cases annually worldwide [13]. Eastern Mediterranean Region (EMR) is endemic to old world CL caused by *Leishmania major*, *Leishmania tropica*, and *Leishmania aethiopia* in most cases [14]. To date, different sources of heat have been applied in trials for the treatment of leishmaniasis including hot water soaks, circulating hot water in heating pads, Infrared (IR) heat, and ultrasonically induced hyperthermia of the skin [15]. Of note, a recent trial for CL in Afghanistan compared the efficacy of one session of thermotherapy by radiofrequency with five sessions of intralesional Glucantime injection and found that the former was more effective, shorter in duration, had fewer side effects, and had better patient compliance [10].

In the current study, the majority of patients had multiple lesions and nodular type was the most common. The most commonly affected site was the upper limbs (50%) followed by lower extremity (36.7%) and face (13.3%). In agreement with our study, Al-Mutairi, et al., showed that the course of the disease was mainly acute (84.5%) [11]. The lesions were equally divided into solitary and multiple (53.6% and 46.4%, respectively). The most commonly affected location was the upper limbs (44.5%), followed by the face and neck (25.4%) and lower limbs (20%). The majority of patients with multiple lesions had two to three lesions, except those having sporotrichoid, zosteriform, subcutaneous, and disseminated forms.

In the present study, patients treated with dapsone and radiofrequency (90%) were cleared in 1-2 months more than patients treated with radiofrequency (70%) or dapsone (60%) alone. In agreement with our study, Asilian, et al. showed that a combination of cryotherapy plus meglumine antimoniate MA is superior to MA alone or cryotherapy alone [16]. In this manuscript, the combination of intralesional MA and cryotherapy is called classic local therapy, and the combination of Intramuscular (IM) MA and cryotherapy is called classic systemic therapy. In case of contraindication for classic treatment of CL, other treatment options could be used.

Al-Mutairi, et al., showed that cryotherapy used as monotherapy cured CL in 30 of the 44 patients (68.18%) receiving this mode of therapy [11]. The majority of the patients required three sittings. Most of the patients had solitary small lesions. Local transient pain was described by most patients, and blister formation occurred in seven cases. No cases of secondary infection or lymphangitic dissemination were observed. The topical immune modulator imiquimod cream was applied as monotherapy thrice weekly for 6 weeks in a standard manner. Two patients did not improve at all, and the lesions in four patients progressed after showing initial improvement at 4 weeks. Systemic treatment with oral itraconazole, 100 mg twice daily, alone showed a "good to excellent response" in seven of the 12 cases (58.3%) receiving this mode of therapy. Dapsone (100-150 mg daily) alone showed similar results in 43.8% (7/16) of patients. Combination therapy was offered to 69 patients, including those with a poor response (cryotherapy, 14; imiquimod, 6; itraconazole, 5; dapsone, 9). The combination approach gave a better overall response (69.56%) than monotherapy alone (56.41%), except for cryotherapy alone (68.18%). The combination therapy with the best response was itraconazole plus cryotherapy (80.95%), followed by itraconazole plus imiquimod (70%). In Iran, Sadeghian, et al., have found only one report on the effect of radiofrequency-induced heat for the treatment of anthroponotic CL in comparison with intralesional injection of meglumine antimoniate ILMA [17]. The study population was divided

into two groups, and treated with radiofrequency heat therapy (group A) or ILMA (group B). Group A was treated for one month on a weekly basis with RF heat of 50 °C for 30 seconds. Group B was treated with ILMA once weekly for one month. Complete response occurred in 80.7% of group A, versus 55.3% of group B. Valencia, et al., first described the use of thermotherapy for the treatment of CL in Peru [18]. Twenty-five patients with confirmed CL were treated with this method for 7 days and followed for 6 months. 68.4% of patients showed complete cure with 2 cases of second-degree burn. The authors suggested further study to evaluate this technique as adjuvant or monotherapy. Shah, et al., performed their study in Pakistan, and found that the patients were treated with thermotherapy for 7 days, with an initial temperature of 51.6°C for 3 min, at 6 months of follow-up, out of 23 patients who completed the study, 19 (83%) patients were completely cured [19]. The treatment was well tolerated and showed no side effects.

Contrary to our study, a recent prospective study, also in Pakistan, showed a high failure rate of 3 min, 7 continuous days of handheld exothermic crystallization thermotherapy heat pack therapy for CL due to *L. tropica* in 56 patients. They reported a 91% failure rate and suggested that this finding might be due to low heat sensitivity and slower spontaneous healing of *L. tropica* [20]. Goyonlo, et al., showed that all together, from the 53 lesions treated by thermotherapy, a complete response was achieved in 13 lesions (24.5%) [9]. Thirty-one lesions (58.5%) showed a good response and 9 lesions (17%) showed mild or no improvement. In terms of side effects, only mild and transient erythema was seen in four lesions. The remaining 49 lesions (92.45%) did not show any side effects in response to the treatment. The treatment response was not statistically related to sex, age, lesion size, or duration of lesions ($P>0.05$). Although chronic and non-healing forms of Old World CL (OWCL) are most commonly seen in sun-exposed sites of the body and it was expected to find more resistant lesions in these areas, they detected complete/good responses in 46.50% (20 out of 43 lesions) of sun-exposed lesions compared with 30% of lesions (3 out of 10) in sun-protected areas, with Fisher's exact test revealing that this difference was not statistically significant ($P=0.45$). In other words, CL lesions in areas of sun exposure were more responsive to thermotherapy, although the difference was not statistically significant. Dapsone (diaminodiphenyl sulfone) is a very cheap, widely available, and safe antimicrobial agent, which is effective in many dermatoses. In addition to its main use as part of the highly successful multidrug treatment regimen for leprosy, studies from India have shown good efficacy of dapsone in the treatment of CL [21,22]. In agreement with our study, Al-Mutairi, et al. observed a good/ excellent response with dapsone alone in only 48.8% of CL patients, a figure similar to our results [11]. Miranda-Verástegui, et al. and Arevalo, et al., found that dapsone in combination with Imiquimod gave a better response than when either of the modalities was used alone [23,24]. These observations indicate that dapsone, as an immunomodulator, may have a synergistic action with other antileishmanial drugs, as revealed in the successful treatment of New World CL in South America. The concept of combination therapy is recommended for the treatment of CL, similar to the management of other chronic infectious granulomatous diseases, such as leprosy and tuberculosis [25].

Conclusion

Cutaneous Leishmaniasis (CL) is a significant public health problem with an incidence of around 1500,000 cases annually

worldwide. Different sources of heat have been applied in trials for the treatment of CL, including hot water soaks, circulating hot water in heating pads, Infrared (IR) heat, and ultrasonically induced hyperthermia of the skin. A recent trial for CL in Afghanistan compared the efficacy of one session of thermotherapy by radiofrequency with five sessions of intralesional Glucantime injection. In the current study, patients treated with dapsone and radiofrequency cleared CL in 1-2 months more than those treated with cryotherapy or meglumine antimoniate MA alone. Cryotherapy used as monotherapy cured CL in 30 of the 44 patients receiving this mode of therapy. Systemic treatment with oral itraconazole, 100 mg twice daily, alone showed a good to excellent response in seven of the 12 cases. In case of contraindication for classic treatment, other treatment options could be used.

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