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# Comparison between the Efficacy and Safety of Intralesional Sodium Stibogluconate Solution and Intralesional Metronidazole Solution in the Treatment of Cutaneous Leishmaniasis

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**Abstract:** ***Background: Leishmaniasis encompasses a spectrum of chronic infections in humans and several animal species.It is caused by over 20 species of the genus LeishmaniaLeishmania is a flagellated protozoa belonging to the order Kinetoplastidae. The cutaneous leishmaniasis is restricted to the skin and is seen more often in the Old World. Transmission is by the bite of infected female sandfly from the genera Phlebotomus and Lutzomyia. The disease has a worldwide distribution, affecting millions of people in South America, Mediterranean basin, and parts of Asia and Africa. There are four major clinical patterns: (1) Cutaneous: which is restricted to the skin and is seen more often in the Old World. (2) Mucocutaneous: which affects both the skin and mucosal surfaces and occurs almost exclusively in the New World. (3) Diffuse cutaneous: which occurs mainly in the New World. (4) Visceral: which affects the organs of the mononuclear phagocyte system, e.g. liver, spleen. Aim of study: To compare the efficacy and safety of Intralesional sodium stibogluconate and Intralesional metronidazole solution in the treatment of cutaneous leishmaniasis. Patients and methods: This is a therapeutic trial intervention study done in dermatology and venereology teaching department in Rezgari hospital, Erbil / Iraq, during the period from November, 16th 2015 to November, 16th 2016 on convenient sample of 60 patients. Two typical cutaneous leishmaniasis lesions from each patient had been selected, labelled by writing its number, patient's full name, type of treatment (sodium stibogluconate solution or metronidazole solution) on a piece of adhesive plaster and putted above or below the lesion, then the lesions is measured by a ruller and documented and then the lesion is photographed by a Samsung mobile camera and all this data had been documented in a handbook for follow up of patients each week until the end of the period of the study . During each visit the perilesional area of one of the lesion is sterilized by povidone iodine 10% and theno.2ml of sodium stibogluconate solution (pentostam;100 mg/ml)is infiltrated through the surrounding normal skin to the lesion for each 1cm$^2$ area of the lesion ,making a wheal and this procedure repeated to cover the whole lesion and the other labelled lesion is infiltrated by 0.2mlof metronidazole solution (Flagyl;5mg/ml)for each 1cm2area of the lesion and this procedure is repeated until blanching of the whole lesion were occurred. this procedure is done weekly for 4 weeks' duration and during each visit the lesions were measured in size and photographed again and documented. Results: A significant association was observed between lesions treated with sodium stibogluconate solution and complete improvement (p<0.001), while no improvement was significantly reported for lesions treated with metronidazole solution. Both Cutaneous Leishmaniasis lesions treated with metronidazole solution and those treated with sodium stibogluconate solution were significantly reduced in size after four sessions of treatment. There was a significant association between severe pain during treatment in patients treated with sodium stibogluconate solution (p<0.001). Conclusion: The sodium stibogluconate solution has a higher efficacy in treatment of cutaneous leishmaniasis. The metronidazole solution has a lower efficacy in the treatment of cutaneous leishmaniasis. The metronidazole solution has the ability to reduce cutaneous leishmaniasis lesional size. The pain severity score was strongly related to the sodium stibogluconate solution but the side effects were more common with metronidazole solution.***

**List of Abbreviations**

| Abbreviations | Meanings |
|---|---|
| HIV | Human Immunodeficiency Virus |
| CL | Cutaneous Leishmaniasis |
| L | Leishmania |
| IFN | Interferon |
| IL | Interleukin |
| NK | Natural Killer |
| TNF-α | Tumor Necrosis Factor-α |
| PCR | Polymerase Chain Reaction |
| FDA | Food and Drug Administration |
| CDC | Centers for Disease Control and Prevention |
| MCL | Mucocutaneous Leishmaniasis |
| SD | Standard Deviation |
| **SPSS** | **Statistical Package for Social Sciences** |
| USA | United States of America |

# 1. Introduction

## Cutaneous leishmaniasis

### 1.1 Definition

Leishmaniasis encompasses a spectrum of chronic infections in humans and several animal species. It is caused by over 20 species of the genus Leishmania. Leishmania is a flagellated protozoa belonging to the order Kinetoplastidae.

Transmission is by the bite of infected female sandfly from the genera Phlebotomus and Lutzomyia. The disease has a worldwide distribution, affecting millions of people in South America, Mediterranean basin, and parts of Asia and Africa [1].

There are four major clinical patterns:

1) Cutaneous: which is restricted to the skin and is seen more often in the Old World.
2) Mucocutaneous: which affects both the skin and mucosal surfaces and occurs almost exclusively in the New World.
3) Diffuse cutaneous: which occurs mainly in the New World.
4) Visceral: which affects the organs of the mononuclear phagocyte system, e.g. liver, spleen[2, 3].

Worldwide, there are approximately 2 million new cases of leishmaniasis annually, with cutaneous or mucocutaneous disease in >75% of affected individuals and it is estimated that 12 million people are currently infected[3]. Over 90% of cutaneous infections occur in the Middle East (Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria), Brazil and Peru, but the disease is also seen in the Mediterranean basin, sub-Saharan Africa, Central Asia, and India.

South-central Texas is the only endemic area for cutaneous leishmaniasis in the US; most infections diagnosed in the United states are acquired outside of the country[4].Mucocutaneous leishmaniasis is endemic in Central America and northern regions of South America.

Although the visceral form of leishmaniasis has a worldwide distribution, it is seen most frequently in Africa and Asia[1, 2, 5]. Old World cutaneous leishmaniasis is usually due to Leishmania major or leishmania tropica and less often due to Leishmania infantum (Europe) or Leishmania aethiopica (Ethiopia and Kenya).

New World cutaneous leishmaniasis is caused primarily by subspecies of Leishmania Mexicana and mucocutaneous leishmaniasis is caused by Leishmania braziliensis. Diffuse cutaneous leishmaniasis is most commonly caused by Leishmania amazonensis[3].

Visceral leishmaniasis are caused by Leishmania donovani (e.g. in India, Bangladesh and Sudan), Leishmania infantum (e.g. Europe, especially in the setting of HIV infection) and Leishmania chagasi (e.g. in Central and South America).

The species of Leishmania can also vary within a particular geographic region. For example, in the Middle East, Leishmania major is found in rural areas where the primary animal reservoirs are desert rodents, whereas Leishmania tropica is endemic in urban areas[5].Canine and rodent species act as reservoirs for Leishmania.

Transmission between these species (as well as to humans) is via sand flies, primarily of the genera Phlebotomus (Old World) and Lutzomyia (New World). Human-to-human spread of Leishmania tropica can also occur. In general, humans acquire leishmaniasis as accidental hosts when they intrude into the sandfly's habitat. Overall, the disease is seen most commonly in men between 20 and 40 years of age, but Old World cutaneous leishmaniasis occurs more often in children[2].

### 1.2 Pathogenesis of leishmaniasis

Leishmania species are obligate intracellular parasites that exist in two forms: the promastigote and the amastigote. In the gut of the sandfly, the organisms multiply as extracellular flagellated promastigotes. Following migration to the proboscis, the parasites are inoculated (in the promastigote form) via the sandfly bite. Once inoculated into the skin, the parasites are rapidly engulfed by the host's mononuclear phagocytes, where they transform into amastigotes and multiply by binary division.

The incubation period from the bite until the first clinical manifestation can vary from ≤2 weeks (cutaneous lesions; typically, several weeks to 2 months) to more than 2 years (mucocutaneous lesions or visceral involvement; typically, 3 to 9 months)[6].

The clinical manifestations of leishmaniasis primarily depend on the host's cell-mediated immune response and the species of Leishmania involved. A robust Th1 response (i.e. production of interleukin-2[IL-2] and interferon-γ [IFN-γ]) is associated with quicker resolution, whereas a lack of a Th1 response or the development of a Th2 response (i.e. production of IL-4 and IL-10) is associated with progression of the disease[7–9].

Other factors that play a role in the parasite–human interaction include the amount of exposure and the virulence of the parasite (e.g. macrophage-resistant strains of Leishmania).

Mucocutaneous disease is associated with infection of the Leishmania organisms with Leishmania RNA virus-1; this virus is recognized by human Toll-like receptor 3, leading to a proinflammatory cascade that subverts the immune response to Leishmania, leading to persistence of the parasite and disease progression[9a]. IFN-γ is the most potent cytokine involved in the induction of cidal activity against the organisms residing within the macrophage phagolysosomes .It leads to the production of oxygen species and activates naïve CD4+ cells to become Th1 cells, the latter differentiation process is aided by IL-12, which stimulates natural killer (NK) cells to produce IFN-γ[7,9,10].

Tumor necrosis factor-α (TNF-α) is also important for the control of Leishmania infections[8]. It is Produced by macrophages and Natural Killer cells, it amplifies the macrophage activation triggered by IFN-γ. Use of TNF-α

inhibitors increases the risk of developing leishmaniasis, especially the visceral form[11].

Animals that have recovered from Leishmania tropica or Leishmania donovani infections acquire immunity against re-infection from the same species of Leishmania, but not against other species. Similarly, humans with the New World form of cutaneous leishmaniasis have been inoculated successfully with Leishmania tropica. However, it has been reported that surviving an episode of visceral leishmaniasis confers lifelong immunity against all types of leishmaniasis[11].

### 1.3. Clinical Features

#### 1.3.1 Cutaneous leishmaniasis

Cutaneous leishmaniasis is divided into two subsets based on the geographic region where the infection is acquired: Old World and New World.

These two groups differ with regard to the causative organisms, vectors, reservoirs, clinical presentation, and prognosis[3].

Both Old World and New World cutaneous leishmaniasis usually begin as a small, well-circumscribed papule at the inoculation site.This lesion may slowly enlarge over several weeks into a nodule or plaque, and thenbecome ulcerated or verrucous. Exposed sites such as the face, neck, arms, and legs are most commonly involved.

The lesions of leishmaniasis are often solitary but may be multiple, with the formation of satellites or lymphatic spread (sporotrichoid pattern).

The majority of acute cutaneous infections resolve spontaneously within several months with scarring (cicatricial stage), but a minority become chronic or disseminated. Several clinical forms of Old World cutaneous leishmaniasis have been described, including zoonotic, anthroponotic, recidivans, and lupoid leishmaniasis[12].

Zoonotic cutaneous leishmaniasis (rural, moist, or early ulcerative form) usually has a mild, rapid course and is caused by Leishmania major.

Anthroponotic cutaneous leishmaniasis (urban, dry, or late ulcerative form), has a more chronic course and is caused by Leishmania tropica[3].

Leishmaniasis recidivans is a chronic, destructive form that is characterized by recurrence at the site of an original ulcer, generally within 2years and often at the edge of the scar[12].

Anthroponotic or, less frequent, zoonotic cutaneous leishmaniasis occasionally develops into chronic lupoid leishmaniasis, which is clinically and histopathologically (epithelioid granulomas surrounded by lymphocytes) resembles the lupus vulgaris form of cutaneous tuberculosis. The amastigotes are few in number and difficult to be find in lupoid leishmaniasis, making establishment of the diagnosis more challenging.

New World cutaneous leishmaniasis has a wide clinical spectrum, including patterns such as sporotrichoid, pustular, impetigo-like, eczematoid, sarcoidosis-like, erysipeloid, papulotuberous, and verrucous[12].

#### 1.3.2 Diffuse (disseminated) cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis usually develops in the setting of reduced cell-mediated immunity. Leishmania aethiopica (in Africa) and Leishmania amazonensis (in the Americas) are the most common causes. Multiple keloid-like lesions on the face and limbs are usuallyobserved[3]. Nasal infiltration and ulceration may be present, but without destruction of the nasal septum. There may be also laryngeal and pharyngealinvolvement[12].

#### 1.3.3 Mucocutaneous leishmaniasis

After a time period ranging from a few months to more than 20 years, some patients infected with Leishmania species in the Viannia subgenus (most commonly Leishmania braziliensis; and rarely Leishmania panamensis, Leishmania guyanensis or hybrid genotypes) develop mucocutaneous disease[13].Mucosal lesions range from edema of the lips and nose to perforation of the nasal and laryngeal cartilage as well as the palate. Infiltration and/or ulceration of the nose, lips and oropharynx is characteristic. Rarely the ocular or genital mucosa is involved.

In some patients, there is extensive loss of tissue in both the mouth and nose, causing a characteristic “tapir face” known as espundia.Alterations in phonation because of destruction of the vocal cords also may occur[12–14].

#### 1.3.4 Visceral leishmaniasis (kala-azar)

Visceral leishmaniasis, or kala-azar, occurs when the parasite spreads to the bone marrow, spleen, and liver[3].
It is most commonly caused by infection with Leishmania donovani in adults and Leishmania infantum or Leishmania chagasi in children.

The incubation period ranges from 1 to 36 months. Fever, wasting, cough, lymphadenopathy and hepatosplenomegaly are the most common systemic findings.

There may be an abrupt onset or slow progression, and the fever may be continuous or intermittent. complications include enteritis, oronasal or gastrointestinal hemorrhage, pneumonia and nephritis, which may lead todeath[12].

Cutaneous findings may be disease-specific (e.g. papules, nodules or ulcers at infected sites) or nonspecific (e.g. purpura, hyperpigmentation, xerosis and kwashiorkor-like hair discoloration).

#### 1.3.5 Post-kala-azar dermal leishmaniasis:

Develops as sequelae of untreated or treated visceral leishmaniasis[3]. This form of cutaneous leishmaniasis is most commonly seen in Sudan and India, where it occurs in 50% and 10% of patients cured of visceral leishmaniasis, respectively[15].The onset can be during treatment or up to 20 years after treatment[15].

Skin findings can include hypopigmented macules, malar erythema, skin-colored nodules and verrucous papules[16].

### 1.4 Pathology

Histologically, cutaneous lesions show areas of ulceration, pseudoepitheliomatous hyperplasia and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, plasma cells and neutrophils. Amastigotes are present within dermal macrophages.

Overtime, lesions develop an increase in the number of giant cells and a decline in the number of parasites; in chronic cutaneous leishmaniasis, Caseous necrosis may be observed[14].

In the scarring stage, the epidermis becomes flattened and hyperpigmented in areas with dermal fibrosis. Identical changes are seen in mucosal lesions.

The parasites can also be detected in the lymph nodes, bone marrow and spleen in patients with visceral leishmaniasis.

### 1.5 Diagnosis

The diagnosis of cutaneous leishmaniasis can be confirmed by Demonstrating the presence of amastigotes within the dermal macrophages in the skin biopsy specimens, tissue impression smears (touch preparations), and smears of dermal scrapings[2, 12, 17]. Giemsa stain, Wright stain or Feulgen stains are used to identify the organisms in the smears and tissue.

The cytoplasm appears blue, the nucleus pink and the kinetoplast has a deep red[12]. The edge of a relatively new ulcer is the location of choice for obtaining dermal scrapings, biopsy specimen or a needle aspirate; the latter two types of samples may be used for culture and polymerase chain reaction(PCR)-based assays[3,17]. In longer standing lesions of cutaneous leishmaniasis, parasites may be scarce. In this context, the delayed skin reaction test (Montenegro skin test or Leishman reaction), which uses leishmanial antigens to induce a cell mediated response, has traditionally been an important diagnostic tool.

A phenolated suspension of killed promastigotes is injected intradermally, usually on the volar aspect of the forearm. The test is considered positive if a papule >5 mm in diameter forms at the site of inoculation after 48–72 hours [12]. It is positive in up to 90% of patients with cutaneous and mucocutaneous leishmaniasis of over 3month's duration[3] and is invariably negative in patients with diffuse cutaneous (anergic) leishmaniasis[12]. However, the test (which is not approved by the USA Food and Drug Administration [FDA]) cannot distinguish between past and present infections; positivity appears while the skin lesions are still active, and the test remains positive long after spontaneous cure.

The test is usually negative during the febrile phase of visceral leishmaniasis, but it often becomes positive after cure.

For culturing Leishmania, specialized media are required, e.g. Nicolle–Novy–MacNeal media or chick embryo media. Cultures are positive in approximately 40% of cases. Serologic and immunologic tests are also available, e.g. indirect immunofluorescence, ELISA, immunoprecipitation and isoenzyme electrophoresis.

Serologic testing is most useful for visceral (and occasionally mucocutaneous) disease. although it is not specific due to cross-reactivity (e.g. with Chagas disease antibodies) [18].

PCR-based methods represent the most sensitive and specific diagnostic tests, and their availability is increasing[2,12]. The USA FDA recently approved a real-time PCR assay for the diagnosis of leishmaniasis, and it is available through the Centers for Disease Control and Prevention (CDC) [17].

### 1.6. Treatment

Factors to be considered when planning the treatment of leishmaniasis include[19]:

The region of the world in which the infection was acquired, species of Leishmania, the site(s) and severity of the infection, host factors such as immune status and age, and risks and benefits of therapy need to be balanced, with goals of maximizing effectiveness while minimizing drug toxicity.

Without treatment, Old World cutaneous leishmaniasis typically resolves within 2–4 months (Leishmania major) or 6–15 months (Leishmania tropica).

New World cutaneous leishmaniasis caused by Leishmania Mexicana resolves within 3 months in >75% of cases. In contrast,cutaneous diseasecaused by Braziliensis and Leishmania panamensis spontaneously heals in less than 10% and 35% of cases, respectively.

Indications for treatment of cutaneous leishmaniasis include: Persistence for >6 months, Presence of multiple (≥5–10) or large (≥4–5 cm) lesions[19, 20], location over a joint, decrease scarring (especially important for lesions in the cosmetically sensitive sites), accelerate healing and prevent dissemination or relapse.

**a) Local therapy**

Is appropriate for small, non-inflamed and localized lesions that are not at risk of progression to Mucocutaneous leishmaniasis: it include; Intralesional antimonialcombined with cryotherapy[35], intralesional metronidazole[47], hypertonic sodium chloride[42]. topical or intralesional zinc sulfate [11], Intralesional interferon-γ [11]. Cryotherapy [22], thermotherapy [23], electrotherapy [24], photodynamic therapy [25], Paromomycin ointment[26, 31, 36]alone or combined with 12% methylbenzethonium chloride[26], Topical azoles[38], Topical glyceryl trinitrate[41], Topical Imiquimod alone is ineffective [44], Excision/curettage or laser ablation [21]and Others like ethanolic formulation of amphotericin B[39, 40].

**b) Systemic therapy**

Is used for complicated cutaneous leishmaniasis[41] such as: Diffuse cutaneous leishmaniasis, Chronic cutaneous leishmaniasis, Mucocutaneous leishmaniasis, Visceral

leishmaniasis, relapsing disease and disease complicated by HIV coinfection.

Systemic drugs used in leishmaniasis include[53]:

**Pentavalent antimonials**: **sodium stibogluconate** (Pentostam) and **meglumine antimoniate** (Glucantime):
DOSE: 20 mg/kg/day for 20–30days.IM/IV. Mechanism of Action: Inhibition of glycolysis and oxidation of fatty acids of the parasite.

Indications[43, 44]: Complicated Old World-Localized cutaneous leishmaniasis, New World-Localized cutaneous leishmaniasis, Potential of mucosal dissemination, diffuse cutaneous leishmaniasis, Mucocutaneous leishmaniasis and Visceral leishmaniasis.

Effectiveness[45]: Superior to all other drugs except Pentamidine in New World-Localized Cutaneous Leishmania, Cure rate variable depending on species and disease: ranges from 35%–95% and high treatment failure in India and Iran.

Adverse Effects: Dose dependent and resolve after discontinuation of the drug. Include;Pain at the injection site, Myalgias (68%), Pancreatitis (18%), Hepatitis, bone Marrow suppression, QT prolongation, fatigue, headache, rash, and nausea.

**Pentamidine[52]:**
DOSE: 2–4 mg/kg/day IV or IM or every other day for 4–7days.
Mechanism of Action: Not established yet.

Indications: New world –localized cutaneous leishmaniasis in French, Guyana (first-line treatment) Mucocutaneous leishmaniasis.

Effectiveness: Superior to all other drugs in NW-LCL.
Adverse Effects: Risk of diabetes mellitus in high dose course, Nephrotoxicity, hypotension, Arrhythmias, Nausea, vomiting, diarrhea, pancytopenia, cough, bronchospasm, confusion, and hallucinations.

**Amphotericin B[47]:**
DOSE: 1 mg/kg IV every other day for up to 30 days.
Mechanism of Action: is by binding to the sterol present in the parasite's plasma membrane, causing a change in the permeability of the membrane.
Indications: Second-line therapy when other lines of treatments fail in LCL, MCL.
Effectiveness: > 97% efficacy for Visceral Leishmaniasis in all regions.
Adverse effects: Hyperpyrexia, hypotension, thrombophlebitis, renal complications, anemia, and hepatitis.

**Liposomal amphotericin B[48]**:
DOSE: 3 mg/kg/day IV for 5 days, then on day 10.
Mechanism of Action: is by binding to the sterols present in the parasite's membrane causing a change in the permeability of the membrane.
Indications: Visceral leishmaniasis, not yet studied for localized cutaneous leishmaniasis.
Effectiveness:100% cure rate against Leishmania braziliensis, Single dose (10 mg/kg) as efficacious as conventional Amphotericin B (1 mg/kg every other day for 15doses) for Visceral Leishmaniasis in India.
Adverse Effects: Less renal toxicity than amphotericin B.

**Imidazoles[49]:**
Fluconazole 200 mg/day orally for 42 days.
Itraconazole 200 mg/day orally for 6 weeks.
Ketoconazole 600 mg/day orally for 28–30 days.
Mechanism of Action: Inhibition of demethylation of lanosterol, blockingergosterol synthesis.
Indications: Localized cutaneous leishmaniasis.

Effectiveness:Oral fluconazole: effective against Leishmania major, Oral itraconazole: good efficacy against Leishmania tropica, Oral ketoconazole: 89% efficacy against both L. major and L. tropica, and 76% against Leishmania panamensis.
Adverse Effects: No significant side effects, hepatotoxicity.

**Miltefosine[50]:**
DOSE: 2.5 mg/kg/day orally for 28 days.
Mechanism of Action: Inhibits phosphatidylcholine biosynthesis in the parasites.
Indications: Visceral Leishmaniasis (Indian), Localized cutaneous leishmaniasis and Paromomycin sulfate:
DOSE: 15 mg/kg IM daily for 21 days.
Mechanism of Action: Inhibition of protein synthesis.
Indications: Indian Visceral Leishmaniasis.
Effectiveness: 94% efficacy in Indian Visceral Leishmaniasis, 2.59% efficacy against L. braziliensis and L. Mexicana, under investigation for Visceral Leishmaniasis in Africa.
Adverse Effects: Rarely; hepatotoxic, nephrotoxic and ototoxic.

**Zinc sulfate[51]**:
DOSE: 2.5–10 mg/kg/day orally for30–40 days.
Mechanism of Action: Boosting of Th1 reaction as well as phagocytosis of Parasites.
Indications: Localized Cutaneous Leishmaniasis.
Effectiveness: 84%–97% efficacy against L. major or L. tropica.

**Pentoxifylline[52]**:
DOSE: 400 mg 2–3 times/day orally (with pentavalent antimony).
Mechanism of Action: Inhibits TNF-α.
Indications: mucocutaneous leishmaniasis, Localized Cutaneous Leishmaniasis.

Effectiveness:
Reduces healing time as well as need for second course of pentavalent antimony, effective for Mucocutaneous leishmaniasis patients' resistant to pentavalent antimony, can prevent renal function alterations induced by meglumine antimonate in rats.

Adverse Effects: No significant side effects is related to pentoxifylline.

**Other reported systemic therapies:**
Terbinafine[46], Metronidazole[54, 55], Dapsone[56, 57], interferon-γ [58]. Allopurinol [52,55], Trimethoprim-sulfamethoxazole [57], Rifampin[58], Nifurtimox[59,60], Quinolones[61], Pyrimethamine[62], Anti-interleukin-10 (experimentally lead to sterile cure)and Azithromycin[63].

**Aim of the study**

The aim of the study is to compare the efficacy and safety of Intralesional sodium stibogluconate (Pentostam® 100mg/ml) and Intralesional metronidazole (flagyl; 5 mg /ml) solution in the treatment of cutaneous leishmaniasis (CL).

## 2. Patients and Methods

This is a therapeutic trial interventional study done in Dermatology and venereology teaching department in Rezgari hospital, Erbil / Iraq, during the period from November, 16th 2015 to November, 16th 2016.

A Total of 60 patients (36 males and 24 females), their ages ranged from 2 to 45 years (mean age: 32.9 years old, SD ±15.6) with typical two or more lesions of cutaneous leishmaniasis have been included in this study.

Patients with the following criteria were excluded from this study:

Lesions of more than 12 weeks' duration were excluded due to the possibility of self-healing, Lesions with surface area more than 10 $cm^2$ or lesions close to the eyes, Patients who received local or systemic anti-Leishmanial treatment during the last 6 weeks, Pregnancy, Chronic diseases like Diabetes mellitus, peripheral neuropathy, poor peripheral circulation and Prolonged corticosteroid therapy.

A history was taken from each patient regarding the followings:
Age, gender, Occupation, Nationality, Address, Refuge history, Duration of the lesions, Recurrence of the lesion, history of previous therapy, Past medical history, Past drug history, Obstetric history in females in the reproductive period and Family history.

- A Close physical examination was performed for each patient regarding the: Type of lesion(s), Number, Size, Site and Regional lymphadenopathy.
- After full interrogation and explanation to each patient about the nature of the disease including its course and prognosis, treatment modalities and their complications, the formal consent was taken from each patient.
- In All 60 patients, the diagnosis of cutaneous leishmaniasis were made on the clinical base of an a typical, non-healing, indurated papule, nodule, or plaque…. etc. with or without crusting in patients coming from geographic areas previously delineated as endemic areas of leishmaniasis.

For this study ,Two typical cutaneous leishmaniasis lesions from each patient had been selected,labelled by writing its number, patients full name , type of treatment (sodium stibogluconate solution (pentostam 100 mg/ml)or metronidazole solution (5mg/ml) on a piece of adhesive plaster and putted above or below the lesion , then the lesions is measured by a ruller and documented and then the lesion is photographed by a Samsung mobile camera and all this data had been documented in a handbook for follow up of patients each week until the end of the period of the study . During each visit the perilesional area of one of the lesion is sterilized by povidone iodine 10% and theno.2ml of sodium stibogluconate solution (pentostam;100 mg/ml)is infiltrated through the surrounding normal skin to the lesion for each $1cm^2$ area of the lesion ,making a wheal and this procedure repeated to cover the whole lesion and the other labelled lesion is infiltrated by 0.2mlof metronidazole solution (Flagyl;5mg/ml)for each $1cm^2$area of the lesion and this procedure is repeated until blanching of the whole lesion were occurred.

This procedure is done weekly for 4 weeks' duration and during each visit the lesions were measured in size and photographed again and documented.
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At the end of 4th week, the response to therapy was graded according to the fallowing scale:
1)… **Complete improvement** (full re-epithelialization of the lesions).
2)… **Partial improvement** (Decrease in induration size between 50% and 75%).
3)…**No improvement** (Decrease in induration size < 25%).
During follow up we evaluate side effects of the two treatment options like Pain, Bleeding, edema, blistering, excessive granulation, infection, hyperpigmentation, hypopigmentation, atrophy, hypertrophic scar, milia, alopecia, altered sensation, vasovagal syncope and ulceration.

**Statistical Analysis**

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 17 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables and Fissures. Exact test was used when expected variables were less than 20%. ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist.

## 3. Results

### 3.1. Sociodemographic characteristics of patients

The Mean age of Cutaneous Leishmaniasis patients was 32.9±15.6 years; 33.4% of them were aging ≥40 years and 6.7% of them were children. Males were more than females with male to female ratio as 1.5:1. Urban residents constituted 53.3% of Cutaneous Leishmaniasis patients and

46.7% of them were rural residents. Public servants represent 40% of Cutaneous Leishmaniasis patients and housewives represented 35% of them. All these findings were shown in Table 1 and figures 1, 2

**Table 1:** Sociodemographic characteristics of patients

| Variable | No. | % |
|---|---|---|
| **Age** mean±SD (32.9±15.6 years) | | |
| <10 years | 4 | 6.7 |
| 10-19 years | 8 | 13.3 |
| 20-29 years | 11 | 18.3 |
| 30-39 years | 17 | 28.3 |
| ≥40 years | 20 | 33.4 |
| Total | 60 | 100.0 |
| **Gender** | | |
| Male | 36 | 60.0 |
| Female | 24 | 40.0 |
| Total | 60 | 100.0 |
| **Residence** | | |
| Urban | 32 | 53.3 |
| Rural | 28 | 46.7 |
| Total | 60 | 100.0 |
| **Occupation** | | |
| Child | 2 | 3.3 |
| Student | 8 | 13.3 |
| Housewife | 21 | 35.0 |
| Self employed | 4 | 6.7 |
| Public servant | 24 | 40.0 |
| Retired | 1 | 1.7 |
| Total | 60 | 100.0 |

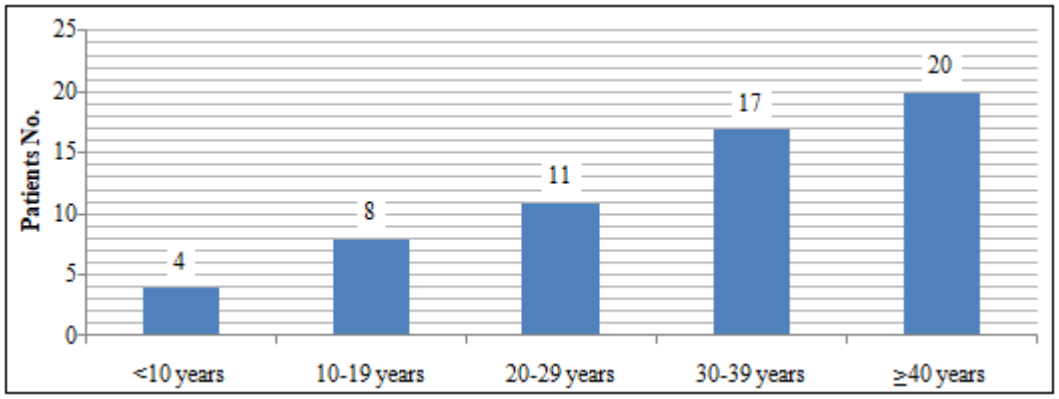



**Figure 1:** Age distribution

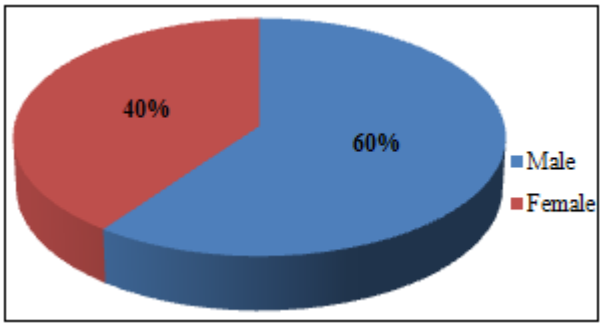



**Figure 2:** Gender distribution

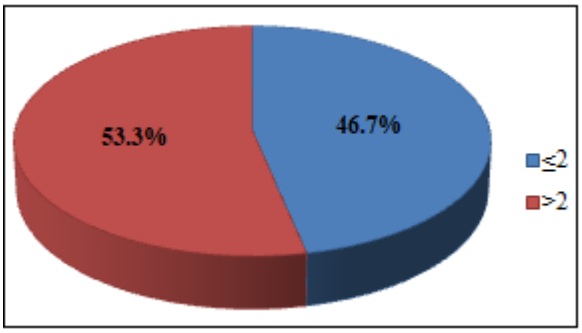



**Figure 3:** lesions number distribution

### 3.2 Cutaneoonsus Leishmaniasis characteristics

Mean Cutaneous Leishmaniasis lesions number was 3±2; 53.3% of patients had more than two lesions and Mean Cutaneous lesion's duration was 2.9±2.1 months; 53.3% of patients had lesion's duration of ≤2 months, this feature is shown in Table 2 and figure 3, 4.

**Table 2:** Cutaneous Leishmaniasis lesions number and duration

| Variable | No. | % |
|---|---|---|
| **Cutaneous Leishmaniasis lesions number** mean±SD (3±2) | | |
| ≤2 | 28 | 46.7 |
| >2 | 32 | 53.3 |
| Total | 60 | 100 |
| **Cutaneous Leishmaniasis lesions duration** (2.9±2.1months) | | |
| ≤2 months | 32 | 53.3 |
| >2 months | 28 | 46.7 |
| Total | 60 | 100 |

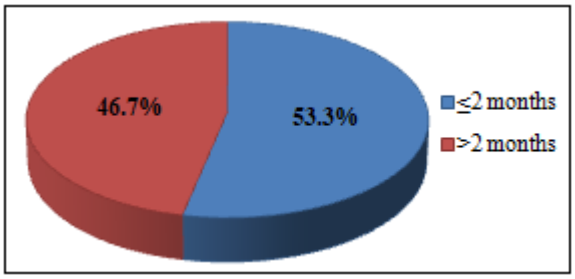



**Figure 4:** lesions duration distribution

The Prevalent lesion types among studied patients were: plague (27.5%), papular (16.7%), ulcerative (15.8%), nodulo-ulcerative (15%) and nodular (15%). The prevalent lesion sites among Cutaneous Leishmaniasis patients was:

Head and neck (33.3%), upper limbs (29.2%), lower limbs (17.5%), multiple sites (11.7%), Trunk (8.3%). This features are shown in Table 3 and figures 5, 6

**Table 3:** Lesion types and sites

| Variable | No. | % |
|---|---|---|
| **Lesion types** | | |
| Plaque | 33 | 27.5 |
| Papular | 20 | 16.7 |
| Ulcerative | 19 | 15.8 |
| Nodulo-ulcerative | 18 | 15 |
| Nodular | 18 | 15 |
| Impetiginous | 3 | 2.5 |
| Nodular+lymphangitis | 3 | 2.5 |
| Sporotichoid | 3 | 2.5 |
| Papular+lymphangitis | 3 | 2.5 |
| Total | 120 | 100 |
| Lesion sites | | |
| Head and neck | 40 | 33.3 |
| Upper limbs | 35 | 29.2 |
| Lower limbs | 21 | 17.5 |
| Multiple sites | 14 | 11.7 |
| Trunk | 10 | 8.3 |
| Total | 120 | 100 |

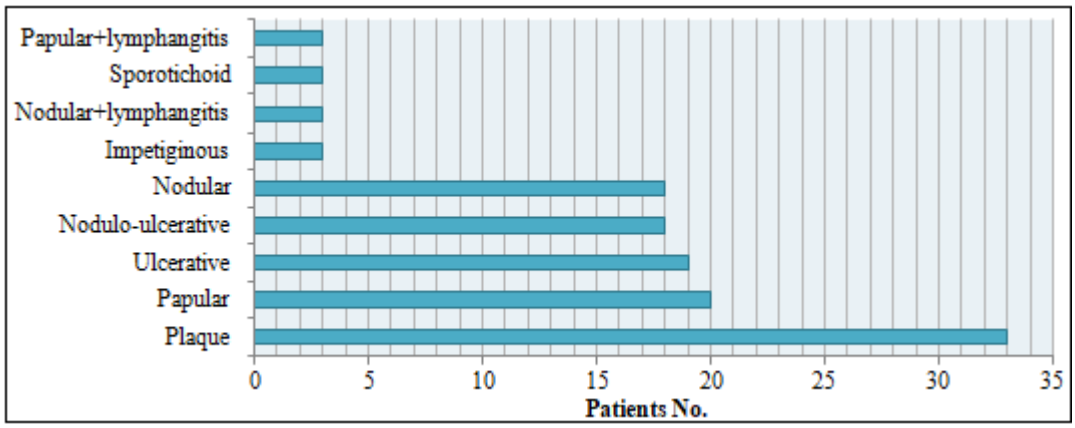



**Figure 5:** Lesion types distribution

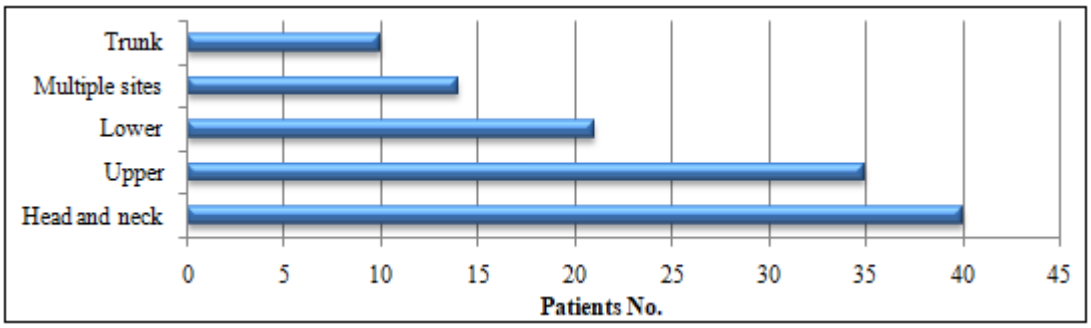



**Figure 6:** Lesion sites distribution

### 3.3 Treatment history & outcome of treated patients

#### 3.3.1. History

A Total of 60 patients with Cutaneous Leishmaniasis (CL) were included in this study and completed their management and follow up. Treatment history for Cutaneous Leishmaniasis were negative for all studied patients. sodium stibogluconate solution (Pentostam;100mg/ml) was used for treatment of 60 lesions of 60 patients with cutaneous leishmaniasis and metronidazole solution (flagyl;5mg/ml) was used for the treatment of another 60 lesions of the same patients. All these findings were shown in Table 4.

**Table 4:** previous treatment history and Present Treatment models of patients with cutaneous leishmania

| Variable | No. | % |
|---|---|---|
| **Previous Treatment history** | | |
| No | 60 | 100 |
| Total | 60 | 100 |
| **Present Treatment model of Cutaneous Leishmaniasis lesions** | | |
| Sodium stibogluconate | 60 | 100 |
| Metronidazole | 60 | 100 |
| Total | 120 | 100 |

The complete follow up and 4 session's management with sodium stibogluconate solution revealed that 52 of Cutaneous Leishmaniasis lesions had complete clearance of lesions and 8 lesions had partial improvement and no lesions

with failure of treatment. The Cutaneous lesions treated with metronidazole solution had complete improvement for 32 Cutaneous Leishmaniasis lesions, partial improvement for 19 lesions and no improvement for 9 lesions. All these findings were shown in Table 5 and figures 7, 8.

**Table 5:** Treatment outcome of cutaneous leishmania patients

| Variable | No. | % |
|---|---|---|
| **Outcome of treatment with sodium stibogluconate solution** | | |
| Complete improvement | 52 | 86.7 |
| Partial improvement | 8 | 13.3 |
| No improvement | 0 | - |
| Total | 60 | 100 |
| **Outcome of treatment with metronidazole solution** | | |
| Complete improvement | 32 | 53.3 |
| Partial improvement | 19 | 31.7 |
| No improvement | 9 | 15 |
| Total | 60 | 100 |

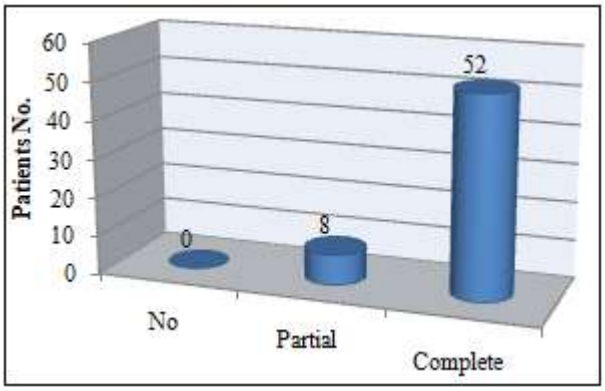



**Figure 7:** Treatment outcome of sodium stibogluconate solution

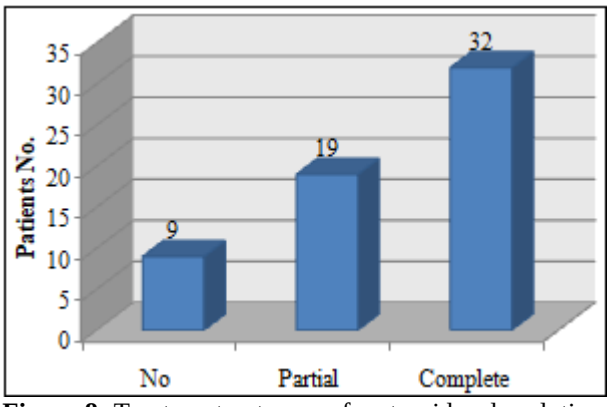



**Figure 8:** Treatment outcome of metronidazole solution

### 3.3.2. Outcome

A significant association was observed between lesions treated with sodium stibogluconate solution and complete improvement ($p<0.001$), while no improvement was significantly reported for lesions treated with metronidazole solution. Table 6 and figure 9.

**Table 6:** Distribution of Treatment outcome by metronidazole solution and sodium stibogluconate solution

| Outcome | Metronidazole | | Sodium stibogluconate | | $\chi^2$ | P |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Complete improvement | 32 | 53.3 | 52 | 86.7 | 18.4 | <0.001 S |
| Partial improvement | 19 | 31.7 | 8 | 13.3 | | |
| No improvement | 9 | 15 | 0 | - | | |

*S: Significant.

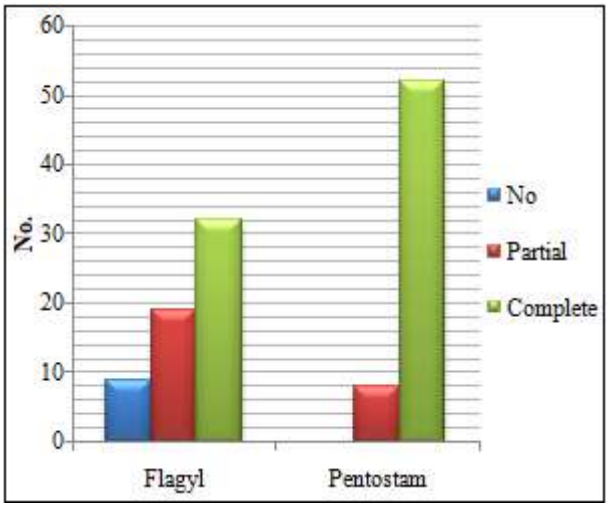



**Figure 9:** Treatment outcome for metronidazole and sodium stibogluconate solution.

### 3.4. Sizes of cutaneous leishmaniasis lesions during treatment period

### 3.4.1. Characteristics

The Mean size of Cutaneous Lesions treated with metronidazole solution at first week was 5.2±4.1cm$^2$, while at 4$^{th}$ week the mean size of Cutaneous Lesion treated with metronidazole was 2.1±1.1cm$^2$.

The Mean sizes of Cutaneous Lesions treated with sodium stibogluconate solution at first week was 5.2±4.1 cm$^2$, while at 4$^{th}$ week the mean sizes of Cutaneous Lesions treated with sodium stibogluconate was 1.7±0.4cm$^2$. This feature is shown in Table 7.

**Table 7:** Mean sizes of cutaneous lesions treated by both treatments at 1$^{th}$, 2$^{th}$,3$^{th}$ and 4$^{th}$ weeks.

| Variable | Mean | SD |
|---|---|---|
| Mean Lesion's size treated with metronidazole solution (cm$^2$) at | | |
| 1$^{st}$ week | 5.2 | 4.1 |
| 2$^{nd}$ week | 4.3 | 2.2 |
| 3$^{rd}$ week | 3.1 | 1.5 |
| 4$^{th}$ week | 2.1 | 1.1 |
| Mean lesion's size treated with sodium stibogluconate solution(cm$^2$) at : | | |
| 1$^{st}$ week | 5.2 | 4.1 |
| 2$^{nd}$ week | 3.5 | 2.3 |
| 3$^{rd}$ week | 2.8 | 1.2 |
| 4$^{th}$ week | 1.7 | 0.4 |

### 3.4.2. Comparison of both treatment models regarding Cutaneous Leishmaniasis mean lesion's size at the different 4 sessions

Both Cutaneous Leishmaniasis lesions treated with metronidazole solution and those treated with sodium stibogluconate solution were significantly reduced in size after four sessions of treatment. This features are shown in Table 8 and figure 10.

**Table 8:** Distribution of Cutaneous Leishmaniasis mean lesion's size treated with metronidazole solution and those treated with sodium stibogluconate solution according to sessions.

| Session | Lesion size | |
|---|---|---|
| | Metronidazole | Sodium stibogluconate |
| | Mean±SD | Mean±SD |
| 1st week | 5.2±4.1 | 5.2±4.1 |
| 2nd week | 4.3±2.2 | 3.5±2.3 |
| 3rd week | 3.1±1.5 | 2.8±1.2 |
| 4th week | 2.1±1.1 | 1.7±0.4 |
| ANOVA (P value) | 0.003 | <0.001 |

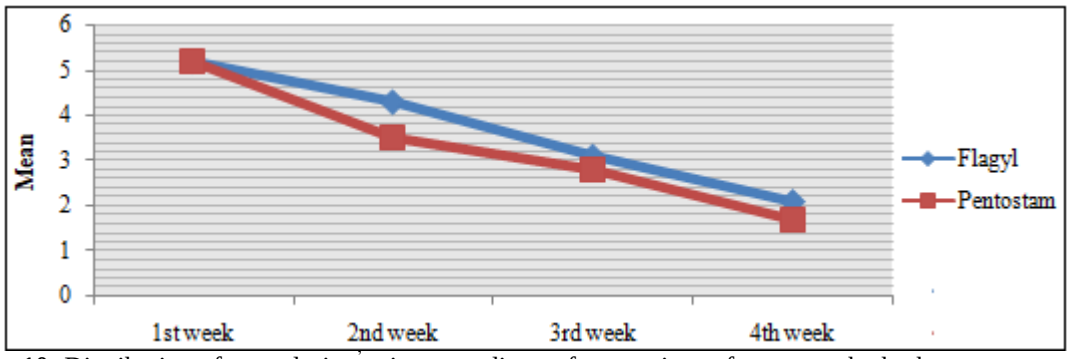



**Figure 10:** Distribution of mean lesion's size according to four sessions of treatment by both treatment models.

### 3.5.1. Pain outcome

There was a significant association between severe pain during treatment in patients treated with sodium stibogluconate solution (p<0.001). This feature is shown in Table 9 and figure 11.

**Table 9:** Distribution of pain scales according to treatment models

| Variable | Metronidazole | | Sodium stibogluconate | | $\chi^2$ | P |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Pain | | | | | 15.7 | <0.001 |
| Mild | 5 | 8.3 | 0 | - | | |
| Moderate | 35 | 58.3 | 20 | 33.3 | | |
| Severe | 20 | 33.4 | 40 | 66.7 | | |

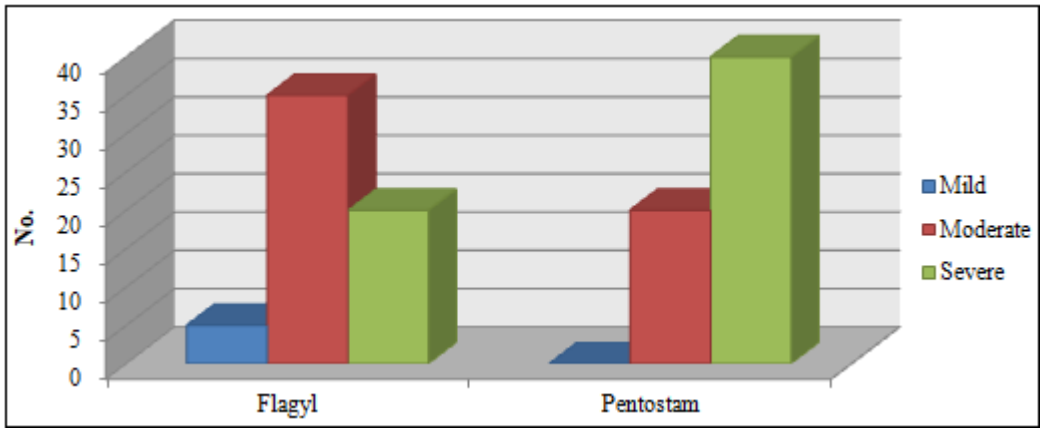



**Figure 11:** Distribution of pain according to treatment type

### 3.5.2. Pain scores outcome

A significant association was observed between high pain score during treatment by Sodium stibogluconate solution (p<0.001). This feature is shown in Table 10.

**Table 10:** Distribution of pain scores according to treatment models

| Treatment models | Pain scores |
|---|---|
| | Mean±SD |
| Sodium stibogluconate | 7.7±0.9 |
| Metronidazole | 4.2±0.8 |
| t-test (P value) | <0.001 |

### 3.6. Treatment complications

The main side effects reported in patients treated with sodium stibogluconate solution were severe pain and hyperpigmentation, While The side effects reported for patients treated with metronidazole solution were severe pain, failure of treatment, hyperpigmentation, scarring and recurrences of the lesions. All these findings were shown in Table 11.

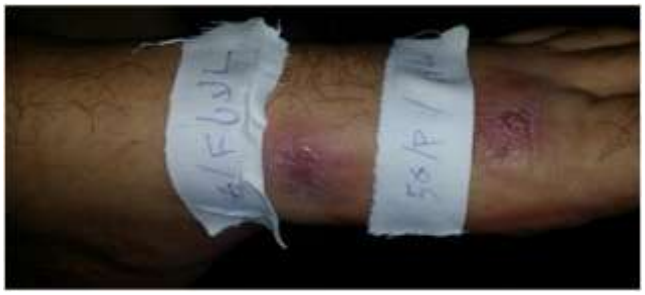
**Table 11:** Complications of both treatment models

| Complications | Metronidazole | | Sodium stibogluconate | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Severe pain | 20 | 57.2 | 40 | 95.2 |
| Failure of treatment | 9 | 25.8 | 0 | - |
| Hyperpigmentation | 4 | 11.4 | 2 | 4.8 |
| Scarring | 1 | 2.8 | 0 | - |
| Recurrences | 1 | 2.8 | 0 | - |
| Total | 35 | 100 | 42 | 100 |

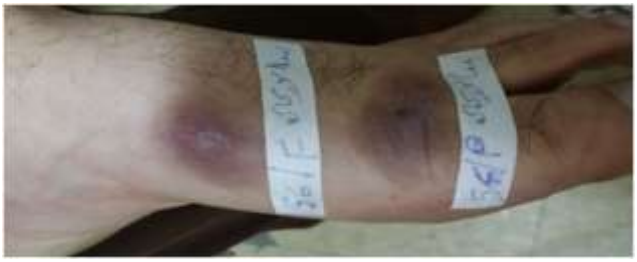

**A**


**B**

**Figure 12 :** A. Metronidazole (flagyl) solution . B. Sodium stibogluconate (pentostam) solution used in this study.

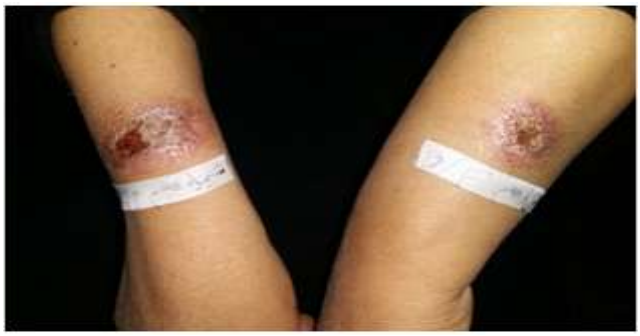


A

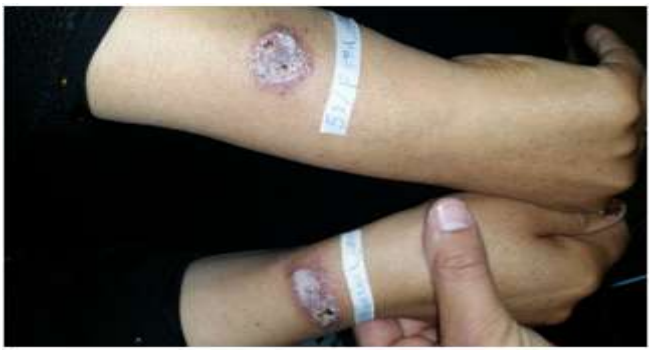


B

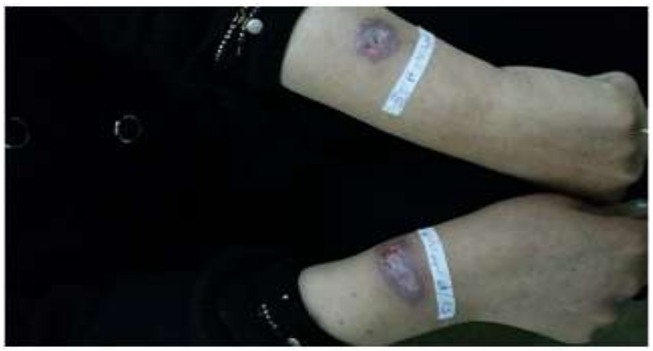
**Figure 13:** Two Cutaneous Leishmaniasis lesions, one treated with sodium stibogluconate and the other with metronidazole. A. before treatment. B. At 4$^{th}$week of treatment.



A

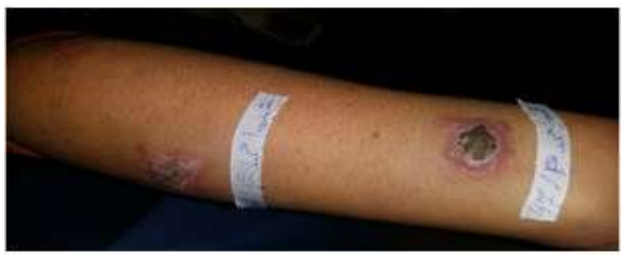


B

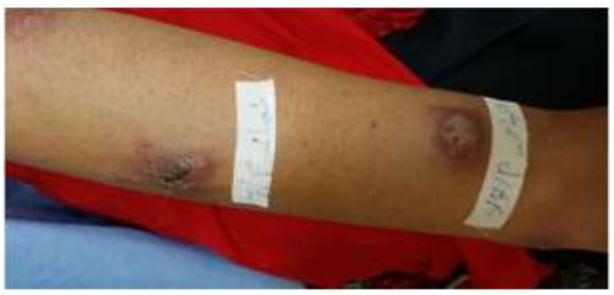


C

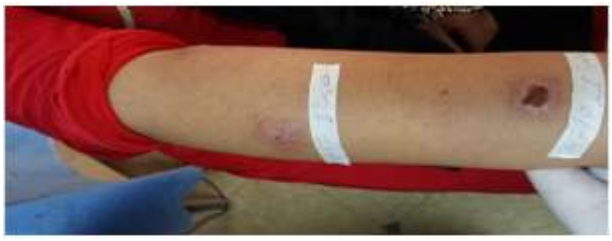
**Figure 14:** Response of both treatment models at A. before treatment. B.2$^{nd}$ week and C.4$^{th}$ week of treatment.



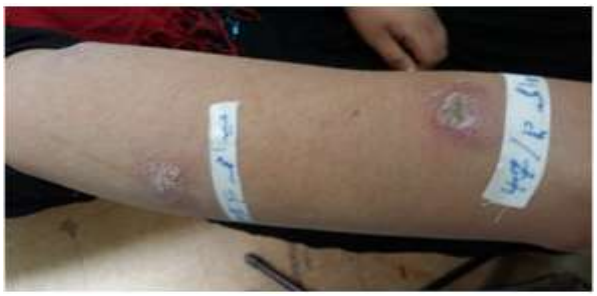
A



B



C



D

**Figure 15:** Response to both treatment options: A. before treatment. B. at 2nd week. C. at 3rd week and D. at 4th week.

## 4. Discussion

Cutaneous Leishmaniasis is not a severe disease; however, it may be hardly tolerated by patients because of three reasons:

First: its particular localization in uncovered areas which makes an aesthetic bother for the patient especially when it lies on the face.

Second: its spontaneous evolution is long (some lesions may require years to heal). Finally: an aesthetic scar that may be caused by the disease particularly if it was not well treated.

For these reasons, therapeutic abstention is rarely admitted, despite the high rate of spontaneous recovery specially noted with Old World Cutaneous Leishmaniasis[66].

In the present study, Cutaneous Leishmaniasis treated with sodium stibogluconate solution had significantly higher efficacy in improvement (86.7%) in comparison to patients treated with metronidazole solution (53.3%) ($p<0.001$). This finding is consistent with the results of Kellapatha et al [67] study in Sri Lanka which reported that the standard treatment of sodium stibogluconate solution shows superior efficacy to metronidazole in treating Cutaneous Leishmaniasis.

Sharquie et al [68] study in Iraq recommended intralesional sodium stibogluconate solution as a safe and effective method of treating acute cutaneous leishmaniasis. Pentavalent antimony compounds, 'the best drug of a bad bunch' still remain the mainstay of treatment in the majority of cases.

However, these have the disadvantage of both toxicity and clinical resistance in at least 40% of cases in certain regions.

Physical methods to control transmission of Cutaneous Leishmaniasis as a preventive measure have also been tried with some success[73].

For simple lesions which are few in number and where there is no risk of disfigurement or joint mobility restriction, the treatment option; parenteral antimony compounds, because of their unwanted side effects, inconvenience and cost, are not recommended.

Topical application or local treatment of cutaneous lesions, therefore, would be a valuable option. Local therapy is of value because it is simple to administer and less toxic than systemic ones[74].

Although there is a significant efficacy of sodium stibogluconate solution in comparison to metronidazole solution, 53.3% of patients treated with metronidazole solution in current study had complete improvement, 31.7% of them had partial improvement and only 15% of them had no improvement.

These findings are similar to the results of Mapar et al [74] study in Iran which stated that intralesional metronidazole injections have little effect for the treatment of cutaneous leishmaniasis.

Metronidazole was discovered in France in 1957 and became the drug of choice for treatment of trichomoniasis. It was subsequently proven to be effective for both amebiasis and giardiasis[75] and for cutaneous leishmaniasis; however, in further studies its efficacy in cutaneous leishmaniasis was not proved[76]. So the effectiveness of oral metronidazole for the treatment of cutaneous leishmaniasis remains controversial[77].

Our study revealed that Cutaneous Leishmaniasis lesion size was significantly reduced after four sessions of treatment with either sodium stibogluconate solution or metronidazole solution, but the reduction of lesion size was higher for patients treated with sodium stibogluconate solution. This is consistent with the results of Masmoudi et al [76] study in Tunisia.

Many studies have shown that metronidazole solution may be considered as a therapeutic alternative against Old World Cutaneous Leishmaniasis leading to 66% recovery [77, 78]. Considering the self-limiting aspect of Leishmania tropica and Leishmania major, such low rate may not be significant and there is a need for more controlled studies to confirm the real contribution of metronidazole solution in Cutaneous Leishmaniasis healing [67].

The common complications reported in the present study for Cutaneous Leishmaniasis patients treated with sodium stibogluconate solution were severe pain and hyperpigmentation and pain score was significantly higher for patients treated with sodium stibogluconate ($p<0.001$). This is similar to the results of Oliveira et al study in Brazil [78]. However, there are concerns about their cost, toxicity and the development of drug resistance.

Parenteral antimonial drugs are associated with severe adverse effects, including nausea, vomiting, diarrhea, skin eruptions, dizziness, cardiac arrhythmia, hypotension, arthralgia, myalgia, abdominal discomfort, headache and

reversible elevation of hepatocellular enzymes, occasional anemia and thrombocytopenia which are often dose-dependent. Pain at the site of the injection was greater when administered Intralesionally than IV/IM [80].

While there is no general agreement on optimum treatment, alternatives to the systemic antimonials are under active investigation. Combination therapies may also help to reduce the drug resistance [30].

For Cutaneous Leishmaniasis patients treated with metronidazole solution, the complications reported by our study were pain, hyperpigmentation, scarring, failure of treatment and recurrences. Mapar et al [74] reported a very painful pain at site of metronidazole injection in addition to failure of treatment and recurrences.

## 5. Conclusions

The sodium stibogluconate solution has a higher efficacy in the treatment of cutaneous leishmaniasis. The metronidazole solution has a lower efficacy in the treatment of cutaneous leishmaniasis. The metronidazole solution has the ability to reduce cutaneous leishmaniasis lesional size. The pain severity score was strongly related to the sodium stibogluconate solution but the side effects were more common with metronidazole solution.

## 6. Recommendations

Ensuring the availability and use of sodium stibogluconate solution as the first choice for the treatment of cutaneous leishmaniasis, encouraging the use of metronidazole solution as an alternative treatment of cutaneous leishmaniasis especially with sodium stibogluconate solution deprivation due to cost reasons and Further national multi-center studies on the efficacy of sodium stibogluconate solution and its alternatives must be supported.

## 7. Acknowledgement

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