# Treatment, prevention and control of leishmaniasis in Sri Lanka

E S N Samaraweera[1]

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## Abstract

Treatment options for leishmaniasis consist of no treatment option, medical treatment and surgical treatment. Always treat visceral, mucocutaneous, severe form of cutaneous leishmaniasis and new world cutaneous leishmaniasis with a tendency to develop into mucocutaneous form. Old world cutaneous leishmaniasis tends to resolve spontaneously need no treatment but should receive treatment if the lesions are disfiguring, painful, infected, over joints or slow to heal.

Sodium stibogluconate is the gold standard therapy for leishmaniasis. For localized cutaneous leishmaniasis topical therapy (intralesional and local application) is recommended as the first line therapy. Intralesional sodium stibogluconate is the widely accepted intralesional treatment in Sri Lanka. Intralesional hypertonic sodium chloride solution, zinc sulphate or metronidazole also proven to be effective. Cryotherapy is used to treat few localized lesions. For complicated cutaneous leishmanisis and for diffuse cutaneous leishmaniasis intramuscular sodium stibogluconate is being used. Mucocutaneous leishmaniasis is treated with sodium stibogluconate (IM) or amphotericin B. For visceral leishmaniasis sodium stibogluconate (IM/IV) is recommended. In addition to antileishmanial therapy intercurrent infections require antibiotics. Reticuloendothelial failure with visceral leishmaniasis need appropriate supportive measures. Severe mucocutaneous leishmaniasis may require orofacial reconstructive surgery.

Prevention of bites is important to reduce the prevalence of the disease in the country.


## Introduction

Causative species of leishmaniasis determines the clinical features and courses and treatments. In Sri Lanka only *Leishmania donavani* Mon 37 has been identified so far from the endogenous cases[1]. This can cause both visceral and cutaneous leishmaniasis. Appropriate treatment is essential to cure patients, to minimize scaring and to save lives from this emerging infection. Adequate measures need to be taken to prevent and control this vector born disease.

### Treatment of leishmaniasis

Treatment consists of no treatment option, medical treatment and surgical treatment. No treatment option is considered for old world cutaneous leishmaniasis which tends to resolve spontaneously. The lesions judged to be inactive (without raised margins) are healing spontaneously should be left alone. These patients can be reassured and reviewed in one month to see whether they are healing[2]. Given the associated morbidity always treat visceral, mucocutaneous and severe form of cutaneous leishmaniasis. Given its potential to progress into mucocutaneous leishmaniasis certain types of new world cutaneous leishmaniasis need to be treated. Some forms of cutaneous leishmaniasis of old world, for eg. severe forms, if the lesions are disfiguring, painful, infected over joints or slow to heel need to be treated.

Choice of correct therapy depends on experience of the physician, preference of the patient or the family, their ability to co-operate, the position of the lesion, stage and severity of the disease, immune status of the patient, geographic location, availability of drugs and cost effectiveness considerations for the patient and for the health care system[2,3]. Therapeutic response is dependent on host immune response and genetic makeup[4].

Treatment of leishmaniasis will help to save lives in case of visceral leislmaniasis and to minimize scaring and subsequent deformities in case of mucocutaneous leishmaniasis and cutaneous leishmaniasis. Furthermore the treatment will help to prevent more severe form of disease and will help to reduce the spread of the disease.

Treatment of cutaneous leishmaniasis consists, intralesional injections, topical treatment, oral treatment, intramuscular and intravenous drugs. Pentavalent antimony (sodium stibogluconate and meglumine antimoniate) is the gold standared treatment for leishmaniasis. In Sri Lanka only antimony available is sodium stibogluconate. This can be given intralesionally, intramuscularly or intravenously. Same preparation is being used for all three routes. Local injections of hypertonic sodium chloride solution, zinc sulphate and metranidazole also reported to be as effective [5,6,7]. In a study conducted

[1]*Consultant Dermatologist, Teaching Hospital, Kurunegala, Sri Lanka.*

by Ranawaka RR *et al*[8] sodium stibogluconate showed 100% cure within 1-6 injections (mean 3.24); while 7% hypertonic saline 92.2% cure within 1-10 (mean 5.27) injections.

Indications for intralesional stibogluconate include lesions less than 4 cm in diameter, lesions where the surrounding tissue is fairly soft and where the lesion is accessible and the patient is co-operative. Sodium stibogluconate vial contains 100ml of 100mg/ml solution. Dose and duration of sodium stibogluconate is 1-3ml in every 5-7 days for 2-5 doses[2]. If the response is inadequate treatment may extend up to 10 weeks. Alternatively 2-5ml of sodium stibogluconate can be given on day 1, 3, 7, 10, and 30. Trained staff is needed to administer the intralesional injections. The drug has to be injected into the dermis until complete blanching of the lesion occurs[2]. Advantages of intralesional stibogluconate include targeting higher drug concentrations to the site of infection, lower systemic toxicity, decreased cost and faster healing time[4]. Other advantages are that it does not require hospital admission, monitoring investigations and restriction of exercise[9]. Disadvatntages of intralesional stibogluconate includes bacterial superinfection, stibo intolerance (in cephalic locations), evolution to sporotricoid lesions, recurrence of the disease and non response[8].

Topical therapy for cutaneous leishmaniasis includes cryotherapy, paramomycin ointments, imiquimod cream, topical amphotericin B, localized control heat, $CO_2$ laser and photodynamic therapy. Cryotherapy is commonly being used in our country for localized lesions as it is less expensive and freely available. Two cycles of 10-30s freezing time are sufficient for leishmania tropica lesions in Greece[10]. 1-3 sessions of 2 applications (15-20 freezing time with a thaw of 1 minute each) are used in jordan) for *Leishmania tropica* and *Leishmania major*[11]. Disadvantages of cryotherapy include pain, and post inflammatory hypopigmentation.

Oral treatments for cutaneous leishmaniasis include azoles, azithromycin, miltefosine and oral zinc sulphate. Oral miltefosine in a dose of 2.5mg/kg/day for 28 days is given in visceral leishmaniasis due to *Leishmania donovani*[8].

Intramuscular and intravenous drugs for leishmaniasis include systemic antimonials, drug combinations with antimonials, pentamidine, amphotericin B and other treatments like bisophosphonate. Indications for intramuscular sodium stibogluconate includes larger diameter lesions (>5cm, lesions), larger number of lesions, lesions at the sites those are difficult to inject (ear, eye lid and nose lesions), lesions where there is lymphatic spread, children who need treatment but cannot be restrained for intralesional treatment and in whom 10 weeks sodium stibogluconate treatment has failed. Dose and duration of intralesional sodium stibogluconate include 10-20mg/kg/daily for 14 days (with a break of one day for the week end). If the response is poor by 14 days, treatment can be continued for further 7 days. The injection should be given to upper outer quadrant of the buttock on alternating sides. This is a relatively safe drug and few side effects are experienced. Special cautions for intra muscular sodium stibogluconate include anaphylactic response, cardiac arrhythmias, hepatic and renal side effects and immunosuppression. Emergency tray should be kept ready before giving the injection. Patients with irregular cardiac rhythm or a history of cardiac disease should not be given the injections. If the patient has a febrile illness or pulmonary TB they should not be treated[2].

For mucocutaneous leishmaniasis intramuscular and intravenous pentavalent antimony can be used. Amphotericin B also is being used. Diffuse cocutaneous leishmaniasis is treated with pentavalent antimony intramuscularly or intravenously. Visceral leishmaniasis is treated with pentavalent antimony intramuscularly or intravenously, intravenous amphotericin B (deoxy cholate and liposomal forms), intramuscular pentamidine and oral miltefosine. Miltefosine is being under trial in India for the treatment of visceral leishmaniasis by *Leishmania donovani*. Miltefosine is not yet available in the country. Combinations of various oral and parentral treatments are under study.

Dose of intravenous stibogluconate is 20mg/kg/day (with no upper limit). Duration of treatment varies depending on the species involved and the type of disease. For new world cutaneous leishmaniasis 20mg/kg should be given for 20 days. For old world cutaneous leishmaniasis 20mg/kg for 10 days may be sufficient. For visceral leishmanisis 10-20mg/kg/day for a minimum period of 20 days should be given. Sodium stibogluconate should be given via a series of butterfly needles or intravenous cannulae which should be changed frequently to avoid phlebitis. Intravenous sodium stibogluconate should be diluted in 5% dextrose and administered over 30 minutes. Filtration, cardiac monitoring and

keeping the infusion in dark place are not necessary. Patients receiving intravenous sodium stibogluconate do not need hospital admission but need to avoid exercise and alcohol during treatment and one week thereafter[9]. Adverse effects of sodium stibogluconate include anorexia, nausea, vomiting, diarrhoea, malaise, myalgia, arthralgia, headache and lethargy. These patients should undergo twice weekly monitoring investigations including full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFT), serum amylase and electrocardiographs (ECG). The treatment should be interrupted if FBC changes become significantly abnormal, U&E changes become significantly abnormal, liver transaminases exceed 15 times the upper limit of normal, serum amylase exceeds 4 times upper limit of normal or if the features of pancreatitis develop or ECG changes becomes significantly abnormal (QTc prolongation>500 milliseconds)[9]. Commonest reason for interruption of treatment is musculoskeletal symptoms. This may be severe in older patients and may settle with non-steroidal anti-inflammatory drugs. Treatment can be restarted once the abnormality in question returns to normal. There are no special recommendations for different age groups. Antimonials efficacy was significantly reduced in children under 5 years (11-25%) regardless of the duration of treatment[8].

Additional therapy for leishmanisis includes treatment of intercurrent infection with antibiotics and additional supportive care (like blood transfusions) with reticuloendothelial failure in visceral leishmaniasis. Surgical therapy with orofacial surgery is indicated sometimes for the treatment of mucocutaneous leishmaniasis. Surgical removal is not recommended. On the other hand surgery may exacerbate quiescent disease.

Military personnel receving intravenous sodium stibogluconate for 20 days should be given 20 days sick leave and advised to avoid exercise and alcohol for one week after treatment. They also need gradually increasing exercise to regain full fitness[9].

Once the treatment is completed patients should be reviewed after 2 months and six months to see the response.

## Prevention and control

Both anthroponotic (AL) and zoonotic (ZL) leishmaniasis need different methods of control. Prevention of AL is very similar to malaria prevention[2]. Here the sandflies bite at night and indoor. They are more sensitive to insecticides than mosquitoes. Therefore main means of prevention are residual spraying of rooms, use of repellents and use of impregnated bed nets. Treatment can have a preventive effect if enough cases are treated early in the disease[2].

In ZL sandflies bite out door. Therefore insecticides are unlike to work. Reservoir of infection is seen among burrowing rodents in areas of human habitation. Therefore the most effective strategy is to control the rodent reservoir. In Sri Lanka possible reservoir host is not yet identified[12,13]. Therefore protective measures against sand fly bites is the most important method in prevention of leishmaniasis in Sri Lanka. When we consider the distribution of lesions in our patients, most lesions are seen on exposed areas[14]. Thus protective clothing can benefit most of these patients. Wearing long sleeved shirts and ankle long pajamas and socks and tucking the shirts under pants will definitely help to minimize bites. Avoidance of outdoor activities especially from dusk to dawn when the sand flies are generally most active will further minimize the risk of bites.

## Conclusion

The treatment of leishmanisis depends on the form of the disease, species involved, experience of the clinician, preference of patients and cost effective considerations for the patients and health care system. Except cutaneous leishmaniasis of old world which shows signs of self healing all other forms need to be treated with standard antileishmanial therapy. Response to therapy depends on the species involved, genetic background and immune status of the individual. Sodium stibogluconate is the gold standard therapy for leishmaniasis. In Sri Lanka sodium stibogluconate is used for cutaneous, mucocutaneous and visceral leishmanisis. Cryo-therapy and intralesional injection of sodium chloride is used for localized disease. Main problem we encounter is the erratic supply of sodium stibo-gluconate. In order to reduce mortality and morbidity from this emerging infection we need to have a regular supply of sodium stibogluconate .

Prevention of bites is the most effective method of prevention of disease at the moment as there is no definitive reservoir host identified up to date in the country. Further studies needed to understand the vector, reservoir host and transmission of the disease in the country in order to control the disease prevalence in the country.

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