

# Combined intralesional and intramuscular sodium stibogluconate appears more effective in the treatment of localized cutaneous leishmaniasis lesions: An experimental study

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## Abstract

**Background** Intralesional sodium stibogluconate (SSG) is now the preferred therapy for Localized Cutaneous Leishmaniasis (LCL). The objective of this study was to analyse the effectiveness of intralesional SSG alone with intralesional SSG combined with intramuscular SSG.

**Methods** This randomized controlled intervention study was conducted at the department of Dermatology, King Khalid Hospital in Najran, Saudi Arabia. A total of 40 patients with LCL were assigned randomly to Group-1 (n=20) or Group-2 (n=20). Patients in Group-1 were given a total of three intralesional SSG injections on alternate days; Patients in Group-2 were given a total of three injections of intralesional SSG on the same regimen as Group-1 with simultaneous intramuscular injections. The total dose given to patients in Group-2 was the same as that given to patients in Group-1 (15-20 mg/ Kg/ day). Five treatment cycles were carried out through monthly follow-up visits during the subsequent five months to assess the treatment outcome in both groups.

**Results** The patients in Group-2 showed overall better improvement than that of the patients in Group-1 across all treatment cycles. Almost all lesions (plaque, multiple and mucosal) were cured after one to two treatment cycles in Group-2, patients in Group-1 with similar lesions required two or more cycles to achieve similar results. The scarring after healing among the patients in Group-2 was more even and cosmetically better than that observed among the patients in Group-1.

**Conclusion** A regimen of intralesional and intramuscular SSG showed more efficacy than intralesional SSG alone to treat LCL.

## Key words

Localized cutaneous leishmaniasis, Intralesional SSG, Combined Intralesional intramuscular SSG.

## Introduction

Leishmaniasis is a parasitic disease caused by Leishmania species. Its worldwide prevalence is approximately 12 million cases, with two million annual new cases, of which 1.5 million are cutaneous leishmania.<sup>1</sup> Leishmaniasis occurs throughout the Americas and is also prevalent in

the Middle East and North Africa.<sup>2</sup>

Cutaneous leishmaniasis can be of the acute, chronic, mucocutaneous and post kala azar type. Acute leishmaniasis can be localized or present diffuse lesions, and the chronic variant manifests as a recurrence following the original infection or papules that grow, plaque, or a clustering of papules that leave centralized scarring following healing.<sup>3</sup> Localized cutaneous lesions often appear as a nonspecific ulcer that can indicate numerous other infectious and noninfectious skin conditions.<sup>4</sup> In addition, for patients manifesting the diffuse localized type, papules,

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nodules, and plaques appear all over the skin that are usually therapy resistant. This often leads to the condition becoming chronic.<sup>5</sup>

Although intralesional treatment is often the first treatment option for LCL, IM or IV is recommended for the highest cure rates (90 to 95% cure).<sup>6</sup>

In addition, researchers have suggested combining intramuscular SSG with intralesional SSG for effective treatment and to minimize the risk of resistance to treatment.<sup>7,8</sup>

Cutaneous leishmaniasis is prevalent in Najran province in the southwestern region of Saudi Arabia. Ineffective treatment, either due to inadequate dosage or poor technique, is also common in the region. This is a serious issue because incomplete treatment raises the risk of drug resistance. For this reason, it is essential to understand the exact treatment regimen appropriate for various cases of Cutaneous leishmaniasis. Moreover, because the treatment of a large number of cases in a particular area can reduce the spread of the disease, the treatment strategy is also important from the perspective of public health and infectious disease control.

### **Objectives and goals**

This study aimed to assess the efficacy of intralesional Sodium Stibogluconate given alone compared to efficacy of combined intralesional and intramuscular Sodium Stibogluconate in treatment of localized cutaneous leishmaniasis.

### **Subjects and methods**

This study comprised a randomized controlled intervention conducted at the Dermatology Department, King Khalid Hospital in Najran, Saudi Arabia. A total of 40 diagnosed LCL patients were recruited in study during the study period.

Formal approval was obtained from the hospital authority to conduct this study and photographs were taken after obtaining special consents from the patients.

The diagnostic criteria for LCL was mainly clinical. A typical case of LCL in this study was from an area that was suspected as endemic for the condition. They presented with non-healing indurated papules, nodules or plaque that may have had crusting. To confirm the diagnosis, a smear and/or skin biopsy was carried out. Patients were examined individually, and body weight, laboratory results and type of skin lesions were recorded. Exclusion criteria included those already receiving treatment for LCL, pregnant and nursing women, children below five years of age, and patients with known hypersensitivity to Sodium Stibogluconate (SSG).

The study subjects were assigned randomly to Group-1 or Group-2, with each group containing 20 patients. In Group-1, each patient received an intralesional injection of SSG on alternate days. In Group-2, a combination of intralesional and intramuscular SSG was given to each patient. The dose of SSG did not exceed 20 mg/ kg/ day for both groups. Group-2 received half of the dose as intralesional and the other half dose as intramuscular SSG. A total of five treatment cycles were carried out at monthly follow-up visits over the next five months to assess the treatment outcomes among patients in both groups.

The therapeutic responses were determined by examining the improvement of lesions (i.e. changes in size, erythema, induration and ulceration) during each follow-up visit (every four weeks). These clinical examinations were performed by the study team. The therapeutic responses were categorized and ranked subjectively by the study team (applying clinical knowledge, skills and experience) as follows:

Category	Rank
No response	0
Minimal response	1
Mild response	2
Moderate response	3
Excellent response	4
Cured (healing of lesions)	5

Finally, the study team assessed the effects of two different treatment options (one for each group) and compared their effects.

Descriptive statistical analyses were performed by creating cross-tables, and calculating proportion, range, and frequency.

**Results**

40 of a total of 1759 patients who attended the clinic during the study period were suffering from cutaneous leishmaniasis. The majority of patients were males (n=32; 75%), Saudis (n=27; 67.5%) and their ages ranged from 5 to 65 years. Tissue smears were positive in 30 patients (75%) while skin biopsies were positive in six patients

only (15%).

**Table 1** shows the demographic, clinical, and investigative characteristics of the patients with LCL in both groups, and a comparison of anatomical distribution of lesions between patients in the two groups is illustrated in **Table 2**. A variety of LCL lesions presented by the study patients are shown in **Figures 1-3**.

**Table 3** provides a summary of the treatment outcomes for each of the therapeutic options for the patients in each groups. Of the 20 patients in Group-1 (intralesional injection of SSG only), two patients did not appear at the first follow-up visit after the first cycle of treatment. Similarly, six patients did not come back for the first follow-up of the 20 patients in Group-2. In Group-1, two patients were found to be completely cured at the first follow-up visit. One of them had presented with a single small nodule on the forearm for two months (smear- and culture-negative), and the other had presented with a papular lesion over the cheek for two

**Table 1** Demographic, clinical, and investigative profile of patients with localized cutaneous leishmaniasis in two groups, Najran, Saudi Arabia.

Characteristics	Group-1 (n=20) [IL SSG]	Group-2 (n=20) [IL+IM SSG]	Total (n=40)
Sex (Male : Female)	17 : 3	15 : 5	32 : 8
Age (range in years)	5-55	10-65	5-65
Duration of disease (range in months)	1-19	2-18	1-19
Number of lesions	38	57	95
Positive tissue smear	12	18	30
Positive skin biopsy	4	2	6

IL = intralesional; IM = intramuscular; SSG = sodium stibogluconate.

**Table 2** Anatomical distribution of lesions among patients with localized cutaneous leishmaniasis in two groups, Najran, Saudi Arabia.

Site	Number of lesions	
	Group-1 (n=20) [IL SSG]	Group-2 (n=20) [IL+IM SSG]
Face	19	27
Neck	01	02
Chest	09	08
Upper limb	05	11
Lower limb	04	09
Total number of lesions	38	57

IL = intralesional; IM = intramuscular; SSG = sodium stibogluconate.

**Table 3** comparison of therapeutic responses among patients with localized cutaneous leishmaniasis in two groups.

Therapeutic response*	Follow up									
	1 <sup>st</sup> (4th week)		2 <sup>nd</sup> (8th week)		3 <sup>rd</sup> (12th week)		4 <sup>th</sup> (16th week)		5 <sup>th</sup> (20th week)	
	Gr-1 (n=20)	Gr-2 (n=20)	Gr-1 (n=16)	Gr-2 (n=14)	Gr-1 (n=6)	Gr-2 (n=4)	Gr-1 (n=2)	Gr-2 (n=0)	Gr-1 (n=2)	Gr-2 (n=0)
Lost to follow up	2	6	4	4	-	-	-	-	-	-
No response	-	-	-	-	-	-	-	-	-	-
Minimal response	-	-	-	-	-	-	-	-	-	-
Mild response	14	-	2	-	2	-	2	-	2	-
Moderate response	2	5	3	-	-	-	-	-	-	-
Excellent response	-	9	1	4	-	-	-	-	-	-
Cured (healing of lesions)	2	-	6	6	4	4	-	-	-	-

\*Categorizing and ranking technique of the therapeutic responses has been described in the *Subject and Methods* section.

n = No. of patients booked at the follow up visit (i.e. excluding 'no show' patients and excluding cured patients from previous visit).



**Figure 1** A 20-year-old male presented with 2 crusted lesions.



**Figure 2** A 25-year-old male presented with single nodule on his right arm.



**Figure 3** A 7-year-old male presented with multiple lesions on his chest.

months (smear- and culture-positive). No further treatment was advised. However, at the first follow-up visit, no patients were found to be cured from Group-2 (combined intralesional and intramuscular injection of SSG). No patients showed 'excellent' therapeutic response in Group-1, while a total of nine patients showed 'excellent' therapeutic responses in Group-2, indicating overall better responses than Group-1.

At the end of eighth week, four patients from Group-1 and four from Group-2 did not report to the clinic for the second follow-up visit. A total of six patients from Group-1 and another six from Group-2 were found to be totally cured after the second cycle of treatment. Only one patient showed 'excellent' therapeutic response in Group-1, while a total of four patients presented 'excellent' therapeutic responses in Group-2, again indicating overall superior responses compared to the patients in Group-1. Among the six remaining patients in Group-1, four were found to be cured at the third follow-up visit, and of the four remaining patients in Group-2, all four had been cured. The remaining two patients in Group-1 showed unchanged status ('mild' response) at the third, fourth and fifth follow-up visits. Thus, the patients in Group-2 showed overall better improvement than the responses of the patients in Group-1 at all follow-up visits.

Moreover, the majority of the lesions (plaque,

multiple, mucosal) were cured after one to two treatment cycles of combined IM and IL SSG in Group-2. Group-1 patients required two or more treatment cycles to achieve similar results. In addition, the resultant scarring post-healing among the patients in Group-2 was more uniform than scarring among the patients in Group-1.

No systemic side effects were observed in both the groups. Only pain and swelling were developed at the injection site that subsided after a short period of time. Baseline routine investigations were carried out at the beginning of the treatment, and the subsequent routine investigations did not show any significant deviation in any patient during the treatment course. No side effects occurred that necessitated early termination of treatment in any of the patients.

## **Discussion**

The World Health Organization (WHO) advises using intralesional SSG therapy, especially if patients are diagnosed with for early and localized LCL lesions.<sup>9</sup> Tallab *et al.* (1996) standardized the schedule for intralesional SSG (as 0.3-3 ml of SSG) and recommended a regimen of three injections on alternate days in a week. This proved more effective than daily or weekly injections.<sup>10</sup> This regimen has also been shown to be consistently effective. It also appears to be better than injections given once or twice every eight days<sup>11</sup> or 18-20 injections, as recommended by Kellum.<sup>12</sup> Furthermore, this regimen requires fewer injections than the latter treatment option and causes reduced side effects (such as necrosis of the tissue) at the site of injection. It has also been noted that the best outcomes occur when lesions are treated as early as possible

In this present study, the administration of IM SSG to patients in Group-2 improved the

therapeutic outcome for all 12 patients compared to patients in Group-1. More specifically, an excellent response was observed after one or two treatment cycles whereas patients in Group-2 required more treatment cycles for similar responses. Healing of the lesions was more uniform and devoid of 'cobble-stoning' in Group-2 patients. Positive smear/culture tests had no impact on therapeutic outcome.

IM SSG injected at increased concentrations in the lesions after IL infiltration achieved better therapeutic responses. The optimal therapeutic dose of SSG (15-20 mg/ Kg/ day) also achieved better results than the dose administered through IL infiltration alone. Administering the full dose of SSG (IL+IM) in Group-2 patients, resulted in less treatment cycles being required for clinical cure.

No severe side effects, such as cardiovascular toxicity, neurotoxicity, bone marrow hypoplasia or renal toxicity (all commonly associated with systemic SSG therapy), were observed in any patients from either group. Pain and swelling at the injection site were commonly noted among all patients, but this only lasted for a short period of days and did not require discontinuing of the therapy.

Furthermore, the majority of the lesions were observed on the faces of patients, and these lesions were multiple in nature, indicating that this outbreak in Najran province might have been caused by the anthroponotic type of cutaneous leishmaniasis. Early treatment of the diagnosed cases using an effective regimen is therefore important to control any outbreak.

There are a number of limitations to this study. Firstly, the numbers of 'no show' patients was fairly high (but not equal) in both groups. The likely reason for the dropout, as often stated by some patients, could be that the drug is very expensive. Early cure after the first or second

treatment cycle in both groups could have been another potential cause for the dropout at the initial stages of the study. Moreover, the long distance to the treatment center for many of the participants further added to the cost and inconvenience of continuing the trial. The final limitation of the study is the small sample size.

## Conclusion

Although the current study included a relatively low patient number, results showed increased efficacy of intralesional and intramuscular SSG combined to treat and heal LCL compared to intralesional SSG. No added side effects were observed with this combination treatment. Therefore, we recommend future studies assess the same combination regimen with larger sample sizes to support and more firmly establish the findings of the present study.

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**Competing interests** The author declares that he has no conflict of interests regarding the publication of this paper.

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