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Original Article

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) has become the first line therapy for localized cutaneous leishmaniasis (LCL). The objective of this study was to compare the efficacy of intralesional SSG given alone with that of 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). Group-1 received three injections of intralesional SSG on alternate days, while Group-2 received three injections of intralesional SSG similar to Group-1 and the rest of the calculated dose as a simultaneous intramuscular injection. Five treatment cycles were carried out through monthly follow-up visits during 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 in all treatment cycles. Most of the plaque lesions, multiple lesions and mucosal lesions were cured after 1 to 2 treatment cycles in Group-2, compared to the patients in Group-1 having similar lesions required 2 or more cycles for cure. The resultant scarring after healing among the patients in Group-2 was even and cosmetically more acceptable than that was observed among the patients in Group-1.

Conclusion Combination regimen of intralesional and intramuscular SSG appeared to be more effective than intralesional SSG given alone in the treatment of LCL.

Key words
Localized cutaneous leishmaniasis, Intralesional SSG, combined Intralesional intramuscular SSG.

Introduction

Leishmaniasis is a parasitic disease caused by Leishmania species of Trypanosomatidae. Its worldwide prevalence is approximately about 12 million cases with 2 million annual new cases, and 1.5 million out of these new cases are cutaneous leishmanial.[1] Leishmaniasis occurs throughout the America, and is also prevalent in the Middle East and North Africa.[2]

Cutaneous leishmaniasis can be an acute, chronic, mucocutaneous and post kala azar types. The acute leishmaniasis can be localized or diffuse lesions, the chronic disease manifests as a recurrence of healed disease after the original infection or an enlarging papule, plaque, or coalescence of papules that heals with central

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scarring.[3] Localized cutaneous lesions usually manifests as a nonspecific ulcer that can mimic many other infectious and noninfectious skin conditions.[4] In diffuses localized type patients develop many papules, nodules, and plaques throughout the skin and often resistant to therapy and may assume a chronic course.[5]

Although intralesional treatment has been widely used as the first therapeutic line in LCL, IM or IV is recommended for high cure rate (90 to 95% cure).[6]

Some researcher suggested to combine intramuscular SSG with intralesional SSG for effective treatment and to minimize the resistance to treatment.[7,8]

Cutaneous Leishmaniasis is prevalent in Najran province, the Southwest part of Saudi Arabia. Occurrence of ineffective treatment, either due to inadequate dose or poor technique, is common in the region. Incomplete treatment causes drug resistance. It is essential to make the precise decision regarding the treatment strategy of Cutaneous Leishmaniasis. Because the treatment of a large proportion of cases in a particular area can reduce the spread of the disease, the treatment strategy is important in 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 (LCL).

Subjects and methods

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

A 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 was presented with non-healing indurated papule, nodule or plaque with or without crusting in patients coming from a suspected endemic area. In addition, tissue smear and/ or skin biopsy was carried out to confirm the diagnosis. Patients were examined individually, and body weight, laboratory results and type of skin lesions were recorded. However, patients already receiving the treatment for LCL, pregnant and nursing women, children below five years of age, and patients with known hypersensitivity to Sodium Stibogluconate (SSG) were excluded from the study.

The study subjects were assigned randomly to Group-1 or Group-2. Each group included 20 patients. In Group-1, every patient received an intralesional injection of SSG only on the alternate days. On the other hand, a combination of intralesional and intramuscular SSG was given to each patient in Group-2. The dose of SSG did not exceed 20 mg/kg/day in both groups. A total of five treatment cycles were carried out through monthly follow up visits during next five months to assess the treatment outcome among the patients in both group.

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 4 weeks), and 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 experiences) 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 in both groups and compared their effects.

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

Results

40 out of 1759 patients who were seen in the clinic during the study period were suffering from cutaneous leishmaniasis. The patients were predominantly males 32 (75 %), Saudis (67.5%) and their age ranging from 5 to 65 years. Tissue smears were positive in 30 patients (75%) while skin biopsies were positive in 6 patients only (15%).

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

Table 3 shows the summary of the treatment outcomes comparing therapeutic responses among the patients in two groups. Of 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

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*									
	1st (4th week)		*2nd (8th week)*		*3rd (12th week)*		*4th (16th week)*		*5th (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).

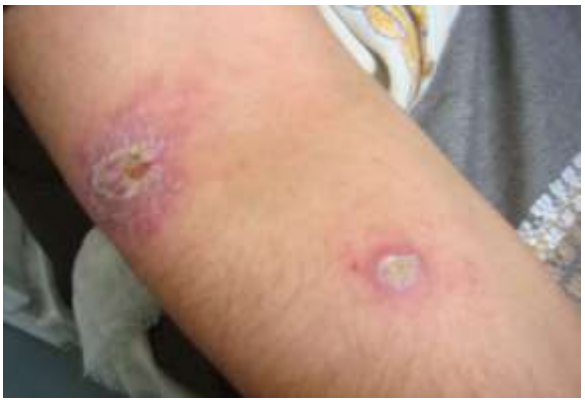

Figure 1 A 20 years old male presented with 2 crusted lesions.

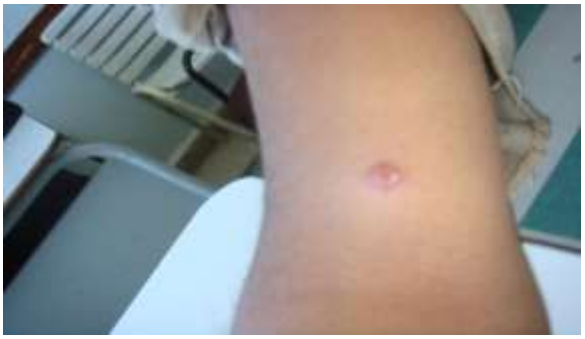

Figure 2 A 25 years old male presented with single nodule on his right arm.

Figure 3 A 7 years old male presented with multiple lesions on his chest.

Similarly, six patients did not come back for the first follow-up among 20 patients in Group-2. In Group-1, two patients were found completely cured at the first follow-up visit. One of them had a single small nodule on the forearm for two months (smear- and culture-negative) and the other had a papular lesion over the cheek for two months (smear- and culture-positive). No further treatment was advised to them. 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 9 patients confirmed 'excellent' therapeutic responses in Group-2 indicating overall better responses over Group-1 **(Table 3)**.

At the end of eighth weeks, 4 patients from Group-1 and another 4 patients from Group-2 did not report to the clinic for the second follow up. A total of 6 patients from Group-1 and another 6 patients from Group-2 were found totally cured after second cycle of treatment. Only one patient showed 'excellent' therapeutic response in Group-1, while a total of 4 patients presented 'excellent' therapeutic responses in Group-2 indicating overall superior responses comparing to the patients in Group-1 **(Table 3)**. Among 6 patients in Group-1, 4 patients were found cured at the third follow up visit, while among 4 patients in Group-2, all four became cured. The remaining 2 patients in Group-1

showed unchanged status ('mild' response) at third, fourth and fifth follow up visits **(Table 3)**. Thus, the patients in Group-2 showed overall better improvement than that of the patients in Group-1 at all follow up visits.

Moreover, it was observed that most of the plaque lesions, multiple lesions and mucosal lesions were cured after 1 to 2 treatment cycles of combined IM and IL SSG in Group-2, compared to the patients in Group-1 having similar lesions required 2 or more treatment cycles for cure. It was also observed that the resultant scarring after healing among the patients in Group-2 was even and cosmetically more acceptable than that was seen 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. None of the cases warranted discontinuation of treatment due to side effects.

Discussion

The World Health Organization (WHO) recommends intralesional SSG therapy particularly for early and localized LCL lesions.[9] Tallab *et al.*, 1996: standardized the schedule for intralesional SSG (as 0.3-3 ml of SSG) and recommended to give it on alternate days as three injections in a week, and found it was superior to the daily or weekly schedules.[10] This regimen has also been consistently effective. It also appears to be better than injections given once or twice every eight days[11] or 18-20 injections as recommended by Kellum.[12] Furthermore, this regimen is convenient, requires less number of injections, has fewer side effects such as necrosis of the tissue at the injection site. Treatment of early lesions is imperative for good therapeutic response.

Addition of IM SSG to the patients in Group-2 further improved the therapeutic outcome as observed in 12 patients. In Group-2, patients having lesions of variable sizes and duration, excellent response was observed after one treatment cycle itself compared to the patients of Group-1 with similar lesions who needed 2 or more treatment cycles for similar response. Healing of the lesions were more uniform and devoid of 'cobble-stoning' in Group-2 patients. The smear/culture positivity did not affect the therapeutic outcome.

It appeared that IM SSG with higher concentrations in the lesions after IL infiltration achieved better therapeutic response. It might be a fact that the optimum therapeutic dose of SSG was much more effective than that the patient received after IL infiltration alone. By giving the full dose of SSG (IL+IM) in Group-2 patients, albeit for short periods, fewer treatment cycles were required for clinical cure.

None of the patients in both the groups developed any serious side effects like cardiovascular toxicity, neurotoxicity, bone marrow hypoplasia or renal toxicity associated with systemic SSG therapy. Pain and swelling at the injection site that was noted in all patients for a few days, is well documented. However, it did not warrant discontinuation of the therapy.

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

important to control any outbreak.

The numbers of 'no show' patients were not equal in both the groups. This was a limitation of the present study. The probable reason for the dropout, as often stated by some patients, could be the drug which was very expensive. Early cure after first or second treatment cycle in both the groups could be another possible reason for the dropout at the initial stages of the study. Moreover, the long distance commutes to the treatment center further increased the cost and inconveniences for the patients. Small sample size was another limitation of this study.

Conclusion

Although the current study examined only a small number of patients, the combination regimen of intralesional and intramuscular SSG appeared to be more effective and provided qualitatively superior healing than intralesional SSG given alone while treating large or old lesions in LCL without occurring any added side effects. We recommend initiating further future studies with large sample sizes in order to support and establish the findings of the present study.

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