

Comparative efficacy of intralesional sodium stibogluconate (SSG) alone and its combination with intramuscular SSG to treat localized cutaneous leishmaniasis: Results of a pilot study

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ABSTRACT

Background: Intralesional sodium stibogluconate (SSG) has become first line therapy for localized cutaneous leishmaniasis (LCL). **Aims:** This study compares the efficacy of intralesional SSG given alone with that of intralesional SSG combined with intramuscular SSG. **Methods:** Thirty-two patients aged between 5-56 years were included in the study. The first group received three injections of intralesional SSG on alternate days while the other group received three injections of intralesional SSG similar to the first group and the rest of the calculated dose as a simultaneous, intramuscular injection. Patients were followed up every four weeks to assess for cure/ the need for repeating the treatment. **Results:** Five patients from group 1 having small nodular lesions of < six months duration were cured after 1-2 treatment cycles. However, six patients with mucosal lesions, large lesions and lesions of > six months duration needed 3-5 treatment schedules. Most plaques and mucosal lesions in seven patients in group 2 cleared with two treatment cycles. **Conclusion:** Intralesional combined with intramuscular SSG appears more effective in LCL and gave qualitatively superior healing than intralesional SSG given alone

Key words: Localized cutaneous leishmaniasis, Intralesional sodium stibogluconate, Intramuscular sodium stibogluconate

Localized cutaneous leishmaniasis (LCL) is a major health problem worldwide caused by parasites of the *Leishmania* species, which are transmitted by the female sand fly (*Phlebotomus* spp.) both in the sylvatic and peridomestic cycles. Afghanistan, Brazil, Saudi Arabia, Iran, Peru and Syria account for about 90% of cutaneous leishmaniasis.^[1] In North America and Northern Europe, CL is a disease seen in returning travelers, such as those conducting rural field studies, tourists and the military personnel.^[2] New endemic foci are also being recognized due to activities like horticultural development, setting up of new residential colonies leading to clearing of forests, war-like conditions, movement of a nonimmune population into previously sparsely inhabited areas and intrusions into the sylvatic cycle.^[3]

A typical LCL lesion begins at the site of the sand fly bite, mostly on exposed body parts, as a papulo-nodulo-ulcerative plaque that develops a crust (oriental sore). As the crust falls off, a shallow ulcer is formed. This has well defined, raised, erythematous borders and granulation tissue in the centre.^[4] Clinical diagnosis is usually easy in patients coming from an endemic area having discrete, relatively painless skin lesions. The demonstration of Leishman-Donovan bodies (amastigotes) in Giemsa-stained tissue smears or histology sections from lesions and culture of *Leishmania* organisms on Novy, MacNeal and Nicoll's (NNN) medium are considered to be confirmatory tests of CL.

Pentavalent antimonials with their consistent efficacy

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remain the drug of choice for treating LCL till date.^[5-7] These compounds are given intravenously (IV), intramuscularly (IM) or intralesionally (IL). Intolerable side effects are common when large doses are used for IV or IM (as in visceral leishmaniasis or VL) therapy and even the LCL lesion may take long time to resolve. We have been routinely using intralesional sodium stibogluconate (SSG) since the 1990's.^[3,8] It has been observed that most of the cases respond well to this treatment without major side effects. However some lesions, particularly the larger ones, show patchy resolution and uneven 'cobble-stone' surface after healing [Figure 1] and such nodules even persist for a longer period. This is either due to lack of thorough infiltration of the whole lesion or perhaps the drug is not able to reach all the areas / parasites despite attaining high concentrations at the injection site. The latter appears plausible as invasion of deeper organs by these primarily dermatropic *Leishmania* spp. as well as their culture from blood samples of CL patients is well recognized.^[9-13]

In this pilot study, we compared the efficacy and safety of intralesional SSG given alone to that of the hitherto untried combination of intralesional and intramuscular SSG. Our objectives were to achieve the maximum drug concentration in the lesion and to reach those tissues / disseminated / distant parasites via the intramuscular route, which are not accessed by intralesional administration alone.

METHODS

This study was undertaken in the department of Dermatology, Venereology and Leprosy, I. G. Medical College, Shimla, during March 2005 to February 2006. After receiving informed consent, all new cases of LCL diagnosed consecutively in this one year period were included in the study. Patients already



Figure 1: Lesion of cutaneous leishmaniasis after intralesional sodium stibogluconate

on treatment for LCL, pregnant and nursing women, children < five years of age and patients with known hypersensitivity to SSG were excluded from the study.

After the diagnosis, the patients were assigned alternately to group 1 or group 2. Complete blood counts, urinalysis, random blood glucose, serum proteins, blood urea, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase and electrocardiogram (ECG) were carried out at the first visit as well as during follow-up in all patients. The diagnosis was mainly clinical - a typical chronic nonhealing indurated papule, nodule or plaque with or without crusting in patients coming from a previously delineated endemic area.^[14] Tissue smear and / or culture from skin biopsy was carried out to establish the diagnosis.

Skin biopsies were taken from the active indurated margin of the lesion under aseptic conditions. A 4 mm tissue sample was taken using a sterile biopsy punch. The biopsy was cut into two parts by a sterile blade. One part of the biopsy was used to make imprint smears while the other part was used for culture. When necessary, the slit smear technique was used for smear preparation. Smears were air-dried and Giemsa-stained. The second piece of biopsy was teased and inoculated in modified NNN medium with RPMI 1640 + 10% heat-inactivated fetal bovine serum. The culture was incubated at $25 \pm 1^\circ\text{C}$ and examined for growth of promastigotes from the third day onwards on every alternate day. The culture specimen was discarded if no growth was observed in three weeks or when bacterial or fungal contamination occurred.

Schedule of treatment

Group 1 patients were given an IL injection of SSG (100 mg/ml) following a treatment schedule on alternate days as described by Tallab *et al.*^[6] The lesions were infiltrated until blanching. The dose in this group of patients varied from 1-4 ml, but did not exceed 20 mg/kg/day or 8.5 g/day of SSG. Repeat injections were given on days 3 and 5 in one sitting.

All the patients of group 2 were hospitalized for the period of treatment. A part of the dose calculated (20 mg/kg/day) was injected intralesionally on days 1, 3 and 5 as in group 1 patients. The remaining amount of the total dose was given intramuscularly simultaneously on the same day.

All patients were followed up for repeat treatment or clinical cure at monthly intervals. Criteria for improvement were reduction in lesional erythema, size and induration. Cure was

defined as complete disappearance of erythema, induration and healing of ulceration after four weeks of last injection. No improvement or worsening of lesion was considered as failure of treatment. Follow-up assessment was done by the treating clinician, the patient and by comparing serial photographs. The response was graded as mild (25% improvement), moderate (26-50% improvement), good (51-75% improvement) and excellent (76-100%). The scarring was ignored. At the end of study period, the response in both groups was compared with the respective pretreatment values and their percentage reduction was statistically analyzed by paired t-test. $P < 0.05$, calculated at 5% level (95% confidence limits), was considered to be statistically significant.

RESULTS

The study included 32 newly diagnosed LCL patients (M:F = 20:12) divided in two groups of 16 patients each. Their demographic, clinical and investigative profiles are shown in Tables 1 and 2.

Therapeutic response

Group 1

Group 1 consisted of 16 patients who were given only intralesional SSG. One patient did not turn up for the first follow-up visit four weeks after the first cycle of treatment. All other patients showed moderate to excellent therapeutic response. The response to treatment in group 1 is shown in Table 3. Two patients were labeled as being cured (100% response) at the 1st follow-up four weeks after the first treatment cycle itself. One of them had a single small nodule over the face 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 given to them. Two other patients having plaque lesions over the face of ten and 19 months duration (both smear-negative, one culture-positive) respectively showed 60% (good) regression. The remaining 11 patients (four smear-positive,

Table 2: Anatomical distribution and types of localized cutaneous leishmaniasis lesions

Sites	Number of lesions Group 1	Number of lesions Group 2	Total number of lesions
Face	17	15	32 (56.14)
Cheek	08	06	14
Nose	04	06	10
Chin	02	02	04
Fore head	01	00	01
Mouth angle	02	01	03
Mucosal	02	02	04 (07.02)
Upper lip	00	02	02
Lower lip	02	00	02
Neck	00	03	03 (05.27)
Chest	01	03	04 (07.02)
Upper limb	03	08	11 (19.29)
Fore arm	02	07	09
Arm	01	01	02
Lower limb	00	03	03 (05.27)
Total	23	34	57

There were one (in 22 patients) to eight (in one patient) lesions. There were 29 (50.87%) nodulo-ulcerative plaques in 23 patients, 19 (33.3%) papules in nine patients, nine (15.7%) small nodules in seven patients respectively. Figures in parentheses are in percentage.

five culture-positive) had 40-50% (moderate) regression. These 13 patients received the 2nd treatment cycle.

Four of the 11 patients, who had moderate response at the 1st follow-up, did not report for the 2nd follow-up at the end of eight weeks. The other three patients showed 90-100% response - two had one papular lesion each and the third had a small nodule of two, four and 11 months' duration respectively. They were labeled as cured and treatment was discontinued. Another patient with a plaque lesion over the lip of five months' duration (smear- and culture-negative) showed 80% response. Five other patients showed 60-70% response. Four of these five patients had a single plaque lesion over the face of four, nine, ten and 19 months' duration respectively. One of them was tissue smear-positive. The fifth patient had a nodular lesion on the root of the nose of four months' duration (tissue smear- and culture-positive). These six patients were given the 3rd cycle of intralesional SSG.

At the 3rd follow-up after 12 weeks, four patients got (100% response) cured. Three had plaque lesions and the fourth had a nodular lesion on the face (three smear-positive and one culture-positive). One plaque over the lower lip was of five months' duration (smear- and culture-negative) while two lesions were of four and one of nine months' duration. The remaining two patients showed 70-80% response and both progressed to the 4th cycle of treatment.

One patient who had a plaque lesion over the cheek of 19 months' duration (smear- and culture-negative) was cured after the 4th treatment cycle. The second patient who showed

Table 1: Baseline characteristics

Characteristics	Group-1 (I/L SSG) (n =16)	Group-2 (I/L+I/M SSG) (n =16)	Total (n =32)
Sex (m/f)	9:7	11:5	20:12
Age (range in years)	5-49	12-56	5-56
Duration of disease (range in months)	2-19	1-14	1-19
Number of lesions	23	34	57
Positive tissue smears	6	11	17 (53.12%)
Positive cultures in NNN medium	6	8	14 (46.66%)

IL = Intralesional, I M = Intramuscular, SSG = Sodium stibogluconate, NNN = Novy, MacNeal and Nicoll's. Only five (15.62%) patients were children of ≤ 14 years. Smear and culture positivity were higher in 12 (70.58%) and ten (71.42%) patients respectively having lesions of \leq six months' duration. Only 12 (40%) patients had both smears and cultures positive.

Table 3: Response to treatment in Group 1

Response	1 st follow-up (at 4 weeks) n = 16	2 nd follow-up (at 8 weeks) n = 13	3 rd follow-up (at 12 weeks) n = 6	4 th follow-up (at 16 weeks) n = 2	5 th follow-up (at 20 weeks) n = 1
Lost to follow-up	1	4	0	0	0
Mild (up to 25%)	0	0	0	0	0
Moderate (26-50%)	11	0	0	0	0
Good (51-75%)	2	05	2	0	0
Excellent (76-100%)	2	4	4	2	1
Cured	2	3	4	1	1

Those labeled cured were not given further treatment.

80% response in the 4th cycle, required a 5th cycle of treatment for cure. She had a plaque lesion over the nose for ten months (smear-negative, culture-positive).

In general, small lesions and lesions of short duration (< six months) in five patients responded well and required only 1-2 treatment schedules. On the other hand, mucosal lesions, large lesions and lesions of > six months' duration in six patients were cured after 3-5 treatment cycles.

Group 2

This group of 16 patients received intralesional and intramuscular SSG simultaneously. The response to treatment in group 2 is shown in Table 4. Out of 16 patients, five patients did not come back for the 1st follow-up four weeks after completing the first treatment schedule. Seven patients who had nodulo-ulcerative plaques showed excellent (80-90%) response. Four of them had single lesions of < six months (all smear- and culture-positive) while the other three patients had two, four and eight papulonodular lesions respectively of > six months' duration. Four patients (three smear-positive, one culture-positive) showed good (60-70%) response. All these 11 patients were given the 2nd cycle of treatment.

One of the seven patients who had an excellent response after the first treatment cycle, was lost for the 2nd follow-up

Table 4: Response to treatment in Group 2

Response	1 st follow-up (at 4 weeks) n = 16	2 nd follow-up (at 8 weeks) n = 11	3 rd follow-up (at 12 weeks) n = 3
Lost to Follow-up	5	1	0
Mild (up to 25%)	0	0	0
Moderate (26-50%)	0	0	0
Good (51-75%)	4		0
Excellent (76-100%)	7	10	3
Cured	0	7	3

Those labeled cured were not given further treatment.

at eight weeks. The other six patients showed 100% response and were considered cured. One of the other four patients having a good response at the 1st follow-up showed 100% response (cured) after the second treatment cycle. No further treatment was given. This patient had a single plaque lesion over the cheek of 12 months' duration. The remaining three patients showed 80-90% response and were given the third cycle of SSG. At the 3rd follow-up after 12 weeks, these three patients having nodulo-ulcerative plaques of three, four and six months' duration (two smear- and culture-positive) and 80-90% response at the 2nd follow up, showed 100% response and further treatment was stopped.

It was observed that most of the plaque lesions, multiple lesions and mucosal lesions in seven patients were cured after two cycles of combined IM and IL SSG regimen in group 2 as compare to the six patients in group 1 having similar lesions requiring 3-5 treatment cycles for cure. It was observed that after healing, the resultant scarring in group 2 patients [Figure 2] was even and cosmetically more acceptable than that seen in group 1 patients.

Side effects

No systemic side effects were observed in any of the patients



Figure 2: Intralesional sodium stibogluconate administration and intramuscular sodium stibogluconate therapy; Pretreatment (A), Post treatment (B).

in both the groups. All patients complained of pain and swelling at the intralesional injection site that subsided on its own in one to two days and did not require any intervention except for oral analgesics. Oozing of blood from the injection site while infiltrating the lesions could be controlled by pressure with a sterile piece of gauze. Intramuscular SSG was associated with pain at the injection site due to which the patients had difficulty in walking for a day or two. Various investigations carried out at the beginning of the treatment and during follow-up did not show any significant deviation from the baseline values in any patient. None of the cases warranted discontinuation of treatment due to side effects.

DISCUSSION

The demographic, clinical and investigative profiles of our cases [Tables 1 and 2] were similar to what has been described in the literature and by us previously.^[3,8,15,16]

WHO recommends intralesional SSG therapy particularly for early and localized LCL lesions.^[17] Tallab *et al.*^[6] standardized the schedule for IL SSG-0.3-3 ml of SSG was given on alternate days as three injections in a month and found it superior to their own daily or weekly schedules. This regimen has also been consistently effective in our previous studies.^[3,8] It also appears to be better than injections given once or twice every eight days as described by Sharquie *et al.*^[7] or 18-20 injections given by Kellum.^[18] This regimen is convenient, requires less number of injections, has fewer side effects such as necrosis of the tissue at the injection site and an almost similar cure rate of 99.2% vs 68-100% reported in the other two studies.^[7,18] Similar observations were also made in 11 patients of group 1 who completed our study. Five patients having small lesions of \leq six months' duration required only 1-2 treatment cycles for cure. Mucosal lesions, large lesions and lesions of $>$ six months' duration, needed 3-5 treatment cycles for a similar therapeutic response. Treatment of early lesions is therefore imperative for good therapeutic response. Addition of IM SSG in group 2 patients further improved the therapeutic outcome as was observed in ten patients who could be followed up till the end of the study. In group -2 patients having lesions of variable sizes and duration, excellent (80-90%) response was observed after one treatment cycle itself as compared to seven patients of group 1 with similar lesions who needed 2-4 treatment cycles for 70-80% response. While only two treatment cycles were sufficient for cure in ten patients of group 2, as many as nine patients in group 1 needed 2-5 treatment cycles. Healing of the lesions was more uniform and devoid of 'cobble-stoning' in group

2 patients. The smear / culture positivity did not affect the therapeutic outcome. It appears that IM SSG acting in tandem with higher concentrations in the lesions after IL infiltration, achieved better therapeutic response. It is also possible that the optimum therapeutic dose of SSG is much more than what the patient receives 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 sufficient 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.^[19-22] Pain and swelling at the injection site that was noted in all patients for a few days, is well documented.^[6] However, it did not warrant discontinuation of the therapy. The numbers of dropouts are almost equal in both the groups. The probable reason for dropouts, as often stated by these patients, could be apprehension for losing wages due to frequent hospitalization. Early cure after only one treatment cycle at least in six patients in both the groups, could be another possible reason for dropout in initial stages of the study.

The long distance commutes to the treatment center further increased the cost and inconvenience for them.

Although this study examines only a small number of patients, the combination regimen of intralesional and intramuscular SSG in LCL appears more effective and gave qualitatively superior healing than intralesional SSG given alone while treating large or old lesions without any added side effects. However, small lesions like papules, small nodules and lesions of short duration respond equally well to intralesional SSG alone.

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