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Randomized, double-blind, controlled, comparative study on intralesional 10% and 15% hypertonic saline versus intralesional sodium stibogluconate in *Leishmania donovani* cutaneous leishmaniasis

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Abstract

Background Intralesional 7% hypertonic saline (HS) has been shown to be effective and safe against *Leishmania donovani* and *Leishmania major* cutaneous leishmaniasis (CL), with cure rates of 92% and 96%, respectively. This study was designed to assess the efficacy and safety of 10% and 15% HS in CL.

Methods A total of 444 patients (643 lesions) were randomly allocated to sodium stibogluconate (SSG), 10% HS and 15% HS at a ratio of 2 : 2 : 1, taking into consideration any unwanted side effects that might arise with 15% HS. The follow-up period was 18 months. Survival analysis using Cox proportional hazard regression was performed to assess the effectiveness of the three treatment modalities. The clinical trial was registered at the Sri Lanka Clinical Trial Registry (SLCTR/2013/024).

Results Treatment with SSG resulted in a cure rate of 96.3% within one to seven injections (mean: 3.6 injections); the mean (median) duration of treatment was six weeks (6 weeks) per lesion. Treatment with 10% HS showed a cure rate of 93.0% within one to 10 injections (mean: 5.28 injections); the mean (median) duration of treatment was 9.3 weeks (9 weeks) per lesion. Treatment with 15% HS showed a cure rate of 93.6% within two to 10 injections (mean: 5.3 injections); the mean (median) duration of treatment was 11.3 weeks (10.0 weeks) per lesion. Treatment with 10% HS and 15% HS caused cutaneous necrosis in 3.1% and 30.6% of lesions, respectively. Despite continuous data collection for 14 months, we were unable to recruit a sample of sufficient size. Seventeen (3.8%) patients were lost to follow-up, and 24 (5.4%) were partial or non-responders.

Conclusions This study found 10% HS to be an effective and safe alternative to SSG. Treatment with HS at concentrations of 15% or above was not safe as a result of cutaneous necrosis. Safety was not studied for concentrations of 11–14%, and these concentrations should be avoided pending further evidence. Hypertonic saline is very cheap (< US$1 per 100 ml, whereas SSG is priced at US$160 per 100 ml), is prepared locally and has no systemic side effects and minimal local side effects.

Introduction

Leishmaniasis has been recorded in Sri Lanka for more than 100 years.[1–3] In 2003, the causative species was identified as *Leishmania donovani* zymodeme MON-37.[4] More than 99% of cases represent cutaneous leishmaniasis (CL), although mucocutaneous and visceral involvement caused by the same species are also reported.[5–7]

Cutaneous leishmaniasis is known to heal spontaneously. Therefore, treatment must be non-toxic and must result in a cosmetic appearance superior to that of natural healing. During the period of the present study, intralesional sodium stibogluconate (SSG)[8–11] and liquid nitrogen cryotherapy[12,13] were widely used as therapies for CL in Sri Lanka.

Sharquie *et al.*[14,15] reported that intralesionally administered 7% hypertonic sodium chloride (96.1% cure rate) is as effective as SSG (96.4% cure rate) against CL caused by *Leishmania major* and *Leishmania tropica* in Iraq.

Ranawaka and Weerakoon[16] reported that both 7% hypertonic sodium chloride solution (7% hypertonic saline [HS]) and SSG are safe as intralesional injections in *L. donovani* CL in Sri Lanka. The most effective therapy

in this study was intralesional SSG, for which the average number of injections required per lesion was 3.24 (range: 1–6), and the average duration of treatment was 5.11 weeks. Treatment with 7% HS showed a 92.2% cure rate within one to 10 injections; in addition, the number of injections required per lesion and average duration of treatment were longer, at 5.27 injections and 8.78 weeks, respectively. Other than post-inflammatory hyperpigmentation, there were no local or systemic side effects with either SSG or 7% HS.

As 7% HS had proven effective in *L. donovani* CL,[14–16] we wondered whether treatment should adhere strictly to this 7% concentration or whether a range of concentrations might be safe. Therefore, we determined to establish the effective and safe maximum concentration of intralesional HS in the treatment of CL. This randomized, double-blind, controlled, comparative study was designed to assess the efficacy and safety of 10% and 15% concentrations of HS in *L. donovani* CL.

Materials and methods

Study setting and study population

This study took place at the skin clinic of Anuradhapura Teaching Hospital, Sri Lanka, over 14 months from January 2012 to February 2013. The Teaching Hospital was the only treatment center for CL in Anuradhapura district. Anuradhapura is the largest district in the country of Sri Lanka and is situated in North Central Province, which has a low population density of 129 persons per square km. The majority (94.6%) of the population is rural and is engaged in farming (http://www.statistics.gov.lk/PopHouSat/CPH2011/Pages/Activities/Reports/CPH_2012_5Per_Rpt.pdf).

Patient selection

The study recruited patients with suspected CL who consented to participation. Pregnant or lactating women and subjects with a history of cardiac, renal, or hepatic disease were excluded. The completed clinical research form included demographic data, details of the subject's occupation, data on when and how CL was acquired, history of overseas travel, and history of affected family members and people in the neighborhood. Patients were examined for the sites and number of lesions, local features such as itchiness, pain, and discharge, and systemic features such as fever, lymphadenopathy, and hepatosplenomegaly.

The study protocol was approved by the Ethics Review Committee, Sri Lanka Medical Association, Colombo. The clinical trial was registered at the Sri Lanka Clinical Trial Registry (SLCTR/2013/024).

Randomization and blinding

All patients with CL who consented to participate in the study and who fulfilled the inclusion and exclusion criteria were assigned to one of three treatment groups. The treatment options were documented separately and packed in opaque envelopes numbered consecutively according to the randomization schedule at a ratio of 2 : 2 : 1 for the SSG, 10% HS, and 15% HS treatment groups, respectively, taking into consideration any unwanted side effects that might arise with the 15% HS injections. The allocation sequence was concealed from the researcher who enrolled and assessed the participants by the use of sequentially numbered, opaque, sealed, and stapled envelopes that were impermeable even to intense light.

The participants and the investigator (who assessed the patients for their clinical response) were blind to the type of therapy allocated. The same investigator performed a clinical assessment in all participants at each visit until cure. Two medical officers were trained to perform intralesional injections and continued to do so throughout the study period.

Parasitological investigations

A leishmania slit-skin smear (SSS) was performed in all patients. The smear was stained with Giemsa stain. In patients with a negative SSS, if lesions were clinically indicative, a skin biopsy was performed for confirmation. Polymerase chain reaction (PCR) and culture were not performed routinely.

Preparation of hypertonic sodium chloride

Concentrations of 10% and 15% HS were prepared by dissolving 18.2 and 28.2 g, respectively, of medical sodium chloride in 200 ml of 0.9% sodium chloride (normal saline) solutions. The solutions were sterilized in an autoclave at 121 °C for 20 minutes in a screw-capped bottle. Fresh solutions were prepared monthly.

Technique for infiltration

A disposable 2-ml syringe with a fine-gauge needle was used. The lesion was infiltrated with the drug solution thoroughly until the base of the lesion was completely blanched. The amount of solution required ranged from 0.2 to 4.0 ml per lesion, depending on the size of the lesion. No local anesthesia was added. The solutions were injected intralesionally and not subcutaneously.

Frequency of infiltration and follow-up

Patients were seen weekly for the first three injections, fortnightly for the fourth and fifth injections, and then monthly until a cure was achieved. At each visit, the patient was examined by the primary investigator, who was blinded to the therapy. Patients were followed up every three months after cure for six months to assess recurrences and evidence of visceralization.

Outcome measures

The outcome measures of the study were status of the skin lesion, side effects at the site of the lesion caused by the

injections, duration of treatment, and time required to achieve the cure of the lesion.

At each clinic visit, lesions were examined and responses were graded by an investigator who did not perform the injections. Responses were graded as slight (10% improvement from the initial status of the lesion), mild (20–30% improvement), moderate (50% improvement), marked (80–90% improvement), or as total if the lesion had cleared and parasites were not detected in the affected area by smear or culture. Both marked improvements and total clearance were considered to represent a cure.

Self-healing control group

In this part of the study, we intended to assess whether any treatment response that might be achieved was really attributable to treatment and not to self-healing. Therefore, in each of 50 patients with two or more lesions, who consented to join the control group, one non-secondarily infected lesion in an area that was usually covered (the head and exposed parts of limbs were excluded) was left untreated as a control lesion against which to compare the response of the treated lesion(s). The remaining lesions in each of the 50 patients were treated. After the treated lesions were cured, the untreated lesions were treated. These formerly untreated lesions were treated soon after the clear improvement of the treated lesions had become evident. The treatment regimen used was similar to that in the study group, and data were included in the final analysis.

Statistical analysis

The different treatment groups were checked for demographic characteristics (age, gender) and behavior-related variables (employment) and clinical variables such as clinical presentation, sites of lesions, and number of lesions. No differences in these variables emerged between subjects who completed the study and participants lost from follow-up as the latter group was very small.

Simple descriptive analysis was used to compare the treatment groups for the variables described above. Survival analysis techniques, such as Cox proportional hazard models, were used to assess the effectiveness of the three treatments. In the assessment of the treatment groups, the sex, age in completed years, and occupation (summarized into outdoor and indoor occupations) of the individual, and the site of the lesion (grouped into face, neck, trunk, upper limbs, and lower limbs) were used to construct the regression model. All analyses were performed using IBM SPSS Version 21.0 (IBM Corp., Armonk, New York, NY, USA).

The primary analysis referred to intention to treat and involved all patients who were randomly assigned to one of the three groups. Intention-to-treat analysis was considered as there was no possibility that treatment would be contaminated because no other treatment facilities were available and because the clients were blinded to the treatment. Patients who had dropped out (or were lost from follow-up) and those who remained on treatment without any obvious improvement were censored from the survival analysis in order to compare the effectiveness of the three treatment modalities.

Sample size calculation and trial limitations

The sample size was calculated as for an equivalence study with the anticipation that there would be no major difference in effectiveness among the treatments but that one treatment (i.e. hypertonic saline) would demonstrate practical advantages such as lower cost. Therefore, the sample size required was large. Approximately 473 patients per group were required to enable the detection of a treatment difference of 5% with a lowest cure rate of one group of 90%.

Despite continuous data collection for 14 months, we failed to recruit the desired number of study participants and achieved a final sample of only 444 participants divided into the three groups. This failure to recruit the required number of participants may limit the internal validity of the findings. Measures taken to ensure the random allocation of participants to the three treatment groups and measures for the concealment of allocation, and the blinding of investigators at the treatment and outcome assessments minimized bias at these stages. To minimize the bias caused by our subjective assessment of response according to the size of the lesion, this assessment was undertaken by a single investigator who was blind to the treatment method used. The limitation caused by attrition may be considered minimal as the numbers of participants lost from follow-up amounted to fewer than 5% and because intention-to-treat analysis was used.

Subgroup analyses are known to pose concerns of multiplicity, whereby if enough subgroups are tested, a false positive result might emerge by chance alone.[17] Therefore, in order to counter concerns related to multiplicity of analysis, subgroup analysis was not attempted by the researchers, and analysis was limited to the three intervention groups.

Results

Figure 1 shows a flow chart depicting the study participants. A total of 503 patients were invited to participate in the study, and 468 (93.0%) consented to do so. Following the application of exclusion criteria, 444 patients remained. Of these 444 participants, 17 (3.8%) were lost from follow-up and were excluded from the final analysis.

Clinico-epidemiological profile of the study group

Of the 444 patients in the study group, 286 were men and 158 were women; the male : female ratio was 1.8 : 1 (Table 1). The average age of the study population was 32.7 years (range: 14 months to 88 years). The majority (60.8%) of participants belonged to the 16–45-year age groups.

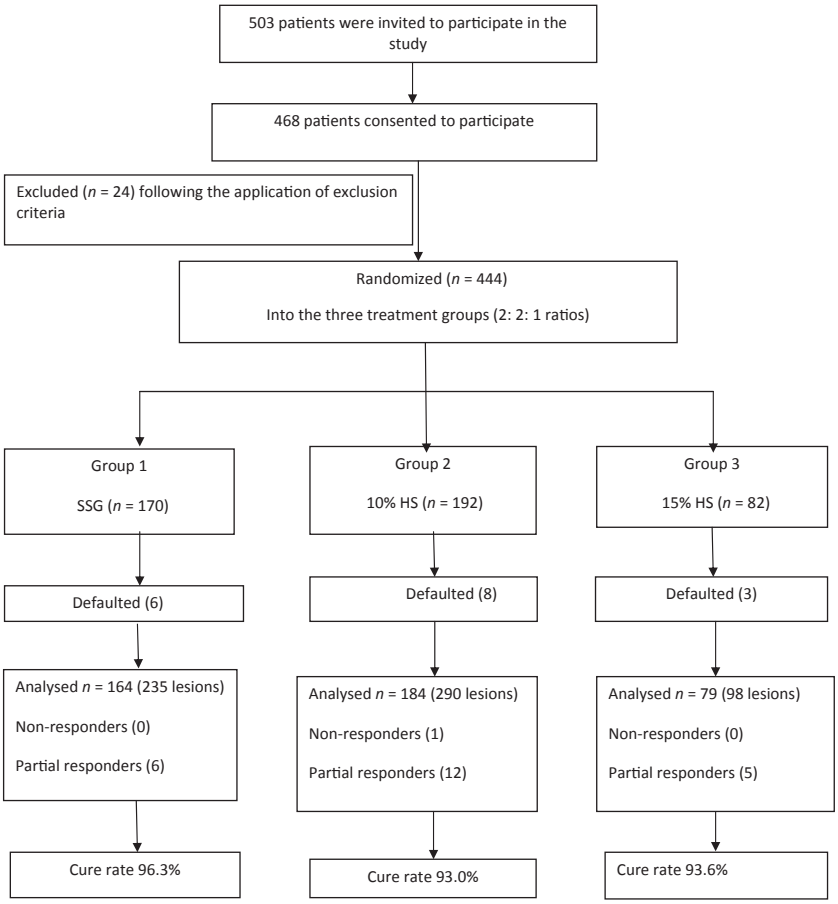


Figure 1 Flow diagram showing participation in the study. SSG, sodium stibogluconate; 10% HS, 10% hypertonic saline; 15% HS, 15% hypertonic saline

A total of 74.8% of participants were civilians who had acquired the disease locally; 45.3% were farmers or children. Military personnel who had acquired the disease in the jungle accounted for 25.2% of participants.

The average delay in presentation was eight months (range: 4 weeks to 5 years). A total of 91.0% of lesions were located on exposed areas of the body. The majority (69.8%) of participants had a single lesion. None of the participants had evidence of visceralization, such as fever, lymphadenopathy, and/or hepatosplenomegaly at the time of presentation. A total of 14.3% of participants had associated photodermatitis which disappeared when CL healed. A total of 43.7% of cutaneous lesions were surrounded by a hypopigmented halo.

Except for two women who had acquired the disease while in Dubai, all cases were autochthonous.

Effectiveness of the three treatment modalities

The cure rate was highest for SSG (96.3%), followed by 15% HS (93.6%) and 10% HS (93.0%) (Table 2). The estimated mean and median time taken for cure was considerably shorter for SSG (Table 3). Kaplan–Meier curves for the efficacies of the three treatment methods demonstrated that treatment with SSG was more effective than the other two treatment methods throughout the study (Fig. 2). This suggests that SSG gives faster relief than 10% HS and 15% HS; the very similar plots for the latter two suggest that there is very little difference in efficacy between these two methods.

The percentages of lesions cured with SSG and 10% HS, and the total number of injections required per lesion, are shown in Figure 3. Treatment with SSG resulted in the cure of 96.3% of lesions within one to seven injections (mean: 3.67 injections). In the SSG group, 59.9% and 89.6% of lesions were cured within three and four injections, respectively. One lesion that had been initially treated with SSG recurred after 13 months.

Treatment with 10% HS resulted in the cure of 93.0% of lesions within one to 10 injections (mean: 5.28

Table 1 Characteristics of the study sample by age, sex and occupation, and clinical presentation, site and number of cutaneous leishmaniasis lesions[a]

	n		
	Male	**Female**	**%**
Age, years (*n* = 396)			
0–15	23	35	14.6
16–30	112	35	37.1
31–45	78	16	23.7
46–59	43	34	19.4
≥60	11	9	5.0
Occupation (*n* = 397)			
Farmers	102		25.7
Military personnel	100		25.2
Schoolchildren	78		19.6
Housewives	32		8.1
Teachers	10		2.5
Others	75		18.9
Clinical presentation (*n* = 548)			
Papules (≤ 1 cm diameter)	181		33.0
Nodules (> 1 cm diameter)	56		10.2
Plaques	31		5.7
Nodulo-ulcerative lesion	271		49.4
Chronic non-healing ulcers	9		1.6
Site of lesion (*n* = 520)			
Face	98		18.8
Upper limb	252		48.5
Lower limb	116		22.3
Trunk	54		10.4
Number of lesions (*n* = 384)			
1	268		69.8
2	77		20.1
3	21		5.5
4	7		1.8
>4 (5–11 lesions)	11		2.9

[a]Totals vary as a result of missing data.

injections). With 10% HS, 21.5% and 35.2% of lesions were cured with three and four injections, respectively; 64.8% of lesions required between five and 10 injections to achieve cure. Nineteen lesions (6.3%) which showed 30–50% improvement with 10% HS, were considered partial responders and were then cured with one to three SSG injections. Treatment with 10% HS caused necrosis in 3.1% of lesions. This did not recur during six months of follow-up.

Although 15% HS cured 93.6% of CL lesions within two to 10 injections (mean: 5.5 injections), it caused cutaneous necrosis in 30.6% of treated lesions, which healed with an unsightly scar (Table 2).

Other than post-inflammatory hyperpigmentation, which faded over 6–8 months, we found no systemic or significant local side effects with either SSG or 10% HS. There was no significant difference in treatment response to 10% HS with regard to the size, type (ulcerative or papular), or location (head, neck, upper and lower extremities) of lesions (Tables 4 and 5).

Leishmania recidivans developed in three (1.2%), five (1.6%), and three (2.9%) lesions treated with SSG, 10% HS, and 15% HS, respectively. These lesions were subsequently treated with liquid nitrogen cryotherapy.

The 50 lesions that had remained untreated did not change during the period of therapy.

Discussion

Leishmaniasis predominantly affects people in developing countries. Therefore, treatment should be cost-effective, cheap, and available at all times. Although occasional cases are reported from all provinces in Sri Lanka, the disease is endemic in the Southern[18] and North Central Provinces,[19] and more than 1500 cases were reported in 2012. This study was conducted at Anuradhapura Teaching Hospital, which was the only leishmania treatment center in Anuradhapura district.

There have been various recommendations about the frequency of repeat intralesional injections. The World Health Organization (WHO) recommends that injections should be repeated at intervals of 1–2 days.[20] Bumb *et al.*[9] showed twice weekly (73%) injections to be superior to weekly (62%) injections of stibogluconate. Faris *et al.*[21] repeated injections every other day between eight and 24 times, and Sharquie *et al.*[8] recommended an interval of 10–15 days. Tallab *et al.*[22] proved that alternate-day (97%) and weekly (91%) intralesional SSG was more effective than daily (67%) treatments. We carried out a regimen designed for the convenience of patients who traveled from 120 km away and achieved a high cure rate with the minimum number of injections.

Sodium stibogluconate was the most effective treatment and achieved the most rapid relief. However, SSG is expensive (US$160 per 100 ml) and its supply is interrupted, and moreover SSG resistance is emerging in Sri Lanka.[23–26] In the present study, SSG was found to have a 4% failure rate. In hyperendemic districts of North Bihar, India, treatment with SSG has been reported to fail in 50–65% of patients.[23]

Given the high costs and severe systemic side effects associated with IM and IV infiltrations, the use of SSG was limited to dermatology units in Sri Lanka, the nearest of which was situated 120 km distant from the hyperendemic areas in North Central Province. Weekly travel to the treatment center represented a significant financial burden on patients, the majority of whom were farmers; we estimated this cost to amount to approximately SLR15,000 (US$115) per full treatment course, excluding the costs of lost working days. The monthly income of

Table 2 Summary of treatment with sodium stibogluconate (SSG), and 10% and 15% hypertonic saline (HS) against cutaneous leishmaniasis caused by *Leishmania donovani* in Sri Lanka

Treatment	SSG	10% HS	15% HS
Total patients, *n*	170	192	82
Total lesions, *n*	245	297	101
Mode of treatment	Intralesional injections in all three therapies		
Injections per lesion, mean (range)	3.6 (1–7)	5.28 (1–10)	5.5 (2–10)
Duration of therapy per lesion, weeks, mean (range)	6 (1–29)	11.2 (1–30)	12.65 (2–30)
Non-responders, *n*	0	1 (0.5%)	0
Partial responders, *n* (%)	6 (3.7%)	12 (6.5%)	5 (6.4%)
Cure rate,%	96.3%	93.0%	93.6%
Lost from follow-up, *n*	6	8	3
Cost	US$160 per 100 ml	US$1 per 500 ml	
Local side effects			
Pain during injections	In all patients	In all patients	More painful
Post-inflammatory hyperpigmentation	Yes; faded over 6–8 months	Yes; faded over 6–8 months	Yes; faded over 6–8 months
Scarring	No	No	Yes, scarring +
Post-inflammatory depigmentation	No	No	No
Ulceration and necrosis	No	9/289 (3.1%)	30/98 (30.6%)
Leishmania recidivans	3 (1.2%)	4 (1.4%)	4 (4.3%)
Systemic side effects	None	None	None
Availability	Interrupted supply	Can prepare at local hospitals	

Table 3 Mean and median times taken for cure for the different treatment groups under study

	Mean time, weeks		Median time, weeks	
Treatment	Estimated mean	95% CI	Estimated median	95% CI
SSG	6.0	5.5–6.6	6	5.5–6.5
10% HS	11.2	10.2–12.2	9	7.7–10.3
15% HS	12.65	9.9–15.6	10	9.4–10.6

ANOVAS *F*-value = 44.3; significance: $P < 0.001$.
Independent-sample median test significance: $P < 0.001$.
95% CI, 95% confidence interval; SSG, sodium stibogluconate; HS, hypertonic saline.

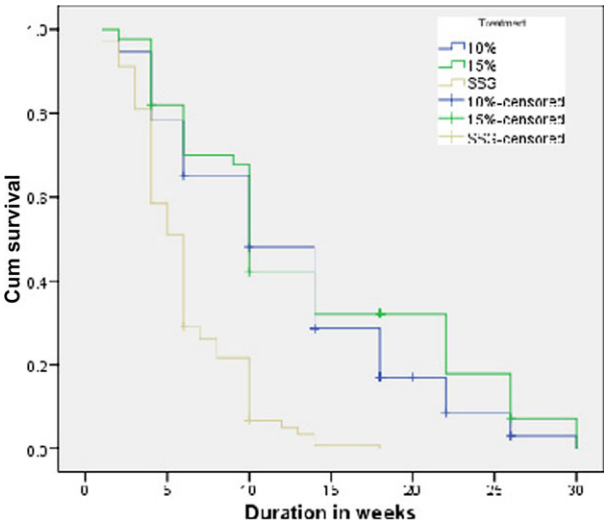


Figure 2 Kaplan–Meier curves for cure in the three treatment groups. SSG, sodium stibogluconate; 10% HS, 10% hypertonic saline; 15% HS, 15% hypertonic saline

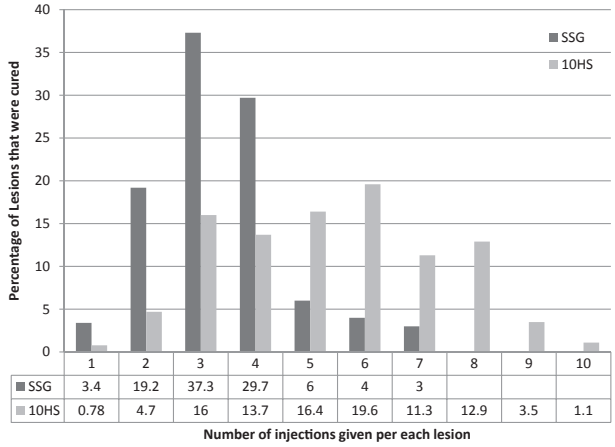
Sri Lankan farmers in 2012 was SLR 20,000–30,000 (US $175–260).

Although the treatment duration was prolonged, 10% HS was found to be effective and safe in *L. donovani* CL. The period of treatment was much shorter than the time required for the natural healing of *L. major* (≥9 months), *L. tropica* (≥12 months),[14,15] and *L. donovani* (≥12 months) CL.[16] Hypertonic saline is very cheap (< US$1 per 100 ml) and can be prepared easily at local hospitals; it also carries no systemic side effects and minimal local side effects.

However, 15% HS caused cutaneous necrosis in 30.6% of infiltrated lesions and was not considered to be safe.

Hypertonic saline at a concentration of 7% was found to be a safe and effective alternative to SSG in treatments of CL caused by *L. major*, *L. tropica*,[14,15] and *L. donovani*.[16] The present study provides proof that in concentrations up to 10%, HS is an effective and safe alternative to SSG.

At present, no disease control methods are implemented in endemic areas in Sri Lanka. Although research has been carried out to identify possible vectors, the vector, reservoir host, and pattern of disease transmission in Sri Lanka have not yet been elucidated.[27,28] Strategies to



	1	2	3	4	5	6	7	8	9	10
SSG	3.4	19.2	37.3	29.7	6	4	3			
10HS	0.78	4.7	16	13.7	16.4	19.6	11.3	12.9	3.5	1.1

Figure 3 Percentages of cutaneous leishmaniasis lesions cured with sodium stibogluconate (SSG) and 10% hypertonic sodium chloride (10% HS) and numbers of injections per lesion in total

control or eradicate the vector by insecticide spraying are discouraged in the context of this lack of information. Reducing or eradicating parasitic density with early treatment is a realistic method of disease control and should ideally be achieved with a cheap, non-toxic, orally administered drug. As no effective oral drugs are available in Sri Lanka, these aims can be achieved by introducing treatment with HS in endemic areas.

The mechanism of action of HS may refer to its high osmolality, which kills the parasite by osmotic stress.

The self-healing nature of CL makes it difficult to assess the efficacy of treatment in uncontrolled therapeutic trials. As our patients were travelling distances of up to 120 km, the decision to leave a lesion untreated for the purposes of a clinical study was difficult to make. Therefore, a few selected patients who consented to act as controls were maintained. Our data demonstrated that the response was attributable to treatment rather than to self-healing.

In conclusion, this study proved that intralesional 10% HS was an effective and safe alternative to intralesional SSG in *L. donovani* CL. Hypertonic saline at concentrations of 15% and above caused cutaneous necrosis and was not safe in intralesional injections. The safety of HS at concentrations of 11–14% was not investigated and

Table 4 Efficacy of sodium stibogluconate and 10% hypertonic saline on ulcerative and papular cutaneous leishmaniasis lesions according to size of lesion

Treatment	**Sodium stibogluconate**				**10% hypertonic saline**			
Type of lesion	Ulcer		Papule		Ulcer		Papule	
Diameter of lesion, mm	<25	≥25	≤10	>10	<25	≥25	≤10	>10
Total number of lesions	55	35	53	18	63	39	147	44
Injections per lesion, mean (range)	3.44 (1–5)	3.57 (2–6)	3.25 (1–5)	3.55 (2–6)	5.24 (2–8)	5.68 (2–10)	5.33 (1–10)	5.56 (2–10)
Treatment per lesion, weeks, mean (range)	4.86 (1–11)	5 (2–11)	4.52 (1–13)	5.5 (2–12)	8.3(2–17)	9.6 (2–18)	10.8 (2–18)	7.9 (5–13)

Table 5 Efficacy of sodium stibogluconate and 10% hypertonic saline on cutaneous leishmaniasis lesions according to the location of lesions: head, trunk, and upper and lower extremities

Treatment	**Sodium stibogluconate**				**10% hypertonic saline**			
Type of lesion	Head	Upper	Lower	Trunk	Head	Upper	Lower	Trunk
Total number of lesions	41	102	57	25	57	138	62	38
Injections per lesion, mean (range)	3 (1–7)	3.4 (2–5)	3.9 (2–6)	3.25 (2–6)	5.57 (1–10)	5.42 (2–10)	5.28 (2–9)	5.3 (2–9)
Treatment per lesion, weeks, mean (range)	5.46 (2–13)	4.45 (1–9)	5.14 (1–11)	5.13 (3–9)	12 (2–17)	7.8 (2–18)	8.2 (3–15)	10.8 (5–16)

thus these concentrations should be avoided until further evidence indicates otherwise.

In view of the benefits of low cost, preparation at local hospitals, lack of systemic side effects and minimal local side effects associated with HS, and the emerging resistance to SSG, we recommend that developing countries should introduce treatment with HS in hyperendemic areas and train medical officers and nurses working at local hospitals to treat CL patients. Treatment with SSG can be reserved for partial and non-responders to HS. Such a strategy would be cost-effective to government and convenient and amenable to the local patient population, the majority of whom are farmers.

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