

The effect of intralesional meglumine antimoniate (glucantime) versus a combination of topical trichloroacetic acid 50% and local heat therapy by non-ablative radiofrequency on cutaneous leishmaniasis lesions

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BACKGROUND: Pentavalent antimonial drugs have been the first line of therapy in cutaneous leishmaniasis for many years. However the cure rate of these agents is still not favorable. This study was carried out to compare the effect of 50% topical trichloroacetic acid in combination with non-ablative radiofrequency heat therapy and intralesional glucantime on cutaneous leishmaniasis. **METHODS:** A total of 76 lesions in 60 patients were studied and randomly divided into 2 groups. A total of 30 patients with 38 lesions were treated with intralesional injection of meglumine antimoniate (Glucantime) (Sanofi-Aventis, France) as group-1 and the 38 lesions in the remaining 30 patients were treated with a combination of non-ablative radiofrequency and 50% topical trichloroacetic acid as group-2. Complete cure rate besides the lesion's changes in size and size of scars were assessed and compared between groups especially according to gender and location of initial lesions. **RESULTS:** complete cure of after 4 months of treatment was achieved significantly more in group-1 than group-2 ($p = 0.01$). However, the complete cure rate at month 6 of treatment was not significantly different between groups ($p = 0.06$). Score II-III of the lesions' reduction size (more than 50% reduction in size) was achieved significantly more in group-1 ($p = 0.004$). There was no significant cure rate difference between the two groups according to the location of lesions (head and upper extremities vs. lower extremities) or the patient's sex. Moreover, there was no significant scar size difference between groups according to the location of lesions. **CONCLUSIONS:** The study showed that intralesional glucantime has a significantly higher cure rate of cutaneous leishmaniasis in a shorter time than 50% trichloroacetic acid in combination with non-ablative radiofrequency. Furthermore, it could significantly induced efficient reduction size of more than 50% in most lesions. The analysis reveals that intralesional glucantime still has the superiority to be the first line of therapy in cutaneous leishmaniasis.

KEYWORDS: Meglumine Antimoniate (Glucantime), Trichloroacetic Acid, Non-ablative Radiofrequency, Cutaneous Leishmaniasis, Scar

BACKGROUND

It has been known for years that Iran is one of the seven countries in which over 90% of new cutaneous leishmaniasis (CL) cases emerge each year.^[1-4] After many years of first report, CL is still one of the endemic parasitic infections in many provinces of Iran especially in Isfahan and khorasan.^[3,5-13] In some of our rural areas more than 70% of people bear the scar sign of past CL infection.^[5] Despite the self-resolving and healing characteristic of CL lesions, it can cause disfigurement and deep scars especially in areas that are not usually covered by cloths.^[9,14] In the past decades several studies have focused on different CL treatment schedules comprising of administration of intramuscular or intralesional pentavalent antimonial agents alone or in

combination with other drugs like ketoconazole and pentoxifylline, utilizing peeling agents, cryotherapy, and lately heat therapy. However, there is no single definite treatment available for CL with the ability to cure in a short period of time.

During the past years we performed a series of studies regarding efficacy of glucantime, trichloroacetic acid (TCA), and radiofrequency (RF) heat therapy. They showed that TCA could be a potential alternative for intralesional glucantime with an appropriate effectiveness however its combination with intralesional glucantime could shorten the healing process time.^[3,15,16] Moreover, based on previous studies, especially our 2007 study,^[16] heat therapy with ablative RF could be used as an efficacious treatment for CL even more than conventional treatment with

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glucantime. These results encouraged us to compare the efficacy of intralesional glucantime and combination of topical TCA 50% and less invasive non-ablative RF in treatment of CL.

METHODS

A. Study Population

This computer-based randomized clinical trial was conducted from March 2008 to March 2009, (286046 Isfahan University of Medical Sciences) and recruited patients (age range, 5–50 years) who were scheduled for treatment of documented acute cutaneous leishmaniasis in the Skin Disease and Leishmaniasis Research center (SDLRC) (Sedigheh Tahere), Isfahan University of Medical Science, Isfahan, Iran.

The study was approved by the SDLRC's ethics committee, and written and informed consents were obtained from the patients.

Pregnant patients, children less than 5 years of age, patients who had palpebral lesions (less than 20 mm from palpebral margin), more than 5 lesions, more than 12 weeks duration of leishmaniasis, history of any specific anti-leishmaniasis therapy, or significant underlying diseases were excluded from the study.

A total of 80 lesions were studied and randomly divided into 2 groups. However, only 76 lesions in 60 patients were analyzed after excluding the missing data.

A total of 30 patients with 38 lesions that were treated with intralesional injection of meglumine antimoniate (Glucantime) (Sanofi-Aventis, France) were considered as group-1 and the 38 lesions in the remaining patients were treated with a combination of non-ablative radiofrequency and topical TCA 50% as group-2.

B. Lesion's characteristics

Number, location and clinical feature of the lesions, along with presence of indurations, erythematic areas, ulcers or scars were examined and recorded. Each induration, erythematic area, and lesion size was measured via its two greatest perpendicular diameters in millimeters and photographed before administration of the treatment, and 4 and 6 months after completion of the treatment course. The examinations and measurements were performed by the investigators who were blinded to the type of treatment.

C. Treatment methods

-Intralesional Glucantime

Intralesional injection of glucantime was administered

twice a week and continued up to 8 weeks until absolute healing of lesions, by means of complete epithelialization of surface of lesions, was achieved. Glucantime was injected into the intact margin of the lesion until the injection site and 1 mm rim of the surrounding normal skin were bleached. The procedure was replicated all around the lesion to achieve a completely blanched lesion.^[17]

-Combination of topical TCA 50% and local heat therapy by non-ablative RF

After cleansing the lesion with alcohol, TCA 50% (Merck, Berlin, Germany) was applied onto the lesion using a cotton swab, until frosting the lesion, once a week and for up to 2 weeks.

Afterward, a controlled localized heating of the lesions was performed using an RF heat generator (4 MHz, maximum output 90 W; Ellman International Inc, NY, USA) as was described in detail in our previous study.^[17] The area was heated to 42 C surface temperature for 30 seconds once a week and for 4 consecutive weeks.

D. Treatment responses

Clinical improvement and lesion changes were assessed at the end of the treatment, and in 4 and 6 months follow up.

-Complete cure

Complete clinical healing was defined as complete re-epithelialization of the lesions, flattening of the lesions and lack of indurations along with negative direct smear.^[17]

- Partial cure

Partial clinical improvement along with decreased size of indurations, erythematic areas, and lesions were considered as partial cure at the end of the treatment.^[17]

-Non-cure or treatment failure

No clinical improvements along with unchanged or even increased size of lesions.^[17,18]

It is important to say that if neither complete nor partial cure was achieved in 8 weeks (failure to cure) the case was removed from the study and underwent standard systemic treatment.

E. Reduction size scores in month 6

Standard quartile grading was used for scoring the size reduction percentage of lesions and scars as follow:

Score 0 was considered for reduction in size of 25% or

less. Score I was considered for the reduction of more than 25% but less than 50%. Score II was considered for the reduction of equal to or more than 50% but less than 75%. Finally if the reduction was equal to or more than 75% it was considered as score III.^[17]

F. Statistical Analysis

The univariate analysis of the continuous variables was performed with the Student t-test, and the categorical variables were compared using the chi square test and Fisher's exact test, as appropriate. Moreover, independent t-test was used for comparison between groups and paired t-test was used for intragroup comparison. For the statistical analyses, SPSS version 15.0 (SPSS Inc, Chicago, IL) was used. All P-values were 2-tailed. A P-value of less than 0.05 was considered significant.

RESULTS

A total of 60 patients with 76 lesions and mean age of 25.11 ± 13.3 (range of 5-50 years of age) were enrolled into the study. A total of 30 patients with 38 lesions were treated with glutamine only (group-1) and the remaining 30 cases were treated with a combination of TCA 50% and non-ablative RF (group-2). Demographic and lesion characteristics are shown in table 1. There was no significant difference between the groups according to the sex distribution ($p = 0.11$).

A. Location of lesions

61 lesions of the total 76 were located in the upper extremities or head and the 15 remaining lesions (19.73%) were in the lower extremities.

31 of 38 lesions (81.5%) in group-1 and 30 of 38 lesions (78.9%) in group-2 were located in the upper extremities or head. 7 lesions (18.4%) of group-1 and 8 lesions (21.05%) of group-2 were located in the lower extremities. There was no significant difference between groups according to distribution of lesion in the different locations ($p = 0.99$).

B. size of lesions and scars

-At the beginning

The mean size of lesions at the beginning of study was not different between groups ($p = 0.58$) and was 3.18 ± 0.89 cm in group-1 and 2.66 ± 0.37 cm in group-2.

-At the month 6

At the end of month 6 of treatment the remaining

lesions or scars were measured. This showed the mean size of lesions or scars to be 0.85 ± 0.33 cm in group-1 and 1.30 ± 0.42 cm in group-2 that was not significantly different between groups ($p = 0.40$).

-Reduction size scores in month 6

Reduction size score of 0, I, II and III were achieved in 0, 2 (8%), 5 (20%) and 18 (72%) of lesions in group-1, respectively. Furthermore, reduction size score of 0, I, II and III were achieved in 2 (11.8%), 6 (35.3%), 3 (17.6%) and 6 (35.3%) of lesions in group-2, respectively.

The reduction size score of II and III (reduction size of more than 50%) was achieved significantly more in group-1 than group-2 ($p = 0.004$).

C. size of lesions and scars according to the location of lesions

Mean size of lesions after 6 months of treatment was not significantly different between or within groups according to location of lesions in head and upper extremities or lower extremities (Table 1).

D. Complete cure

-Month 4

In month 4 of treatment, complete cure was achieved in 21 patients (55.3%) of group-1 and 10 patients (26.3%) of group-2, which was significantly higher in group-1 ($P = 0.01$). There was no significant between groups or intragroup cure difference according to the male or female gender (Table 1).

-Month 6

Moreover, in month 6 of treatment complete cure was achieved in 24 patients (63.2%) of group-1 and 16 patients (42.1%) of group-2 ($p = 0.06$) that was not significant between groups ($p = 0.06$). There was no significant between groups or intragroup difference according to male or female gender (Table 1).

E. Complete cure of lesions according to the location of lesions

We also compared the complete cure rate of lesions between groups in month 6 of treatment according to the location of lesions. There was no significant complete cure rate difference between groups according to the location of lesions, $p = 0.717$.

Furthermore, there was no significant complete cure rate difference within groups, $p = 0.22$ and $p = 0.99$ for group-1 and 2, respectively (Table 1).

Table 1. Characteristics of lesions before and after treatment and complete cure rate between groups

Characteristics	Intralesional Glucan-time (Group-1)	TCA 50% and RF (group-2)	Total	P-value (between groups)
Number of patients	30	30	60	
Number of lesions	38	38	76	
lesions according to sex				0.11
-Male	15(39.5%)	22(57.9%)	37.76(48.7%)	
-Female	23(60.5%)	16(42.1%)	39.76(51.3%)	
4 month complete cure of lesions	21.38(55.3%)	10.38(26.3%)	31.76(40.8%)	0.01
-Male	6.15(40%)	3.22(13.6%)	9.37(24.3%)	0.06
-Female	15.23(65.2%)	7.16(43.8%)	22.39(56.4%)	0.18
P-value(within groups)	0.126	0.06		
6 month complete cure of lesions	24.38(63.2%)	16.38(42.1%)	40.76(52.6%)	0.06
-Male	8.15(53.3%)	8.22(36.4%)	16.37(43.2%)	0.30
-Female	16.23(69.6%)	8.16(50%)	24.39(61.5%)	0.21
P-value(within groups)	0.31	0.40		
Mean size of lesions and scars (mm)				
-Before treatment	3.18 ± 0.89(SE)	2.66 ± 0.37(SE)		0.58
-After 6 months of treatment	0.85 ± 0.33(SE)	1.30 ± 0.42(SE)		0.40
-Reduction size score II ,III during 6 months of treatment	23(92%)	9(53%)		0.004
Location of lesions before treatment				0.99
-Head and Upper extremities	31.38(81.58%)	30.38(78.95%)	61.76(80.26%)	
- Lower extremities	7.38(18.42%)	8.38(21.05%)	15.76(19.73%)	
Complete cure according to the location of lesions				
- Head and Upper extremities	18.31(58.1%)	12.30(40%)	30.61(50.8%)	0.15
-Lower extremities	6.6(85.7%)	4.8(50%)	10.15(66.7%)	0.20
P-value(within groups)	0.22	0.99		
Size of lesions before treatment				0.717
-Head and Upper extremities	2.06 ± 0.54	2.48 ± 0.35		0.518
-Lower extremities	8.14 ± 3.86	3.46 ± 1.35		0.288
Size of scars according to the location of lesions				
-Head and Upper extremities	0.57 ± 0.27	1.12 ± 0.38		0.238
-Lower extremities	1.77 ± 1.05	1.93 ± 1.45		0.930
P-value(within groups)	0.124	0.440		

Data are presented as n (%) and mean ± standard deviation. Trichloroacetic acid; TCA, radiofrequency, RF

DISCUSSION

CL is an endemic disease in Iran and is even a hyper-endemic disease in some of our rural areas. Despite the high resistance rate and side effects of intralesional

glucantime, it is still the first line of therapy for CL in our country as in other countries of the world. In the past decade, several studies have been performed to identify some alternatives like ketoconazole for penta-

valent antimonial agents.^[19] Our latest studies, which are in line with others, have revealed that heat therapy by different methods of delivery like ablative radiofrequency could be an efficacious alternative schedule for conventional treatment with intralesional glucantime.^[14,17] The highest reported efficacy rate for intralesional glucantime in Iran is 55%^[20] that could be alternatively achieved by topical TCA 50% according to our previous studies.^[3,15,16]

The present randomized prospective study showed that there is no significant difference in complete cure rate after 6 months of treatment between groups (62.2% in intralesional glucantime group vs. 42.1% in combination of TCA 50% and non-ablative RF group) ($p = 0.06$). However, after 4 months of treatment intralesional glucantime showed a significantly higher complete cure rate of 55.3% in comparison with 26.3% of TCA and non-ablative RF group ($p = 0.01$). This means that glucantime still has superiority in treating CL lesions over the combination of TCA 50% and non-ablative RF as its healing process is significantly faster ($p = 0.01$).

The analysis showed no significant cure rate differences between or within groups according to the patient's gender or location of lesions (head and upper extremities vs. lower extremities).

The mean size of scars and remaining lesions were not significantly differed between groups at the end of month 6 of treatment. On the other hand, the analysis of reduction size scoring system showed that 92% of lesions in the glucantime group had more than 50% reduction in size after 6 months of treatment. However, this amount of reduction in size was achieved only in 53% of lesions in the combination therapy group ($p = 0.004$). This is strong evidence that glucantime is more effective in the treatment of CL lesions according to the reduction size of lesions and scars.

These results are not exactly in line with our previous work which was about superiority of ablative RF heat therapy in comparison with intralesional glucantime on treatment of CL lesions.^[16] In the present work we decide to evaluate non-ablative accent RF for treatment of CL lesions as it is a less invasive method of heat delivery with fewer side effects, however, the results are not comparable. This seems to be related to some rational reasons such as inflexible metal-plate electrodes of the accent RF device that could reduce its contact surface with CL lesions in comparison with ablative RF. Moreover, the CL lesions are not smooth enough to allow the inflexible

metal-plate electrode to be placed appropriately on their surface.

This study has some limitations. For instance more favorable results may have been achieved if we could use more flexible probes to affect more of the surface of the lesions.

We utilized TCA 50% before applying accent RF to dry the wet CL lesion enough to achieve appropriate results. However, we now hypothesize that utilizing combination therapy of topical peeling agent TCA 50% and non-ablative RF heat therapy could probably postpone the healing process of lesions due to excessive damaging of cells and causing new onset wheals on the lesions.

There is another limitation in this study; as we only followed up the patients for a longer period of time than the other study (6 months vs. 3 months) that could easily affect the results of the studies.

In conclusion, the present study strongly showed that intralesional glucantime has a significantly higher complete cure rate in a shorter time than TCA 50% in combination with non-ablative RF. Furthermore, it could induce a significant reduction in size of more than 50% in most of the lesions. The data demonstrate that intralesional glucantime still has superiority to be first line of treatment in CL lesions. However, we suggest performing further studies to eliminate the effect of the above mentioned limitations and to compare the effect of ablative and non-ablative methods of RF heat delivery on treatment of CL lesions.

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