Efficacy of Cryotherapy versus Intralesional Meglumine Antimoniate (Glucantime) for Treatment of Cutaneous Leishmaniasis in Children

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Abstract. We compared intralesional glucantime and cryotherapy for treatment of children with cutaneous leishmaniasis in Iran. We observed that cryotherapy is an effective treatment for cutaneous leishmaniasis in children. No serious post-treatment side effects were observed in either group. At six months of follow-up, no recurrence of disease was observed in cured patients in either group. Because of its simplicity, lower cost, low rate of serious complications, and greater tolerability, cryotherapy should be recommended as an appropriate alternative treatment for leishmaniasis in children.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a chronic parasitic disease that is endemic in many regions of the world. Khorasan Province in Iran is one of the most prominent sites of CL in this country. Leishmania tropica is endemic in this region and its prevalence is not age dependent.1

Treatment for CL aims to hasten recovery and prevent further transmission and secondary bacterial infection. However, response to treatment is often unpredictable and unsatisfactory.2 Different treatments for leishmaniasis include local and systemic methods, in which cryotherapy with liquid nitrogen and intralesional glucantime are more commonly used.3 If one considers the special concern for children, a simple more convenient method with high efficacy and fewer side effects has always been of interest.

Meglumine antimoniate, which is the first-line drug for treatment of all forms of leishmaniasis, has a lower efficacy in children than in adults. This finding might be caused by the pathogenicity of the organism or the pharmacokinetics of the drug, which causes a lower response rate in this age group.4,5 If one considers host factors that affect the response to treatment, the immune response, either innate or acquired, may be different in adults than in children.

To the best of our knowledge, no comparisons of the efficacies of the two most widely used treatment modalities for leishmaniasis in children, cryotherapy and intralesional glucantime, have been reported. Therefore, we compared these treatment modalities for children in an area endemic for leishmaniasis.

MATERIALS AND METHODS

Patients. The study was a randomized clinical trial of children with leishmaniasis who came to the Dermatology Clinic of Qaem Hospital in Mashad, Iran, over a 10-month period. Diagnosis was made clinically in each patient and confirmed parasitologically by direct examination of an ulcer smear or skin-slit smear stained with Giemsa. Lesions of all patients were photographed. Treatment was performed on an outpatient basis. Study goals were explained to all patients and informed consent was obtained from the parents of each patient. The study protocol was reviewed and approved by the Ethics Research Committee of Mashad University of Medical Sciences.

Patients were enrolled in the study if they had positive direct skin smears for CL, were ≤13 years of age, had visited the dermatology clinic from September 2006 through June 2007, and had lesions with a duration of <12 weeks to exclude any natural self-healing during follow-up. Patients were excluded if they were >13 years of age, had a lesion history >3 months, were allergic to antimonial drugs, and were simultaneously using any other therapeutic method.

To detect a 22% difference in the cure rate between cryotherapy and glucantime groups and assuming a 57% cure rate in the cryotherapy group, with a 65% power and a 10% two-sided type I error, 40 persons were needed in each group. The 79 patients who met our criteria were randomly divided into two groups: 40 patients received cryotherapy and 39 patients received intralesional glucantime.

Patients were asked to visit the clinic on a weekly basis for up to six weeks to complete the treatment course and six months later for follow-up. They were strongly advised not to use any other medication during this period.

Treatment. For the glucantime group, intralesional glucantime (Glucantine®; Specia, Paris, France) in a volume of 0.5–2 cm³ was injected into each lesion until the lesion was completely infiltrated (blanched). For the cryotherapy group, liquid nitrogen (−195°C) was applied twice to the lesion. Each cycle was 10–15 seconds of freezing time with a thawing interval of 20 seconds. Care was taken to ensure that freezing reached up to a few millimeters within the healthy skin surrounding the lesion. Cryotherapy was repeated weekly up to six weeks. Post-operative care included daily cleansing with an antiseptic solution and topical application of tetracycline cream.

Follow-up and outcome. Clinical evaluations were performed every week during the treatment course by one observer for both groups. The last evaluation was six months after the sixth week of treatment. At each visit, clinical response was determined on the basis of the following criteria: 1) complete improvement (full re-epithelialization of the lesions and a negative direct skin smear result), 2) significant improvement (decrease in induration size >75%), 3) partial improvement (decrease in induration size between 50% and 75%), 4) slight improvement (decrease in induration size between 25% and 50%), and 5) no improvement (decrease in induration size <25%). The study end points were time required to complete healing of all skin lesions or withdrawal from the study.

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Complete cure was defined as full re-epithelialization; disappearance of edema, induration, and other signs of inflammation; and a negative direct skin smear result. On the follow-up visits, all patients were clinically re-examined for response rate and recurrence.

**Statistical analysis.** We used three approaches to compare treatment outcomes between the two groups. The first approach was an intention-to-treat analysis that included all 79 patients enrolled at the beginning of the trial and considered patients with irregular treatments and follow-ups as therapeutic failures. The second approach was more stringent and included the 72 patients with regular treatment and follow-up. They were considered good compliers and better represented an explanatory approach that enabled interpretation of data in terms of effectively treated patients. The third approach used the Kaplan-Meier method to compare time-to-failure data of the 79 initially enrolled patients. The log-rank test was used to compare the two survival curves. The chi-square test was used to test for significance ($P < 0.05$) between groups.

**RESULTS**

Four patients in the cryotherapy group and three patients in the glucantime group were excluded because they received two medications simultaneously, did not complete the treatment course, did not visit the clinic for follow-up six months later, or changed their address and were lost to follow-up.

The demographic characteristics of patients in both groups are summarized in Table 1. The two groups were similar in terms of sex, age, and lesion duration, type, and location ($P > 0.05$) and only varied in the number of lesions, which was slightly higher in the cryotherapy group.

The most common lesion sites were the head, neck, and the upper limbs. The most common lesion type was papulonodular. The median (range) number of treatment sessions was 4 (3–6) in the cryotherapy group and 5 (4–6) in the glucantime group. There were no significant differences in treatment responses in either group between males and females ($P = 0.108$), but the risk of no improvement in females was 2.8 times higher than that in males ($P < 0.05$, 95% confidence interval [CI] = 1.1–7.3)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cryotherapy</th>
<th>Intrallesional glucantime</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>40</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>20</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>6.8 ± 3.4</td>
<td>6.2 ± 3.4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD no. lesions</td>
<td>1.91 ± 1.02</td>
<td>1.4 ± 0.76</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD durations of lesions, weeks</td>
<td>11.2 ± 11.8</td>
<td>12.1 ± 18.4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papuloplaque</td>
<td>35</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>2</td>
<td>3</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Ulcer</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Location of lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>24</td>
<td>31</td>
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</tr>
<tr>
<td>Hand</td>
<td>10</td>
<td>13</td>
<td>&gt; 0.05</td>
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<tr>
<td>Foot</td>
<td>4</td>
<td>3</td>
<td></td>
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</tbody>
</table>

Results of the intention-to-treat approach and analysis of only compliers by comparing therapeutic failure rates are summarized in Table 2. Analysis of time to failure data by the Kaplan-Meier method showed no significant shorter mean time to failure in the glucantime group (5.67 weeks, 95% CI = 5.51–5.82 for the cryotherapy group and 5.69 weeks, 95% CI = 5.50–5.89 for the glucantime group, log rank = 2.62, $P = 0.1059$) (Figure 1).

No serious post-treatment side effects were observed in either group. In 36 patients receiving cryotherapy, the most common adverse reactions were erythema and edema of the treated site, which appeared during the initial hours of treatment, and blistering of the treatment site, which became evident 1–2 days after treatment and responded well to local treatment. Slight changes in pigmentation also occurred post-inflammation as either hypopigmentation (2 patients, 5.5%) or hyperpigmentation (7 patients, 19.4%), which cured spontaneously a year after treatment ended. Three children in the glucantime group showed erythema and mild pruritus at the injection site. At six months of follow-up, no recurrence of the disease was noted in cured patients in both groups.

**DISCUSSION**

Choosing the best therapeutic method for treatment of CL has always been one of the greatest health problems in leishmaniasis-endemic areas. Despite many therapeutic modalities available, there is still no consistency regarding treatment of choice. Therefore, choosing a treatment method that is painless, effective, and has fewer side effects in children, who represent 7–10% of patients in disease-endemic areas, has always been an issue of great importance. Methods used for treating children with leishmaniasis are similar to those used for treating adults.

Visceral leishmaniasis and CL are endemic in different parts of Iran, and glucantime has been the treatment of choice. With recent detection of antimonial resistance as a result of intermittent drug use by parenteral and intrallesional routes and low compliance caused by painful injections, the need for an alternative therapeutic method has become widely apparent.

Cryotherapy is an effective treatment for leishmaniasis. All *Leishmania* species are markedly thermosensitive and cryosurgery has several advantages in the treatment of CL. Although cryotherapy is a painful procedure, it does not have any systemic side effects. This method is simple, does not require local anesthesia, produces rapid destruction of the *Leishmania* spp. parasites, is comparatively inexpensive, and is not associated with serious complications. Cosmetic results are excellent and well accepted by most patients. However, it usually requires multiple sessions with treatment failures rates of up to 50% and relapse rates of up to 8%.

Antimonial compounds are associated with significant side effects but have lower failure rates. Several studies have compared intrallesional glucantime with cryotherapy either alone or as a combined therapy. Khatami and others in a systematic review evaluated randomized controlled trials in which cryotherapy alone or in combination with other therapeutic modalities was used in the treatment of Old World CL. They concluded that these treatment modalities had good efficacies and negligible side effects. In a recent report by Mosleh and others that evaluated the efficacy of a weekly cryotherapy regimen in patients infected with *L. major*, all patients were cured, no relapses occurred, and cosmetic results were good.
Asilian and others reported response rates of 55.63% for glucantime, 57.15% for cryotherapy, and 41.4% for combined (glucantime plus cryotherapy) therapy. Gurei and others in a clinical trial compared the efficacy of intralesional sodium stibogluconate (pentostam) with cryotherapy in the treatment of CL. A total of 92% of those who received pentostam and 78% of those who received cryotherapy were clinically cured at the end of the three-month follow-up period. In another study, 14 patients with acute CL who were treated with cryotherapy were clinically and parasitologically cured within 3–8 weeks, with no noticeable scars at lesion sites.

Variation has been observed in cure rates for leishmaniasis in response to cryotherapy in different studies. Therefore, factors such as diagnosis; type of CL; causative species; size, duration, and location of lesions; population variations; cryotherapy regimen; and accuracy and consistency in performance might be responsible and should be taken into consideration. However, most of the reported results showed a high efficacy for this therapeutic method.

In the current study, the complete response rate in those completing the study was significantly higher in the cryotherapy group than in the intralesional glucantime group (31 of 40 patients versus 10 of 39 patients; P = 0.012). Because of the small sample size, appropriate statistical results could not be obtained on the relationship between improvement rates on the basis of the treatment regimens and location or type of lesions. Therefore, further studies with larger sample sizes are needed.

The results of this survey also confirm the efficacy of cryotherapy in treatment for leishmaniasis. In addition, in comparison with adults, a shorter duration of time was used in each cycle (10–15 second versus 10–30 seconds) for children, but this change did not affect the final response rate. This finding might be caused by more delicate skin in children. Furthermore, patients less than five years of age with CL have not been previously included in a controlled clinical trial on the efficacy of antimonials and cryotherapy despite the importance of this age group in disease-endemic areas.

Our results in children verified results of similar trials on the advantages of cryotherapy in comparison with glucantime in other age groups. Because of its simplicity, lower cost, low rate of serious complications, and greater tolerability, cryotherapy should be recommended as an appropriate alternative treatment for leishmaniasis in children.

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References