The Use of Intralesional Metronidazole in the Treatment of Cutaneous Leishmaniasis

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Abstract
Seventy patients (70 lesion , 48 dry, 22 wet) with typical acute cutaneous leishmaniasis in mirjan teaching hospital in Hilla city from January to May,2004 were included in this project. Thirty eight(55%) of them were females and thirty two(45%) were males .Their ages ranged from 1-50 years, 53 patients had few lesion (1-5 lesions) 75%, 17 patients had multiple lesions above (5 lesions) 25%. Duration of lesions was 2 weeks - 6 months.

The patients were divided into 3 groups, the first group included 33 patients how were given 1% metronidazole solution intralesionally. The cure rate was 75% in one to two injections required for complete cure, 1-2 weeks intervals between each injection,12% in the third injection, 9% in the fourth injection, and 4% in the fifth injection. Each patient followed up for 6 weeks. The second group included 20 patients, metronidazole was given orally in a dose of 200 mg , 3 times daily for 4 weeks, no apparent clinical improvement was observed.

The third group included 17 patients how were given placebo treatment as a control for this study. No clinical improvement was observed during 6weeks follow up.

Introduction
Cutaneous leishmaniasis (Baghdad Boil) is specific cutaneous infection caused by Leishmania tropica and is commonly seen in tropical and subtropical areas [1]. It affect all races and there is no sex predilection. It is most common in children and young adults. The reservoir of infection usually domestic and wild animals like doges and rodents, the parasite transmitted from those animals to human through a bite of infective female of sand fly [2].The incubation period is variable from few weeks to several months depends on the size of the inoculum, the individuals susceptibility and perhaps virulence of the organism.

Usually the disease affect the exposed parts of the body and each individual skin lesions occur at the site of
bite. The rapidity of evolution of skin lesion depends on dose of parasite injected into the skin and the immunity of the individual. So the number of skin lesions variable, could be single or may reach a high number like 50, 70 or more [3]. Temperature is an important factor that helps to determine the localization of leishmanial lesions. Species causing visceral leishmaniasis are able to grow at core temperatures, while those responsible for cutaneous type grow best at lower temperatures [2].

The lesion start as erythematous spot then becomes papule, nodule or plaque and this may ulcerate to form ulcerative Baghdad boil. The untreated cases may remain several months and some time years before complete healing leaving a disfiguring scars especially on the face. So the aim of therapy is to prevent this scaring. The disease was endemic in certain geographical area mainly in Baghdad, but after 1980 the disease become wide spread areas of country and reaches an epidemic state [1], and was found to be important problem in the out patient clinic among infectious skin diseases (3.2%) in children ages ranged from 1-2 years. The diagnosis is established by demonstrating the parasite in histological sections and by cultures, skin testing may be helpful, but is of limited usefulness in endemic areas when most individuals have acquired natural immunity, following exposure [4].

The main stages in the therapy includes:
1- Local treatment in the form of cryotherapy, infra red therapy and surgical excision.
2- Local intralesional of drugs and chemicals.
3- Systemic treatment which is indicated when there are multiple skin lesions.

Aim of the Study
Because of unavailability of the drugs especially the pentostam injection and shortage of glucontine injection, and because of the important of this parasite in making scars in untreated cases this lead us to find other available drug. The present work was arranged to assess the effectiveness of intralesional injection of metronidazole solution.

Patients and Methods
Seventy patients with typical acute cutaneous leishmaniasis, were seen in the Department of Dermatology, Mirigan Teaching Hospital, Babylon from January to May 2004. They were 38 females and 32 males. Their ages ranged from 2-45 years. Diagnosis was confirmed in every patients clinically and by laboratory diagnosis by demonstration of the parasite by microscopical examination of blood film and biopsy materials [5, 6], most of the patients had multiple skin lesion. Duration of lesions ranged from 2 weeks to 6 months. 8 lesions were associated with satellite papules. The patients divided into 3 groups.

1- Patients treated with intralesional 1% solution metronidazole in which lesions infiltrated until completed blanching of whole lesion had occurred. The amount of solution required was 1-3ml or more depending on the size of each lesion. The injection was repeated according to the response of 7-14 days intervals. The solution was injected by ordinary disposable insulin syringes using fine gauge needles. The lesions were examined almost every week for 6 weeks. On the follow up of the treated lesions, the therapeutic response was assessed by decreasing of erythema, oedema, reduction in the size of the lesion and dry of the lesion.
2- Patients treated with systemic metronidazole 200mg, 3 times daily and examined every 7-14 days for 4 weeks.
3- 17 patients lefted as control without treatment.
Results and Discussion

Table (1) shows the incidence of cutaneous leishmaniasis according to the age and sex, there was no statistical significance, females are more commonly infected than males, most likely because of their increased exposure to sand flies [7]. As shown in table (2) the 33 patients treated with 1% metronidazole explain marked improvement by the first and second injection (75%) within 1-2 weeks intervals between each injection. While 12% of the lesions improved by the 3rd injection of 1% metronidazole and the remaining lesions improved by the 4th and 5th injection (9%, 4%) respectively and statistically significant (p<0.001). Each patient followed up for 6 weeks.

As shown in table (3), the dry lesion respond more rapid than the ulcerative type (wet) and statistically significant. There were no side effects following the treatment, after healing scarring was minimal or absent but hyperpigmentation was noted in most of the patients, which later disappeared.

Control lesions (17patients) that left with out treatment showed no signs of improvement during a period of 6 weeks follow up. The remaining 20 patients treated with oral metronidazole were showed no improvement with 6 weeks follow up also.

There are only few effective systemic therapies in cutaneous leishmaniasis such as stibogluconate [8]. However most recently oral zinc sulfate has been found to be extremely effective in the treatment of Baghdad Boil [9, 10].

Metronidazole had been reported as uneffective treatment of cutaneous leishmaniasis. However, there are many controversial results concerning the drug [11, 12]. The present work has proved its uneffectiveness in all patients treated orally while the local infiltration with 1% metronidazole has given a high cure rate (75%) which was comparable to hypertonic sodium chloroide (7%) [9].

The mode of action of metronidazole against parasite explained. Nevertheless the in vitro study using the slide method [1], it suggested that meronidazole could locally interfere with osmotic pressure in addition to its direct lethal effect on parasites causing their death.

Table 1 The incidence of cutaneous leishmaniasis according to the age and sex for the first group of patients.

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>11-20</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>21-30</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>31-40</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>41-50</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 2 Improvement of the patients treated with intralesional 1% metronidazole.

<table>
<thead>
<tr>
<th>Number of injection</th>
<th>Female</th>
<th>Male</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First injection</td>
<td>10</td>
<td>10</td>
<td>60%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Second injection</td>
<td>4</td>
<td>1</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Third injection</td>
<td>2</td>
<td>1</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Fourth injection</td>
<td>1</td>
<td>2</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Fifth injection</td>
<td>1</td>
<td>1</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Improvement by the first injection of 1% metronidazole.

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Total number</th>
<th>Improved number</th>
<th>% of improvement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry type</td>
<td>48</td>
<td>14</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Ulcerative type (wet)</td>
<td>22</td>
<td>7</td>
<td>33%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Recommendation
Metronidazole can be recommended as an effective alternative mode of therapy in healing cutaneous leishmaniasis lesions.

References
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leishmaniasis with 2% zinc sulfate. PATENT. (1996). No.2595.