Therapy of Tungiasis: a Double-blind Randomized Controlled Trial with Oral Ivermectin

Jörg Heukelbach/*, Sabine Franck/**, Hermann Feldmeier/**

Departamento de Saúde Comunitária, Faculdade de Medicina, Universidade Federal do Ceará, Rua Prof. Costa Mendes 1608, 5º andar, 60430-140 Fortaleza, CE, Brasil *Fundação de Educação e Saúde Mandacaru, Fortaleza, CE, Brasil **Institute for Infection Medicine, Department of Microbiology, Charité University of Medicine, Berlin, Germany

Tungiasis is an ectoparasitosis causing considerable pathology in endemic areas. Standard therapy consists of removing the embedded parasite with a sterile needle. There is no effective chemotherapy at hand. To fill this gap, a double-blind randomized controlled trial with oral ivermectin was conducted. A total of 54 individuals (27 in the placebo group, 27 in the ivermectin group) was followed up for seven days. They presented a total of 192 lesions. Patients received either ivermectin (300 µg/kg body weight at a single dose, repeated after 24 h) or placebo. Outcome measures included the clinical stage of lesion, presence of erythema, pain, itching, signs of viability of the parasite, and total lysis of flea. The ratio of fleas with total lysis per total number of fleas was slightly higher in the ivermectin group; however, this difference was not statistically significant. There was no significant difference in any of the other outcome measures between the treatment and the placebo group. The results show that oral ivermectin is without any clinically significant efficacy against embedded sand fleas at the dose given.

Key words: tungiasis - Tunga penetrans - therapy - ivermectin - randomized controlled trial - Brazil

...
each). Patients, investigators and the auxiliary nurse were blinded with respect to the treatment given. None of the investigators involved in the design or realization of the trial had access to the code book before finalization of the trial. Coded ivermectin and placebo tablets were supplied by a pharmaceutical producer of ivermectin (Solvay Farma S.A., São Paulo, Brazil). Treatment consisted of two doses of 300 µg/kg body weight ivermectin or placebo given 24 h apart.

The patients were examined immediately before as well as once per day during six days after treatment. All clinical examinations were performed by the same investigator (SF). The lesions were examined thoroughly with a magnifying glass. The following variables were used as outcome measures and noted for each lesion: clinical stage of lesion according to the Fortaleza classification (Eisele et al. 2003), presence of erythema, pain, itching, total lysis of flea, and vital signs (flea’s faeces, eggs, pulsation). Total lysis of the flea was defined as the clearance of an embedded flea or its carcass from the skin either by tissue repair mechanisms or by falling out. Faeces, eggs and pulsation of the embedded fleas were identified when present and considered as clear indicators for the flea’s viability (Eisele et al. 2003). Before examination, the feet were washed with tap water. Patients were asked for the presence of itching and pain associated with embedded sand fleas and, if present, to grade their complaints into weak, moderate or severe for each of the lesions. Swallowing of ivermectin/placebo tablets was controlled. Adverse events were assessed at each follow-up examination.

To estimate the sample size, a clinically significant efficacy was defined as a difference of the ratios of fleas with total lysis per total number of fleas of 0.3 in the ivermectin group as compared to 0.6 in the placebo group at any of the follow-up examinations. Conclusively, 63 viable lesions in each treatment arm are necessary to detect a clinical difference with a power of 90 to 95% significance level. Considering possible loss to follow-up, in each group, 30 patients were randomized with a total of 192 viable tungiasis lesions.

Data were entered twice into a database using version 6.04d of the Epi Info software package (Centers for Disease Control and Prevention, Atlanta, GA) and checked for errors that could have occurred during their entry. In the analysis, morphological aspects of the lesions were compared in each treatment group rather than comparing the outcome measures in individual patients. Relative frequencies were compared between treatment groups using the chi-squared test. The Wilcoxon rank sum test was used to compare ordinal data between the two groups.

**RESULTS**

Descriptive characteristics of the study groups are depicted in the Table. Both treatment arms consisted of 30 patients. Six patients (three of the ivermectin group and of the placebo group, respectively) were lost to follow-up as they felt homesick and asked to leave the mountain resort after two days. These were excluded from data analysis. Parasite load of those lost to follow-up was similar to the remaining study participants. There were no drop-outs in follow-up in the remaining 54 study participants. The total number of lesions followed up was 103 in the ivermectin arm and 89 in the placebo arm. There was no statistically significant difference in age (p = 0.8) or the number of lesions per patient between the treatment groups (p = 0.5). There were more males in the placebo group; however, the difference was not statistically significant (p = 0.06).

The Figure presents the proportion of lesions showing total lysis of the flea in relation to the total number of lesions in each treatment arm. The ratio was slightly higher in the ivermectin group for the days of follow-up indicating some insecticidal activity of the drug. However, the difference never gained statistical significance (p > 0.3 in all cases).

Both treatment groups were also compared with respect to the other outcome measures such as itching and pain but again there was no statistically significant difference between the two groups at any time point of the follow-up.

Adverse events were reported in 12 cases. In the treatment group 3 patients complained of headache, 2 of abdominal pain and 1 of sore throat. In the placebo group, 3 patients complained of headache and 3 of itching.

**DISCUSSION**

Ivermectin is a comparatively cheap drug, and its use has been suggested in individuals infected with intestinal helminths and ectoparasites when specific diagnoses are difficult to establish due to lack of appropriate health infrastructure (Heukelbach & Feldmeier 2004, Heukelbach

### TABLE

<table>
<thead>
<tr>
<th>Characteristics of study participants</th>
<th>Ivermectin group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals randomized</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Number of individuals followed-up for 6 days</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Age (median and range)</td>
<td>12 (5-17)</td>
<td>12 (6-34)</td>
</tr>
<tr>
<td>Sex (males/females)</td>
<td>11/16</td>
<td>18/9</td>
</tr>
<tr>
<td>Number of lesions per patient (median and range)</td>
<td>3 (1-10)</td>
<td>3 (1-10)</td>
</tr>
<tr>
<td>Total number of lesions before treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Stage III</td>
<td>74</td>
<td>59</td>
</tr>
<tr>
<td>Total number of lesions evaluated</td>
<td>103</td>
<td>89</td>
</tr>
</tbody>
</table>
support their notion by anecdotal observations. In fact, gists claim a good efficacy of ivermectin in tungiasis and randomized controlled trials to conclude on the therapeutic efficacy of ivermectin on embedded sand fleas.

That even a higher dose would not significantly improve larva migrans (usually 200 µg/kg body weight) we think that the efficacy of topical ivermectin as compared to a topical placebo lotion and a control group without any treatment (Heukelbach et al. 2003a). Thus, such a broad-spectrum antiparasiticidal drug is of considerable benefit in mass treatment campaigns in populations concomitantly infected with various species of intestinal helminths and ectoparasites (Heukelbach et al. 2004).

Using an appropriate study design, we were unable to confirm anecdotal reports on the efficacy of ivermectin in tungiasis (Saraceno et al. 1999). A previous trial reported some efficacy of topical ivermectin as compared to a topical placebo lotion and a control group without any treatment (Heukelbach et al. 2003a). In this study, the relatively small effect of the drug on sand fleas was explained by the type of application: it was assumed that not sufficient quantity of the active compound would reach the skin lesions in the placebo (n = 89) and ivermectin (n = 103) group.

The efficacy of ivermectin on embedded sand fleas (Valença et al. 1972, Cardoso 1981). Similarly, other authors suggest oral thibendazole to be effective against embedded sand fleas (Valença et al. 1972, Cardoso 1981). Probably the effect observed by these authors is due to the fact that patients were severely infested and were hospitalized and thereby taken out from the endemic area, consequently preventing re-infestation. According to their developmental stage, fleas will die anyway after two to three weeks independently whether the patient is treated or not (Eisele et al. 2003).

The only randomized controlled trial in tungiasis with an oral drug has been realized more than 20 years ago with niridazole, an anti-schistosomal compound with severe neurological adverse events, which has been taken from the market since long (Ade-Serrano et al. 1982). In this study, the therapeutic efficacy of niridazole was claimed to be very good. However, the outcome measures were not well defined and the study showed other methodological problems which limit the interpretation of results.

The reduced prevalence of tungiasis observed in an endemic community after selective mass treatment with ivermectin may be explained by seasonal variation in transmission dynamics rather than intrinsic activity of the drug on T. penetrans (Heukelbach et al. 2004).

Our study did not show any significant difference between oral ivermectin and a placebo at the dose chosen. This may be attributable to the relative small number of patients treated, however the study size was sufficient to detect a clinical significant difference between treatment and placebo group with a high power.

Recently, a small case series using a natural repellent on the basis of coconut and jojoba oil showed an impressive regression of clinical pathology in patients severely infested by prevention of re-infection (Schwalfenberg et al. 2004). It is conceivable that in endemic communities the use of an effective repellent would be a better approach to reduce tungiasis-associated morbidity than treatment after infestation has occurred.

ACKNOWLEDGEMENTS

Ivermectin and placebo were provided free of charge by Solvay Farma, São Paulo, Brazil. To Vanja Andrade dos Santos and Antonia Valéria Assunção Santos. The data form part of a medical thesis by SF.

REFERENCES


References

Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 99(8), December 2004 875


