A Randomized Placebo-Controlled Trial of Mebendazole for Halitosis

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Objective: To test whether mebendazole, an antiparasitic drug, would affect recovery from halitosis.

Design: We conducted a randomized, double-blind, placebo-controlled trial between April 1999 and September 2001.

Setting: A referral medical center.

Patients: One hundred sixty-two children aged 5 to 16 years whose parents complained about their chronic bad breath.

Interventions: Children were randomly assigned to receive mebendazole (n=82) or placebo (n=80).

Main Outcome Measure: Parents whose children had halitosis were evaluated for halitosis at 2 months of treatment by questionnaire. The microbiologist investigated the stool samples of children for parasitosis at the beginning of the trial and also at the end of the trial in children who were treated with mebendazole.

Results: Among those children who had evidence of parasites in stool samples at the beginning of the trial, 18 of 28 who were treated with mebendazole recovered from halitosis, compared with 2 of 24 who received placebo (relative risk [RR] for recovery, 7.7; 95% confidence interval [CI], 2.0-29.9). Among those who did not have stool parasites, 14 of 52 improved with mebendazole, compared with 10 of 48 taking placebo (RR, 1.3; 95% CI, 0.6-2.6). Mebendazole intake made a significant difference whether or not the children had parasites (P=.002).

Conclusions: Parasitosis should be considered as a possible cause of halitosis in the pediatric patient population. Mebendazole therapy seems to offer benefit to those children with parasites as a potential cause of their halitosis.

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dalitosis (bad breath) is defined as a foul odor arising from a person’s oral cavity or nasal passages.1 It is a common ailment in children and adults, and 50% to 60% of the general population has chronic halitosis.2-4 Most cases of halitosis may have oral causes.2,5-7 Besides the oral cavity problems, it is associated with chronic sinusitis, upper and lower respiratory tract diseases, various systemic diseases, and usage of certain drugs.1,6-9 Bad breath originating from gastrointestinal disorders is considered to be extremely rare.10 It was reported in 1941 that 19% of the children visiting an outpatient clinic at Children’s Hospital of Boston (Boston, Mass) were infected with pinworms.11 Prevalence levels as high as 100% have been recorded for some parasites, especially Enterobius vermicularis in the United States and northwestern Europe.12 Using standard methods, the prevalence levels have been shown to be around 35% to 87% in Turkey.13,14 Although most of the children infested with parasites may be asymptomatic, others suffer from deficits in their physical, intellectual, and cognitive growth.15

We have no knowledge of medical literature reporting the relationship between halitosis and parasitosis. When a mother stated that the bad breath of her child, who was infested with E vermicularis, disappeared after antiparasitic treatment with mebendazole, we became suspicious that halitosis might be a consequence of parasitic infection and decided to see if a randomized trial with mebendazole could influence recovery from halitosis.

PATIENTS AND METHODS

We conducted a randomized, double-blind, placebo-controlled trial. The Ethical Committee of Karaelmas University (Zonguldak, Turkey) approved the trial. Parents were informed, and their consent was obtained before enrollment.
PATIENTS AND SETTING

Children aged 5 to 16 years whose parents complained about their chronic bad breath were included in the trial. Participants were enrolled between April 1999 and September 2001 from the outpatient clinics of the Department of Pediatrics at the Research Hospital of Karaelmas University.

INCLUSION CRITERIA

When parents spontaneously reported bad breath in their children who were taken to outpatient clinics for various non-pathologic reasons (well-child care, growth follow-up, lack of appetite, etc.), these children were included. The parents reported no recent acute infection.

EXCLUSION CRITERIA

A pediatrician, an otorhinolaryngologist, and a dentist examined all of the children. If needed, their pulmonary and/or Water view radiographs were taken. According to any suspicion of adenoiditis or sinusitis during the ear-nose-throat examination, endoscopic and tomographic investigations were done. Also, liver function tests (alanine aminotransferase and aspartate aminotransferase levels), serum urea nitrogen levels, creatinine levels, fasting blood glucose levels, uric acid levels, and hemograms were studied for all children.

RANDOMIZATION

A random-number table was used to generate random sequences of allocation, which were generated by a research coordinator. Numbered containers were used for allocation concealment. The investigators, who were blinded to the trial, were assigned participants to their treatment groups. The parents, investigators, and the research coordinator were unaware of the assigned treatment. Follow-up data collection and effectiveness of blinding were evaluated by questionnaire at the end of the trial.

We assumed a 30% difference in children who had parasites, and a 40% clinical success rate in the mebendazole group. To achieve 80% power with $\alpha = .05$, we needed to enroll 29 children with parasites (risk ratios) and 95% confidence intervals (CIs).

LABORATORY INVESTIGATIONS

Fresh stool specimens were submitted to the laboratory in sterile containers with tight-fitting lids, and these containers were then placed into plastic bags before transport. All fresh and liquid specimens were examined within 1 hour or 30 minutes of passage, respectively. Examination of 3 specimens collected every other day was considered the minimum necessary to perform an adequate ova and parasite evaluation (National Committee for Clinical Laboratory Standards, Wayne, Pa, unpublished data, 1993).

Direct wet mounts and iodine (1:5 dilution of Lugol iodine) staining of fresh stool specimens were examined microscopically for motile trophozoites or helminth larvae. We performed either a Faust zinc sulfate centrifugal flotation technique or the Richie technique of formalin-ether sedimentation to increase yield, in addition to direct wet mount examinations according to the standard procedures. For false-negative test results, attention must be paid to the recommended speed and time of centrifugation, as well as excessive amounts of fat content in feces.16

The eggs, or occasionally, the adult worms of the pinworm, *E ventricularis*, may be detected on examination of a clear adhesive cellophane tape pressed against the perianal region. Specimens were collected late at night, when the worms are most active, or first thing in the early morning before bathing or defecation, then evaluated by microscopic examination in the standard manner.

In children who had parasites, 37 were found in the first, 14 were found in the second, and 7 were found in the third stool samples to be positive for parasites. The parents were not informed about parasitosis during follow-up. The stool samples that had parasites were investigated once at the end of the trial in the mebendazole group.

TREATMENT

Children were randomly assigned to receive mebendazole (100 mg twice daily for 3 consecutive days) or placebo. Pills were administered by the parents and were taken on an empty stomach 30 minutes before meals.

EVALUATION OF TREATMENT RESPONSE

A clinical improvement was acknowledged if parents declared the disappearance or notable decrease of their children’s bad breath. Clinical failure was defined as parents sustaining reports of bad breath in their children.

STATISTICAL ANALYSIS

The differences between groups were analyzed by using the Pearson $\chi^2$ test. A Mantel-Haenszel test was used for point estimates (risk ratios) and 95% confidence intervals (CIs).

RESULTS

Of the 190 children, 28 (6 also had parasites) were excluded from the trial: 8 had tonsillitis and/or adenoiditis, 6 had chronic sinusitis, 7 had dental problems, 1 had chronic persisting hepatitis, and 6 refused to participate in the trial. Of the 58 children who had parasites, 6 were not meeting eligibility criteria (refused to participate and/or had other etiological reasons for halitosis) and were excluded from the trial. One hundred sixty-two children met the eligibility criteria and were randomized as shown in the Figure. Ten children were excluded from the trial during follow-up: 5 were lost to follow-up, 2 were excluded for unknown reasons, 2 had varicella, and 1 child was excluded for non-compliance (Figure). Follow-up interviews were successfully completed in 93% of children. The characteristics of the study group and the parasites detected in stool samples are presented in Table 1. Stool examinations revealed that 28 children (35%) in the mebendazole group had parasites vs 24 (33%) in the placebo group. Of the 28 children with parasites who were treated with mebendazole, 18 (64%) recovered from halitosis vs only 2 (8%) of the 24 children with parasites who received placebo (relative risk [RR] for recovery, 7.7, 95% CI, 2.0-29.9). Among those who did not have stool parasites, 14 of 52 improved with mebendazole, compared with 10 of 48 taking placebo (RR, 1.3, 95% CI, 0.6-2.6). Mebendazole intake made a significant difference whether or not the children had parasites ($P=.002$) (Table 2).

Those 18 children who had parasites and improved for halitosis with mebendazole therapy were also
Table 2. Recovery From Halitosis in Children With or Without Parasites*

<table>
<thead>
<tr>
<th></th>
<th>Mebendazole Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>18 (64.3)</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>No recovery</td>
<td>10 (35.7)</td>
<td>38 (79.2)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (100)</td>
<td>48 (100)</td>
</tr>
</tbody>
</table>

*All data are presented as number (percentage) of patients. For children with parasites, 18 of 28 improved who were given mebendazole treatment compared with 2 of 24 who received placebo. Relative risk for recovery was 7.7 (95% confidence interval [CI], 2.0-29.9). For children with no stool parasites, 14 of 52 improved with mebendazole treatment, compared with 10 of 48 who received placebo. Relative risk was 1.3 (95% CI, 0.6-2.6). Mebendazole intake made a significant difference in whether the children had parasites (P = .002).

Halitosis is defined as a foul odor arising from a person’s oral cavity or nasal passages. It is a common ailment in children and adults, and 50% to 60% of the general population suffers from chronic halitosis. In this trial, we have presented an association between mebendazole therapy and resolution of halitosis through the resolution of parasitosis.

Table 1. Characteristics of Children and Parasites Detected on Stool Examination*

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Mebendazole Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td>10 (12.5)</td>
<td>8 (13.9)</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>4 (5)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
<td>10 (12.5)</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>2 (2.5)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Negative stool test</td>
<td>52 (65.3)</td>
<td>48 (66.7)</td>
</tr>
</tbody>
</table>

*All data are presented as number (percentage) of patients unless otherwise indicated.

Stool examinations revealed that 28 children (35%) in the mebendazole group had parasites vs 24 (33%) in the placebo group. Of the 28 children with parasites who were treated with mebendazole, 18 (64%) recovered from halitosis vs only 2 (8%) of the 24 children with parasites who received placebo (RR for recovery, 7.7; 95% CI, 2.0-29.9).

In our preliminary trial, mebendazole treatment seemed to encourage recovery from bad breath. It seemed to work in children with evidence of parasitic infection. By a search of MEDLINE, we do not find any literature to date regarding a relationship between halitosis and parasitosis. There might be several possible explanations for parasitosis as the cause of halitosis. First, excess saliva secretion stimulated by parasites leads to stasis, which may be a more convenient environment for bacterial overgrowth, especially during sleeping.17 Second, pulmonary migrations of some parasites and their larvae (eg, A lumbricoides and Trichuris trichiura). Third, it is suggested that halitosis should be considered in the presence of an increased formation of intestinal gases.18

At usual recommended dosages (100-200 mg daily), mebendazole seems to cause minimal adverse effects. Adverse effects seem to occur more frequently when higher dosages are used, and they may be related to effects resulting from drug-induced killing of the parasites in some cases.19 Transient diarrhea, abdominal pain, nausea, vomiting, headache, tinnitus, and dizziness also have been occasionally reported during mebendazole therapy. Myelosuppression manifesting as neutropenia and/or thrombocytopenia has also been reported in patients receiving high-dose (30-50 mg/kg daily) mebendazole therapy for extraintestinal infections.20 However, international trials have shown that mebendazole is safe and effective in eradicating many parasites.15,20,21 Biddulph22 has reported that widespread use of mebendazole in less-developed countries indicates that it is probably safe for infants and children, except for children with blood dyscrasias, leukopenia, or liver diseases.

Limitations to our study design included the fact that some parents reported that a child’s bad breath showed a notable decrease, but did not disappear, and we accepted this to be a positive response to treatment. It may have been better to develop some grading for the improvement, or to use more objective tests for the assessment of halitosis.

In this trial, we found an association between mebendazole therapy and the resolution of halitosis...
through the resolution of parasitosis. We think that mebendazole improved bad-smelling breath among children who were infected with parasites.

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REFERENCES


