Helicobacter pylori and halitosis: A comparative quasi-experimental clinical trial study

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Halitosis or mouth malodor is a known problem for many years. The knowledge regarding the possible association of Helicobacter pylori infection is quite limited in literature. A comparative quasi-experimental clinical trial study was conducted on 17 H. pylori positive patients and 16 H. pylori negative patients who were complaining of halitosis. All patients, regardless of H. pylori infection, received two-week’s treatment of clarithromycin (500 mg BID) and amoxicillin (1 g BID) along with three month’s long omeprazole; a pretested questionnaire was used for self-reported measurement of halitosis. Halitosis was assessed after three and six months of continued treatment. Patients were also checked for eradication of H. pylori infection. Mean estimated time for improvement was 74.4 days for H. pylori negative group compared to 46.8 days for H. pylori positive group. 12 out of 17 patients in this group improved during the treatment time, while only 4 of the 16 patients in H. pylori negative group improved (P<0.01). The relative risks of halitosis resolution in H. pylori positive group over H. pylori negative group were 2.8 and 3.3, respectively after 3 and 6 months. H. pylori eradication can resolve halitosis in majority of patients without an oral pathology causing halitosis. H. pylori may be a probable rather than a possible cause of halitosis.

Key words: Halitosis, Helicobacter pylori, eradication.

INTRODUCTION

The discovery of Helicobacter pylori (H. pylori) and its relationship with peptic ulcer and gastric cancer raised overall curiosity that it may cause other problems like non-ulcer dyspepsia. This in turn led to a debate for eradication therapy to improve such problems (McColl et al., 1998; Rauws and Tytgat, 1990; Talley, 1996; Talley et al., 1999). The organism can also be found in mouth spaces and saliva. Maybe this is the reason for dental researchers and gastroenterologists to think of a common problem, the halitosis.

Halitosis or mouth malodor is a known problem for many years. It may be such severe to prevent a normal life, or result in something to suffer and tolerate. Up to 50 percent of the U.S. population report that their own “bad breath” has been a concern to them during some point in the course of their lifetime. Half of this group is indeed likely to have an ongoing sporadic or a chronic breath malodor problem (Lee et al., 2007). Halitosis is defined as an unpleasant odor that emanates from the oral cavity with intra-oral and/or extra-oral origins. Fifty percent of people worldwide view themselves as having halitosis, with 85 to 90% of the etiology reported to be intra-oral (Armstrong et al., 2010; Scully and Greenman, 2008). Halitosis frequently causes embarrassment, may affect interpersonal social communication and has also become an important market for the pharmacological and cosmetic industries (Scully and Greenman, 2008).

The knowledge regarding the possible association of H. pylori infection is quite insufficient in literature, leading to a much conservative statement of H. pylori infection as the possible cause of halitosis. More research in different settings and using different study designs is needed to make stronger assumptions on the association between halitosis and H. pylori infection. The aim of this study was to determine effect of H. pylori infection eradication on resolution of halitosis as a clue for investigating the...
Sinusitis and main oral pathologies were among the excluding criteria. Patients were enrolled from internal medicine outpatient clinics of Tabriz University of Medical Sciences. All the 33 patients were complaining of halitosis. 17 of these patients were found to have \textit{H. pylori} infection, while 16 patients were \textit{H. pylori} negative. All cases complaining of dyspepsia were assessed through upper GI endoscopy and RUT. The procedures were done after ensuring two week PPI free period. UBT was done for those not complaining of dyspepsia. All patients, regardless of \textit{H. pylori} (HP) infection, received two-week treatment of clarithromycin (500 mg BID) and amoxicillin (1 g BID) along with three month long omeprazole. Regarding the post eradication being tested, it should be mentioned that in patients with primary negative HP it was not tested at all and just disappearance of halitosis was observed. In those with primarily positive HP, it was tested by urea breath test even if the primary test had been oesophagogastroduodenoscopy (OGD). The first OGD was because of dyspepsia so that we could check the patients for both halitosis and dyspepsia and not missing concomitant ulcers and other pathologies. As OGD is more invasive than urea breath test we did not repeat it just to check the HP condition after the treatment.

A pretested likert scaled questionnaire was used for self-reported measurement of halitosis. To improve the validity, questionnaire was reviewed by four experts and the reliability was checked before conducting the research. Although the measures in this assessment were semi-objective, the reliability analysis was done using Cronbach’s alpha which was above 0.6.

Halitosis was assessed after three and six months of continued treatment. Patients were also checked for eradication of \textit{H. pylori} infection. The main variables measured included age, gender, length of time suffering from halitosis, dyspepsia, gastro-esophageal reflux disease (GERD), history of previous eradication therapy, time to resolution of halitosis and existence of halitosis at the beginning, after 3 months and after 6 months from the beginning of the study. McNemar test was used to assess before-after results in each group. To compare the efficacy of treatment in \textit{H. pylori} positive and \textit{H. pylori} negative patients, a preliminary chi-squared test was used to compare the proportions. Then relative risk, risk difference and number needed to treat statistics were computed along with their 95% confidence intervals. Cox multivariate regression analysis was used to control measured possible confounders to assess the effect of eradication therapy on halitosis in both groups. A p-value lower than 0.05, was considered as indicative of statistically significant results. Committee of ethics in Tabriz University of Medical Sciences approved the study protocol and data collection methods.

RESULTS

Fifteen of 33 patients were males and 18 were females. The age ranged between 17 to 59 years old. Average of age among the participants was (33 ± 10.6) years. Mean time length of suffering from halitosis before treatment was 5 years.

Mean estimated time improvement was 74.4 days for \textit{H. pylori} negative group compared to 46.8 days for \textit{H. pylori} positive group. Compared Kaplan- Meier graphs for time improvement is given in Figure 1. Five patients had coincidental halitosis and dyspepsia and one patient had halitosis coincidental with gastro esophageal reflux disease (GERD). All the 17 patients who had a positive UBT test for \textit{H. pylori} turned to a negative \textit{H. pylori} result during the 3 month period, after treatment. 12 out of 17 patients in this group improved during the treatment time, while only 4 of the 16 patients in \textit{H. pylori} negative group improved (P<0.01). The efficacy indices of treatment in \textit{H. pylori} positive patients compared to \textit{H. pylori} negative group along with 95% confidence intervals are provided in Table 1. Two of the patients that improved at 3 months relapsed at the end of 6 months.

Cox regression model found that efficacy of treatment assessed as hazards was higher in \textit{H. pylori} positive group, even after controlling age, sex and length of the time patients suffered from halitosis.

DISCUSSION

In addition to specific questions about \textit{H. pylori} eradication therapy, there is controversy regarding whether or not patients with chronic \textit{H. pylori} infection exhibit unique symptoms. Finding an association between \textit{H. pylori} and halitosis may be more useful in guiding these therapy decisions. In an effort to find a parameter that would facilitate stronger decision-making in this area, we examined the association of \textit{H. pylori} infection and halitosis and effect of \textit{H. pylori} infection on resolution of halitosis.

Based on the idea that halitosis is caused by bacterial decomposition of food particles and other material encrypted in mouth space, a substantial role of gastrointestinal causes for halitosis has always been a source of discussion. Another interfering assumption is related to considering the halitosis as a respiratory symptom (Hoshi et al., 2002; Spielman et al., 1996). However, halitosis is reported in pathologic locations isolated from respiratory system from a gross anatomical point of view (Mosimann, 1995; Tolliver et al., 1995). Dental reviews have considered several microorganisms as the cause of halitosis namely Centipeda periodontii, Eikenella corroden, Enterobacteriaceae, Fusobacterium nucleatum subsp. nucleatum, Fusobacterium nucleatum subsp. polymorphum, Fusobacterium nucleatum subsp. vincentii, Fusobacterium periodonticum, Porphyromonas endodontalis, Porphyromonas gingivalis, Prevotella melaninogena, Prevotella intermedia, Bacteroides loescheii, Solobacterium moorei, Tannerella forsythia and Treponema denticola. \textit{H. pylori} is only considered to be a possible cause of halitosis and more research is needed to determine existence of such an association (Scully and Greenman, 2008). This association, suggested in a dental review article, was made...
Figure 1. Kaplan-Meier improvement hazard graphs compared for two groups.

Table 1. Relative risk, risk difference and number needed to treat calculated to assess efficacy of treatment in H. pylori positive vs. H. pylori negative halitosis patients.

<table>
<thead>
<tr>
<th>Efficacy statistics</th>
<th>3 months after treatment</th>
<th>6 months after treatment</th>
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<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>95% CI</td>
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<tr>
<td>Relative risk</td>
<td>2.8</td>
<td>1.15 - 6.96</td>
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<tr>
<td>Risk difference (%)</td>
<td>45</td>
<td>15 - 75</td>
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<tr>
<td>NNT*</td>
<td>2.2</td>
<td>1.3 - 6.6</td>
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* Number needed to treat

In this study, we used an adaptive clinical trial design to study the possible association between halitosis and H. pylori infection, and also assessed possible benefit of eradicating H. pylori infection on resolution of halitosis. Other than what is discussed above, association of halitosis and H. pylori infection is investigated in some cross-sectional studies, finding a support for the hypothesis on such an association to be tested in prospective studies (Adler et al., 2005; Chen et al., 2007). We found that eradication therapy resolves the halitosis in 70% of halitosis patients who are H. pylori positive. This indicates that halitosis can be considered as an objective in H. pylori positive patients. However, from methodological point of view this does not mean that H. pylori is a cause for halitosis because the strong antibiotic package used for eradication can be assumed to affect any other microorganism in causal chain of halitosis, which is also sensitive to the H. pylori eradication regimen.

The first report of H. pylori infection as a possible...
Cause of halitosis goes back to 1985 during a scientific experiment through which the researcher ingested a culture of *H. pylori* (Marshall et al., 1985). Several studies have investigated the effect of *H. pylori* infection on improvement of halitosis. The first in time order was a case study of three couples by Tiomny et al. (1992) whose halitosis impressively improved after *H. pylori* eradication (Tiomny et al., 1992). The second study conducted on 30 patients with halitosis, found that *H. pylori* eradication led to improved halitosis in all patients in whom the infection was eradicated. Halitosis in patients with unsuccessful eradication persisted even after receiving antiseptic mouthwashes. The halitosis in these patients disappeared only after a successful *H. pylori* eradication (Tiomny et al., 1992). The second study conducted on 30 patients with halitosis, found that *H. pylori* eradication led to improved halitosis in all patients in whom the infection was eradicated. Halitosis in patients with unsuccessful eradication persisted even after receiving antiseptic mouthwashes. The halitosis in these patients disappeared only after a successful *H. pylori* eradication (Tiomny et al., 1992). The third study was also a before-after study conducted on 148 *H. pylori* positive patients; 61% of whom suffered from halitosis. The halitosis proportion decreased to 13% among all patients treated for *H. pylori* infection and 3% among those with successful eradication (Serin et al., 2003). The fourth study conducted on 18 *H. pylori* positive halitosis patients resolution of halitosis was observed in 78% of patients, all of whom achieved *H. pylori* eradication (Katsinelos et al., 2007). The fifth study published in 2007, Korea red ginseng was given to 68 *H. pylori* positive halitosis patients. 55% of subjects became free of halitosis. The resolution rate among the 15 patients receiving Korea red ginseng along with *H. pylori* eradication regimen, 93% turned free of halitosis. Interestingly among 20 *H. pylori* negative patients, also treated with Korea red ginseng, 13 patients became free of halitosis (Lee et al., 2009).

Eradication of *H. pylori* in patients with functional dyspepsia and halitosis results in sustained resolution of halitosis during long-term follow-up in the majority of cases. This finding supports although *H. pylori* eradication might be considered in patients with halitosis (Katsinelos et al., 2007), we are not convinced with the conclusion drawn by the authors of the aforementioned article that such findings can indicate the existence of a link between *H. pylori* infection and halitosis. The reason for our argument is that *H. pylori* eradication may affect the halitosis through another unknown causal pathway. As all the treated patients had *H. pylori* infection at baseline, without being compared with those free of *H. pylori* infection, and also it was eradicated in all 188 patients, from an epidemiological point of view resolution of *H. pylori* can only be attributed to treatment not to *H. pylori*. Regardless of its limitations, the merit in our study was the inclusion of *H. pylori* negative patients in the study. So the resolution rate compared between *H. pylori* positive and *H. pylori* negative patients in our study can be a sign of possible causal relationship between *H. pylori* and halitosis, given the minimum selection bias and comparable variability of subjective measurement. The current methodology, although due to including a control group, was a bit stronger than previous clinical studies in showing a possible link between *H. pylori* and halitosis. But to be reasonable it shows *H. pylori* eradication is associated with improvement of halitosis and not directly indicative of a causal relationship. This is because in case of an association between *H. pylori* infection and existence of other known causes of halitosis with gastric or oral origin, this may confound the causal relationship.

Another fact that should be taken into account studying the association between *H. pylori* and halitosis is that based on available information including the results of this study, even if there is an association between *H. pylori* infection and halitosis, we do not know what the mechanism is and what is the share of oral vs. gastric *H. pylori* infection.

**Conclusion**

Considering the consistency of findings in several interventional studies, we assume it may be the time to think about *H. pylori* as a probable cause of halitosis rather than a possible cause of halitosis. No doubt, there is a long way in research to make a stronger assumption regarding the association of *H. pylori* and halitosis or taking into account the existence of this association in decision making on *H. pylori* eradication therapy.

**LIMITATIONS AND STRENGTHS**

A limitation in our study was the subjective measurement of halitosis. Subjective measurement of halitosis is common in literature maybe due to the fact that it is mainly a subjective problem rather than an insidious major health complication. From a clinical perspective, it also must be considered that current objective measures may not be reasonable end-points in clinical trials to decide on starting a heavy treatment if we find a statistical mean difference in objective measures. Another assuring fact regarding this limitation of our study is that a previous trial has found concordance in objective and subjective measures of halitosis and a high concordance was also found in repeated measurement of halitosis in our study. Nevertheless, from methodological point of view objective measurements are more reliable than subjective measurements and maybe the best choice regarding halitosis is the dual objective-subjective assessment of halitosis. Another limitation of our study was the smaller sample size. Although this carries lesser importance when null hypotheses are significantly rejected as in this study, but larger sample size is often recommended because it provides narrower confidence intervals of association measurements like in relative risks. In contrast to some previous studies, the methodological strength in our study was inclusion of a control group suffering from halitosis without *H. pylori* infection.
REFERENCES


