Lycopene an Adjunctive Therapy for Helicobacter Pylori Eradication: a Quasi-Control Trial

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Abstract

Although some herbal remedies in association with vitamin therapy have been investigated in eradicating HP, no research has been done to investigate the effects of lycopene it. Our aim was to understand if lycopene could be effective in eradication of HP. In this parallel group quasi-control trial, a total of 54 patients whose diagnosis of HP had been confirmed by rapid urease test (RUT) were enrolled. Group 1 received the standard 4-drug therapy to eradicate HP (Metronidazole 500 mg/BD, Amoxicillin 1g/BD, Omeprazole 20mg/BD, and Bismuth 240 mg/BD) and group 2 received the same regimen in association with Lycopene (30 mg/daily). One month after the initiation of the treatment, the patients were evaluated for HP eradication by RUT. Although eradication rate was higher in the second group, bivariate analysis showed no significant statistical difference between the two groups. In contrast with other nutrients, it seems that Lycopene does not have any significant effects on eradicating HP in comparison with the standard antibiotic therapy. The prevalence of HP is in association with socioeconomic situation, so the patients in different studies should be paid more attention about their own lifestyle. We recommend that more studies can be designed by considering control group and placebo administration.

KEYWORDS: Lycopene, Helicobacter Pylori, Antibiotic therapy

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Introduction

Helicobacter Pylori (HP) can infect all people regardless of the family history or the age; however, the elderly people are more prone to this infection in the United States (Andreica et al, 2004).

New mutations of HP are more resistant to Metronidazole, one of the standard antibiotics used for eradicating HP. Using antibiotics can flare the microbes which are in competition with the pathogenic ones. To replace the antibiotics with herbal remedies, lots of studies have been performed (Tabak et al, 1996; Krausse et al, 2004; Fukai et al, 2002). Previous studies verified the effect of antioxidant agents specially lycopene on reducing the incidence rate of malignancies, diabetes, aging, and cardiovascular and eye diseases. It is associated with oxidative processes (John et al 2009; Bjelakovic et al 2008). In the last decade, many studies were devoted to the benefits of fruits and vegetables especially carotenoids. Among them, lycopene has been considered as an anti-carcinogenic substance. This motivates further investigations on the advantages of lycopene (Lenore et al, 2001). Based on the review of the literature, although the effects of anti-oxidants, vitamin A, and vitamin E have been investigated on the eradication of HP in some articles, there was no research to show the effects of lycopene on it. While lycopene supplements are nowadays provided, their consumption is not widespread. Based on the daily diet in US (tomato sauce, tomato paste) the consumption of Lycopene in that country is relatively more than Thailand, China, and India. No similar evaluations have been performed in Iran (Lenore et al; Food and Nutrition Board, 2001; Yang et al, 1984; Das et al, 1996; Thurnham, 1990).

Considering the benefits of lycopene, we designed our study to determine if lycopene affected on HP eradication.

Methods

Ethical approval

This study was approved and supported by the institutional review board of Tehran University of Medical Sciences (TUMS), Tehran, Iran, and was conducted in Rasul-e-Akram hospital from July 2010 to December 2010. Before starting the study, written informed consents were taken from the patients. Also, the use of drug and its probable side effects were clarified for them. Lycopene is a nutrient anti-oxidant. No side effect has been reported in the previous studies with dose of 30 mg.

Study design and Participants
This study was a parallel group quasi-control trial (drug interventional trial). All 54 patients who had been referred to the endoscopy ward of the Rasool-e-Akram hospital between July and December 2010 and their diagnosis of HP had been confirmed by rapid urease test (RTU), were legally convinced by the investigators to participate in the study. The patients were then consecutively assigned into two groups. Those patients who would not like to accept the new regimen were enrolled into the first group. However, we could not randomize the groups and this difference made this intervention a quasi-control trial.

The inclusion criteria included the age of 15-75 year-old, no previous gastric surgery, no history of cancer or other aggressive diseases of gastrointestinal (GI) tract, no history of esophagitis of grade 2 and more (by Savariet Miller classifying), no history of allergy to the administrated drugs, and no history of use of antibiotic within the last 4 weeks in the patients whose diagnoses were confirmed by RUT. Those who did not use their medications, pregnant women, and those with the history of allergy to the medications or peptic ulcer were excluded.

**Interventions**
Before starting the two approaches for treatment, all patients were advised to continue their previous nutritional and physical habits. They also wrote their dairy diet in a table. The tables were checked by a nutritionist every 2 weeks. The amount of lycopene in the diet received by group 1 (treated by the routine regimen) was estimated. Group 1 received a standard 4-drug therapy to eradicate HP (Metronidazole 500mg/BD, Amoxicillin 1g/BD, Omeprazole 20mg/BD, and Bismuth 240mg/BD) and the second group received the same regimen as well as Lycopene (30mg/daily). Daily nutritional regimen was observed as mentioned above.

**Clinical assessment**
The patient’s demographic characteristics including gender, age, drug history (especially NSAID), and the last result for HP eradication were recorded in a self-made checklist by a nutritionist. To re-assure the equality of the regimen, the checklist contained a specific table for daily diet that was filled by the patient him/herself.

All patients were followed for 1 month by the nutritionist regarding their conserved nutrition and also drug regimen. At the end of the first month, the patients were evaluated for HP eradication by RUT.

**Statistical analysis**
Statistical analysis was performed using chi square test via SPSS software version 18. A P value less than 0.05 was considered to be statistically significant.
Results

Characteristic of the Patients
From 27 patients allocated as group 1, two did not follow the nutritionist and were excluded. Of the remainder, 13 were male (male/female: 1.08) and the average age was 42.7± , (range; 21 to 73 years). From 27 patients enrolled as group 2, all terminated the treatment successfully. Of them 11 were male (male/female: 0.68) and the average age was 39.35±12.37 (range; 22 to 74 years). All patients’ characteristics are illustrated in table 1.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Patients’ characteristic</th>
<th>Group 1 (4 common drugs)</th>
<th>Group 2 (4 common drugs+ Lycopene)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean:42.7± Rang:21-73</td>
<td>Mean:39.35±12.37,Range:22-74</td>
<td>0.9*</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1.08 (13 Male)</td>
<td>0.68 (11 Male)</td>
<td>0.2*</td>
</tr>
<tr>
<td>Usage of NSAID</td>
<td>4(16%)</td>
<td>1(3.07%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Positive UBT test after treatment</td>
<td>8 (32% of 25 patients)</td>
<td>6(22.2% of 27 patients)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*: The insignificant P value shows that the characteristics did not have any significant differences in the two groups

Analysis
Using the 4-drug regimen in group 1, HP was eradicated in 68% of the patients (17/25). On the other hand, in group 2, by adding lycopene, HP was eradicated in 77.8% of the patients (21/27). Although the percentage of eradication was more in group 2, bivariate analysis showed no significant statistical difference in HP eradication (P=0.27).
Discussion

Considering the circulation half-life (12-33 days) of lycopene (Rock and Swendseid, 1992), all patients were evaluated for HP eradication 30 days after taking the regimens. We evaluated the patients for HP by RUT. There was no significant difference in HP eradication between the 2 groups. New mutations of HP are going to be resistant to two of the three standard antibiotics (Tabak et al, 1996; Krausse et al, 2004; Fukai et al, 2002), thus, various investigations have been performed to understand if antibiotics can be replaced by herbal treatments.

By Kist, the director of Germany’s National Reference Center for HP, HP resistance to metronidazole, one of the three standard antibiotics used for eradicating HP, has been increased to 40-50% from 30% in 1980s (Reuters, 2002). Apart from the new resistant mutations, antibiotic therapy can suppress the effect of normal bacterial colonies of the GI tract. The bacteria compete with other microbes and reduce the risk of infection. Considering these expressions, some herbal diets have been investigated to see if they could facilitate HP eradication. In 2003, by the university of Illinois, Chicago, it was found that ginger root extracts suppress the growth of HP in vitro. In 1996, food researchers at Technion, recommended more studies for the effect of thyme on HP (Tabak). Terminalia Chebula extract (black myrobalan), a herb from an Indian tree was found to have a significant inhibitory effect on HP by Malekzade et al (Malekzadeh, 2001). In 2004, a study at the institute of medical microbiology and virology, Kiel, Germany, suggested that clarithromycin, one of the standard antibiotics used for HP, can be replaced by licorice extract in patients who are infected by resistant generations of HP (Krausse).

Other researchers at Toho University, Chiba, Japan, found that licorice extracts were effective against HP strains that were resistant to both amoxicillin and clarithromycin (Fukai). Berberine and Curcumin have also been demonstrated to be effective against HP (Mahady et al, 2002a; Nostro et al, 2005; Foryst-Ludwig et al, 2004; Mahady et al, 2003b).

Beyond herbal remedies, vitamins and micronutrients are necessary for life. Only a few studies about the effect of nutrients on HP eradication have been done. In 2010, Mustafa Akcam, et al studied about some nutrition and HP in Turkey. They revealed that HP growth might be decreased by micronutrition supplementation especially in developing countries (Mustafa, 2010).

Among all carotenoids, lycopene plays the most effective role as an in vitro antioxidant.

In 1995, the National Cancer Institute and the Beijing Institute for Cancer research began a randomized, double-blind, placebo-controlled factorial trial, to determine if the prevalence of precancerous gastric lesions and gastric cancer (GC) would be reduced by tree treatments, alone or in combination. Those
treatments were amoxicillin and omeprazole (only in individuals with HP infection), dietary supplementation with vitamins E and C and selenium, and dietary supplementation with steam-distilled garlic oil and ethanol-aqueous aged garlic extract. Before that, it was showed that the risk of GC was decreased by increasing consumption of garlic and other allium-containing vegetables (You, 1989). Also, higher serum concentrations of vitamin C result in decreased risk of advanced precancerous gastric lesions (Zhang et al, 1994a).

From carotenoids, beta carotene was proved to be effective on GC by a review article in 2000. The authors declared that the effect of beta-carotene on GC and intestinal metaplasia was similar to the usage of anti-HP treatment and ascorbic acid (Lenore; Correa et al, 2000). In 2008, Christina Persson et al revealed that the risk of GC was inversely associated with plasma level of β caroten (compared with the lowest quartile: OR 5 0.63, 95% CI 5 0.31–0.75; OR 5 0.48, 95% CI 5 0.31–0.75 and OR 5 0.46, 95% CI 5 0.28–0.75, for quartile 2, 3 and 4, respectively, P trend < 0.01). Inverse associations for α carotene and β carotene were obvious in men (P trend 5 0.04 and P trend < 0.01, respectively), but not in women, who had relatively higher plasma levels than men. They did not find any significant association between plasma levels of lutein/zeaxanthin, lycopene, retinol, α- or g-tocopherol and risk of GC. Altogether, they suggested that patients with very low plasma levels of α and β carotene were more prone to GC than who have higher plasma levels (Persson et al, 2008).

From other antioxidants, carotenoids, retinol, and Tocopherol had been studied, but the results were in conflict (Nouraie et al, 2005; Serafini et al, 2002; Ito et al, 2003; Botterweck et al, 2000; Abnet, et al, 2003; Larsson et al, 2007; Yuan et al, 2004; Jenab et al, 2006). It seems that using different methods such as food frequency questionnaires or direct measure plasma levels caused these conflicts. Some authors believe that different plasma level of carotenoids is in association with HP infection but some did not agree with them (Jenab; Salgueiro et al, 2004). Helicobacter pylori can reduce the absorption of many nutrients. In HP-infected patients, β carotene concentration is decreased in gastric fluid but not in plasma. Also, α tocopherol concentration is decreased in corpus of stomach while HP is present in antrum (Salgueiro). In 2008, in a study on 140 420 patients in Tokyo, Japan, it was found that plasma levels of β cryptoxanthin, α and β carotene, and lycopene in HP positive patients were lower than the non-infected group (Persson).

Among all studies done about nutrients and HP, in 2007, a strong association was found between HP infection and iron deficiency by Akcam M et al (Akcam et al, 2007; Kurekci et al, 2005; Seo et al, 2002; Süoglu et al, 2007; Marignani et al, 1997). Treatment with iron in patients with iron deficiency was associated with HP eradication (Barabino et al, 1999). In 2005, Mahalanabis D et
al compared 2 groups for HP after a period of 8 weeks of iron therapy. They saw that the response was better in the HP negative group (Mahalanabis et al, 2005). The prevalence of vitamin B12 deficiency was reported to be 28% in HP positive patients and 11% in HP negative patients by Akcam, et al. In 2005, Kim et al found that the role of HP as a risk factor of GC in the low vitamin C intake group was more significant than the high vitamin C intake group (Kim et al, 2005). Park JH et al hypothesized that vitamin C concentration could have a role in HP progression; therefore, vitamin C supplementation can be considered as one of the approaches to HP treatment (Park et al, 2003). Also, in other studies, it was suggested that vitamin C could act on HP like antimicrobial agents (Chuang et al, 2007). In 1993, it was theorized that low β caroten in plasma was accompanied by HP infection and gastric atrophy (Tsugane et al, 1993). In 2000, Zhang ZW et al revealed that gastric fluid β carotene concentration in HP positive patients was lower than the negative group; but, there was no significant difference in serum or gastric mucosal β carotene concentration between the 2 groups. By their study, the mucosal β carotene concentration was associated with gastric atrophy and intestinal metaplasia (Zhang et al, 2000b).

Chatterjee A, in 2005, revealed that vitamin E did not have any significant effect on HP progression comparing to the control group (Chatterjee et al, 2005). In 1998, Hep A. et al revealed that vitamin E and C supplementation in patients with gastritis associated with HP reduced the malignant changes (Hep et al, 1998). In 2006, Sugimoto N et al suggested that vitamin E reduced activated neutrophil aggregation and gastric mucosa injury induced by HP (Sugimoto et al, 2006). There was not enough study on zinc and HP. Two studies (one in 2000 and one in 2007) did not see any correlation between zinc concentration and HP (Akcam; Zullo et al, 2000). The only study about this relation in children, found that there is no relation between zinc concentration and HP (Akcam).

Studies about fulate concentration and HP revealed the negative relation between HP and fulate in adults. About selenium, it was seen that high intake of selenium reduced HP growth in the guinea pig (Sjunnesson et al, 2001).

The strength of our study was that we compared 2 positive HP groups because we did not find any previous studies that especially investigated the influence of lycopene on HP eradication. Our sample size was not as much as some previous studies about other micronutrients. The weakness of our study was not being a double-blinded RCT and we had not considered a control group with placebo administration. Also, it seems that the duration of using lycopene for eradicating HP should be considered longer. We did not consider life style profile and other risk factors such as smoking, as well. The prevalence of HP is in association with socioeconomic situation; thus, more attention should be paid to hygiene, life style such as smoking habits, physical exercise, higher consumption.
of fruits and vegetables, and habitual intake of vitamins and nicotine in different studies

More studies in this regard considering these defects and comparing the groups using lycopene and placebo for a longer duration are warranted.

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