Helikobakteri Pylori Eradikasyonunun Atrofik Gastrit ve İntestinal Metaplazi üzerine olan etkisi

The Efect of Helicobacter Pylori Eradication on Atrophic Gastritis and Intestinal metaplasia

Helikobakteri Eradikasyonu / Helicobacter Eradication

Güldem Kilciler, Zülfikar Polat, Ahmet Uygun, Murat Kantarcıoğlu, Mustafa Gülşen
Department of Gastroenterology, Gülhane Military Medical Academy Ankara, Türkiye.

Özet

Amaç

Bu prospektif çalışmanın amacı helikobakter pilori eradikasyonunun intestinal metaplazi yada atrofik gastriti iyileştirip iyileştirmediğini değerlendirmektir.

Gereç ve Yöntemler

Helikobakter pilori enfeksiyonu olan 42 hasta merkezimizde atrofik gastrit ve intestinal metaplazi yönünden değerlendirildi. Helikobakter pilori eradikasyonundan önce ve altı ay sonra antrumdan ve korpusdan ikişer biyopsi alındı. Tedaviden 2 ve 6 ay sonra üre nefes testi ile helikobakter pilori durumuna bakıldı. Atrofik gastrit ve intestinal metaplazi derecesi güncelleştirilmiş Sydney klasifikasyonuna göre ciddi, orta ve hafif olarak sınıflandırıldı.

Bulgular

Altı ay sonra helikobakter pilori eradike edilen grupta gastrik atrofi skoru anlamlı olarak azalırken, helikobakter pilori eradike edilmeyen grupta ise anlamlı bir değişiklik olmadı. İntestinal metaplazi helikobakter pilori eradike edilen ve edilmeyen grupta değişmedi.

Sonuç

Atrofi ve intestinal metaplazinin kaybolmasının yıllar içinde olabileceği beklendiğinden eradikasyon tedavisinden sonraki pozitif etkiler uzun süreli takiplerde daha iyi görülebilir. Bunlar bizim 6. aydaki erken sonuçlarımızdır.

Anahtar Kelimeler

Helikobakter Pilori, Eradikasyon, Atrofik Gastrit, İntestinal Metaplazi.

Abstract

Aim

The aim of this prospective study was to evaluate whether helicobacter pylori eradication could improve gastric atropy or intestinal metaplasia.

Material and Method

Forty-two pylori infected patients were evaluated for the status of atrophic gastritis and intestinal metaplasia. Two biopsy specimens from antrum and two biopsy specimens from corpus were taken before and 6 months after the helicobacter pylori eradication therapy. Helicobacter pylori status was determined by C-urea breath test 2 and 6 months after for helicobacter pylori eradication. Severity of gastric atrophy and intestinal metaplasia was classified as mild, moderate or severe according to the updated Sydney classification.

Results

The scoring of gastric atrophy was found significantly decreased in helicobacter pylori eradicated group after 6 months, while no significant change was found in H. pylori non-eradicated group. Intestinal metaplasia wasn't recorded as improved in neither helicobacter pylori eradicated group nor helicobacter pylori non-eradicated group.

Conclusion

It can be suggested that reversal of atrophy and intestinal metaplasia may occur even after several years, so the positive effect of eradication therapy might have been even better with a longer follow-up period. The results reported here are those obtained during the 6 months period.

Keywords

Helicobacter Pylori, Eradication, Atrophic Gastritis, Intestinal Metaplasia.

DOI: 10.4328/JCAM.191 Received: 23.01.2010 Accepted: 19.02.2010 Printed: 01.01.2011 J Clin Anal Med 2011;2(1):17-20
Corresponding Author: Güldem Kilciler, Department of Gastroenterology, Gülhane Military Medical Academy Ankara, Türkiye.
Phone:+903123041118 E-mail: mkilciler@yahoo.com

Introduction

Chronic gastritis is generally associated with Helicobacter pylori infection. The infection is associated with increased cancer risk only when it induces atrophy.[1] Atrophic gastritis is considered a precursor of gastric intestinal metaplasia, dysplasia, and carcinoma. H. pylori infection is perhaps the most frequent cause of both atrophic gastritis and intestinal metaplasia.[2,3] The type of atrophic gastritis most commonly related to H. pylori infection involves primarily and predominantly the antrum and the antrum-corpus junction. It is also known as multifocal atrophic gastritis.[4] H. Pylori is also known as the cause of the gastric carcinogenesis by activating the growth factors, induction of apoptosis, induction of unlimited replication, promotion of angiogenesis, and disruption of cell-cell contacts. Diets with high fresh vegetables and fruits protect against atrophic gastritis and gastric cancer.[5] This protective effect may be due to dietary antioxidants, ascorbic acid and β-carotene.[6]

Material and Methods

This prospective study was carried out at Gulhane Military Medical Academy, department of Gastroenterology between October 2004 and December 2007. Gastric biopsy procedures were performed on patients with dyspeptic symptoms in our clinic. C-urea breath test was applied to patients with H. Pylori, atrophic gastritis and/or intestinal metaplasia at biopsy. In all patients, gastric mucosa was histologically evaluated by performing biopsy. 42 patients who have positive H. pylori with atrophic gastritis or intestinal metaplasia or both atrophic gastritis and intestinal metaplasia with biopsy were included in the study. Four biopsy specimens from each patient were taken with biopsy forceps as a standardized procedure.. Two of the four biopsies were from antrum and two were from corpus. Smoking, alcohal intake, any drug use, duodenal or gastric ulcus were the exclusion criterias.

Twenty (47.61%) patients were male and 22 (52.38%) patients were female. Mean age of the patients was 50.3 (25-70).

Helicobacter pylori status was assessed by using histologic results. Eligible patients were treated for 14 days with proton-pump inhibitor (pantaprazole), tetracycline, metranidazole, and bismute sulphate. Two months later following the eradication therapy H. pylori status was determined by C-urea breath test to all patients. At 6 months after eradication therapy, patients again uderwent upper gastrointestinal endoscopy and gastric biopsy, and C-urea breath test. The results were evaluated six months later.

Two biopsy samples from the antrum (smaller and greater curve, anterior or posterior walls) and two from the mid-body along the greater curve were taken with a standard biopsy forceps. The specimens were immediately fixed in Boun's solution for 4-8 h at room temperature, rinsed in 0.1 M phosphate-buffered saline, pH 7.4 and routinely processed to wax. Serial praffin sections (5 μm) were stained with haematoxylin-eosin for routine histological determination and with Giemsa stain for H. pylori evaluation. The same patholologists examined specimens in a blinded manner.

The assessment of the degree of gastric atrophy and intestinal metaplasia was performed according to the visual analogue scales of the updated Sydney system. The following scores were assigned to each graded variable: 0, absence; 1, mild; 2, moderate; 3, severe.[7]

Patients with possible allergy to tetracycline, metranidazole, or proton-pump inhibitors and those with previous gastrectomy were excluded. Written informed consent was obtained from participants in accordance with the Declaration of Helsinki and its later revision. The protocol was approved by the institutional review board of Gulhane Military Medical Academy, Ankara, Türkiye.

For the statistical evaluation, we divided patients into two groups on the basis of the success or failure of H. pylori eradication. We examined background factors and histologic findings at baseline to identify pretreatment differences between the two groups. Data were expressed as the mean ± S.E.M. and/or median (range). The t-test for paired data or the Wilcoxon test was used as appropriate. $P < .05$ was considered to be statistically significant.

Results

Before the H. pylori eradication treatment 8 patients had gastric atrophy, 13 patients had intestinal metaplasia and 21 patients had both atrophic gastritis and intestinal metaplasia. All the 42 patients had H. pylori eradication thrapy. H. pylori was eradicated without serious side effects in 35 (83.3%) of the 42 patients who had treated for H. pylori.

At the second month after the H. pylori eradication therapy, just one patient had positive H. pylori by C-urea breath test. But at C-urea breath test that was performed 6 months later we realised that this patient had negative H. pylori status. At biopsies six months later, this patient had both gastric atrophy and intestinal metaplasia.

After 6 months later we observed at the biopsies that 35 patients had negative H. pylori, 7 patients had positive H. pylori. After this results we called these 35 patients were H. pylori eradication group.

Before the treatment there were 8 patients with atrophic gastritis, 8 patients intestinal metaplasia and 19 patients with both atrophic gastritis and intestinal metaplasia at the H. pylori eradication group.

After the treatment there were 2 patients with atrophic gastritis, 18 patients with intestinal metaplasia and 6 patients with both atrophic gastritis and intestinal metaplasia at the H. pylori eradication group.

At the H. pylori positive group after the eradication therapy (H. pylori non-eradicated group) there were 4 patients with intestinal metaplasia, 3 patients with both atrophic gastritis and intestinal metaplasia before and after the treatment.

Table 1. Number of patients with positive H. Pylori, gastric atrophy and intestinal metaplasia before and six months later after H. Pylori eradication therapy.

	Before Treatment			After Treatment		
Positive pathology of the gastric mucosa	H.Pylori	Atrophic Gastritis	Intestinal Metaplasia	H.Pylori	Atrophic Gastritis	Intestinal Metaplasia
Number of Patients	42	29	34	7	11	31

Table 2. Status of gastric atrophy and intestinal metaplasia before and after the treatment in HP eradicated, HP non-eradicated and all groups.

	Before Treatment			After Treatment				
	IM	AG	IM+AG	IM	AG	IM+AG	Non IM-Non AG	Total
HP eradicated group	9	8	18	18	2	6	9	35
HP non-eradicated group	4	0	3	4	0	3	0	7
All Group	13	8	21	22	2	9	9	42

IM: Intestinal Metaplasia, AG: Atrophic Gastritis

Table 3. Status of gastric atrophy and intestinal metaplasia after H. pylori eradication therapy in the world.

Autors	Year	Country	Patients (n)	Follow up (months)	Improvement in G.A.	Improvement in I.M.
Perttu E et al.	2006	Finland	76	12	+	No data
You et al.	2006	China	3365	120	+	+
Mera et al.	2005	Colombia	795	144	+	+
Ley et al.	2004	USA	316	12	+	+
Kuipers et al.	2004	The Netherlands	144	24	+	-
Leung et al.	2004	China	435	60	+	+
Zhou et al.	2003	China	552	60	-	+
Kokkoa et al.	2002	Finland	22	30	+	+
Ito et al.	2002	Japan	22	60	+	+
Ohkusa et al.	2001	Japan	163	15	+	+
Hsu et al.	2000	Taiwan	63	12	-	-
Annibale et al.	2000	Italy	35	12	-	-
Kyzekova et al.	1999	Czech	25	6	-	-
Satoh et al.	1998	Japan	20	33	-	-
Van der Hulst et al.	1997	The Netherlands	155	12	-	-
Forbes et al.	1996	Australia	54	85	-	-

G.A.: Gastric atrophy, I.M.: Intestinal metaplasia, + : There is improvement, -: There is no improvement

None of the patients stopped treatment as a result of side-effects. 35 patients, (83.3 %) were successfully cured from H. pylori.

Pre-cancerous lesions were cured at 9 patients (25.71%) of 35 H. pylori eradication group at 6 months after the H. pylori therapy.

Pre-cancerous lesions were not cured at 26 patients of H. pylori eradication group. There were 2 patients with atrophic gastritis, 18 patients with intestinal metaplasia and 6 patients with both atrophic gastritis and intestinal metaplasia at this group.

There was an increase at the number of intestinal metaplasia from 8 to 18. Because only atrophic gastritis were cured at some of the patients with atrophic gastritis and intestinal metaplasia group.

H. Pylori, gastric atrophy and intestinal metaplasia status of all patients before and six months later after H. Pylori eradication therapy are shown in table 1.

Status of H. Pylori, gastric atrophy and intestinal metaplasia in all groups before the treatment are shown in table 2.

Status of gastric atrophy and intestinal metaplasia before and after treatment HP eradicated and HP non-eradicated groups are shown in table 2.

After 6 months follow-up the scoring of gastric atrophy was found decreased significantly in H. pylori eradicated group, ($P < .05$) while no significant change was found in H. pylori non-eradicated group ($P > .05$). The proportion of change in intestinal metaplasia was higher in H. pylori eradicated group than in H. pylori non-eradicated group, but it was not statistically significant ($P > .05$).

Discussion

Many epidemiological reports indicate that H. pylori infection plays an important role in gastric carcinogenesis. H. pylori infection is a significant risk factor for the development of atrophic gastritis and intestinal metaplasia.[8] By eradicating H. pylori, gastric inflammation can be cured; the therapy decreases the levels not only of inflammatory cell infiltration, but also atrophy and intestinal metaplasia in part. Most randomized controlled trials revealed that the eradication therapy diminished the gastric cancer prevalence. However, it is stil controversial as to the improvement of glandular atrophy or intestinal metaplasia after the eradication therapy.

H. pylori infection plays a major causative role in intestinal metaplasia, especially in the antrum, where both gastritis and intestinal metaplasia are more severe and more common than in the corpus.[9,10,11] However it is difficult to evaluate intestinal metaplasia, because it shows a patchy distribution and is not visible endoscopically. Thus, sampling error is virtually unavoidable. In our cases we detected the intestinal metaplasia and atrophic gastritis with the biopsy.

Intestinal metaplasia can be found also in duodenal ulcus patients, especially in the antrum, althought these patients are reported to have a reduced risk of gastric cancer development.[12] These findings suggest that intestinal metaplasia in patients with duodenal ulcus and benign gastric ulcus may have different implications and can react differently to H. pylori eradication. Similarly, the corpus and antrum show different reactions to H. pylori, causing different manifestations of gastritis, atrophy, and intestinal metaplasia.[13] That is why we excluded the patients who have duodenal

ulcus and gastric ulcus in our study.

Premalignant lesions of the stomach representing a continuum from normal to carcinoma has been well documented. To complete this process, a duration of more than two decades has been considered.[14] Eradication H. pylori would be sufficient for populations with low prevalence of this infection, but recurrence or reinfection following successful antibiotic treatment is common in developing counties.[15] In our cases we performed the second biopsies 6 months later after the H. pylori eradication treatment. If there was a reinfection we excluded these patients as well.

Conflicting results had been reported about the precancerous lesions following eradication therapy of H. pylori infection (Table 3). These studies demonstrated that H. pylori eradication could not induce regression of precancerous lesions before the 2000. But, then, a significant regression of precancerous lesions has been observed. Although there is no changes in the treatment, these changes still remain unclear.

In a study H. pylori eradication results in at least partial resolution of atrophic gastritis.[16,17] Tucci and colleagues reported that atrophic gastritis of the stomach had regressed during by 12 months after discontinuation of treatment in 10 of 20 patients with fundic atrophic gastritis in whom H. pylori was successfully eradicated.[18] In an other study, it is shown that there is an improvement of atrophy and intestinal metaplasia in the corpus after treatment, but no change in the antrum.19 In contrast, Annibale et al. reported that eradication therapy does not improve mucosal atrophy.[20] Sung et al. Reported the results of a large-scale prospective randomized study and concluded that eradication therapy prevents the progression of athrophy which was not reversible.[21]

Take et al. reported that they followed up more then thousand peptic ulcer patients with eradication therapy prospectively and found that gastric cancer is more frequently detected in patients with failed eradication than those with successful eradication.[22] On the other hand, in a study there is a relative decrease in cancer incidence in patients with eradication therapy in the overall population, but this difference did not reach a level of significance.[23]

Bin Lu et al. reported that in order to prevent gastric carcinoma, eradication of H. pylori infection will be more beneficial, if the therapy is given at the early stage of lesions, i.e. before the formation of pre-cancerous lesions.[24] But in our study we initiated therapy of H. pylori eradication when we detected the precancerous lesions like other studies.

In our study, after 6 months follow-up the scoring of gastric atrophy decreased significantly in H. pylori eradicated group, ($P < .05$) while no significant change was found in H. Pylori non-eradicated group ($P > .05$). The proportion of change in intestinal metaplasia was higher in H. pylori eradicated group than in H. pylori non-eradicated group, but it was not statistically significant ($P > .05$).

It has been published that reversal and healing of atrophy may occur even after several years. To see the positive effect of eradication therapy, a longer follow-up duration might be needed. These are our early results. For our patients clinical trials and follow up are continuing.

References

1. Ruiz B, Garay J, Correa P, Fontham ET, Bravo JC, Bravo LE et al. Morphometric evaluation of gastric antral atrophy: improvement after cure of Helicobacter pylori infection. Am J Gastroenterol. 2001; 96(12):3281-7.
2. Kuipers EJ, Klinkenberg-Knol EC, Vandenbroucke-Grauls CM, Appelmelk BJ, Schenk BE, Meuwissen SG. Role of Helicobacter pylori in the pathogenesis of atrophic gastritis. Scand J Gastroenterol Suppl. 1997;223:28-34.
3. Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y et al. Helicobacter pylori eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther. 2002;16(8):1449-56.
4. Rugge M, Genta RM. Staging and grading of chronic gastritis. Hum Pathol. 2005;36(3):228-33.
5. Potter JD. Diet and cancer: possible explanations for the higher risk of cancer in the poor. IARC Sci Publ. 1997;(138):265-83.
6. Buiatti E, Muñoz N, Kato I, Vivas J, Muggli R, Plummer M, et al. Determinants of plasma anti-oxidant vitamin levels in a population at high risk for stomach cancer. Int J Cancer. 1996;65(3):317-22.
7. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol. 1996;20(10):1161-81.
8. Kuipers EJ, Uyterlinde AM, Peña AS, Roosendaal R, Pals G, Nelis GF, et al. Long-term sequelae of Helicobacter pylori gastritis. Lancet. 1995;345(8964):1525-8.
9. Stolte M, Eidt S, Ohnsmann A. Differences in Helicobacter pylori associated gastritis in the antrum and body of the stomach. Z Gastroenterol. 1990;28(5):229-33.
10. Satoh K, Kimura K, Yoshida Y, Kasano T, Kihira K, Taniguchi Y. A topographical relationship between Helicobacter pylori and gastritis: quantitative assessment of Helicobacter pylori in the gastric mucosa. Am J Gastroenterol. 1991;86(3):285-91.
11. Eidt S, Stolte M. Prevalence of intestinal metaplasia in Helicobacter pylori gastritis. Scand J Gastroenterol. 1994;29(7):607-10.
12. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. Helicobacter pylori infection and the risk of gastric carcinoma. N Engl J Med. 1991;325(16):1127-31.
13. Eidt S, Stolte M. Prevalence of intestinal metaplasia in Helicobacter pylori gastritis. Scand J Gastroenterol. 1994;29(7):607-10.
14. Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, et al. Gastric precancerous process in a high risk population: cross-sectional studies. Cancer Res. 1990;50(15):4731-6.
15. Xia HX, Talley NJ, Keane CT, O'Morain CA. Recurrence of Helicobacter pylori infection after successful eradication: nature and possible causes. Dig Dis Sci. 1997;42(9):1821-34.
16. Annibale B, Di Giulio E, Caruana P, Lahner E, Capurso G, Bordi C, et al. The long-term effects of cure of Helicobacter pylori infection on patients with atrophic body gastritis. Aliment Pharmacol Ther. 2002;16(10):1723-31.
17. Kokkola A, Sipponen P, Rautelin H, Härkönen M, Kosunen TU, Haapiainen R, et al. The effect of Helicobacter pylori eradication on the natural course of atrophic gastritis with dysplasia. Aliment Pharmacol Ther. 2002;16(3):515-20.
18. Tucci A, Poli L, Tosetti C, Biasco G, Grigioni W, Varoli O, et al. Reversal of fundic atrophy after eradication of Helicobacter pylori. Am J Gastroenterol. 1998;93(9):1425-31.
19. Yamada T, Miwa H, Fujino T, Hirai S, Yokoyama T, Sato N. Improvement of gastric atrophy after Helicobacter pylori eradication therapy. J Clin Gastroenterol. 2003;36(5):405-10.
20. Annibale B, Aprile MR, D'ambra G, Caruana P, Bordi C, Delle Fave G. Cure of Helicobacter pylori infection in atrophic body gastritis patients does not improve mucosal atrophy but reduces hypergastrinemia and its related effects on body ECL-cell hyperplasia. Aliment Pharmacol Ther. 2000;14(5):625-34.
21. Sung JJ, Lin SR, Ching JY, Zhou LY, To KF, Wang RT, et al. Atrophy and intestinal metaplasia one year after cure of H. pylori infection: a prospective, randomized study. Gastroenterology. 2000;119(1):7-14.
22. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, et al. The effect of eradicating helicobacter pylori on the development of gastric cancer in patients with peptic ulcer disease. Am J Gastroenterol. 2005;100(5):1037-42.
23. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE,et al. China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA. 2004;291(2):187-94.
24. Lu B, Chen MT, Fan YH, Liu Y, Meng LN. Effects of Helicobacter pylori eradication on atrophic gastritis and intestinal metaplasia: a 3-year follow-up study. World J Gastroenterol. 2005;11(41):6518-20.