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Original Article

How Should Helicobacter Pylori Infection Be Diagnosed by Endoscopy? Is It Enough to Have Received a Biopsy?

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ABSTRACT

Objective: To demonstrate the effectiveness of standardizing the endoscopic gastric biopsy site and sufficient quantity of biopsies in the detection of *Helicobacter pylori* (HP) infection, lymphoid aggregates, and gastrointestinal metaplasia.

Methods: Having undergone gastroscopy due to dyspeptic complaints, 146 patients were included in the study. The data of the study were collected retrospectively. The patients whose biopsies were taken from two stomach regions, namely the corpus and antrum, were included in the study.

Results: There were 58 (39.7%) patients with HP infection detected in the biopsies taken from the antrum and 57 (39%) patients with HP infection detected in the biopsies taken from the corpus. In total, there were 74 (50.7%) patients with HP positive. Sensitivity and specificity for antral biopsy were 78% and 100%, respectively. As for the corpus, the values were 77% and 100%, respectively. When the biopsy results of patients with lymphoid aggregate and intestinal metaplasia in one and both regions were compared, the p-values were found to be <0.001 and <0.001,respectively.

Conclusion: The quantity and location of endoscopic gastric biopsies are of importance to correctly identify HP infection and also to detect lymphoid aggregates and gastrointestinal metaplasia because biopsy specimens taken only from the antrum or only from the corpus increase the rate of false negativity.

INTRODUCTION

Diagnosing *Helicobacter pylori* (HP) infection is a significant step in the treatment of gastroduodenal diseases. HP infection increases the risk of chronic active gastritis, peptic ulcer diseases, atrophic gastritis, mucosa-associated lymphoid tissue (MALT) lymphoma, and noncardia gastric cancer. HP infection affects more than half of the adult population worldwide, yet the prevalence of HP infection varies greatly by geographic region, age, race, and socioeconomic status.[1] HP accounts for more than 80% of cases of peptic ulcer diseases.[2]

Although there are quite a lot of invasive or noninvasive methods to diagnose HP infection, most researchers consider the histopathological diagnosis of HP infection to be the "gold standard."[3] Each method has its own advantages, disadvantages, and limitations. Invasive diagnostic tests include endoscopic imaging, histology, rapid urease test, culture, and molecular methods. Noninvasive diagnostic tests include urea breath test (UBT), stool antigen test, serological, and molecular examinations. In our clinical practice, we use invasive diagnostic methods such as endoscopic biopsy and Giemsa staining for the diagnosis of HP infection.

A standardization for endoscopic gastric biopsy was established in the updated Sydney Classification.[4] According to this classification, it is recommended to take five biopsies in total – from both the small and large curvatures of both the antrum (2–3 cm proximal from the pylorus) and the corpus (approximately 8 cm distal from the cardia) and one from the incisura angularis (Fig. 1). However, in daily practice, these rules are not obeyed because this provides convenience to both the endoscopist and the patient. While Niccoli et al.[5] argued that a single biopsy from the antrum is sufficient, in other studies, at least one corpus biopsy is recommended.[6,7] Figura et al.[8] reported that biopsies should be taken from both the antrum and the corpus.

Our aim in this study is to demonstrate the effectiveness of standardizing the endoscopic biopsy site and sufficient quantity of biopsies in detecting HP infection, lymphoid aggregates, and gastrointestinal metaplasia.

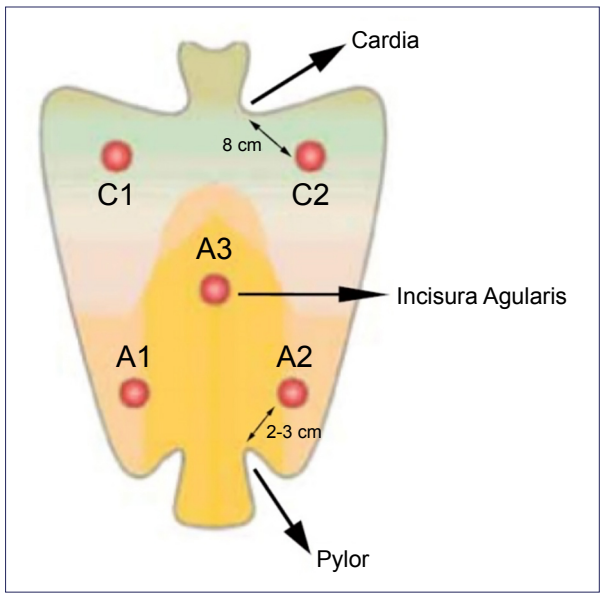

Figure 1. Stomach biopsy sampling protocol.

MATERIALS AND METHODS

Having undergone gastroscopy due to dyspeptic complaints and having given biopsy specimens from the antrum and the corpus specifically for HP diagnosis in the general surgery clinic between January 2018 and December 2020, 146 patients were included in the study retrospectively. Approval was obtained from the Ethics Committee of our hospital (2021/514/195/7) for this study. Those who had previously undergone gastric surgery had been diagnosed with malignancy (carcinoma, lymphoma, and stromal tumor) and had received antibiotics or proton pump inhibitors (PPIs) 2 weeks before due to HP infection were excluded from the study. The patients who had given a biopsy from both the small curvature and the large curvature of the stomach antrum and corpus and whose biopsies taken from the antrum and the corpus had been placed in separate biopsy containers were included in the study.

If HP infection was detected via Giemsa staining in at least one of the biopsies, the patients were considered as HP infection positive. If both were negative, the patients were considered HP infection negative. In addition, HP-positive patients were classified as corpus and antrum regions.

SPSS (Statistical Package for Social Sciences) 20.0 for Windows was used. The data were summarized as mean±standard deviation, numbers (n), and percentage (%). Categorical variables were compared using the Chi-squared test or Fisher's exact test. All statistical calculations were two-sided and showed statistical significance at $p<0.05$ and at 95% confidence interval.

RESULTS

Of the patients, 58 (39.7%) were male and 88 (60.3%) were female. The mean age was 52.2±14.2 years.

Table 1. Helicobacter pylori results of biopsies taken

	Helicobacter pylori		p
	Negative	Positive	
Corpus H. pylori			
Negative	72	17	<0.001
Positive	0	57	
Antrum H. pylori			
Negative	72	16	<0.001
Positive	0	58	

Table 2. Lymphoid aggregate results of biopsies taken

	Lymphoid aggregates		p
	Negative	Positive	
Corpus lymphoid aggregates			
Negative	60	32	<0.001
Positive	0	54	
Antrum lymphoid aggregates			
Negative	60	36	<0.001
Positive	0	50	

There were 58 (39.7%) patients with HP infection detected in biopsies taken from the antrum and 57 (39%) patients with HP detected in biopsies taken from the corpus. In total, there were 74 (50.7%) patients with HP positive ($p<0.001$) (Table 1).

Sensitivity and specificity for antral biopsy were 78% and 100%, respectively. For the corpus, they were 77% and 100%, respectively.

Lymphoid aggregates were detected in the samples of 86 (58.9%) patients. While lymphoid aggregates were detected in antral biopsy specimens in 50 (34.2%) patients, there were 54 (36.9%) patients with lymphoid aggregates in the corpus biopsy specimens. Sensitivity and specificity to detect lymphoid aggregates were 58% and 62%, respectively. When biopsy results of patients with lymphoid aggregation were compared in one region and in both regions, the p-value was found to be <0.001 (Table 2).

Intestinal metaplasia was detected in the biopsies taken from both regions in 35 (23.9%) patients. There were 24 (16.4%) patients with intestinal metaplasia who underwent a biopsy from the antrum and 19 (13%) from the corpus. Sensitivity was 68% and 54%, respectively. When the biopsy results of patients with intestinal metaplasia in one and both regions were compared, the p-value was found to be <0.001.

DISCUSSION

Endoscopic diagnosis of HP infection can be difficult despite existing guidelines.[3,9] The region where the endoscopic biopsy was taken, insufficient quantity of biopsies

and/or that proton pump inhibitors were not stopped 2 weeks before the biopsy may cause false-negative results. In this case, patients were diagnosed incorrectly and treated inappropriately. UBT is recommended as the gold standard test in asymptomatic patients.[10] However, there is no common test accepted as the gold standard in the diagnosis of HP infection in symptomatic patients. Invasive methods (such as endoscopic biopsy) are recommended to diagnose HP infection in patients with dyspeptic complaints.[11] Routinely, modified Giemsa stain is more suitable in detecting HP because the modified Giemsa stain is very straightforward, inexpensive, takes about 5 min to perform, excluding the time in the solution, and rarely requires repeat stains (none were required in our study). This method is easily reproducible. The major disadvantage is that there is little contrast between organisms and tissue.[12]

Biopsy-based tests are important diagnostic tools in the diagnosis of HP infection. However, a review of recent studies indicates that there is no consensus on either the optimal biopsy site or the adequate quantity of biopsies. Diagnostic approaches using the antrum alone, the corpus alone, or a combination of both as the biopsy site appear largely arbitrary.[13–15] A standard approach is required to reveal the benefits of these biopsy sites. Unfortunately, very few endoscopists follow the biopsy sampling recommendations of the Sydney System.[4] As a result, histological evaluation of endoscopic biopsy results in false-negative results in some patients, which creates a serious problem. These problems are usually associated with gastritis or peptic ulcer disease. Usually, symptoms are abdominal pain, nausea, vomiting, or dyspepsia.Also, various extraintestinal manifestations are associated with HP infection such as iron deficiency anemia and chronic immune thrombocytopenia. The most important problem associated with HP infection is gastric cancer. HP is associated with gastric cancer. A group I carcinogen can lead to gastric adenocarcinoma through a sequence of pathology starting from gastritis, atrophy, intestinal metaplasia, dysplasia, and finally carcinoma. Endoscopists should be aware whether the patient is on or has recently been on PPIs or antibiotics, or had recently undergone *Helicobacter* eradication therapy, all of which can reduce the number of organisms to low or undetectable levels. One of the other reasons for false negativity is the absence of classical histological pictures in hematoxylin and eosin sections.[16]

In our study, the number of patients with HP infection detected in the biopsies taken from the antrum and the corpus was 58 (39.7%) and 57 (39%), respectively. In total, the number of patients with positive HP infection was 74 (50.7%) ($p<0.001$). Sensitivity and specificity for antral biopsy were 78% and 100%, respectively. Sensitivity and specificity for a biopsy taken from the corpus were 77% and 100%, respectively. These data suggest that biopsy should be taken from both the antrum and the corpus to obtain more accurate results and minimize the possibility of wrong treatment. In previous studies on HP, it was reported that biopsy specimens histologically close to normal werefound especially in the stomach corpus.[17] In the study conducted by El-Zimaity et al.,[18] it was reported that the false negativity rate was 33% in the biopsy taken only from the antrum and that only from the corpus. These results are consistent with our study. On the other hand, Genta et al.[5] argued that a single biopsy from the antrum is sufficient, whereas, in other studies, at least one corpus biopsy is recommended.[6,7] Figura et al.[8] reported that biopsies should be taken from both the antrum and the corpus.

According to the Sydney System, two biopsies from the antrum and the corpus each are sufficient during gastroscopy, while an additional biopsy from the incisura angularis is recommended in the updated Sydney System.[4,19] We took two biopsies from each of the two regions in accordance with the first Sydney System. We concluded that taking a biopsy from a single site is not sufficient for the diagnosis of HP infection. If we had only taken an antrum biopsy, it would have resulted in 22% false negativity;if we had only taken a corpus biopsy, it would have resulted in 23% false negativity. When we compared these results with all HP-positive patients, the p-value was found to be <0.001 in both groups. Therefore, statistically, we found that a biopsy from a site is not sufficient to diagnose HP infection accurately. It should be kept in mind that the quantity of biopsies is also an important parameter in reducing the false-negativity rate.

Although there are available guidelines on the detection of HP infection, and these are taught, these rules are not followed in daily and practical approaches. Endoscopists should be aware that they should take biopsies from the mucosae of both the antrum and the corpus (ideally from the small and large curvatures of both topographic regions).

HP infection initiates a local immune response in the gastric mucosa. One of its morphological manifestations is the formation of MALT, which is an organized form of lymphocyte aggregate with germinal centers that are in close contact with the epithelium.[1] Low-grade B-cell lymphomas can arise from these lymphoid follicles through a series of mutations and translocations.[20] Intestinal metaplasia is also a precursor of stomach cancer.[21] Under normal conditions, HP induces inflammatory mucosal damage that spreads from the antrum to the corpus. As it moves proximally, it leaves an atrophic corpus mucosa behind and becomes pseudopyloric metaplasia.[22] In the small curvature, the distance between the angle of the stomach and the esophagogastric junction is shorter than that in the large curvature. This anatomical situation may explain why incisura angularis is the first site where atrophy occurs and is a targeted biopsy site in the Sydney Biopsy System.[19] In our study, lymphoid aggregates were detected in 86 (58.9%) patients by taking biopsies from two regions. If only antrum biopsy had been performed, we could have detected lymphoid aggregates in 50 (34.2%) patients; if only corpus biopsy had been performed,we could have detected lym-

phoid aggregates in 54 (36.9%) patients. The p-value was found to be <0.001 in both. Similarly, we detected intestinal metaplasia in a total of 35 patients. Intestinal metaplasia was detected in 24 (16.4%) patients who had a biopsy from the antrum and in 19 (13%) patients from the corpus. The p-value was found to be <0.001 in both. Therefore, to receive information about gastric atrophy, intestinal metaplasia, or gastric lymphoid aggregates, endoscopists should take biopsies from both regions, preferably from the lesser curvature. In addition, pathologists should also consider lymphocytic gastritis in which the bacterial load is low, especially in the oxyntic mucosa; lymphocytic gastritis is a significantly less common cause of gastritis that responds to Helicobacter eradication therapy.[18]

CONCLUSION

The quantity and site of endoscopic gastric biopsy are significant in correctly identifying HP infection and also detecting lymphoid aggregates and gastrointestinal metaplasia because biopsy samples taken only from the antrum or only from the corpus increase the rate of false negativity. It should be kept in mind that the success rate can only be increased by biopsies taken from the large and small curvatures of both the antrum and the corpus.

Ethics Committee Approval

This study approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (Date: 10.02.2021, Decision No: 2021/514/195/7).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.M.A.; Design: F.M.; Supervision: A.E.K.; Fundings: S.K.; Materials: A.Ç.; Data: N.İ.; Analysis: Y.Ö.; Literature search: M.M.A.; Writing: F.M.; Critical revision: A.E.K.

Conflict of Interest

None declared.

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Helicobacter Pylori Enfeksiyonunu Endoskopi ile Nasıl Teşhis Etmeliyiz? Biyopsi Almış Olmak Yeterli Mi?

Amaç: *Helicobacter pylori* (HP) enfeksiyonunun, lenfoid agregatlarının ve mide bağırsak metaplazisinin tespitinde endoskopik mide biyopsi bölgesini ve yeterli biyopsi sayısını standartlaştırmanın etkinliğini ortaya koymaktır.

Gereç ve Yöntem: Ocak 2018–Aralık 2020 tarihleri arasında hastanemiz genel cerrahi kliniğinde dispeptik şikayetler nedeniyle gastroskopi yapılan 146 hasta çalışmaya dahil edildi. Çalışmanın verileri geriye dönük olarak toplandı. Çalışmaya korpus ve antrum olmak üzere iki mide bölgesinden biyopsi alınan hastalar dahil edildi.

Bulgular: Antrumdan alınan biyopsilerde HP enfeksiyonu saptanan 58 (%39.7) hasta vardı. Korpustan alınan biyopsilerde HP saptanan 57 (%39) hasta vardı. Toplamda HP pozitif saptanan 74 (%50.7) hasta vardı. Antral biyopsi için duyarlılık ve özgüllük sırasıyla %78 ve %100 bulundu. Korpus için sırasıyla %77 ve %100 idi. Lenfoid agregalı hastaların biyopsi sonuçları bir bölgede ve her iki bölgede de karşılaştırıldığında, p değeri <0.05. Tek ve her iki bölgedeki intestinal metaplazili hastaların biyopsi sonuçları karşılaştırıldığında p değeri <0.05.

Sonuç: HP enfeksiyonunu doğru tanımlamak ve ayrıca lenfoid agregatlarını, mide bağırsak metaplazisini tespit etmek için endoskopik mide biyopsilerinin sayısı ve yeri önemlidir. Çünkü yalnızca antrum ya da yalnızca korpustan alınan biyopsi örnekleri yanlış negatiflik oranını artırmaktadır. Başarı oranını arttırmanın yolu hem antrum hemde korpusun büyük ve küçük kurvaturundan alınan biyopsilerden elde edilebileceği akılda tutulmalıdır.

Anahtar Sözcükler: Biyopsi yeri; endoskopi; *Helikobakter pilori*; tanı doğruluğu.