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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

What Should Be the Optimum Biopsy Time for *Helicobactery Pylori* in Upper Gastrointestinal System Bleeding Due to Peptic Ulcer?

Peptik Ülsere Bağlı Üst Gastrointestinal Sistem Kanamalarında *Helikobakter Pilori* için Optimum Biyopsi Zamanı Ne Olmalı?

Cemal Seyhun, Mehmet Abdussamet Bozkurt, Bahadır Kartal

Department of General Surgery, İstanbul Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: Upper gastrointestinal system (GIS) bleedings are common in the daily practice of general surgeons and are still an emergency situation with high morbidity and mortality despite advanced medical and endoscopic treatments. The most common cause of upper gastrointestinal bleeding is peptic ulcer; Helicobacter pylori (HP) has been implicated in the etiology of peptic ulcers. In this study, we aimed to determine the optimum time of biopsy for HP and the optimum time to start HP treatment in patients who applied to the hospital with upper gastrointestinal bleeding and had gastric or duodenal ulcers during their gastroscopic evaluation.

Method: Patients who were diagnosed with upper GIS bleeding and had bleeding due to peptic ulcer disease were divided into two groups. In the first group, patients whose bleeding was stopped and who were discharged with medical therapy, and underwent biopsy for HP diagnosis from antrum after 4–6 weeks at control gastroscopy were included. In the second group, patients who underwent a biopsy for HP diagnosis from gastric antrum during the first gastroscopy performed within 6–24 h after admission were included. Endoscopic findings of patients were estimated with Forrest classification and HP densities in biopsy were estimated according to the Sydney classification, and the two groups were compared.

Results: When groups were divided into subgroups according to age, gender, comorbid disease, and history of previous surgery, no significant difference was found between the two groups statistically ($p>0.05$). When the two groups were considered in terms of rebleeding rates, no statistically significant difference was found between them ($p>0.05$). No statistically significant difference was found between the groups for HP according to the Sydney classification and Forrest classification in the first endoscopic evaluation ($p>0.05$).

Conclusion: In patients who presented with acute upper GIS bleeding and were hemodynamically stable and had no coagulopathy, we thought that biopsy for HP could be performed safely after bleeding was stopped regardless of the presence of active bleeding in the first endoscopy. Furthermore, biopsy for HP during the first endoscopy may help to reduce the rate of false negativity that may occur due to the proton pump inhibitor treatment that patients will use up to the control endoscopy. We think that there is a need for further studies with large series on this subject.

Keywords: Forrest classification, gastroscopy, *helicobacter pylori*, Sydney classification, upper gastrointestinal system bleeding

ÖZ

Amaç: Üst gastrointestinal sistem (GIS) kanamaları genel cerrahların günlük pratiğinde sık görülen ve ileri tıbbi ve endoskopik tedavilere rağmen halen yüksek morbidite ve mortalitesi olan acil bir durumdur. ileri tıbbi ve endoskopik tedavilere rağmen hala yüksek morbidite ve mortalite ile acil bir durumdur. Üst gastrointestinal kanamanın en yaygın nedeni peptik ülserdir; Helikobakter Pylori (HP), peptik ülser etiyolojisinde yer almaktadır. Bu çalışmada üst gastrointestinal kanama ile hastaneye başvuran ve gastroskopik değerlendirmeleri sırasında mide veya duodenum ülseri tespit edilen hastalarda. HP için optimum biyopsi zamanını ve HP tedavisine optimum başlama zamanını belirlemeyi amaçladık.

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Address for Correspondence/Yazışma Adresi: Cemal Seyhun, İstanbul Bakirköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
E-mail: seyhuncemal@gmail.com **ORCID ID:** 0000-0002-1568-3743

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Yöntem: Üst GİS kanaması tanısı alan ve peptik ülser hastalığı nedeniyle kanaması olan hastalar iki gruba ayrıldı. Birinci gruba, kanaması ilk gastroskopi sırasında durdurulup medikal tedavi ile taburcu edilen ve 4-6 hafta sonra yapılan kontrol gastroskopide antrumdan HP tanısı için biyopsi yapılan hastalar dahil edildi. İkinci gruba ise başvurudan sonraki 6-24 saat içinde yapılan ilk gastroskopi sırasında mide antrumundan HP tanısı için biyopsi yapılan hastalar dahil edildi. Hastaların endoskopik bulguları Forrest sınıflaması ve biyopsideki HP yoğunlukları Sydney sınıflamasına göre değerlendirildi ve iki grup karşılaştırıldı.

Bulgular: Gruplar yaş, cinsiyet, komorbid hastalık ve geçirilmiş cerrahi öyküsüne göre alt gruplara ayrıldığında iki grup arasında istatistiksel olarak anlamlı fark bulunmadı (p>0.05). İki grup tekrar kanama oranları açısından değerlendirildiğinde aralarında istatistiksel olarak anlamlı fark bulunmadı (p>0.05). İlk endoskopik değerlendirmede Sydney sınıflamasına ve Forrest sınıflamasına göre HP açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmadı (p>0.05).

Sonuç: Akut üst GİS kanaması ile başvurup hemodinamik olarak stabil ve koagülopatisi olmayan hastalarda ilk endoskopide aktif kanama olup olmadığına bakılmaksızın kanama durdurulduktan sonra HP biyopsisinin güvenle yapılabileceğini düşünmekteyiz. Dahası. ilk endoskopi sırasında HP için biyopsi yapılması hastaların kontrol endoskopisine kadar kullanacağı proton pompa inhibitörü tedavisine bağlı oluşabilecek yanlış negatiflik oranını azaltmaya yardımcı olabilir .Bu konuda daha geniş serili çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar kelimeler: Forrest sınıflaması, gastroskopi, *helikobakter pilori*, Sydney sınıflaması, üst gastrointestinal sistem kanaması

INTRODUCTION

Acute gastrointestinal bleeding is a common life-threatening emergency.[1] Despite advances in pharmacological and interventional treatment methods, the mortality rate varies between 2% and 10%.[2] Gastric and duodenal ulcers are the most common causes of upper gastrointestinal bleeding.[3] Patients should be evaluated gastroscopically after the first evaluation, preferably within the first 6 h or at the latest within 24 h. If active bleeding is detected, bleeding should be stopped by endoscopic or surgical intervention.

There is much evidence supporting the central role of *Helicobacter pylori* (HP) in the pathophysiology of peptic ulcer disease (PUD). HP infection has been shown in 90% of patients with duodenal ulcer and 70–90% of patients with gastric ulcer.[4] Diagnosis and treatment of HP infection is one of the basic principles of upper GIS bleeding treatment. However, controversy continues regarding the optimal time to obtain a biopsy for HP from the antrum in patients presenting with upper gastrointestinal bleeding and who have ulcers detected by first gastroscopic evaluation.

In the general approach, a biopsy is taken during the control gastroscopy 4–6 weeks after the bleeding is stopped because biopsy taken during the first gastroscopy may lead to rebleeding, but this approach causes the patient to be discharged with proton pump inhibitor (PPI) treatment which may lead to false-negative results in the pathological diagnosis of HP and delay in HP treatment. In this study, we compared patients who underwent gastroscopic biopsy at the time of bleeding for HP and those who had a biopsy at control gastroscopy 4 weeks after bleeding and aimed to determine the optimal biopsy time and the optimal time to start the HP treatment.

METHOD

The study was designed as a prospective randomized study following the approval of the local ethics committee. Between January 1, 2017 and January 1, 2019, all patients admitted to the emergency department with acute upper gastrointestinal bleeding were evaluated, and patients who had active or stopped bleeding from gastric or duodenal ulcer during the gastroscopic evaluation were included. Patients admitted to the emergency department with acute upper gastrointestinal bleeding were randomized according to protocol numbers. The first group included patients who had an odd protocol number. In this group, patients were discharged with high-dose PPI after gastroscopic control of bleeding, and a biopsy was taken from the antrum for the diagnosis of HP during control upper gastrointestinal system (GIS) gastroscopy performed 4–6 weeks later. The second group included patients who had an even protocol number. Biopsies taken from from the antrum for the diagnosis of HP during the upper GIS gastroscopy performed at the time of the first admission, and according to the results of the biopsy, treatment was arranged when they were discharged.

The demographic data of patients in both groups were examined. In addition, patients in both groups were divided into subgroups according to endoscopic Forrest classification and pathologically HP positivity according to the Sydney Classification and were compared. Both groups and subgroups were compared according to HP positivity and degree of positivity. Time to begin treatment of patients with HP infection was noted in both groups. Finally, recurrent bleeding was noted in both groups, and the two groups were compared.

Inclusion Criteria

1. Patients older than 18 years,
2. Patients who were hemodynamically stable or unstable at first admission and stabilized by resuscitation,
3. Patients with upper gastrointestinal bleeding and gastric or duodenal ulcer detected during gastroscopy.

Exclusion Criteria

1. Patients younger than 18 years,
2. Patients who were unstable at the time of the first admission and who did not respond to resuscitation and operated,
3. Patients with coagulation disorders,
4. Patients with impaired activated partial thromboplastin time and prothrombin time,
5. Patients with bleeding due to esophageal varices, Mallory-Weiss syndrome, tumors, vascular anomalies, Boerhaave syndrome, and aortoenteric fistula,
6. Patients who previously had antibiotic treatment for Helicobacter eradication,
7. Patients without consent for the study.

Statistical Analysis

Frequency and percentage values were given for categorical variables. Mean, standard deviation, median, minimum, and maximum values were given for continuous variables. The normal distribution of continuous variables was tested by Kolmogorov-Smirnov test. Chi-squared analysis was made for categorical relationships. Where appropriate, categorical variables were evaluated by Fisher-Freeman-Halton test. When variables did not fulfill the normal distribution assumption, Mann-Whitney U test was used to compare two independent groups. $P<0.05$ was considered to be statistically significant. Analyses were performed with NCSS 11 (Number Cruncher Statistical System, 2017 Statistical Software).

RESULTS

A total of 220 patients who have upper gastrointestinal system bleeding were included in the study (Fig. 1). 20 patient did not want to consent to the study. Of these 200 patients who consent to study. 97 patients in the first group and 103 patients in the second group gave consent to participate in the study. Another 2 patients were excluded because of coagulation disorder. Only the remaining 4 were included in the study because they were hemodynamically stable and stopped bleeding. Two patients were hemodynamically stable but had coagulation disorder and therefore were excluded. Two patients who previously received antibiotic therapy for Helicobacter eradication and 2 patients who had gastric adenocarcinoma in their biopsy specimen were excluded. Finally, 3 patients who had esophageal variceal bleeding, 2 patients who had bleeding due to Dieulafoy lesion, and 1 patient who had bleeding due to the Mallory-Weiss lesion were excluded from the study.

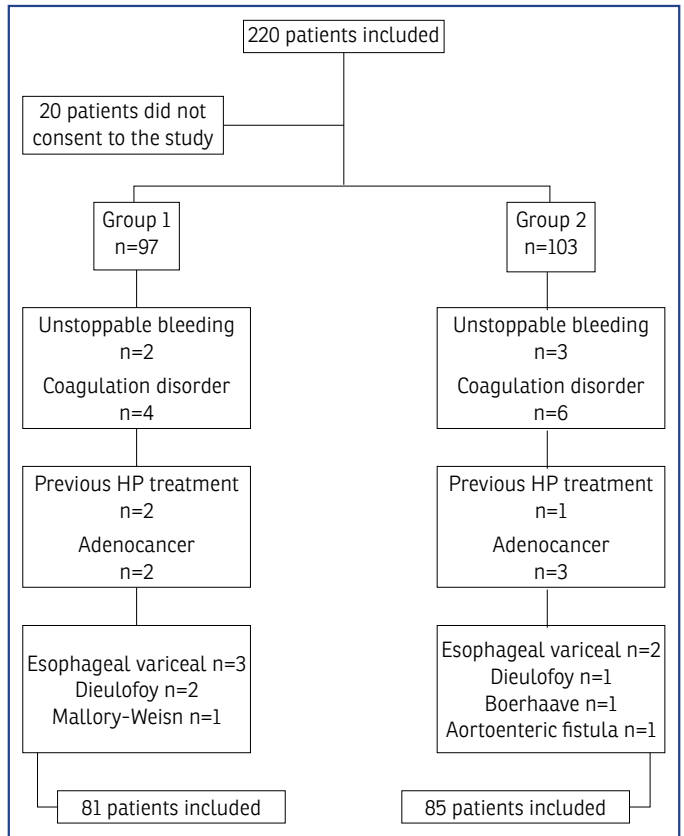

Figure 1. Distribution of groups according to inclusion criteria

Seven of 103 patients in the second group were not hemodynamically stable at first admission. Three of those 7 patients were excluded because of being taken to emergency operation due to unstoppable bleeding and another 2 were excluded because of coagulation disorder. The other 2 were included in the study because they became hemodynamically stable and stopped bleeding. Four patients were hemodynamically stable but had coagulation disorder and therefore were excluded. One patient who previously received antibiotic therapy for Helicobacter eradication and 3 patients who had gastric adenocarcinoma in their biopsy specimen were excluded. Finally, 2 patients who had esophageal variceal bleeding, 1 patient who had bleeding due to Dieulafoy lesion, 1 patient who had bleeding due to Boerhaave syndrome, and

Table 1. Comparison of age levels by groups

	Group 1	Group 2
n	81	85
Mean±SD	53.99±20.22	56.99±20.01
Median (min-max)	56 (19–89)	59 (18–91)

Mann-Whitney U test. P=0.334

1 patient who had bleeding due to aortoenteric fistula were excluded from the study.

When 166 patients included in the study were evaluated according to their age levels, the mean age of 81 patients in the first group was 53.99±20.22 years and the median age was 56 years (19–89). The mean age of the 85 patients in the second group was 56.99±20.01 years and the median age was 59 years (18–91). There was no statistically significant difference between the groups in terms of age (p=0.334) (Table 1).

Of the 81 patients in the first group, 17 (20.99%) were females and 64 (79.01%) were males. Of the 85 patients in the second group, 29 (34.12%) were females and 56 (65.88%) were males. There was no statistically significant difference between the two groups in terms of gender distribution (p=0.059) (Table 2).

Forty-three (53.09%) patients in the first group and 48 (56.47%) patients in the second group had an additional disease. There was no statistically significant difference between the groups in terms of the presence of additional disease (p=0.661) (Table 2).

When the groups were subdivided according to HT, DM, and bypass/angiography, there was no statistically significant difference between the two groups. p=0.815 for HT, p=0.508 for type 2 DM, and p=0.995 for bypass/angio. When the groups were evaluated in terms of anticoagulant and aspirin use, no statistically significant difference was found between the two groups (p=0.349) (Table 2).

When the groups were compared according to the Sydney classification for HP and the Forrest classification in the first endoscopic evaluation, there was no statistically significant difference between them. p=0.054 for the Sydney classification and p=0.194 for the Forrest classification (Table 2).

In addition, anticoagulant/aspirin-treated and nontreated patients were divided into two groups and compared according to the Sydney classification and Forrest classification in the first endoscopy. As a result, there was no statistically significant difference between the two groups according to both the Sydney classification (p=0.520) and the Forrest classification (p=0.141) (Table 3).

Finally, although 6 patients in the first group and 5 patients in the second group had active bleeding detected during the first endoscopy and stopped by intervention, the endoscopic intervention was repeated due to rebleeding during hospitalization and the bleeding was stopped. When the two groups were considered, the total rebleeding rate was 7.40% for the first group and 5.88% for the second group. No statistically significant difference was found between the two groups in terms of rebleeding rates (p>0.05) (Table 4).

DISCUSSION

Peptic ulcer bleeding is the most common cause of upper gastrointestinal bleeding.[1] Upper GIS bleeding is seen twice in men compared with women in all age groups, whereas the mortality rate is similar in both sexes.[5] Similar to the literature, the majority of the patients included in our study were males. Of the patients, 120 (72.29%) were males and 46 (27.71%) were females.

The age of the total 161 patients in our study ranged from 19 to 91 years. The median age was 58 years and the mean age was 55.52±20.11 years. In the literature, there are studies supporting upper gastrointestinal bleeding and peptic ulcer-related bleeding more frequently in older age. In their study with 3270 cases, Mino Fugarolas et al.[6] found the mean age to be 57±16.8 years. These results are similar to our results.

One of the most important factors affecting the prognosis of upper gastrointestinal bleeding is the presence of additional disease. In the study of Sung et al.,[7] it was shown that only 2–10% of the mortality due to acute upper gastrointestinal bleeding was caused by bleeding and 80% was due to additional non-bleeding comorbidities. When the literature is evaluated, the presence of additional disease is seen in high rates in patients with upper gastrointestinal bleeding. Yenigün et al.[8] found the incidence of additional disease in upper gastrointestinal bleeding to be 50.8%. Similar to the literature in our study, 91 (54.82%) patients had at least one additional disease when they were evaluated for any additional diseases.

HP is the most common cause of chronic gastric bacterial infection worldwide.[9] There is much evidence supporting HP's central role in PUD pathophysiology. HP infection is present in 90% of patients with duodenal ulcer and 70–90% of patients with gastric ulcer.[4] Similarly, in our study, HP positivity was found in 68.29% (n=112) patients similar to the rates given in the literature.

One of the hypotheses when we designed this study was in the first endoscopy performed in patients presenting to

Table 2. Examination of the distribution of variables according to the distribution of groups

	Group 1		Group 2		
	n	%	n	%	p
Gender					
Women	17	20.99	29	34.12	0.059
Men	64	79.01	56	65.88	
Additional disease					
–	38	46.91	37	43.53	0.661
+	43	53.09	48	56.47	
Hypertension					
–	51	62.96	55	64.71	0.815
+	30	37.04	30	35.29	
Type 2 diabetes mellitus					
–	68	83.95	68	80.00	0.508
+	13	16.05	17	20.00	
Bypass/angio					
–	60	74.07	63	74.12	0.995
+	21	25.93	22	25.88	
Anticoagulant/aspirin					
–	57	70.37	54	63.53	0.349
+	24	29.63	31	36.47	
Sydney classification					
0	31	38.27	21	25.30	0.054*
+1	27	33.33	23	27.71	
+2	20	24.69	29	34.94	
+3	3	3.70	10	12.05	
Forrest classification					
Ia	5	6.17	1	1.18	0.194*
Ib	14	17.28	8	9.41	
IIa	2	2.47	4	4.71	
IIb	8	9.88	5	5.88	
IIc	3	3.70	4	4.71	
3	49	60.49	63	74.12	

*Chi-squared test. *Fisher-Freeman-Halton test

the emergency department with acute upper gastrointestinal bleeding, due to the concern that the biopsy for HP will create a new hemorrhage focus, the biopsy is postponed to control endoscopy after 4–6 weeks and this approach cause delayed for HP treatment and even HP tests could lead to false negativity due to PPIs usage during this period.

PPIs are the most commonly used antisecretory agents worldwide. Drug activities are evaluated according to their ability to maintain intragastric pH 4 or more for 24 h.[10,11] Active PPI or antibiotic use has been shown to lead to false negativity in all invasive tests for HP. False-negative rates have been reported to be at least 30%.[12]

Studies have shown that peptic ulcer-related complications increase with increasing bacterial load.[13,14] In our study, HP colonization density was evaluated according to the current Sydney classification.[15] When HP positive patients were subdivided according to the Sydney classification, there was no statistically significant difference between the two groups

Table 3. Examination of the distribution of variables according to the distribution of anticoagulant/aspirin use

	–		+		
	n	%	n	%	p
Sydney classification					
0	36	32.43	16	30.19	0.520
1	33	29.73	17	32.08	
2	31	27.93	18	33.96	
3	11	9.91	2	3.77	
Endoscopic Forrest classification					
Ia	1	0.90	5	9.09	0.141
Ib	14	12.61	8	14.55	
IIa	4	3.60	2	3.64	
IIb	8	7.21	5	9.09	
IIc	6	5.41	1	1.82	
3	78	70.27	34	61.82	

Fisher-Freeman-Halton test

Table 4. Comparison of rebleeding rates by groups

Diagnosis	Rebleeding				Total	p
	+		–			
	n	%	n	%	n	
Group 1	6	7.40	75	92.59	81	
Group 2	5	5.88	80	94.11	85	0.05
Total	11	6.62	155	93.37	166	

Fisher's exact test

for each subgroup although HP 2+ and HP 3+ patients were higher in the second group (p>0.05).

Barkun et al.[16] showed that 80% of acute upper gastrointestinal bleeding cases stopped spontaneously but 20% required endoscopic or surgical intervention. To identify these high-risk patients, assess the likelihood of rebleeding, and, if necessary, intervene in bleeding at early gastroscopy (in the first 24 h), bleeding lesions and ulcers are graded according to Forrest classification.[17,18]

In the study of Laine and Peterson, it was shown that the risk of rebleeding, need for operation, and mortality increase in patients with severe bleeding than Forrest IIc or III ulcers.[19] The general approach is that endoscopic intervention should be performed for Forrest I and IIa lesions and that this should be considered as an option for Forrest IIb lesions.[20] In our clinic, we perform endoscopic procedures for Forrest Ia, Ib, IIa, and IIb lesions.

In our study, when the patients in both groups were divided into subgroups according to Forrest classification, no statistically significant difference was found between the two groups for each subgroup (p>0.05). Rebleeding is one of the most important prognostic factors in the first hospitalization of upper gastrointestinal bleeding, and early detection and treatment of this condition improves outcomes in these patients. Endoscopic treatment is an effective method for controlling and treating peptic ulcer bleeding. Although injection of hemostasis was achieved in 90% of patients at the first attempt, the risk of rebleeding was as high as 10–30%.[21–24] It has been shown in the literature that the risk of mortality in rebleeding has increased threefold.[25]

Considering all the patients in the two groups in our study, the rate of rebleeding during the first hospitalization was 6.62% (n=11). This rate is seen to be less than the reported rates in the literature. When the two groups were compared in terms of rebleeding rates (7.40% in Group 1 vs 5.88% in Group 2), no statistically significant difference was found (p>0.05).

There are studies showing that PPIs commonly used in the treatment of peptic ulcer complicate HP eradication and cause false negativity in diagnostic studies. In our study, we compared patients who were admitted to the hospital with acute upper gastrointestinal bleeding, those who had a biopsy during the first endoscopy, and those who had a biopsy at the control endoscopy after 4 weeks of the first admission. We found that HP positivity (74.70% vs 61.70%) was higher in patients who had a biopsy at the time of the first admission, but we could not find a statistically significant difference between the two groups.

Finally, in patients presenting with acute upper gastrointestinal bleeding, the traditional opinion is that the biopsy for HP should be postponed after 4–6 weeks of control to avoid extra bleeding. However, in our study, no statistically significant difference was found in age, comorbidity, anticoagulant/aspirin use, Sydney and Forrest classifications in both groups, and the groups were also similar in terms of rebleeding rates. Therefore, contrary to the conventional view, we believe that biopsy can be performed safely for HP after acute hemorrhage is stopped in patients who are hemodynamically stable and have no coagulation disorder, regardless of the presence of active hemorrhage at the first endoscopy, or in the presence of a still bleeding hemorrhage.

Furthermore, although our hypothesis that performing a biopsy at the first endoscopy will reduce the false negativity rates that may occur due to PPI treatment to be used until the control endoscopy is not proven, we believe that further studies on this subject are needed.

CONCLUSION

HP infection plays an important role in ulcer formation in patients presenting with GIS bleeding. Biopsy treatment during the first gastroscopy allows the patient to start treatment early as well as eliminates the need for a second endoscopic procedure. Our study also contributes to the literature by eliminating the concern that the biopsy performed during the first procedure may cause bleeding.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (No: 2019-04-19, Date: 18/02/2019).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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Conflict of Interest: There is no conflict of interest.

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