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Rebleeding rate and predictive factors in patients with peptic ulcers

Peptik ülserli hastalarda tekrar kanama oranları ve risk faktörleri

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Background and Aims: *Upper gastrointestinal bleeding is one of the most common gastroenterological emergencies. Despite endoscopic treatment methods, rebleeding may occur in some patients. Therefore, it is important to clinically predict recurrent bleeding. This study investigated the factors that could predict rebleeding in upper gastrointestinal bleeding.* ***Material and methods:*** *The study included 310 patients with upper gastrointestinal bleeding. Patients diagnosed with upper gastrointestinal bleeding were divided into two groups: those with recurrent bleeding and those without recurrent bleeding. Demographic data such as laboratory parameters, blood groups, age and gender of patients in both groups were statistically analyzed.* ***Results****: Statistically, bleeding was significantly less in patients with ulcer diameters of 10 mm and less than 10 mm ($p < 0.001$). According to the Forrest classification, patients with group 1A had a statistically significant higher rebleeding rate, as expected ($p < 0.001$). It was observed that rebleeding was significantly more common in patients treated with dual therapy ($p < 0.001$). On the other hand, high urea levels were associated with a 1.1-fold increase in the probability of rebleeding.* ***Conclusions:*** *As a result of the study, we determined that age, blood hemoglobin and urea levels, ulcer size and Forrest classification, and the number of endoscopic methods applied increase the risk of rebleeding. By observing these parameters together, high-risk patients can be identified and more care can be taken in bleeding management. It can also give an idea about early endoscopy again.*

Key words: *Upper gastrointestinal system bleeding, rebleeding, risk factors*

Giriş ve Amaç: *Üst gastrointestinal kanama en sık görülen gastroenterolojik acil durumlardan biridir. Endoskopik tedavi yöntemlerine rağmen bazı hastalarda tekrar kanama görülebilir. Bu nedenle riskli hastalarda tekrarlayan kanamaları öngörebilmek önemlidir. Bu çalışmamızda, peptik ülser kanamasıyla takip ettiğimiz ve hastanede yeniden kanaması olan hastalarda bu duruma etki eden faktörleri araştırarak, kendi deneyimimizi sunmayı amaçladık.* ***Gereç ve Yöntem:*** *Üst gastrointestinal sistem kanaması bulguları nedeniyle başvurup endoskopi yapılan ve peptik ülser kanaması teşhisi konulan 310 hasta çalışmaya dahil edildi. Üst gastrointestinal sistem kanaması tanısı alan hastalar, kanaması tekrar edenler ve tekrarlamayan hastalar olmak üzere iki gruba ayrıldı. Her iki gruptaki hastaların laboratuvar parametreleri, kan grupları, yaş ve cinsiyet gibi demografik verileri istatistiksel olarak analiz edildi.* ***Bulgular:*** *Yeniden kanama oranı, ülser çapı 10 mm ve 10 mm'den küçük olan hastalarda anlamlı olarak daha azdı ($p < 0.001$). Forrest sınıflandırmasına göre, Forrest 1A'daki hastaların istatistiksel olarak anlamlı şekilde daha yüksek bir yeniden kanama oranı vardı ($p < 0.001$). Endoskopik olarak kanama kontrolü için dual yöntemler uygulanan hastalarda yeniden kanamanın anlamlı şekilde daha fazla olduğu görüldü ($p < 0.001$). Öte yandan, yüksek üre seviyesinin yeniden kanama olasılığında 1.1 kat artma ile ilişkili olduğu görüldü ($p = 0.023$).* ***Sonuç:*** *Çalışmamız sonucunda yaş, kan hemoglobin ve üre düzeyleri, ülser boyutu ile Forrest sınıflandırması ve uygulanan endoskopik yöntem sayısının tekrar kanama oranlarında etkili faktörler olduğunu belirledik. Bu parametrelerin birlikte kullanılmasıyla yüksek riskli hastalar belirlenebilir. Ayrıca erken veya tekrar endoskopisi hakkında öngörüde bulunulabilir.*

Anahtar kelimeler: *Üst gastrointestinal sistem kanamaları, tekrarlayan kanama, risk faktörleri*

INTRODUCTION

Upper gastrointestinal (GI) bleeding is one of the most common gastroenterological emergencies. However, gastrointestinal bleeding accounts for 5% of emergency department admissions and 2% to 3% of hospitalizations in developed countries each year (1,2). The most common cause of upper GI bleeding is nonvariceal bleeding, and peptic ulcer bleeding occurs in 28% to 59% of cases (3-5). *Helicobacter pylori* infection and/or use of anti-inflammatory drugs, including low-dose aspirin use, are the most important risk factors (6,7).

Endoscopic hemostatic therapy has been proposed as first-line therapy for ulcers with a high bleeding risk and available endoscopic hemostatic modalities include mechanical treatments such as adrenaline injection therapy, thermal coagulation, and hemoclips (8).

Despite these interventions, rebleeding may occur. The rate of rebleeding after endoscopic hemostasis interventions in peptic ulcer bleeding varies between 6.3% and 25.2% (9). Rebleeding is a common complication of peptic ulcers, and the possibility of rebleeding often precludes hospital discharge (10). Therefore, it is important to predict rebleeding clinically. Observational studies have identified predictors of rebleeding, reoperation, and death in patients with peptic ulcer bleeding (11-15).

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In this study, we aimed to present our own experience by investigating the predictors affecting this condition in our patients with rebleeding.

MATERIALS and METHODS

Study Design and Patient Population

Three hundred and ten patients who were admitted to our hospital due to upper GI bleeding findings and underwent endoscopy and diagnosed with peptic ulcer bleeding were included in the study. The recorded files and electronic data of the patients were reviewed retrospectively.

Patient Data and Definitions

Patients diagnosed with upper GI bleeding were basically divided into two groups (with or without endoscopic treatment) as those with recurrent bleeding and those with non-recurrence. Demographic data such as laboratory parameters, blood groups, age and gender of the patients in both groups were statistically analyzed. In addition, these patients were divided into subgroups according to the location, size and severity of the bleeding ulcer. According to the location of the ulcer; they were grouped as esophageal, stomach, duodenal and anastomotic ulcers.

According to the size of the ulcer, it was grouped as 0-10 mm, between 11 mm and 20 mm, and greater than 20 mm.

While grouping according to the meeting of the ulcer; Forrest classification assessing the risk of rebleeding. Accordingly, Forrest Ia, in the gushing blood; Forrest Ib, oozing bleeding; Forrest IIa, presence of visible vessels that do not bleed; Forrest IIb, adherent clot; Forrest IIc was defined as having a hematin pigment base and Forrest III as a clean-based feature (2).

According to the endoscopic hemostasis methods applied in the treatment of ulcers, those who did not apply any endoscopic hemostasis method, those who applied only saline adrenaline, those who applied at least one endoscopic hemostasis method in addition to saline-adrenaline (hemoclips, argon plasma coagulation or heater probe) and other methods were grouped.

Patients with and without rebleeding were consistently analyzed in these subgroups. Thus, it was aimed to determine the factors that affect the possibility of rebleeding in these patients.

Exclusion Criteria

Patients younger than 18 years of age, patients with bleeding etiologies other than peptic ulcer bleeding (oesophagitis, Mallory Weiss tear, varicose bleeding, patients with comorbidities such as esophageal, stomach, duodenal malignancy, patients with endoscopic non-ulcer bleeding etiology, and endoscopic bleeding focus detection) patients were excluded from the study.

Ethics Committee: Approval for this study was received from the Ethics Committee of Turkey Higher Specialization Hospital with the decision dated 24.01.2018 and numbered 31/09.

Statistical Analysis

Kolmogorov-Smirnov, Shapiro-Wilk test, coefficient of variation, skewness and kurtosis methods were used to control the normal distribution of patient data. While mean and standard deviation values were expressed in continuous variables, categorical variables were expressed as percentages. To compare demographic and descriptive parameters such as age and gender of peptic ulcer patients with and without recurrent bleeding; Independent Samples T test or Mann Whitney U test was used. Chi-square test was used to determine whether there was a difference between the two groups in terms of blood group. The Independent Samples T test was used for normally distributed parameters and the Mann Whitney U test was used for non-normally distributed data for the difference between laboratory data between groups. In the analysis of peptic ulcer patients, who were divided into two groups according to rebleeding status, according to the location of the ulcer, the size of the ulcer and Forrest Classification, one-way-ANOVA was applied to the groups with homogeneous variances, and Chi-Square test was applied to groups with non-homogeneous variances. One-way ANOVA test was used to compare treatment methods between the two groups. Binary logistic regression analysis was performed to determine the factors that most affect the probability of rebleeding of peptic ulcer. Exp(B) and 95% CI values were determined. All tests were bilateral and p value < 0.05 was considered statistically significant. Statistical analyzes were performed using SPSS 24.0 for Windows (SPSSInc.Chicago, IL,USA) package program.

RESULTS

Demographic Characteristics and Laboratory Findings

Rebleeding occurred in 44 (14.2%) of a total of 310 patients. There was no significant difference between the patients in terms of gender ($p = 0.560$). The median age of the patients with recurrent bleeding was 67 years and it was found to be statistically significantly higher ($p = 0.011$). There was no significant difference between the groups in terms of blood groups ($p = 0.169$). Detailed data on demographic characteristics are presented in Table 1.

When the laboratory findings of the patients at the first admission were evaluated, the mean hemoglobin value of the patients with recurrent bleeding at the time of admission was

7.97 ± 2.48 g/dl, and it was found to be statistically significantly lower (p = 0.01). In these patients, the mean platelet volume at the time of admission was 8.8 ± 1.29 fl, which was found to be significantly higher (p = 0.047). The mean urea level was found to be significantly higher at 105 ± 78.8 mg/dl in patients with recurrent bleeding (p = 0.041) (Table 2).

Endoscopic Findings

When the bleeding localizations of the patients with recurrent bleeding were evaluated, no difference was found in terms of ulcer location, but it was found that the bleeding was significantly less in patients with ulcer diameters of 10 mm and less than 10 mm (p < 0.001). As expected, patients with group 1A according to Forrest classification had a statistically significant higher rate of rebleeding (p < 0.001). Detailed data on ulcer location, size and Forrest classification are presented in Table 3. When the endoscopic intervention methods applied to the patients were compared, it was seen that rebleeding was more common in the patients who received dual therapy (p < 0.001) (Table 4). In the logistic regression analysis, it was determined that patient age, urea level, ulcer size and Forrest classification were independent risk factors for rebleeding. Age increased the probability of rebleeding 1.04 times in patients with peptic ulcer [p = 0.008; Exp(B) = 0.955]. High urea level, on the other hand, increased the probability of rebleeding by 1.1 times [p = 0.023; Exp(B) = 0.989]. The probability of rebleeding was 3.7 times higher in patients with low hemoglobin [p = 0.001; Exp(B) = 3.709].

Table 1. Distribution of patients with upper GI bleeding according to demographic data and blood groups

	Not Rebleeding (n: 266)	Rebleeding (n: 44)	p
Age (years)	59.7 (20 - 92)	67 (23 - 96)	0.011
Gender (F/M)	60/206 (%22.5 - %75.5)	12/32 (%37.5 - %62.5)	0.560
Blood group			
A Rh (+)	96 (%36.1)	12 (%27.3)	
A Rh (-)	7 (%2.6)	1 (%2.4)	
B Rh (+)	34 (%12.8)	9 (%20.5)	
B Rh (-)	4 (%1.5)	0 (%0)	
AB Rh (+)	14 (%5.3)	5 (%11.3)	0.169
AB Rh (-)	1 (%0.3)	0 (%0)	
0 Rh (+)	101 (%38)	16 (%36.4)	
0 Rh (-)	9 (%3.4)	1 (%2.3)	

Table 2. Laboratory data of patients with upper GI bleeding

	Not Rebleeding (n: 266)	Rebleeding (n: 44)	p
WBC (mm^3)	10187 ± 3583	11240 ± 6876	0.402
Hgb (gr/dl)	10.13 ± 2.91	7.97 ± 2.48	0.001
MCV	87.1 ± 6.8	84.2 ± 9.6	0.158
Platelet ($/mm^3$)	243.529 ± 99.498	209.483 ± 95.908	0.75
MPV	8.38 ± 1.1	8.8 ± 1.29	0.047
Urea (mg/dl)	74.7 ± 45.5	105 ± 78.8	0.041
Creatinine (mg/dl)	0.69 ± 1.36	1.18 ± 2.2	0.232
Albumin (gr/dl)	3.39 ± 2.92	2.66 ± 0.71	0.175
INR	1.15 ± 1.1	1.28 ± 0.95	0.544
Pt (sec)	16.4 ± 18.6	17.3 ± 11.3	0.793
APTT (sec)	31.4 ± 11.2	33 ± 9.6	0.458

APTT: Activated partial thromboplastin time, Hgb: Hemoglobin, INR: International ratio, MCV: Mean corpusculer volume, MPV: Mean platelete volume, Pt: Prothrombine time, SS: Standard deviation, WBC: White blood cell

According to the Forrest Classification, Forrest 1A ulcers were 2.58 times more likely to bleed again than Forrest 2 and 3 ulcers [p = 0.001; Exp(B) = 2.584].

Considering the ulcer size, an ulcer larger than 20 mm was 3.83 times more likely to bleed again than an ulcer smaller than 10 mm [p < 0.001; Exp(B) = 0.261] (Table 5).

Table 3. Comparison of endoscopic findings of patients with rebleeding and non-bleeding Upper GIS bleeding

	Not Rebleeding (n: 266)	Rebleeding (n: 44)	P
Location of ulcer			
Esophagus	13 (4.9%)	1 (2.3%)	
Stomach	85 (32%)	12 (27.3%)	
Duodenum	157 (59%)	28 (63.6%)	0.798*
Anastomosis	5 (1.9%)	1 (2.3%)	
Other	6 (2.2%)	2 (4.5%)	
Ulcer size			
0-10 mm**	169 (63.5%)	12 (27.3%)	
11-20 mm	28 (10.5%)	12 (27.3%)	< 0.001**
> 20 mm	69 (26%)	20 (45.4%)	
Forrest classification			
Forrest 1A**	10 (3.7%)	13 (29.5%)	
Forrest 1B	41 (15.4%)	9 (20.5%)	
Forrest 2A	88 (33.2%)	15 (34.1%)	< 0.001**
Forrest 2B	9 (3.4)	5 (11.4%)	
Forrest 2C	23 (8.6%)	0 (0%)	
Forrest 3	95 (35.7%)	2 (4.5%)	

* Chi Kare test, ** Anova was used.

Table 4. Comparison of treatment methods applied in patients with upper GI bleeding

	Not Rebleeding (n=266)	Rebleeding (n=44)	*P
Did not require endoscopic treatment*	102 (38.3%)	3 (6.8%)	
SA injection	10 (3.7%)	1 (2.3%)	
SA + At least one type of endoscopic hemostasis treatment	145 (54.6%)	37 (84.1%)	< 0.001
Other (surgical, hemostatic spray (ankaferd)	9 (3.4%)	3 (6.8%)	

SA: Saline + Adrenaline. * Oneway Anova test was applied.

Table 5. Logistic regression analysis of factors affecting rebleeding in patients with peptic ulcer

	P	Exp(B)*	95 % CI
Age	0.008	0.955	0.923 - 0.988
Gender	0.220	0.448	0.124 - 1.617
Blood Group	0.998	0.000	0.000
Urea	0.023	0.989	0.980 - 0.998
Hgb	0.001	3.709	1.311 - 4.288
Forrest classification	0.001	2.584	1.476 - 4.525
Location of ulcer	0.127	0.522	0.226 - 1.204
Ulcer size	< 0.001	0.261	0.123 - 0.555
Endoscopic treatment	0.317	0.600	0.220 - 1.633

Hgb: Hemoglobin.

*Binominal logistic regression analysis

DISCUSSION

Despite the reduction in incidence, owing to the widespread use of modern endoscopic techniques in combination with proton pump inhibitors, the mortality rate associated with non-variceal upper gastrointestinal bleeding is still high (16). Therefore, since it is important to evaluate the factors that may affect recurrent bleeding in the early period, we thought that our experience would make an additional contribution to the literature.

In our study, we found that especially ulcer size less than 1 cm significantly reduced the risk of recurrent bleeding. We thought that the reason for this is that small ulcer bleeding can be controlled more easily with endoscopic therapeutic interventions and there is a faster chance of healing. In parallel with our study, Budimir et al. found that ulcers larger than 2 cm significantly increased the risk of rebleeding (2).

We found that low hemoglobin level at the time of admission increased the risk of rebleeding. In such a case, we think that the ulcer causing bleeding may indicate an ulcer that is difficult to control. It has been stated that a hemoglobin level below 10 g/dl has a predictive value in terms of rebleeding (17). In another study, it was reported that low hemoglobin level predicted life-threatening bleeding in patients with acute gastrointestinal bleeding (18). We found that high blood urea level at the time of admission also increased the risk of rebleeding. High blood urea level has been reported to be associated with severe gastrointestinal bleeding (19,20). It is also known that high urea impairs platelet functions and increases the tendency to coagulopathy (21).

It is known that advanced age and ulcer type in Forrest Classification also increase the risk of rebleeding, as in Rockall scoring (22,23). We found these data to be compatible with the literature.

The limitations of our study were that it was retrospective, limited to a single center, comorbid conditions and the use of anticoagulants and antiaggregants were not known. In patients with upper GI bleeding due to peptic ulcer, the strength of our study was to evaluate and analyze many parameters, such as the patient, the lesion causing the bleeding, and the treatment applied, from the moment of admission to the hospital.

When estimating the possibility of rebleeding in upper GI bleeding due to peptic ulcer, it would be more accurate to evaluate many parameters of the patient, as well as the severity of bleeding, the diameter of the ulcer and the endoscopic treatment applied. By observing these parameters together, high-risk patients can be identified and more care can be taken in bleeding management. It can also give an idea about early endoscopy again.

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