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Analysis of rebleeding in cases of an upper gastrointestinal bleed in a single center series

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ABSTRACT

Background: upper gastrointestinal bleeding (UGIB) is one of the main causes of hospital admission in gastroenterology departments and is associated with a significant morbidity and mortality. Rebleeding after initial endoscopic therapy occurs in 10-20% of cases and therefore, there is a need to define predictive factors for rebleeding.

Aim: the aim of our study was to analyze risk factors and outcomes in a population of patients who suffered a rebleed.

Methods: five hundred and seven patients with gastrointestinal bleeding were included. Clinical and biochemical data, as well as procedures and outcome six months after admission, were all collected. Documented clinical outcome included in-hospital and six-month delayed mortality, rebleeding and six-month delayed hemorrhagic and cardiovascular events.

Results: according to a logistic regression analysis, high creatinine levels were independent risk factors for rebleeding of non-variceal and variceal UGIB. In non-variceal UGIB, tachycardia was an independent risk factor, whereas albumin levels were an

independent protective factor. Rebleeding was associated with in-hospital mortality (29.5% *vs* 5.5%; p < 0.0001). In contrast, rebleeding was not related to six-month delayed mortality or delayed cardiovascular and hemorrhagic events.

Conclusions: tachycardia and high creatinine and albumin levels were independent factors associated with rebleeding, suggestive of a potential predictive role of these parameters. The incorporation of these variables into predictive scores may provide improved results for patients with UGIB. Further validation in prospective studies is required.

Key words: Upper gastrointestinal bleeding. Prognosis. Creatinine. Albumin. Rebleeding.

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is one of the main causes of hospital admission and urgent endoscopy in gastroenterology departments, with an estimated incidence of around 100 cases per 100,000 hospitalizations. Compared with prior decades, patients with UGIB tend to be older, have more co-morbidities and are more likely to be receiving anticoagulant and antithrombotic agents (1,2). However, even though the cases treated nowadays are more complicated, in-hospital mortality due to UGIB has decreased throughout the past two decades, with a corresponding increase in the use of endoscopy and endoscopic therapies. This may suggest that improvements in the therapeutic procedures of patients with UGIB could be responsible for the decline in mortality (3). Despite these developments, UGIB represents a true emergency with an associated significant morbidity, mortality and healthcare costs. Thus, patients need to be stratified according to the risk of a poor outcome, such as rebleeding or death. Furthermore, the need for a clinical intervention should be predicted. Several risk scores have been proposed in this regard and their use is consistently recommended by international guidelines (2,4-7).

Furthermore, rebleeding after initial endoscopic therapy is observed in 10-20% of cases and is associated with a higher mortality rate. Therefore, the definition of predictive factors for rebleeding is of paramount importance, as identifying high-risk cases for rebleeding may allow for targeted additional measures in a cost-effective manner (8-11).

Thus, the aim of the study was to analyze risk factors and outcomes in a population of patients who suffered a rebleed with the purpose of identifying predictive factors.

MATERIAL AND METHODS

Study design and population

This was a prospective cohort study that included consecutive patients with UGIB treated at the Hospital Universitario Virgen de las Nieves over a period of 42 months, from January 2013 to July 2016. Upper gastrointestinal (GI) hemorrhage was defined as bleeding from the upper GI tract that manifested as hematemesis and/or melena. Both variceal and non-variceal bleeding cases were included. Rebleeding was defined as the presence of fresh hematemesis and/or melena associated with the development of shock or a reduction in the hemoglobin concentration of more than 2 g/dl over 24 hours. Rebleeding also included cases that required repeated endoscopy, surgery or any interventional radiology procedure.

The inclusion criteria were: a) age over 18 years; and b) an upper GI hemorrhage that was defined as bleeding from the upper GI tract that manifested as hematemesis (including coffee ground vomiting) and/or melena. Pre-endoscopic exclusion criteria were: a) patients unable to provide written informed consent for the study or who refused endoscopy; b) patients with mental impairment, inability or refusal to follow instructions; c) patients with an unstable medical or surgical problem that precluded endoscopy. The study protocol was approved by the Human Research Ethics Committee of the Hospital Universitario Virgen de las Nieves on the 27th of July, 2012. Written informed consent was required from every patient included in the study. In fact, the study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the Human Research Committee of the institution.

Patients were followed-up during hospitalization and six months after discharge. All cases underwent endoscopy. The timing of endoscopy and the need for endoscopic therapy were determined by the on-call gastroenterologist. The need for a transfusion was determined by the treating physicians, who followed strict per protocol criteria that have been previously published (12,13). Patient management was based on guideline recommendations as follows: all patients received high-dose acid suppression therapy

and if variceal bleeding was suspected, treatment with somatostatin was prescribed. The European Society for Gastrointestinal Endoscopy (ESGE) recommends a combination of epinephrine injection with a second hemostasis modality (contact thermal, mechanical therapy or injection of a sclerosing agent) for patients with peptic ulcer bleeding and actively bleeding ulcers (Ia, Ib). With regard to patients with a non-bleeding visible vessel (IIa), mechanical therapy, thermal therapy or injection of a sclerosing agent as a monotherapy or in combination with epinephrine injection was recommended. Epinephrine injection therapy alone was not recommended as an endoscopic monotherapy in any case. Endoscopic band ligation or injection endoscopic sclerotherapy (if band ligation cannot be performed) were used in acute variceal bleeding (14,15).

Data collection

Information with regard to patient demographics, comorbidities, current medications (including antiplatelet drugs, nonsteroidal anti-inflammatory drug and oral anticoagulants), clinical presentation, hemodynamics and laboratory test results were collected at the time of the admission to the Emergency Room. Moreover, endoscopic findings were recorded. Interventions during the study were documented, including the need for a blood transfusion and the number of packed red cells units used per patient, endoscopic therapy, interventional radiology procedures and surgery. Clinical outcomes documented included in-hospital and six-month delayed mortality, in-hospital rebleeding and six-month delayed hemorrhagic and cardiovascular events. All-cause deaths that occurred during the index hospitalization were determined as well as in-hospital mortality. Outcomes (in-hospital and six-month delayed mortality) were prospectively assessed and directly recorded by two of the investigators when the patient was admitted and via phone calls and electronic chart consultations after discharge.

Data analysis

Statistical analysis was performed using the PAWS Statistics 21.0 software (SPSS Inc., Chicago, IL, USA). Comparisons between the different groups (non-rebleeders and rebleeders) were performed using the Chi-square test for categorical variables and the Student's t-test for normally distributed continuous variables. The non-parametric

Wilcoxon rank-sum test was used when variables did not follow a normal distribution. The results of these comparisons are shown in table 1. The absolute frequency is shown with the relative frequency in brackets for non-rebleeder and rebleeder cases. The average and the standard deviation are shown for the continuous variables. Multivariate analysis was performed by means of a logistic regression analysis in order to identify independent risks factors for rebleeding. The area under the receiver-operating characteristic curve (AUROC) with the standard error and 95% confidence intervals were calculated for the association between rebleeding and creatinine levels on admission. AUROCs were tested for equality via the Delong's χ^2 test. Sensitivity and specificity were calculated and the optimal cut-off values were selected.

RESULTS

Five hundred and seven patients with an upper gastrointestinal bleed were included in the study (339 males aged 64.21 ± 16.4) (Table 1). Endoscopy was performed in all cases, usually in the first eight hours after admission. The main endoscopic findings were: duodenal ulcer (24.7%), esophageal varices (19.5%) gastric ulcer (18.9%), acute gastric erosions (11.8%), esophagitis (11.4%), Mallory-Weiss tears and esophageal ulcers (7.7%), angiodysplasia (4.7%), neoplasms (3.7%), post-sphincterotomy bleeding (3.7%) and an unidentified cause (10.8%). A total of 184 (36.3%) patients received endoscopic therapy during the first endoscopy. This consisted of an injection of a sclerosing agent in 14 cases, hemostatic clipping in three, variceal banding in 41, argon plasma coagulation in four and hemostatic powder application (Hemospray™; Cook Medical, Winston-Salem, NC, USA) in two cases; 120 patients received a combined therapy. The most commonly used therapy was a combination of adrenaline and injection of a sclerosing agent (aethoxisclerol) (n = 75), followed by injection plus clipping (n = 32). Combined therapy was the preferred option in non-variceal bleeding (92.6%) and band ligation in variceal bleeding (67.2%). Five patients required surgery due to a massive hemorrhage that was uncontrollable by endoscopy. In-hospital mortality was 9.7%. The incidence of rebleeding was 17.3% (n = 88), 45.5% (n = 40) of cases had a repeated endoscopy, 13 underwent surgery and three had an embolization. The remaining cases did not undergo additional treatment as they were in a poor clinical condition.

The factors that were related to rebleeding according to the univariate analysis included: past history of cirrhosis (39.8% *vs* 22.7%, p = 0.001), hematemesis (62.5% *vs* 52.4%, p = 0.046) and hematochecia (15.9% *vs* 7.9%) as the clinical presentation, low systolic blood pressure (103.16 *vs* 113.14, p < 0.001), tachycardia (96.28 *vs* 88.24, p < 0.001), high creatinine levels (1,527 *vs* 1,155, p < 0.001), low hemoglobin levels (8.32 *vs* 9.81, p < 0.001), low levels of albumin (2,797 *vs* 3,238, p < 0.001), variceal bleeding (28.4% *vs* 17.7%, p = 0.026), the need for endoscopy therapy during the first endoscopy (73.9% *vs* 32.5%, p < 0.001), number of red cell units transfused (7.52 *vs* 1.90, p < 0.001) and length of hospital stay in days (17.41 *vs* 7.29, p < 0.001). Age, sex, past comorbidities other than cirrhosis, drug history, toxic habits, melena as a clinical presentation, urea, international normalized ratio and platelets were also studied but no statistical association was found.

A multivariate analysis was performed that included all the variables that were statistically significant according to the univariate analysis, as well as age. Tachycardia (OR 1,020; CI 95% 1,006-1,033; p = 0.005) and high creatinine levels (OR 1,436; CI 95% 1,099-1,876; p = 0.008) were independent risk factors for rebleeding according to this logistic regression analysis, whereas albumin (OR 0,400; CI 95% 0,263-0,607; p < 0.001) was an independent protective factor.

A separate analysis for non-variceal bleeding was also performed. The following factors were associated with rebleeding according to the univariate analysis: cirrhosis (18.8% *vs* 8.3%, p = 0.020), hematochecia at presentation (17.2% *vs* 7.4%, p = 0.017), low systolic blood pressure (105,39 *vs* 113.26, p < 0.010), tachycardia (98.21 *vs* 88.16, p < 0.001), low hemoglobin levels (8.06 *vs* 9.76, p < 0.001), high creatinine levels (1,553 *vs* 1,175, p < 0.002), low albumin levels (2,760 *vs* 3,311, p < 0.001), the need for endoscopy therapy during the first endoscopy (71.9% *vs* 27.4%, p < 0.001), red cell units transfused (7.81 *vs* 1.87, p < 0.001) and length of hospital stay in days (17.22 *vs* 6.91, p < 0.001). Similar results were found according to the logistic regression analysis. Tachycardia (OR 1,020; IC 95% 1,005-1,037; p < 0.019) and high creatinine levels (OR 1,389; CI 95% 1,059-1,874; p = 0.032) were independent risk factors for rebleeding, whereas albumin (OR 0.430; CI 95% 0.237-0.781; p = 0.006) was an independent protective factor.

Furthermore, an analysis of variceal bleeding was also performed. The factors related to rebleeding according to the univariate analysis were: low systolic blood pressure (99 *vs*

111.08; p = 0.17), high creatinine levels (1,433 *vs* 1,036; p = 0.005), number of red cell units transfused (6.58 *vs* 2.08; p < 0.001) and the length of hospital stay in days (17.31 *vs* 9.68; p = 0.046). Different results were found according to the logistic regression analysis for variceal bleeding. Only high creatinine levels (OR 2,810; CI 95% 1,108-7,128; p = 0.030) were identified as an independent risk factor for rebleeding.

The AUROC for creatinine levels on admission for the prediction of rebleeding in the whole UGIB population and the AUROCs of albumin levels and heart rate on admission in the non-variceal UGIB population for the prediction of rebleeding are shown in figures 1, 2 and 3. Optimal cut-off values for sensitivity (S) and specificity (P) were obtained from the ROC curve in order to achieve the highest performance of the predictive variable. Creatinine had an AUROC of 0.684 (CI 95% 0.562-0.805; p = 0.005) for the prediction of rebleeding in UGIB and the best cut-off value was 0.985 mg/dl with S = 70% and P = 63%. The AUROC of albumin levels to predict rebleeding in non-variceal UGIB was 0.735 (CI 95% 0.661-0.809; p < 0.001) and the best cut-off value was 2,950 g/dl with S = 66% and P = 72%. The AUROC for heart rate was 0.654 (CI 95% 0.578-0.730; p < 0.001) for the prediction of rebleeding in non-variceal UGIB and the best cut-off value was 93 bpm with S = 64% and P = 64%.

Among the rebleeders, 29.5% (n = 26) suffered in-hospital mortality whereas the rate in non-rebleeders was 5.5% (n = 23). Rebleeding was associated with in-hospital mortality (p < 0.0001). By contrast, it was not related with six-month delayed mortality (17.5% *vs* 11.1%; p = 0.188) or delayed cardiovascular (8.8% *vs* 9.4%; p = 0.885) and hemorrhagic events (12.1% *vs* 18.2%; p = 0.588).

DISCUSSION

Rebleeding is an important outcome in UGIB that increases mortality by a rate of ten times and is one of the most significant predictive factors for mortality (8,10). The identification of patients with a high risk of rebleeding is of paramount importance for a close follow-up due to the impact on mortality. The scores currently available (Rockall, Blatchford and AIMS65) were not primarily designed to predict rebleeding and do not work well in this setting. In fact, two recent studies (a systematic review and an international multi-center study) have shown that a no risk score was helpful for the

prediction of rebleeding (7,16). Therefore, it is important from a clinical point of view to develop a specific score for predicting rebleeding. The first step for the development of an accurate score should be the identification of the most important predictive variables for rebleeding and these should be easily accessible and accurate. Many parameters have been studied, including pre-endoscopic and endoscopic factors. Some of the main risk factors previously identified include: hemodynamic instability, active bleeding during endoscopy, a larger ulcer size, ulcer location, hemoglobin and the need for a transfusion, spontaneous bacterial peritonitis, inpatient onset of bleeding, C-reactive protein levels, chronic kidney disease and prior GI bleeding (9-11,17-19).

We first analyzed the entire UGIB patient cohort and then performed a separate analysis for non-variceal and variceal UGIB. This is due to the fact that variceal patients are usually in a very poor condition with important comorbidities and usually have low albumin and high creatinine levels due to the normal progress of the disease. In our cohort, high creatinine was found to be an independent risk factor for rebleeding in non-variceal and variceal UGIB. However, tachycardia and albumin were independent prognosis factors for rebleeding only in non-variceal UGIB. Maybe these were not independent risk factors in variceal bleeding due to the small number of cases that presented with variceal bleeding in our cohort. Although it would be interesting to study the association between rebleeding and endoscopic findings, this was not possible due to the fact that our cohort included several patients with an important heterogeneity, which would result in small sample sizes of some of the diagnosis types.

Previous reports suggested that higher rebleeding rates occur in chronic kidney disease (CKD). CKD was defined as an estimated glomerular filtration rate of < 60 ml/min for ≥ 3 months (11,16). In our study, non-variceal and variceal UGIB patients with increased creatinine levels on admission, with or without a CKD, had a higher risk of rebleeding. As a sole risk factor, this is a new finding that has not been previously described. Indeed, Hoffman et al. observed that creatinine > 0.9 mg/dl in females or > 1.1 mg/dl in males had a predictive role in the composite endpoint of recurrent bleeding, need for intervention and 30-day death (20).

Hemodynamic instability has been reported to be a significant risk factor for rebleeding and mortality (10,11). A systolic blood pressure of < 90 mmHg, tachycardia > 100

beats/min and peripheral signs of shock indicate hemodynamic instability and were evaluated on admission in most studies. We found that patients with non-variceal bleeding and tachycardia on admission had a higher risk of rebleeding, which is consistent with previous findings (11).

In addition, the important role of hypoalbuminemia in the prognosis of patients with UGIB has been previously reported, which results in a worse outcome (6,21-26). Most studies have demonstrated that hypoalbuminemia is a risk factor for mortality. To our knowledge, our study is the first that establishes albumin levels as an independent protective factor for rebleeding in non-variceal bleeding. This finding was also supported by the study by Tung et al., who found a mayor rate of rebleeding in patients with hypoalbuminemia (24). The association between hypoalbuminemia, mortality and rebleeding could be related to the fact that albumin levels on admission may be a surrogate marker of severe comorbidity in patients with UGIB. This points towards a possible association between low albumin levels and the stigmata of recent bleeding. More studies are needed in order to clarify this association (25).

The ability to predict rebleeding was not good enough using the above mentioned prognosis factors, according to the AUROC analysis. The sensitivity and specificity was between 60-70% for the cut-off value selected. In contrast, these parameters are easy to obtain, widely available and cheap. For this reason, we suggest that they be incorporated with other clinical parameters to generate a new prognostic model, which may be useful for guiding the clinical management of patients with UGIB.

The overall rebleeding rate in our study was 17.3%, which is similar to that of other studies (8,9,11,17-19). In our cohort, rebleeding was associated with increased in-hospital mortality, which is consistent with the previously reported results. Nevertheless, it was not related with six-month delayed-mortality or delayed hemorrhagic and cardiovascular events. In this regard, we considered six-month mortality, as most of the studies of UGIB only take into account in hospital mortality or delayed 30-day mortality (17). However, the misbalance caused by UGIB in frail patients can result in a delayed mortality, even months after the acute episode. This was also noted in a previous study by Crooks et al. (27). In this study, patients with non-variceal UGIB had a cumulative excess of all causes of death in the five years following the acute episode compared to matched controls, and

the elevated deaths were not explained by a co-morbidity diagnosed prior to admission. For this reason, we suggest that mortality rate at six months offers advantages over delayed mortality during a shorter period of time (28).

As previously mentioned, before all patients with suspected UGIB receive high-dose acid suppression therapy, we usually use pantoprazole in an 80 mg iv bolus followed by 40 mg iv twice daily or continued infusion of 8 mg per hour. Once the endoscopy is performed and the cause is identified, the need to continue with this treatment is re-evaluated. Administering PPIs before endoscopy significantly decreases the incidence of high-risk stigmata of hemorrhage at the time of index endoscopy (37.2% *vs* 46.5%; OR 0.67, 95% CI 0.54-0.84) and the need for endoscopic hemostasis (8.6% *vs* 11.7%; OR 0.68, 95% CI 0.50-0.93) (29). Moreover, the acute use of PPIs is significantly and independently associated with a lower rate of rebleeding and mortality (30,31). For this reason, it is important to start PPIs as soon as possible in the case of a suspected UGIB, in order to achieve better outcomes.

The main limitation of our study includes its single-center nature. We must highlight that our center is a referral center with a 24-hour availability of endoscopy, as well as the fact that the endoscopists experience might bias the results. However, not all physicians who performed the urgent endoscopies were dedicated endoscopists. Thus, we believe that our experience can be extensible to other centers.

In conclusion, serum creatinine can be a useful prognostic indicator for rebleeding in patients with non-variceal and variceal UGIB. Albumin levels and heart rate can be useful in the case of non-variceal bleeding. All were independent factors related to rebleeding. The incorporation of these variables to the predictive scores may result in a better result for patients with UGIB. However, further validation in prospective studies is required.

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Table 1. Patients' characteristics

	Total	*Non-rebleeders*	*Rebleeders*	p
Age	64.21 ± 16.43	64.45 ± 16.38	63.07 ± 16.68	0.476
Male	339 (66.9%)	276 (65.9%)	63 (71.6%)	0.321
Comorbidities				
COPD	47 (9.3%)	39 (9.3%)	8 (9.1%)	0.949
Chronic renal disease	68 (13.4%)	54 (12.9%)	14 (15.9%)	0.491
Heart failure	51 (10.1%)	43 (10.3%)	8 (9.1%)	0.847
Coronary artery disease	65 (12.8%)	63 (15%)	2 (2.3%)	0.065
Atrial fibrillation	84 (16.6%)	69 (16.5%)	15 (17%)	0.875
Stroke	39 (7.7%)	34 (8.1%)	5 (5.7%)	0.517
Cirrhosis	130 (25.6%)	95 (22.7%)	35 (39.8%)	0.001
Hypertension	200 (39.5%)	165 (39.5%)	35 (39.8%)	0.958
Diabetes	126 (24.9%)	108 (25.8%)	18 (20.5%)	0.343
Neoplasm	63 (12.4%)	48 (11.5%)	15 (17%)	0.156
Drugs history				
Smoke habit	100 (19.7%)	83 (19.8%)	17 (19.3%)	0.916
Alcoholic habit	103 (20.3%)	82 (19.6%)	21 (23.9%)	0.383
NSAIDs	115 (22.7%)	93 (22.2%)	22 (25%)	0.577
Anti-platelets	122 (24.1%)	105 (25.1%)	17 (19.3%)	0.275
Oral anticoagulants	87 (17.2%)	72 (17.2%)	15 (17%)	0.975
Clinical presentation				
Hematemesis	265 (52.4%)	210 (50.2%)	55 (62.5%)	0.046
Melena	351 (69.2%)	291 (69.5%)	60 (68.2%)	0.471
Hematochecia	47 (9.3%)	33 (7.9%)	14 (15.9%)	0.025
Systolic blood pressure	111.40 ± 22.61	113.14 ± 22.08	103.16 ± 23.39	< 0.001
Pulse	89.63 ± 19.04	88.24 ± 18.45	96.28 ± 20.52	< 0.001
Laboratory markers				
Hemoglobin	9.55 ± 2.63	*9.81 ± 2.65*	8.32 ± 2.18	< 0.001
Urea	83.83 ± 58.51	82.19 ± 56.87	91.59 ± 65.49	0.171
Creatinine	1.22 ± 0. 86	1.16 ± 0.76	1.53 ± 1.18	< 0.001
INR	1.52 ± 0.99	1.51 ± 1.04	1.53 ± 0.75	0.913
Platelets	209,993 ±	213,301 ± 123,277	194,318 ±	

	120,910		108,270	0.181
Albumin	3.17 ± 0.67	3.24 ± 0.63	2.80 ± 0.71	< 0.001
Endoscopic findings				
Variceal bleeding	99 (19.5%)	74 (17.7%)	25(28.4%)	0.026
Endoscopy therapy in first endoscopy	201 (39.6%)	136 (32.5%)	65 (73.9%)	< 0.001
Others				
Red cell units transfusion	2.88 ± 3.59	1.90 ± 2.18	7.52 ± 5.06	< 0.001
In-hospital stay	9.04 ±11.23	7.29 ± 9.70	17.41 ± 14.02	< 0.001
Outcomes				
In-hospital mortality	49 (9.7%)	23 (5.5%)	26 (29.5%)	< 0.001
Delayed mortality	54 (11.9%)	44 (11.1%)	10 (17.5%)	0.188
Delayed cardiovascular events	42 (9.3%)	37 (9.4%)	5 (8.8%)	0.885
Delayed hemorrhagic evens	84 (18.6%)	72 (18.2%)	12 (21.1%)	0.588

COPD: Chronic obstructive pulmonary disease; NSAIDs: Nonsteroidal anti-inflammatory drugs; INR: International Normalized Ratio.

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Fig. 1. AUROC of creatinine levels on admission for the prediction of rebleeding in the entire UGIB cohort (non-variceal and variceal), 0.684 (CI 95% 0.562-0.805, p = 0.005).

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Fig. 2. AUROC of albumin levels on admission for the prediction of rebleeding in non-variceal UGIB, 0.735 (CI 95% 0.661-0.809, $p < 0.001$).

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Fig. 3. AUROC of heart rate on admission for the prediction of rebleeding in non-variceal UGIB, 0.654 (CI 95% 0.578-0.730, $p < 0.001$).