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ORIGINAL PAPERS

Antiplatelet agents and/or anticoagulants are not associated with worse outcome following nonvariceal upper gastrointestinal bleeding

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ABSTRACT

Background: Nonvariceal upper gastrointestinal bleeding emerges as a major complication of using antiplatelet agents and/or anticoagulants and represents a clinical challenge in patients undergoing these therapies.

Aim: To characterize patients with nonvariceal upper gastrointestinal bleeding related to antithrombotics and their management, and to determine clinical predictors of adverse outcomes.

Methods: Retrospective cohort of adults who underwent upper gastrointestinal endoscopy after nonvariceal upper gastrointestinal bleeding from 2010 to 2012. The outcomes were compared between patients exposed and not exposed to antithrombotics.

Results: Five hundred and forty-eight patients with nonvariceal upper gastrointestinal bleeding (67% men; mean age 66.5 ± 16.4 years) were included, of which 43% received antithrombotics. Most patients had comorbidities. Peptic ulcer was the main diagnosis and endoscopic therapy was performed in 46% of cases. The 30-day mortality rate was 7.7% (n = 42), and 36% were bleeding-related. The recurrence rate was 9% and 14% of patients with initial endoscopic treatment needed endoscopic retreatment. There were no significant differences between the exposed and non-exposed groups in most outcomes. Co-morbidities, hemodynamic instability, high Rockall score, low hemoglobin (7.76 ± 2.72 g/dL) and higher international normalized ratio (1.63 ± 1.13) were associated significantly with mortality in a univariate analysis.

Conclusions: Adverse outcomes were not associated with antithrombotic use. The management of nonvariceal upper gastrointestinal bleeding constitutes a challenge to clinical performance optimization and clinical cooperation.

Key words: Anticoagulants. Comorbidity. Endoscopy. Gastrointestinal. Gastrointestinal hemorrhage. Outcome assessment. Platelet aggregation inhibitors.

INTRODUCTION

Nonvariceal upper gastrointestinal bleeding (NVUGB), a relevant clinical entity in gastroenterology, continues to be associated with considerable morbidity and mortality and remains a common cause of hospital admission despite pharmacological and endoscopic advances (1,2).

Recently, there have been important changes both in available therapeutics and in epidemiological data regarding NVUGB, consistent with an increase in life expectancy and the prevalence of chronic diseases (3). Mortality in patients with NVUGB seems to be related to comorbidities rather than to bleeding events (1), so management of these patients requires more than successful hemostasis alone (4).

NVUGB is a major complication of antiplatelet agents (APAs) and anticoagulants, and according to the National Drug Authority, the use of these agents has been increasing in Portugal (5). The risk of NVUGB associated with the use of antithrombotics depends on the active substance involved, the dose, duration of treatment, indication, and therapeutic combinations (double antiplatelet aggregation or combination of APAs with anticoagulants) (6). The concomitant use of other gastrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), further increases the risk (7). Age, sex, co-morbidities and past medical history are other relevant factors to be included in risk evaluation (6). Prophylactic co-treatment with proton pump inhibitors (PPIs) is associated with a marked reduction in the risk of NVUGB in patients treated with APAs (while this protective ability does not seem to apply to anticoagulants) and should be considered when there is a high hemorrhagic risk (8,9). Patients treated with antithrombotics with major NVUGB have a high risk of persistence or bleeding recurrence with prolonged use of these agents. However, the optimal duration of treatment discontinuation remains to be defined, as does the best method for reversing hypocoagulation and whether treatment discontinuation should be complete or partial, given the thromboembolic risk (6). In this context, healthcare professionals deal with a permanent and dynamic risk-benefit assessment from diagnosis to therapy. In Portugal, data regarding the impact of this topic are scarce.

The aims of this study are to assess the magnitude of NVUGB associated with the use of APAs and/or anticoag-

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ulants and to define clinical predictors of adverse outcomes that will enable better risk stratification and clinical management of this particular population.

MATERIAL AND METHODS

Type of study and selection criteria

From January 2010 to December 2012, all adult patients referred to the gastroenterology service of a Portuguese hospital for NVUGB (whether from the emergency room, hospital ward [for other reasons] or via transfer from other hospital units) were included in this observational retrospective cohort study. Data collected from medical and endoscopic records was used. The study was approved by the institution's ethics committee.

NVUGB cases were defined by the presence of hematemesis, melena, hematochezia, and/or other clinical or laboratory evidence of blood loss in the upper gastrointestinal tract confirmed by upper gastrointestinal endoscopy (UGE). Exclusion criteria included absence of NVUGB in endoscopy and incomplete records. Patient selection is summarized in figure 1.

Variables

Recorded data included: age, sex, form of presentation of NVUGB, hemodynamic (heart rate and blood pressure) and analytic (hemoglobin and international normalized ratio [INR]) parameters, cause of NVUGB according to UGE, type of endoscopic treatment performed, timing of UGE, comorbidities and the patient's usual medication (APAs, anticoagulants, NSAIDs, PPIs), Rockall score, number of days of hospitalization and units of red blood cells (RBC) transfused, need for surgery or endoscopic retreatment, 30-day rebleeding, 30-day mortality, and cause of death (nosocomial complications, failure to control bleeding, comorbidities or treatment complications).

Statistical analysis

The SPSS software (version 22) was used to perform statistical analysis. Results are presented as mean ± standard deviation (SD) or mean and minimum-maximum values for continuous variables and as absolute (n) and relative (%) frequencies for categorical variables. The level of statistical significance considered was $p < 0.05$. A Chi-squared test or Fisher's exact test (when appropriate) were used to study the relationship between categorical variables. For continuous variables, normal distribution was evaluated first and Student's t-test or Mann-Whitney test were applied when appropriate. Binary logistic regression was used for multivariate analysis, including variables in univariate analysis with $p < 0.05$.

RESULTS

Patient characteristics

A total of 548 patients were included. Baseline demographic and clinical characteristics are listed in table I. The mean age of the exposed group (72.84 ± 11.97) was significantly higher than that of the unexposed group (61.87 ± 17.58).

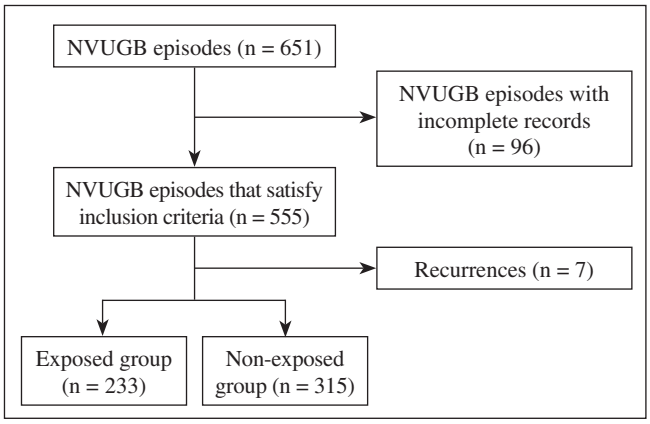

Fig 1. Study population selection. Exposed group: patients using APAs and/or anticoagulants.

Medication used by patients

The distribution of NVUGB episodes by different antithrombotic exposure regimens is represented in figure 2. The most commonly used drug was acetylsalicylic acid (ASA) 100 mg (36.5%). We found that 20.8% of all patients and 21.5% of the exposed group were taking PPIs, without significant differences between exposed and unexposed patients, and that 20.1% used NSAIDs, of which 32.7% were taking APAs, 11.8% anticoagulants and 18.2% a PPI simultaneously.

Characterization of NVUGB

Patients with NVUGB mainly presented with hematemesis (56.6%) or melena (51.8%). In relation to the hemodynamic status, the majority of patients (55.5%) were stable at presentation and 7.5% were admitted with systolic blood pressure (SBP) < 90 mmHg. In the group of unstable patients, 43.9% took antithrombotics. There were no significant differences in hemodynamic status between the exposed and unexposed ($p = 0.571$) groups.

With regard to analytic parameters, the mean hemoglobin value at presentation was 8.96 ± 3.91 g/dL and INR 1.36 ± 1.02. There were no significant differences between the exposed and non-exposed groups in relation to the hemoglobin level, but the INR value was significantly higher in the exposed group (1.65 ± 1.43; p = 0,001).

Approach to NVUGB

UGE was performed within the first 6 hours (inclusive) in 37.9% of the patients and after 24 hours in 9.6% (this

Table I. Baseline patient characteristics (demographic and clinical)

	Global (n = 548)	*Exposed (E) (n = 233)*	*Non-exposed (NE) (n = 315)*	*E/NE P value*
Age (years) - Mean ± standard deviation (SD)	66.53 ± 16.36	72.84 ± 11.97	61.87 ± 17.58	< 0.001
Male (%)	67%	63.5%	69.5%	NS
Co-morbidities (%)	81.6%	96.6%	70.5%	< 0.001
Heart disease	31.6%	51.9%	16.5%	< 0.001
Kidney disease	11.3%	16.7%	7.3%	0.001
Hematological disease	1.5%	0%	2.5%	0.024
Neoplastic disease	13.1%	12%	14%	NS
Metastatic disease	3.6%	2.6%	4.4%	NS
Liver disease	12.8%	3.9%	19.4%	< 0.001
Vascular disease	7.3%	12%	3.8%	< 0.001
Cerebrovascular disease	11.5%	24.9%	1.6%	< 0.001
High blood pressure	45.6%	65.7%	30.8%	< 0.001
Diabetes mellitus	24.6%	36.5%	15.9%	< 0.001
Transplant	1.8%	0.4%	2.9%	0.05
Previous history of PU/gastritis/NVUGB	14.1%	9.9%	17.1%	0.015

NS: Not significant.

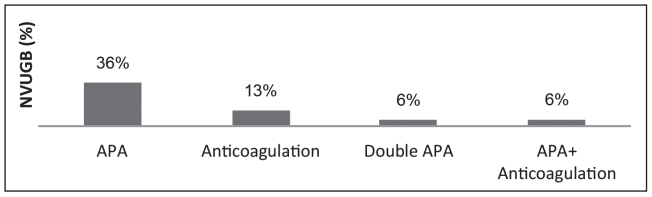

Fig 2. Distribution of NVUGB episodes according to different antithrombotic exposure regimens.

estimate was not calculated in 4 patients due to insufficient information). Of the patients studied, 45.6% underwent endoscopic treatment with no statistically significant differences between the exposed and unexposed groups. The most commonly used endoscopic treatment was drug injection (89.6%). Endoscopic retreatment was necessary in 6.4%. Peptic ulcer (PU) emerged as the main diagnosis, 26.5% were gastric ulcers and 24.6% were duodenal ulcers. In this sample, 46.4% had a high Forrest classification (Ia, Ib, IIa) with no significant differences between exposed and unexposed patients (p = 0.518), or between those who were and were not on PPIs (p = 0.933). The average Rockall score was intermediate-high risk (4.98 ± 2.02) with significant differences between exposed (higher Rockall score) and unexposed patients (p < 0.001).

Outcome

The main outcomes of our cohort are listed in table II. Statistically significant differences were observed in length of hospital stay among patients who were receiving concomitant APAs and anticoagulants *vs* those who did not (10.52 [0-59] *vs* 6.32 [0-191] days, respectively; [p = 0.0014]).

The need for surgery as treatment for NVUGB was recorded in 3.8% patients with significant differences (p = 0.037) between hemodynamically stable and unstable patients (5.7% of the unstable patients required urgent surgery *vs* 2.3% of stable patients) and between patients with (9.4%) and without (2.7%) Forrest lesions classified as "high risk" (p = 0.018).

With regard to the patients who underwent endoscopic retreatment, there was a positive relationship with the need for urgent surgery (p = 0.008), lower hemoglobin values (p = 0.015) (7.78 ± 2.62 *vs* 9.05 ± 3.98) and higher Rockall scores (p = 0.005) (with endoscopic retreatment: Rockall score 5.89 ± 1.62; without retreatment, 4.91 ± 2.03).

Rebleeding was significantly related with the need for endoscopic retreatment (31.4% with recurrence *vs* 3.8% without; [p < 0.001]), a greater duration of hospitalization (10.41 [0-61] *vs* 6.18 [0-191]) and transfused RBC units (4.25 [0-23] *vs* 2.20 [0-18]). Thirty-day mortality (p = 0.061) and need for urgent surgery (p = 0.053) were found to occur less frequently in patients who underwent UGE within the first 24 hours (exclusive) compared to those who underwent UGE after 24 hours (inclusive) (6.9% mortality rate and 3.3% rate of surgeries *vs* 14.3% and 8.9%, respectively), which almost reached statistical significance. Time to UGE ≥ 24 h was significantly related with longer hospital stays (8.34 [0-48] *vs* 6.37 [0-191]; p = 0.033) and more RBC units transfused (3.82 [0-23] *vs* 2.23 [0-18]; p < 0.001).

Table II. Clinical outcome

	Global (n = 548)	*E (n = 233)*	*NE (n = 315)*	*E/NE p value*
Recurrence ≤ 30 days, n (%)	51 (9.3%)	15 (6.4%)	36 (11.4%)	0.047
Mortality ≤ 30 days, n (%)	42 (7.7%)	16 (6.9%)	26 (8.3%)	NS
Failure to control bleeding	12 (2.2%)	3 (1.3%)	9 (2.9%)	
Treatment complications	3 (0.5%)	3 (1.3%)	0 (0%)	
Co-morbidities	23 (4.2%)	9 (3.9%)	14 (4.4%)	
Nosocomial complications	4 (0.7%)	1 (0.4%)	3 (1%)	
Death attributable to NVUGB episode, n (%)	15 (2.7%)	6 (2.6%)	9 (2.9%)	NS
Endoscopic retreatment, n (%)	35 (6.4%)	11 (4.7%)	24 (7.6%)	NS
Urgent surgery, n (%)	21 (3.8%)	7 (3%)	14 (4.4%)	NS
Hospital stay, mean number of days (min-max)	6.57 (0-191)	7.13 (0-191)	6.15 (0-81)	NS
RBC, mean (min-max)	2.39 (0-23)	2.51 (0-18)	2.31 (0-23)	0.015

In the multivariate analysis, the risk of 30-day mortality was found to be about five times higher in patients with one or more comorbidities (95% confidence interval [CI]: 1.18 to 20.98). Metastatic disease was associated with a twelvefold increase in the risk of death (odds ratio [OR] = 12.27; 95% CI: 4.75 to 31.70). Other factors that were significantly associated with mortality were high Rockall score, lower hemoglobin (7.76 ± 2.72 *vs* 9.06 ± 3.98 g/dL) and higher INR (1.63 ± 1.13 *vs* 1.34 ± 1.00).

DISCUSSION

This study allowed us to characterize NVUGB associated with the use of APAs and/or anticoagulants in a Portuguese population and to better understand the complexity of these patients, the clinical entity and the medical approach undertaken, and to identify major factors which impact on short-term results. To the best of our knowledge, this is the first study in Portugal that aims to specifically assess the impact of the consumption of antithrombotics in patients with NVUGB.

According to A. Lanas et al., the NVUGB relative risk is about 1.55 times higher with low-dose ASAs compared to non-use whereas when used in combination with clopidogrel or anticoagulants this increased the risk (OR = 1.86 and OR = 1.93, respectively) (10). The results of our study show that 1 in every 2 to 3 patients with NVUGB were on APAs and/or anticoagulants, a higher proportion than observed (1 in 4) in a similar study conducted in Spain between 2004 and 2007 by P. Wikman-Jorgensen et al. (11). This difference may be due to the fact that the inclusion criteria were different, as they excluded patients who used NSAIDs rather than ASAs, or it may reflect a global trend in increased antithrombotic prescription (12-14) accompanied by an increased prevalence of diseases for which this therapy is recommended.

The characteristics of the patients with NVUGB in the present study represent the demographic evolution of modern society: the vast majority were over 65 years old and had one or more comorbidities.

With regard to the evaluated outcomes, it was found that exposure to antithrombotics had no significant impact on 30-day mortality nor on the need for endoscopic retreatment or urgent surgery. Regarding the 30-day relapse rate, it was found that the exposed group appeared to be protected, since a higher percentage of non-exposed patients (11.4% *vs* 6.4%) showed a new episode of NVUGB after effective hemostasis with a statistically significant difference. These findings are in agreement with T. Solakoglu et al., who have put forth the use of longer duration PPI infusion in the exposed group as a possible explanation. It was recognized that an appropriate duration of this therapy was essential to allow for the healing of the gastrointestinal mucosa and to prevent recurrence in high-risk patients (15). Another possible explanation could be the greater prophylactic use of PPIs in the exposed group (21.5% *vs* 20.3%); however, a lack of statistical significance makes this a less likely hypothesis.

The recurrence rate was also significantly related with longer hospital stay, the need for endoscopic retreatment, and more RBC transfusions, with the subsequent costs involved.

According to evidence currently available, the use of intravenous PPIs reduces relapse rates and the need for endoscopic retreatment and surgery (16-18). The most recent recommendations suggest using a high initial dose of 80 mg in bolus followed by continuous infusion of 8 mg/h for 3 days, since the majority of relapses occur during this period (14,19,20). The benefit of PPI use after endoscopic hemostasis for mortality was observed in patients with active bleeding or visible vessels (16,19,21,22). After intravenous therapy with a PPI, an oral prescription of a single daily dose is suitable for a period of time determined by the etiology of the NVUGB (18,19,22).

The present study did not evaluate the use of PPIs after UGE. However, according to the existing data in the Portuguese population, PPIs are used on almost all patients, but perfusion rates are lower than desirable taking all potentially eligible patients into account (3,23). Thus, there seems to be room for the optimization of acid secretion suppression in addition to endoscopic hemostasis, which may result in lower relapse rates.

The mortality rate associated with NVUGB has remained virtually unchanged at between 5% and 10% (14) in spite of advances in treatment that, according to recent research, have been associated with the fact that the majority of these deaths are related to non-bleeding causes (4). This information is consistent with the results of our study, since the cause of death was not attributable to NVUGB in 64.3% of cases. Another retrospective, multicentre study in Portugal registered a 4.8% mortality rate, 83.3% of which were not attributed to NVUGB (3). Recent data confirm that in these cases, mortality is related primarily to patient comorbidities (3,24), which is consistent with the results of this sample. Thus, attempts to decrease mortality rates need to extend beyond the effective control of hemorrhage, with particular strengthening of supportive treatment and prevention of complications in other organs (4). Reinforcing these findings, we identified other factors that were significantly correlated with mortality: high Rockall score, hemodynamic instability, lower hemoglobin values (7.76 ± 2.72 g/dL) and higher INR (1.63 ± 1.13).

However, in some cases, the outcome can hardly be improved, since the bleeding episode is a terminal event of other underlying disease conditions, including metastatic neoplasm or multiple organ failure (4).

With regard to the timing of UGE, this series found that its implementation within the first 24 hours was associated with better outcome, in agreement with some recent studies (19,25). However, although it seems intuitive that earlier UGE would be associated with the best results, the tendency observed was that no benefits were seen when performed within the first 12 hours with regard to reduction of recurrence, death, and the need for surgery (25,26). This can be justified by the fact that when UGE is performed earlier in the active bleeding period, a large amount of blood and existing clots not only obscure the source of bleeding, but also complicate achieving endoscopic hemostasis (27).

One of the problems that often arise in clinical practice and which led to the planning of this study is how to control and prevent NVUGB relapse in patients being treated with APAs and/or anticoagulation. First, it is recognized that maintenance of this therapy increases the risk of recurrence or the continuation of bleeding; however, these patients have an increased thromboembolic risk due to the underlying disease. Temporary discontinuation of antithrombotic therapy is often necessary to control the bleeding and to prevent an early relapse (15). According to current evidence, the use of APAs as a secondary prophylaxis should be reinitiated as soon as possible after the episode of NVUGB (28), even if this would increase the rebleeding rate as it can potentially reduce overall mortality (29) and its discontinuation increases the risk of death and acute cardiovascular events by around sevenfold (30). In these cases, the protective effect of APAs exceeds their potential gastrotoxic effects. With regard to anticoagulation, the decision to withdraw or restart anticoagulants should be considered on an individual basis. In relation to traditional anticoagulants, it has been verified that thrombosis and mortality decrease without a significant increase of relapse in cases where anticoagulation is reinitiated within 90 days of the NVUGB episode (31).

According to current recommendations, in addition to acid suppression with PPIs after an episode of NVUGB, all patients with PU should also be tested for the presence of *Helicobacter pylori*, and positive cases should undergo eradication therapy (22,25).

One of the strengths of this study is that it was an observational study, which allowed us to evaluate outcomes more reliably since they are representative of the "real clinical practice" without intervention. Furthermore, although this study was conducted in only one central Portuguese hospital, the gastroenterology service of this hospital serves as a regional emergency service at night, and receives patients from several hospitals in the north who were also included in the study. As a result, this case series is representative of a larger group of patients with NVUGB. However, because this was a retrospective study, the results are dependent upon the quality of the medical records obtained. The severity of comorbidities was not considered, which could have allowed us to better characterize patients with unfavorable outcomes. Patients were not excluded for taking other drugs that could potentially increase the risk of NVUGB (non-aspirin NSAIDs, selective serotonin reuptake inhibitors [32,33] or high-dose corticosteroids [7]), which may have introduced a bias in the results. The duration of treatment was also not taken into account, which could have allowed for an estimate to be made regarding the exposure time necessary for an episode of NVUGB to happen. However, this data was difficult to obtain from medical records.

Given that the sample includes inpatients and outpatients, the variable "timing to UGE" likely presents some variability. It is expected that this calculation is closer to reality in hospitalized patients because it is based on the records of healthcare professionals, while it may be less reliable in outpatient cases since the time interval between the NVUGB episode and admission is uncertain.

The results of this study support the current trends found in recent studies: NVUGB increasingly occurs in elderly populations with several comorbidities; adverse outcomes are less associated with iatrogenic causes such as the use of APAs and/or anticoagulants. Although the risk of NVUGB is increased in patients exposed to these drugs, there are some measures that can decrease the incidence of bleeding

and that can be optimized in our population. After an episode of NVUGB, the medical approach needs to assume a broader spectrum: in addition to an efficient endoscopic hemostasis, the implementation of special care to suit the clinical characteristics of patients, including their comorbidities (the leading cause of death in this context), is fundamental.

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