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PREDICTIVE FACTORS FOR POST-ERCP BLEEDING. INFLUENCE OF DIRECT ORAL ANTICOAGULANTS.

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ABSTRACT

Introduction We find a rising number of patients receiving antiplatelet and anticoagulation therapy who require endoscopic retrograde cholangiopancreatography (ERCP), probably due to a higher incidence of the increased morbidity of older patients. Considering the increasingly spreading use of direct oral anticoagulants (DOACs), we want to study about the influence of these factors on the possibility of hemorrhage after ERCP in our center. Material and methods: We collected data from all the examinations carried out in the years 2017 and 2018, which included 797 examinations on 588 patients. Collected data included: personal history of the patients, results of the test and follow-up. Results: In our study, the percentage of post-ERCP bleeding was 4.6% (n=37). With regard to the severity, in 21.6% (n=8) of the cases the bleeding was mild, it was moderate in 59.5% (n=22), and severe in 18.9% (n=7). Previous cardiopathy, antiplatelet therapy, anticoagulation therapy, treatment with DOACs, having a pancreatic stent, and lithiasis removal double the risk of bleeding after ERCP. Having a sphincterotomy represents an over five-fold increase of the risk. Conclusion: In the multivariate analysis, we observed a statistically significant increase of bleeding among patients treated with DOACs, compared to patients who receive anticoagulation with acenocoumarol or low-molecular-weight heparins (LMWH).
Keywords
Gastrointestinal bleeding, ERCP, direct oral anticoagulants.

List of abbreviations
- ERCP: endoscopic retrograde cholangiopancreatography.
- DOAC: direct oral anticoagulants.
- LMWH: low-molecular-weight heparins.
- ESGE: European Society of Gastrointestinal Endoscopy.
- SD: Standard deviation.
- NSAIDs: Non-steroid anti-inflammatory drug.

INTRODUCTION
Endoscopic retrograde cholangiopancreatography (ERCP) was first described in 1968 as a diagnostic technique for pancreatic and biliary diseases (1). In 1973, Kawai and Classen introduced endoscopic biliary sphincterotomy as a therapeutic technique, and it revolutionized the treatment of biliary diseases (2). Since then, ERCP has been progressively implemented as an essential tool in endoscopy units. The main indication for ERCP is the minimally invasive management of a range of pancreatic and biliary conditions, always with therapeutic purposes (3,4,5).
After ERCP, complications may appear. The main ones are pancreatitis, bleeding, cholangitis or cholecystitis and perforation.
Hemorrhage secondary to ERCP is defined as hematemesis and/or melena or a hemoglobin drop over 2 g/dL (7). The incidence of bleeding after therapeutic ERCP is 0.3-2% (8-10). Post-ERCP bleeding is classified by the ESGE, according to its severity, as mild, moderate, or severe, considering different factors, such as the need for transfusion or the admission to a hospital or intensive care unit (4).
The European Society of Gastrointestinal Endoscopy (ESGE) considers the following risk factors for post-ERCP bleeding: use of anticoagulants, platelets <50000/mm3, cirrhosis, end-stage renal disease, intraprocedural bleeding, low endoscopist experience and unsuccessful cannulation with precut sphincterotomy (4).
The initial management must be similar to that of any other cause of upper gastrointestinal bleeding (11).

Given the existing data on the incidence of this complication, professionals who perform ERCP currently feel that the actual rate is higher than what has been described in the published studies. The rising number of patients who receive anticoagulation and antiplatelet therapy over the last decades has increased the number of complications related to bleeding after any type of invasive procedure, despite the use of protocols for the suspension of anticoagulant and/or antiplatelet drugs based on international clinical guidelines.

In order to study these changes in the incidence and accompanying factors of bleeding, our objectives are:

- Determining the current incidence of bleeding as a complication of ERCP.
- Assessing the influence of antiplatelet therapy and anticoagulants as well as other risk factors associated with the appearance of this complication.

**MATERIALS AND METHODS**

Retrospective study of adult patients who underwent ERCP in the years 2017 and 2018 in a tertiary hospital. Patients referred from other centers for examination were ruled out because no follow-up information was available.

The final analysis included 797 examinations of 588 patients with an average follow-up of 265 days (SD=216).

The procedure was carried out following the standard protocols of the endoscopy unit regarding the suspension of previous anticoagulation-antiplatelet treatment, antibiotic prophylaxis, pancreatitis prophylaxis with rectal indomethacin (to all patients except for those allergic or intolerant to NSAIDs), and sedation with continuous infusion controlled by an endoscopist and a trained nurse. We use an ESGE guideline-based protocol for the management of antiplatelet therapy and anticoagulation (12). It is summarized at the Appendix 1.

We recorded the variables related to the patient (personal history, anticoagulation and antiplatelet therapy), the examination (indication, endoscopist, technique and materials used, diagnosis) and the follow-up (complications from the procedure,
severity, follow-up time, death).
Digestive hemorrhage secondary to ERCP was defined as a bleeding episode that required endoscopic treatment and/or RBC transfusion, and its severity was classified according to the ESGE criteria.
In the descriptive analysis of the sample, percentages were used for the qualitative variables, and central tendency measures (mean and/or median) and dispersion measures (standard deviation) were used for quantitative variables. The software program SPSS v. 25.0 (Chicago, Illinois, USA) was used for the statistical analysis. Dichotomous variables were analyzed with the chi-squared test; continuous and categorical variables were analyzed with the ANOVA test, and the Pearson correlation coefficient was used to measure correlation. The multivariate study used binary logistic regression. Statistical significance was established for p<0.05.

RESULTS

Epidemiological variables
Regarding the 797 examinations, 51.4% (n=410) were on men and 48.6% (n=387) on women. The mean age of the patients in the study was 75.34 years (SD=14.14).
With regard to their personal history, 31.7% (n=253) had some type of cardiopathy, 13.6% (n=108) had a respiratory condition, 12.4% (n=99) had chronic kidney disease, and 23.5% (n=187) had diabetes mellitus.
In total, 36.4% (n=290) of the patients received antiplatelet and/or anticoagulation therapy, with 17.2% (n=137) receiving anticoagulation therapy and 21.5% (n=171) receiving antiplatelet therapy. Eighteen patients (2.2%) received both anticoagulation and antiplatelet therapy.
In the anticoagulation group, 75.9% of the patients (n=104) received acenocoumarol or lowmolecularweight heparin (LMWH), and the remaining 24.1% (n=33) received vitamin K nondependent direct oral anticoagulants (DOACs) (apixaban, dabigatran, rivaroxaban, etc.). The number of patients who received each drug is shown in Table 1.
In the antiplatelet group, 77.6% (n=132) of the patients received acetylsalicylic acid (ASA), 14.7% (n=25) received clopidogrel, 5.3% (n=9) received dual antiplatelet therapy, and the other 2.4% (n=4) received a different antiplatelet drug (such as
ticagrelor). Most patients (130) who received ASA were taking a 100mg dose daily, while just 2 of them were taking 300mg daily. We cannot analyze them into two different groups.

The most common indication for ERCP was choledocholithiasis confirmed in an imaging test in 30% of the cases (n=239), followed by the suspicion of biliopancreatic neoplasm in 20.1% of the cases (n=160), and suspicion of choledocholithiasis (not confirmed by an imaging test) in 17.2% of the cases (n=137).

**Characteristics of the procedure**
In 17.1% (n=136) of the examinations, the papilla was next to a diverticulum. Out of all the explorations, 31% (n=247) presented a prior sphincterotomy, and the precut technique was applied in 4.4% (n=35). In the other 472 examinations (59.2%), a biliary sphincterotomy was performed. A pancreatic stent was placed in 3.9% (n=31) of the examinations. Dilation was required in 10.2% (n=81) of the examinations. In 43.4% (n=346), lithiasis was extracted, and a biliary prosthesis was placed in 33.7% (n=267). The different diagnoses are included in Table 2.

**Hemorrhage**
In our study, the percentage of post-ERCP bleeding was 4.6% (n=37). With regard to its severity, it was mild in 21.6% of the cases (n=8), moderate in 59.5% (n=22), and severe in 18.9% (n=7). The average bleeding time was 2.27 days (SD=1.55).

**Comparative study**
A comparative study with the possible variables associated with the development of post-ERCP bleeding was carried out, and it is described in Table 3. Previous cardiopathy, antiplatelet therapy, anticoagulation therapy, treatment with DOACs, placement of a pancreatic prosthesis, and lithiasis extraction double the risk of presenting hemorrhage after ERCP. Having a sphincterotomy increases the risk five-fold.

The multivariate analysis (of those variables with statistical significance at the univariate analysis) shows a statistically significant increase in patients treated with
DOACs, compared with those who receive anticoagulation therapy with acenocoumarol or LMWH, p=0.037; OR=3.63 (IC 95% 1.01-12.8).

DISCUSSION
A study from 2009 carried out in Colombia included 372 patients undergoing ERCP were included, they obtained a 1.3% bleeding rate over the total ERCP (13), which is significantly lower than what was observed in our study (4.6%, n=37). Another study, from 1996, conducted by Freeman et al., identified the different adverse effects of endoscopic biliary sphincterotomy (8). Out of the 2347 patients included in the study, 2% showed significant bleeding, with 30% of those cases classified as mild, 45% as moderate and 25% as severe. In our study, 59.2% (n=472) of the examinations involved an endoscopic biliary sphincterotomy. In this group, 33 patients developed post-sphincterotomy bleeding, which represents a rate of 6.99%, out of which 21.2% (n=7) showed mild bleeding, 60.6% (n=20) showed moderate bleeding, and 18.2% (n=6) showed severe bleeding. These differences with our study are probably due to the higher use of antiplatelet and anticoagulation drugs over the last decade.

More recent studies reveal an increased incidence of bleeding. A retrospective study conducted in South Korea from April 2006 to March 2013 assessed the risk factors for hemorrhage after sphincterotomy in patients at medium risk, and the rate of bleeding was 9.6% (14). Another study carried out in Greece in 2017 showed a post-sphincterotomy/sphincteroplasty bleeding rate of 4.5% (15). In Austria, data from 28319 examinations (for ERCP) from 2008 to 2018 showed 3.8% of cases with bleeding as a complication over the total of ERCP (16). A study undertaken to assess the safety of ERCP in patients with hepatic cirrhosis published in 2019 found a global bleeding rate of 6.3% over the total ERCP, with an incidence of 4.7% for ERCP performed on non-cirrhotic patients (without risk factors), and 10.9% for cirrhotic patients (17).

In 2018, Hyoung-Chul Oh et al. conducted a study that associated post-sphincterotomy bleeding with the use of antiplatelet medication. Out of the 2435 patients included in the study, 2083 did not receive antiplatelet medication. In the group of 352 patients who received antiplatelet drugs (14%), 256 received acetylsalicylic acid, 48 received a different drug (clopidogrel, ticagrelor, prasugrel, etc.), and 48 received dual antiplatelet therapy (18). Bleeding rate of each group was: 0.8% (no antiplatelet
therapy group), 4% (ASA group), 6.3% (other antiplatelet group) and 8.3% (dual antiplatelet therapy group). In our study, a higher percentage of patients in the examinations received antiplatelet therapy (21.5%) and bleeding rate were very similar.

Anticoagulation is also considered a risk factor for bleeding after ERCP with sphincterotomy (19). A study carried out by Hamada in 2015 associated hemorrhage with anticoagulation therapy (0.8% of cases of global bleeding vs 1.6% in anticoagulation patients) (20). In our study, 17.2% (n=137) of the ERCP procedures were performed on patients who received anticoagulation drugs, 13.1% (n=104) acenocoumarol or LMWH, and 4.1% (n=33) DOACs. Out of the 104 patients in the first group, 6 (all of whom received acenocoumarol) presented bleeding after ERCP, which represents 5.8% of the group. On the other hand, in the group of 33 patients who were being treated with DOACs, 6 presented hemorrhage (18.2%).

The use of DOACs has increased notably over the last decade globally. The need for frequent monitoring, their narrow therapeutic range, the restrictions on diet, and the interactions with other drugs that are found in anti-vitamin K anticoagulants (acenocoumarol/warfarin) have been determining factors in the development and spread of DOACs. Due to the increasing number of indications, this group of oral anticoagulants and their complications (including gastrointestinal bleeding) have been studied in detail.

Globally, with regard to DOACs and gastrointestinal hemorrhage, we have found two relevant meta-analyses. In 2013, a meta-analysis of 17 randomized clinical trials with over 150,000 patients showed a higher risk of gastrointestinal hemorrhage for patients treated with DOACs than for those treated with conventional anticoagulation therapy (21). On the other hand, according to the recently published data in the meta-analysis by Zhin-Chun Gu et al. (22) which included randomized clinical trial and real-world studies, DOACs did not involve a significantly higher risk of gastrointestinal bleeding. A higher rate was observed for rivaroxaban, which may increase the risk of digestive hemorrhage up to 39%. In our study, and specifically for post-ERCP hemorrhage, we have observed that DOACs increase the risk when compared with conventional anticoagulants (18.2% vs 5.8%), and this difference is statistically significant. In this
regard, Nagata et al. conducted a study in the years 2014 and 2015 to compare post endoscopy complications in patients who received warfarin and new oral anticoagulants. One of the first parameters assessed in the study was hemorrhage after sphincterotomy, with a sample of 1400 patients in this subgroup. They found a higher rate of bleeding with conventional anticoagulants (warfarin) than with DOACs (6.6% vs 4.4%), contrary to what has been observed in our study, and without statistically significant differences (p>0.05) (23). This effect was also observed in a retrospective study published this year with 149 anticoagulation patients who underwent endoscopic sphincterotomy. They showed a global rate of bleeding of 9.1% with warfarin and 6.5% with DOACs, although without significant differences between both groups (24).

Although the available evidence to date does not support the results of our study, we present a sample of 137 patients for this subgroup, in which there are statistically significant differences showing that the use of DOACs increases the risk of post-ERCP bleeding, compared with acenocoumarol. The use of rivaroxaban in 30% of the anticoagulation patients who receive DOACs may have contributed to the increased risk of bleeding. Three of six patients with DOACs and bleeding were receiving rivaroxaban. Larger case series are required to confirm these results (since a clinical essay on this topic does not seem ethically or methodologically justifiable).

On the other hand, we have obtained a statistically significant higher rate of bleeding for other variables in our study. With regard to pancreatic stent, the ESGE recommends the placement of a pancreatic prosthesis for all patients in which repeated unintentional access to the pancreatic duct occurs (3). Therefore, given that this is a difficult and traumatic cannulation, a higher risk of bleeding may be expected. A similar finding was observed with the extraction of choledocholithiasis because the removal of the stones often causes damage on the sphincterotomy area, which promotes bleeding.

In our study, a history of cardiopathy increases the risk of bleeding after the procedure approximately two-fold. Tae Hoon Lee et al. report that the problem most commonly found in patients with severe cardiovascular disease who must undergo therapeutic ERCP is the risk of hemorrhage due to the use of anticoagulation and/or antiplatelet
therapy (25). A retrospective study carried out by Han-Ra Koh et al. reviewed the records of patients with a history of acute coronary syndrome who underwent therapeutic ERCP from 2007 to 2012. The rate of postsphincterotomy bleeding was 5.6%, and the authors associated this increase to the fact that the patients received antiplatelet therapy with aspirin and clopidogrel (26).

CONCLUSIONS
We observed an increased incidence of post-ERCP bleeding, compared with the classical series published, probably associated with the higher use of anticoagulation and antiplatelet medication among the general population. DOACs seem to increase the risk of post-ERCP hemorrhage, compared with conventional anticoagulants.

REFERENCES


Table 1. Type of anticoagulation.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>N</th>
<th>Valid percentage</th>
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</thead>
<tbody>
<tr>
<td>Conventional anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>89</td>
<td>65</td>
</tr>
<tr>
<td>Heparin</td>
<td>15</td>
<td>11</td>
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### Table 2. ERCP diagnoses.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Valid percentage (%)</th>
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</thead>
<tbody>
<tr>
<td>Ampulloma</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>344</td>
<td>43.2</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>69</td>
<td>8.7</td>
</tr>
<tr>
<td>Unsuccessful cannulation</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td>Normal ERCP</td>
<td>103</td>
<td>12.9</td>
</tr>
<tr>
<td>Pancreatic neoplasm</td>
<td>71</td>
<td>8.9</td>
</tr>
<tr>
<td>Bile leak</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Benign biliary stenosis</td>
<td>47</td>
<td>5.9</td>
</tr>
<tr>
<td>Bile duct dilatation</td>
<td>25</td>
<td>3.1</td>
</tr>
<tr>
<td>Stent removal or control</td>
<td>34</td>
<td>4.3</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>797</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

### Table 3. Statistically significant variables in the univariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (%complications)</th>
<th>No (%complications)</th>
<th>P value</th>
<th>Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
APPENDIX I. ANTICOAGULATION AND ANTIPLATELET THERAPY MANAGEMENT LOCAL PROTOCOL SUMMARY.

Table 1. Antiplatelet therapy.

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>Withdrawal (Days before ERCP)</th>
<th>Bridging therapy (LMWH)</th>
<th>Reintroduction (days after ERCP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 100mg</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>ASA 300mg</td>
<td>5*</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>5</td>
<td>NO</td>
<td>5</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5</td>
<td>NO</td>
<td>5</td>
</tr>
</tbody>
</table>

*Change for ASA 100mg during 5 days previous ERCP.

Table 2. Anticoagulants.

<table>
<thead>
<tr>
<th>ANTICOAGULANTS</th>
<th>Withdrawal (days before ERCP)</th>
<th>Bridging therapy (LMWH)</th>
<th>Reintroduction (days after ERCP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acenocoumarol (Sintron®)</td>
<td>5</td>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>HBPM</td>
<td>1</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>2</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>2</td>
<td>NO</td>
<td>1</td>
</tr>
<tr>
<td>Drug</td>
<td>Score</td>
<td>NO</td>
<td>Other</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>2</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (Lixiana®)</td>
<td>2</td>
<td>NO</td>
<td>1</td>
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