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MESTRADO INTEGRADO EM MEDICINA

Endoscopic Submucosal Dissection in patients on Antiplatelet or Anticoagulant therapy: Assessing Bleeding Risk

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M

2023

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ARTIGO ORIGINAL

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Junho 2023

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Porto, maio de 2023

Obrigado

ao meu orientador, professor Ricardo, pela sua paixão pelo ensino e educação

à Dra. Sara Archer pela revisão

à professora Carolina Lemos pelo apoio na análise e revisão estatística

a todos os membros do serviço de gastroenterologia pela oportunidade e contributo

à minha mãe, Cristina, pelo amor

à minha madrinha, Ana, pelos Mimos

à minha prima Patrícia

ao Bernardo pelas boleias e felicidade

à Morena pela amizade e confidência

à Maravilhosa pelas receitas e crescimento

à Patrícia D. pelo coração feliz

ao João R. pelos desabafos e ajuda

à Carolina V. pela ciclotimia e gargalhadas

E aos restantes amigos e família por acreditarem em mim

Resumo

Introdução: A dissecção endoscópica da submucosa (ESD) é uma técnica endoscópica avançada. A hemorragia é a sua principal complicação. A utilização de fármacos antitrombóticos tem vindo a aumentar ao longo dos anos. A evidência atual em relação ao papel da terapêutica antitrombótica (AT) e da sua gestão peri-procedimento no impacto na hemorragia pós-procedimento não é consensual. Posto isto, identificar que agentes antitrombóticos estão associados a maior taxas de hemorragia e qual o papel da terapêutica de *bridging* no pós-procedimento apresenta elevada relevância clínica.

Objetivos: Avaliar o risco hemorrágico em doentes sob terapêutica antitrombótica submetidos a ESD; Comparar o risco hemorrágico entre diferentes regimes de anticoagulação e antiagregação em pacientes submetidos a ESD.

Métodos: Realizou-se uma análise retrospetiva de todos os doentes submetidos a ESD no período de Junho de 2016 a Janeiro de 2021 num centro hospitalar de referência.

Resultados: Incluíram-se 193 doentes e 233 lesões. Os procedimentos efetuados em doentes sob AT corresponderam a 15.9% (37/233). A taxa global de hemorragia pós-procedimento foi superior no grupo sujeito a AT (18.9% (7/37) vs. 7.1% (14/196)), no entanto não atingiu significância (OR = 3,03; p = 0,053). A hemorragia após a alta hospitalar foi significativamente superior no grupo AT do que no grupo de controlo (OR = 10.1; p = 0.003). Análise aprofundada do grupo AT revelou que os agentes anticoagulantes foram o fator de risco mais forte para hemorragia global pós-procedimento (OR: 6.12; p = 0.003), todavia a toma de agentes antiplaquetários não foi um fator de risco para hemorragia (OR = 0.58; p = 1.000). O tempo até ocorrer hemorragia foi significativamente superior nos procedimentos sob AT (p = 0.004), com uma mediana de 10 dias (IQR: 4-13) após o procedimento e com maior probabilidade de ocorrer após a alta hospitalar, devido maioritariamente aos agentes anticoagulantes. A realização de terapêutica de *bridging* não conduziu a resultados diferentes no grupo dos DOAC (OR: 1.25; p = 1.000).

Conclusão: Os agentes anticoagulantes foram o fator de risco mais forte para hemorragia pós-procedimento, nomeadamente os DOAC. Os agentes antiplaquetários não foram um fator de risco para hemorragia pós-procedimento. O tempo até ocorrer hemorragia foi mais longo nos doentes sob anticoagulantes e foi mais provável de ocorrer após a alta hospitalar. A terapêutica de *bridging* pós-procedimento no grupo dos DOAC não teve impacto no risco hemorrágico.

Palavras-chave: Eventos adversos; terapêutica antitrombótica; terapêutica de *bridging*; dissecção endoscópica da submucosa; hemorragia gastrointestinal.

Abstract

Introduction: Endoscopic Submucosal Dissection (ESD) is an advanced endoscopic technique. Bleeding is its most common complication. Antithrombotic use has been increasing through out the years. Evidence on the role of antithrombotic therapy (AT) and its management in post-procedure bleeding is not consensual. Identifying which antithrombotic agents are linked to higher bleeding rates and the role of post-procedure bridging therapy in bleeding is of prime clinical relevance.

Objectives: Assess the bleeding risk in patients submitted to ESD under antithrombotic therapy; Compare the bleeding risk between different anticoagulant and antiplatelet regimens in patients submitted to ESD.

Methods: All patients submitted to ESD from June of 2016 to January of 2021 in a single referal centre were retrospectively analysed.

Results: A total of 193 patients were included and 233 lesions were analysed. Procedures under AT corresponded to 15.9% (37/233). Overall post-procedure bleeding rate was higher in the AT group (18.9% (7/37) vs. 7.1% (14/196)) but failed to reach significance (OR = 3.03; p = 0.053). Bleeding after hospital discharge was significantly higher in the AT group than in the controls (OR = 10.1; p = 0.003). Subgroup analysis of the AT group revealed that anticoagulant agents were the strongest risk factor for overall post-procedure bleeding (OR: 6.12; p = 0.003), but taking antiplatelet agents was not a risk factor for bleeding (OR = 0.58; p = 1.000). Time to bleed was significantly longer in the procedures under AT (p = 0.004) with a median of 10 days (IQR: 4-13) after the procedure and more likely to occur after hospital discharge due to anticoagulant agents. Undergoing bridging therapy did not lead to different outcomes in the DOAC group (OR: 1.25; p = 1.000).

Conclusion: Anticoagulant agents were the strongest risk factor for post-procedure bleeding, namely DOACs. Antiplatelet agents were not a risk factor for post-procedure bleeding. Timing of bleeding was longer in patients under anticoagulant agents and more likely to occur after hospital discharge. Post-procedure bridging therapy in DOAC group didn't impact the bleeding risk.

Key words: Adverse events; antithrombotic therapy; bridging therapy; endoscopic submucosal dissection; gastrointestinal bleeding.

Abbreviations

ASA – Acetylsalicylic Acid

AT – Antithrombotic Therapy

BSGE – British Society of Gastroenterology

CHUdSA – Centro Hospitalar Universitário de Santo António

DOACs – Direct Oral Anticoagulants

ESD – Endoscopic Submucosal Dissection

ESGE – European Society of Gastroenterology

GI – Gastrointestinal

ICU – Intensive Care Unit

IQR – Interquartilrange

LMWH – Low Molecular Weight Heparin

OR – Odds Ratio

SD – Standard Deviation

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Introduction

The dissemination of gastrointestinal endoscopy and the development of screening programmes for digestive cancer have increased the detection of precancerous and early neoplastic lesions.[1] Treatment has improved, with less invasive procedures when compared to surgery, such as Endoscopic Submucosal Dissection (ESD), being offered in select cases.[2]

Notably, the development of ESD dates back to 1988 in Japan[3]. ESD is nowadays accepted as a safe and minimally invasive treatment for superficial neoplastic lesions without significant submucosal invasion and selected precancerous lesions across the gastrointestinal system, providing en bloc resection regardless of the size plus a detailed histopathological assessment. [2]

ESD is an advanced endoscopic technique that requires a high level of skill and knowhow, training is time-consuming, and learning curves have been lengthy. Given its complexity, this procedure also has higher risk of adverse events[4,5].

Bleeding is the most common complication of ESD. It can present during (immediate) and/or after the procedure (post-procedure). Firstly, immediate bleeding is observed by the operator and immediate intervention is usually required. Secondly, post-procedure bleeding can present with symptoms ranging from melena, hematemesis and haematochezia to drop in the haemoglobin concentration, hypotension and tachycardia[4,6–8]. Other ESD complications include perforation, stenosis and thromboembolism.[9,10]

Antithrombotic use has been increasing through the years as primary and secondary prevention of cerebro-cardiovascular events. Despite reducing thromboembolic events, bleeding risk is increased. [11,12]

As a result, the European Society of Gastroenterology (ESGE) and the British Society of Gastroenterology (BSGE) published a joint guideline regarding endoscopic procedures in patients on antiplatelet or anticoagulant therapy. ESD is considered a high-risk endoscopic technique. Patients should be informed of the bleeding risks of continuing therapy as well as the thrombotic risks of suspending therapy. [13]

Regarding its management, these recommendations suggest that acetylsalicylic acid (ASA) can be continued for most endoscopic procedures considered to be high risk (including ESD). P2Y12 antagonists such as clopidogrel should be suspended 7 days before the procedure in patients at low risk of thrombosis and then restarted 1-2 days after the procedure. On the other hand, in patients at high risk of thrombosis, such as those with coronary stents, P2Y12 regimen should be discussed with cardiology.[13] Furthermore, patients on warfarin with a condition at low risk of thromboembolism (such as xenograft heart valve, atrial fibrillation

without high-risk factores (CHADS2 ≤ 4) and > 3 months after venous thromboembolism) should stop warfarin 5 days before the procedure and restart in the evening of the procedure. Instead, if a high-risk condition is present, warfarin should be suspended 5 days before the procedure and 3 days before the procedure low molecular weight heparin (LMWH) should be started as bridging therapy. In the 24h before the procedure, LMWH is not administered and warfarin is resumed in the evening.[13] In case of direct oral anticoagulants (DOACs), therapy should be suspended 3 days before the procedure and restarted 2-3 days after the procedure[13]. However, these recommendations are broad and valid for any high-risk endoscopic procedure. Hence, case per case analysis, team knowledge and experience currently define the most appropriate approach to each patient undergoing ESD.

Apart from the West, in 2017 the Japanese guidelines published an appendix on anticoagulants including DOACs[14]. The 2012 Japanese guidelines[15] were mainly in tune with ESGE/BSGE, however, later studies reported an increased risk of bleeding in patients taking warfarin undergoing heparin replacement when compared to continuing warfarin regimen without bridging.[16] Post-procedure bleeding risk is reduced by maintaining the PT-INR at the low end of the therapeutic range prior to the procedure. Therefore, bridging therapy with LWMH in patients under warfarin is no longer recommended in Japan according to the 2017 appendix[14].

Some articles indicate that antithrombotic use increases post-ESD bleeding, with dual therapy (with anticoagulant and antiplatelet agents) having the highest risk, followed by anticoagulants and antiplatelet agents. [6,9,10,11,16–23] In contrast, other studies have denied an association between antithrombotic drug use and increased bleeding risk after ESD[24]. Above all, most articles focus on post-ESD bleeding from gastric lesions, with data regarding other portions of gastrointestinal (GI) tract being scarce.

Identifying which antithrombotic agents are linked to higher bleeding rates and the role of post-procedure bridging therapy in bleeding is of prime importance, therefore we conducted this study.

Objectives

- Assess the bleeding risk in patients submitted to ESD under antithrombotic therapy.
- Compare the bleeding risk between different anticoagulant and antiplatelet regimens in patients submitted to ESD.

Methods

This study was conducted at the Gastroenterology department in Centro Hospitalar Universitário de Santo António (CHUdSA). All patients submitted to ESD from June of 2016 to January of 2021 were retrospectively analysed. Undergoing haemodialysis or having a coagulopathy was defined as exclusion criteria. Patient's data regarding demographics, comorbidities, medication, past medical history, surgeries and follow up information was accessed using SClínico® and RSE®. Patient's data was coded and anonymised. Ethics committee approval was granted (REF: 2022-215(173-DEFI/176-CE)).

For patient-oriented statistical analysis in case of the same patient undergoing multiple ESD or having multiple tumours, we selected the procedure in which bleeding was present (priority criteria) or the most recent procedure if no bleeding was present. Each tumour was considered as an independent procedure for lesion-oriented statistical analysis and all tumours were included.

ESD related bleeding is divided into immediate or post-procedure. Immediate bleeding was not considered. We focused only on post-procedure bleeding. It was considered from six hours after the conclusion of the procedure to up to thirty days after the procedure. Bleeding was defined as the cases with classical clinical features and symptoms of bleeding: melena, haematochezia, hematemesis, or drop ≥ 2 g /dL in haemoglobin labels compared to the patient baseline.

Thrombosis was defined as the presence of thrombotic events as stroke, pulmonary embolism, transient ischemic attack, deep vein thrombosis from seven days before the procedure to up to thirty days after the procedure.

Data collected on patient status of antithrombotic therapy included: use of antiplatelet agents (ASA; P2Y12 antagonists; dual antiplatelets); use of anticoagulant agents (vitamin K antagonists such as warfarin, acenocoumarin) and use of DOACs. Antithrombotic suspension before the procedure was conducted according to the latest ESGE/BSGE guidelines – 7 days prior for P2Y12 antagonists and restarted the day after, warfarin 5 days prior with or without LMWH bridging.

Post-procedure antithrombotic management was made in a case per case evaluation with ESGE/BSGE guidelines as a reference and in consultation with cardiology when needed.

The location of the tumour, tumour size, duration of the procedure, day of bleeding, timing of bleeding, blood transfusions, intensive care unit (ICU) stay and the duration of the hospital admission were collected.

Categorical variables were analysed using Chi-square test and Fisher's exact test. Continuous variables are described using the mean± standard deviation (SD), median and

Interquartilrange (IQR), depending on the case. Mann-Whitney U test was used to compare continuous dependent variables with and independent variable with two groups. A *p* value of 0.05 was considered statistically significant. All tests were 2-sided. Analysis was performed using IBM SPSS Statistics version 27.0 (IBM Corp. Armonk, New York, USA).

Results

The baseline characteristics of the patients are presented in Table I. A total of one hundred ninety-three patients were included. No patient met our exclusion criteria. One hundred and sixty-five patients had a single tumour. Twenty-eight had two or more tumours. A total of two hundred and thirty-three tumours were analysed. Four patients underwent ESD more than once. ESD procedures were successfully completed in all cases. Patients were divided into 2 groups: 31 (16.1%) under antithrombotic therapy (AT) and 162 (83.9%) without AT (control group).

Gender proportion between the two groups was similar ($p = 0.257$). Age was significantly higher in the group taking antithrombotics than in the control group (72.6 ± 3.1 vs. 65.5 ± 1.6, $p < 0.001$). Prevalence of hypertension ($p = 0.012$), diabetes mellitus ($p = 0.027$), ischemic heart disease ($p < 0.001$), previous stroke ($p = 0.004$) and chronic kidney disease ($p = 0.024$) were significantly higher in the group taking antithrombotics than in the control group. Multiple tumour resection rate was similar between the two groups (12.9% (4/31) in the patients taking AT vs. 14.8% (24/162) in the control group ($p = 1.000$).

Procedure-related characteristics of the AT group and control group are presented in Table II. There were 37 tumours (15.9%) removed under AT and 196 tumours (83.1%) in the control group. Tumour organ location was similar between the two groups with the highest rate of cases being accounted to the stomach (82.4% (192/233); $p = 0.484$). Tumour size ($p = 0.805$) and the procedure duration ($p = 0.523$) were similar between the two groups.

Post-procedure bleeding rate was higher in the AT group (18.9% (7/37) vs. 7.1% (14/196)) although it was not statistically significant (OR = 3.03; 95%CI: 1.13-8.13; $p = 0.053$). Timing to bleed was longer in the AT group, i.e., patients taking AT had a more delayed bleeding in contrast with the control group (median, IQR; 10 (4-13) days vs. 1 (0-2) days), and this difference was statistically significant ($p = 0.004$). Anticoagulant agents represented 85.7% (6/7) of the post-procedure bleeding cases in the AT group and were responsible for this difference ($p < 0.001$).

Post-procedure bleeding rate was significantly higher after hospital discharge in the group taking AT than in the controls (OR = 10.1; 95%CI: 2.3-44.1; $p = 0.003$). No difference was found between the two groups during hospital stay ($p = 1.000$). All bleeding cases after discharge in the AT group came from anticoagulant agents (100% (5/5); OR: 25.12; 95%CI: 5.44-116.02; $p < 0.001$)), specifically vitamin K antagonists presented an OR of 24.68 (95%CI: 3.46-175.88; $p = 0.010$) and DOACs an OR of 11.67 (95%CI: 2.47-55.24; $p = 0.008$).

No cases of thrombosis were reported.

The rate of procedures requiring blood transfusion was significantly higher in the group

taking AT 8.1% (3/37) than in the control group 0.5% (1/196) (OR = 17.2; 95%CI: 1.7-170.3; p = 0.013). Anticoagulant agents were a risk factor for blood transfusion (OR: 39.94; 95%CI: 3.93-404.19; p = 0.002), specifically DOACs (OR of 18.08 (95%CI: 2.34-139.68; p = 0.019).

One case of post-procedure bleeding that required ICU admission was reported in the control group. The median of hospital stay duration was similar in both groups (2 days; p = 0.385).

A summary of the comparison between antithrombotic therapy regimens and post-procedure bleeding status is presented on Table III. Of the 37 procedures under AT, 43.2% (16/37) were under antiplatelet agents, 51.4% (19/37) were under anticoagulant therapy and 5.4% (2/37) were under antiplatelets and anticoagulants simultaneously.

Taking antiplatelet agents was not linked to post-procedure bleeding (OR = 0.61; 95%CI: 0.77-4.86; p = 1.000). No procedures were performed under dual antiplatelet therapy.

A strong association was found between taking anticoagulant agents and post-procedure bleeding (OR = 6.12; 95%CI: 2.04-18.40; p = 0.003). Overall post-procedure bleeding was significantly higher in the group taking DOACs (OR = 4.75; 95%CI: 1.35-16.77; p = 0.027). Rivaroxaban accounted for half of the bleeding cases (3/6) in the anticoagulant agents group, nevertheless failed to reach significance (OR: 4.88; 95%CI: 1.16-20.51; p = 0.050).

Two procedures were done under dual class antithrombotic therapy but neither bled.

To evaluate differences in bridging therapy regimens we compared post-procedure bleeding with bridging therapy status (Table IV). In the antiplatelet agents group, when needed, bridging therapy was done with ASA. Antiplatelet therapy without bridging was resumed in the majority of the cases the day after the procedure. When bridging was needed, antiplatelet agent was resumed 7 days after the procedure. In the anticoagulant group, all patients under vitamin K antagonists did bridging post-procedure. In the DOAC group, when needed, bridging therapy was done with LMWH.

Post-procedure bridging therapy rate was 35.1% (13/37). Median duration of bridging therapy was 7.0 days (IQR 2.0-21.0 days). Four cases under bridging therapy had post-procedure bleeding. All the cases were in the anticoagulants group – two referred to Vitamin K antagonists and the remaining two to DOACs. To assess if bridging therapy had impact on bleeding each agent needed (1) at least 1 procedure under bridging therapy with bleeding and (2) at least 1 procedure without bridging therapy with bleeding. If both criteria were met, we were able to present the p-value and OR.

To be precise, there was only one subgroup group that met those criteria - DOACs. There were 14 procedures done under DOACs, 5 with post-procedure bridging therapy, 4 presented with post-procedure bleeding and from those 50% (2/4) were from the group with post-

procedure bridging therapy and 50% (2/4) came from the group without post-procedure bridging therapy. No relation could be established between post-procedure bridging therapy and post-procedure bleeding risk in the DOAC's group (OR: 2.33; 95%CI: 0.22-25.25; p = 0.580). DOAC subgroup analysis revealed that apixaban accounted for 25% (1/4) of the post-procedure bleeding cases and rivaroxaban accounted for 75% (3/4). No differences between post-procedure bridging therapy and bleeding risk were observed (OR: 1.25; 95%CI: 0.07-22.88; p = 1.000).

Discussion

Most studies to date focus on post-procedure bleeding from gastric lesions [17,20–23,25,26]. Research focusing on the esophagus[27] and colorectal[7,23,28,29] portions of the GI tract has been emerging. In this study, the majority of the procedures were from the gastric region (82.4%; 192/233).

Post-procedure bleeding rate was 9.0% (21/233). Median time of bleeding was on day 1. Current evidence shows a post-procedure bleeding rate from 4.7% to 9% [4,20,22], with a time of post-procedure bleeding averaging 4 days[22]. Our results are in tune with the available data.

Post-procedure bleeding rate was higher in the procedures group under AT therapy (15.9% (7/37)) despite not reaching significance, (OR = 3.03; 95%CI: 1.13-8.13; p = 0.053). In fact, some studies report that AT therapy is not a risk factor for post-procedure bleeding[24,30,31]. However, large multicentric studies [22] and recent meta-analysis[7,11,20,32] agree on increased bleeding risk with antithrombotic therapy. We believe that AT therapy is a risk factor for post-procedure bleeding and that our study failed to reach significance due to the low number of procedures done under AT (37/233; 15.9%).

When examining AT therapy subgroups, we found that anticoagulant agents were the strongest risk factor for post-procedure bleeding (OR: 6.12; 95%CI: 2.04-18.40; p = 0.003), mainly due to DOACs (OR: 4.75; 95%CI: 1.35-16.77; p = 0.027). Shiroma et al. found DOACs to be the strongest risk factor for post-procedure bleeding (OR: 7.42), followed by warfarin (OR: 3.90) and aspirin (OR: 1.92)[22]. Our results relating to DOACs are similar, but we were unable to link post-procedure bleeding with warfarin and aspirin. In our opinion, the low number of procedures undergone under warfarin (3/233; 1.3%) restrained us from assessing the true impact of this regimen. But unlike warfarin, in the antiplatelet group there were 16 (6.9%) procedures, 11 (4.7%) regarding aspirin use. Studies on the antiplatelet agents impact in post-procedure bleeding are conflicting [33,34] and a lack of association between antiplatelets and post-procedure bleeding may be a plausible conclusion (OR: 0.61; 95%CI: 0.77-4.86; p = 1.000).

Upon reviewing the DOAC group, rivaroxaban was responsible for 75% (3/4) of the bleeding cases in this category, notwithstanding statistically significance (OR: 4.88; 95%CI: 1.16-20.51; p = 0.050). We would like to emphasize this result though, since it was very near our significance value. One study, which reported that DOACs increased the post-procedure bleeding risk, revealed that the post-procedure bleeding rate across all agents (apixaban, dabigatran, edoxaban and rivaroxaban) was similar[29]. Yet, new reports indicate that rivaroxaban may be associated with higher bleeding risk when compared to other DOACs[35]. We believe rivaroxaban is a risk factor for bleeding and that the bleeding rate may be higher than other DOAC.

We had limited data on post-procedure bridging therapy. No differences were found regarding post-procedure bleeding between bridging therapy after the procedure and no bridging therapy (OR: 3.11; 95%CI: 0.58-16.83; p = 0.213). Post-procedure bridging was predominantly accounted to anticoagulant agents (10/13, 76.8%). We were unable calculate the bleeding risk between bridging therapy and no bridging therapy in the vitamin K antagonists group as all the procedures were done under post-procedure bridging therapy. In DOACs no significant difference was observed (OR:2.33; 95%CI: 0.22-25.25; p = 0.580). We couldn't find any connexion too in the rivaroxaban group (OR:1.25; 95%CI: 0.07-22.88; p = 1.000).

Evidence on the impact of post-procedure bridging therapy is not consensual[13,14,16]. Despite being believed to reduce post-procedure bleeding[13], we found that bridging in DOAC group did not lead to different outcomes when compared to the group without bridging. This was an important finding of our study. Post-procedure bridging therapy in patients under DOAC with LMWH is associated with higher costs[36], more complex management and patient education, but without benefits in the bleeding outcome when compared to the group without bridging.

Time to bleed was significantly longer in the procedures under AT therapy (p = 0.004) with a median of 10 days (IQR:4-13) after the procedure. Previous studies suggest that the use of antithrombotic agents is associated with a more delayed bleeding rate[21,22,37], with median time of post-procedure bleeding in DOACs being higher than warfarin (10 days vs. 6 days)[37]. This difference in post-procedure bleeding timing has not been explained yet. Furthermore, we concluded that procedures under antithrombotic therapy are more likely to bleed after the patient discharge (OR: 10.1), despite bleeding rate being similar during hospital stay. We examined which agents were responsible for this result and determined that anticoagulant agents were risk factor for bleeding after discharge.

Studies to date compared the median time of bleeding and the rate of bleeding in antithrombotic therapy group vs. control groups, but without establishing a connection between hospital discharge or during hospital stay. We believe this is a key finding which can be used to create a special approach in the follow up of patients under anticoagulant agents, with emphasis in the re-evaluation 10 days after the ESD.

Moreover, we found that procedures under AT are more likely to need a blood transfusion (OR: 17.2). Previous studies presented mixed results regarding AT use and blood transfusion[17,21,24,37]. We found that taking anticoagulant agents and DOACs were risk factors for post procedure transfusion.

There were limitations to this study: (1) it was performed in a single institution and in a retrospective manner, (2) due to the sample size being small, we couldn't assess differences in

all agents and in the bridging therapy in all regimens, (3) we couldn't discuss thrombotic events because none occurred. (4) there were differences in the baseline characteristics of the patients in the two groups.

On the strengths, (1) this was the first study to our knowledge to connect the bleeding time with hospital stay or discharge, (2) suspension timing of AT agents was uniform across all procedures, (3) AT management was reported in detail; (4) there was a clear definition of post-procedure bleeding; (5) ESD were done by two experienced operators with a high volume of practice.

Conclusion

To sum up, anticoagulant agents were the strongest risk factor for post-procedure bleeding, namely DOACs. Antiplatelet agents were not a risk factor for post-procedure bleeding. Post-procedure bridging therapy in DOAC group didn't impact the bleeding risk.

Timing of bleeding was longer in patients under anticoagulant agents and more likely to occur after hospital discharge.

Tables

Table I – Patient-related baseline characteristics with univariate analysis

	Antithrombotic therapy	Controls	Total patients	p-value
Patients n (%)	31 (16.1)	162 (83.9)	193 (100)	-
Male/female n/n	21/10	92/70	113/80	0.257
Age (years) mean ± SD	72.6 ± 3.1	65.5 ± 1.6	66.1 ± 10.5	**<0.001**
Hypertension n (%)	22 (71.0)	75 (46.3)	124 (64.2)	**0.012**
Diabetes mellitus n (%)	12 (38.7)	33 (20.4)	45 (23.3)	**0.027**
Ischemic heart disease n (%)	13 (41.9)	6 (3.7)	19 (9.8)	**<0.001**
Stroke n (%)	3 (9.7)	0 (0.0)	3 (1.6)	**0.004**
Lung disease n (%)	0 (0.0)	12 (7.4)	12 (6.2)	0.220
Chronic Kidney Disease n (%)	4 (12.9)	4 (2.5)	8 (4.1)	**0.024**
Cirrhosis n (%)	1 (3.2)	3 (1.9)	4 (2.1)	0.507
2 or more tumours n (%)	4 (12.9)	24 (14.8)	28 (14.5)	1.000

Table II – Univariate analysis of procedure-related characteristics of antithrombotic therapy compared to controls

	Antithrombotic therapy	**Controls**	**Total procedures**	**p-value**	**OR** (95% C.I.)
Procedures n (%)	37 (15.9)	196 (84.1)	233 (100)	-	-
Tumour Location					
- **Esophagus** n (%)	1 (2.7)	4 (2.0)	5 (2.1)	0.582	-
- **Stomach** n (%)	29 (78.4)	163 (83.2)	192 (82.4)	0.484	-
- **Colorectal** n (%)	7 (18.9)	29 (14.8)	36 (15.5)	0.619	-
Tumour Size (mm) mean ± SD	21.8 ± 12.0	21.2 ± 13.5	21.3 ± 13.0	0.805	-
Procedure Duration (min) mean ± SD	65.1 ± 52.0	72.6 ± 66.7	71.4 ± 64.5	0.523	-
Post procedure bleeding n (%)	7 (18.9)	14 (7.1)	21 (9.0)	0.053	3.03 (1.13-8.13)
Timing of bleeding					
Bleeding day after ESD (days) median (IQR)	10 (4-13)	1 (0-2)	1 (0-7)	**0.004**	-
- **During Hospital stay** n (%)	2 (5.4)	11 (5.6)	13 (5.6)	1.000	0.96 (0.20-4.53)
Antiplatelet agents n (%)	1 (2.7)	-	-	1.000	1.06 (0.13-8.70)
DOAC n (%)	1 (2.7)	-	-	0.563	1.33 (0.16-11.00)
- **After Discharge** n (%)	5 (13.5)	3 (1.5)	8 (3.4)	**0.003**	10.05 (2.29-44.13)

Anticoagulant agents n (%)	5 (13.5)	-	-	**<0.001**	25.12 (5.44-116.02)
Vitamin K antagonists n (%)	2 (5.4)	-	-	**0.010**	24.68 (3.46-175.88)
DOAC n (%)	3 (8.1)	-	-	**0.008**	11.67 (2.47-55.24)
Thrombosis n (%)	0 (0.0)	0 (0.0)	0 (0.0)		
Transfusion n (%)	3 (8.1)	1 (0.5)	4 (1.7)	**0.013**	17.21 (1.74-170.30)
Anticoagulant agents n (%)	3 (8.1)	-	-	**0.002**	39.94 (3.93-406.19)
Vitamin K antagonists n (%)	1 (2.7)	-	-	0.084	18.75 (1.59-221.60)
DOAC n (%)	2 (5.4)	-	-	**0.019**	18.08 (2.34-139.68)
ICU n (%)	0 (0.0)	1 (0.5)	1 (0.4)	1.000	-
Hospital stay (days) median (range)	2 (0-9)	2 (0-7)	2(0-9)	0.385	-

Table III – Univariate analysis of antithrombotic therapy and bleeding status per procedure

	Total procedures	**No bleeding**	**Bleeding**	**p-value**	**OR** (95% C.I.)
Total n (%)	233 (100)	212 (100)	21 (100)		
Antithrombotic therapy n (%)	37 (15.9)	30 (14.2)	7 (33.3)	0.053	3.03 (1.13-8.13)
Antiplatelet agents n (%)	16 (6.9)	15 (7.1)	1 (4.8)	1.000	0.61 (0.77-4.86)
- **ASA** n (%)	11 (4.7)	10 (4.7)	1 (4.8)	1.000	0.91 (0.11-7.45)
- **Clopidogrel or Ticagrelor** n (%)	5 (2.1)	5 (2.4)	0 (0.0)	1.000	-
- **Dual antiplatelet** n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Anticoagulant agents n (%)	19 (8.2)	13 (6.1)	6 (28.6)	**0.003**	6.12 (2.04-18.40)
• **Vitamin K antagonists** n (%)	5 (2.1)	3 (1.4)	2 (9.5)	0.066	7.33 (1.15-46.63)
- **Warfarin** n (%)	3 (1.3)	2 (0.9)	1 (4.8)	0.248	5.25 (0.46-60.47)
- **Acenocumarol** n (%)	2 (0.9)	1 (0.5)	1 (4.8)	0.172	10.55 (0.64-175.14)
• **DOAC** n (%)	14 (6.0)	10 (4.7)	4 (19.0)	**0.027**	4.75 (1.35-16.77)
- **Apixaban** n (%)	2 (0.9)	1 (0.5)	1 (4.8)	0.172	10.55 (0.64-175.14)
- **Dabigatran** n (%)	1 (0.5)	1 (0.5)	0 (0.0)	1.000	0.91 (0.87-0.95)
- **Edoxaban** n (%)	1 (0.5)	1 (0.5)	0 (0.0)	1.000	0.91 (0.87-0.95)
- **Rivaroxaban** n (%)	10 (4.3)	7 (3.3)	3 (14.3)	0.050	4.88 (1.16-20.51)
Antiplatelet + anticoagulants n (%)	2 (0.9)	2 (0.9)	0 (0.0)	1.000	-

Table IV – Univariate analysis of per procedure bleeding risk comparison in cases with post-procedure bridging therapy and without bridging

	Total procedures under AT n (%)	**Bridging** n (%)	**Bridging days** median (range)	**Bleeding** n (%)	**Bleeding under bridging** n (%)	**p value Bleeding (Bridging vs. no bridging)**	**OR** (95% C.I.)
Antithrombotic therapy	37 (100.0)	13 (100.0)	7.0 (2.0-21.0)	7 (33.3)	4 (100.0)	0.213	3.11 (0.58-16.83)
Antiplatelet agents	16 (43.2)	1 (7.3)	7.0 (7.0-7.0)	1 (4.8)	0 (0.0)	1.000	-
- **ASA**	11 (29.7)	0 (0.0)	-	1 (4.8)	0 (0.0)	-	-
- **Clopidogrel/Ticagrelor**	5 (13.5)	1 (7.3)	7.0 (7.0-7.0)	0 (0.0)	0 (0.0)	1.000	-
- **Dual antiplatelet**	0 (0.0)	-	-	-	-	-	-
Anticoagulant agents	19 (51.4)	10 (76.9)	7.0 (2.0-14.0)	6 (28.6)	4 (100.0)	0.628	2.33 (0.31-17.55)
- **Vitamin K antagonists**	5 (13.5)	5 (38.5)	7.0 (2.0-14.0)	2 (9.5)	2 (50.0)	-	-
- **Warfarin**	3 (8.1)	3 (23.1)	7.0 (2.0-7.0)	1 (4.8)	1 (25.0)	-	-
- **Acenocumarol**	2 (5.4)	2 (15.4)	10.5 (7.0-14.0)	1 (4.8)	1 (25.0)	-	-
- **DOAC**	14 (37.8)	5 (38.5)	6.0 (3.0-7.0)	4 (19.0)	2 (50.0)	0.580	2.33 (0.22-25.25)
- **Apixaban**	2 (5.4)	2 (15.4)	4.5 (3.0-6.0)	1 (4.8)	1 (25.0)	-	-
- **Dabigatran**	1 (2.7)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	-
- **Edoxaban**	1 (2.7)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	-
- **Rivaroxaban**	10 (27.0)	3 (23.1)	7.0 (6.0-7.0)	3 (14.3)	1 (25.0)	1.000	1.25 (0.07-22.88)
Antiplatelet + Anticoagulants	2 (5.4)	2 (5.4)	21.0 (21.0-21.0)	0 (0.0)	0 (0.0)	-	-

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