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ORIGINAL ARTICLE

Acute Upper Gastrointestinal Bleeding in Post COVID-19 Patients Receiving Direct Oral Anticoagulants as Thromboprophylaxis

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Abstract

Background: ***A hypercoagulable state is one of the main pathologic events in COVID-19 patients.***

Aim of the study: ***To assess the possible bleeding sources and proper endoscopic interventions in patients cleared from COVID-19 but still receiving direct oral anticoagulants (DOACs).***

Methods: ***We conducted this prospective study on 305 patients with first-attack upper gastrointestinal bleeding, recently finished COVID-19 treatment, and still using DOACs as a thromboprophylaxis.***

Results: ***DOAC used were Rivaroxaban 10 mg once daily in 150 (49.18%) patients, Apixaban 2.5 mg BID in131 (42.95%) patients, Apixaban 5 mg BID in 15 (4.92%) patients, Rivaroxaban 20 mg in 9 (2.95%) patients. Variceal bleeding occurred in 162 patients, while nonvariceal bleeding occurred in 143 patients. Intervention was endoscopic band ligation (EBL) in 100 (32.79%) patients, Argon plasma coagulation in 71 (23.28%) patients, diluted epinephrine injection in 42 (13.77%) patients, EBL plus cyanoacrylate injection in 25 (8.20%) patients, Hemoclips in 19 (6.23%) patients, Cyanoacrylate injection in 12 (3.93%) patients and Hemospray in 11 (3.61%) patients. 279 (91%) patients improved after the first endoscopic intervention, rebleeding occurred in 21 (7%) of patients, while 5 (2%) of patients died due to different causes.***

Conclusions: ***Esophageal varices were the most common bleeding site in post-COVID-19 patients, and the endoscopic band ligation intervention was the proper endoscopic intervention with 91% improvement. The risk of gastrointestinal bleeding after DOAC use should be considered, and proper patient selection according to the risk-cost-benefit ratio is of value.***

Keywords: Gastrointestinal bleeding, COVID-19, Direct oral anticoagulants

1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-coV-2).[1,2] Due to the hyper-inflammatory process occurring as a consequence of cytokine storm, diffuse micro-thrombosis in lungs and other organs like brain, heart, liver, and kidneys occur.[3,4]

One of the major consequences occurring in COVID-19 is a hypercoagulable state. Therefore, thromboembolic events are one of the life-threatening complications of COVID-19.[5] During the early stages of the COVID-19 pandemic, venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), was seen in up to 1/3 of critical care cases despite using prophylactic anticoagulants.[6,7] However, there has been a general trend over time from a higher VTE risk in hospitalized patients earlier in the pandemic towards a lower risk later in the pandemic, although VTE risk in hospitalized patients remains a serious concern.[8] The use of anticoagulant therapy in these patients can make the prognosis better.[9]

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In COVID-19 cases, the incidence and risk of upper gastrointestinal bleeding (UGIB) are not well studied. Only a few reports in the literature have been done.[10,11,12,13] International guidelines suggest that endoscopists should manage UGIB within 24 hours from clinical stabilization.[14] the study aims to evaluate the possible bleeding sources and proper endoscopic interventions in patients cleared from COVID-19 but still receiving direct oral anticoagulants as thromboprophylaxis.

2. Patients and methods

We conducted this prospective study at Tanta University Emergency Hospital (Gastroenterology and Endoscopy unit), a tertiary referral center in the middle of the Nile Delta of Egypt, from June 2020 to July 2021. The study was done after approval from the Ethical Committee (approval code: 36051/11/22)

2.1.Inclusion criteria were 305 patients presented with first-attack upper gastrointestinal bleeding who had recently finished COVID-19 treatment and were still using direct oral anticoagulants (DOACs) as a thromboprophylaxis measure.

2.2.Exclusion criteria were patients presented with recurrent upper gastrointestinal bleeding, patients who received DOACs before getting COVID-19 infection for any reason, patients with a documented history of being cirrhotic (Child B and C), intensive care unit patients, and COVID-19 patients with thrombotic complications and on treatment.

All patients were evaluated correctly once admitted regarding thorough history taking, monitoring of vital signs and hemodynamics (blood pressure, pulse, temperature, respiratory rate, consciousness level, and urine output), insertion of two large bore cannulas, and resuscitation was done by administration of colloids, crystalloids, and blood transfusion according to hemoglobin level. Routine laboratory investigations, including complete blood count, liver enzymes, D-dimer, serum urea, and creatinine, were done for all patients. All patients were informed to stop taking DOACs immediately once bleeding occurred.

After the stabilization of the case, upper gastrointestinal endoscopy was done within the first 24 hours to identify the possible source of bleeding and proper endoscopic management.

The endoscopy device used was EPK-I5000 High-Definition videos cope-Pentax Medical, Japan. All endoscopy suite staff, including endoscopists, nurses, technicians, and other workers, followed the infection control roles by wearing masks, goggles, face shields, long-sleeved medical gowns or suits, protective gloves, and protective boots. Regular slandered disinfection of hands, accessories, scopes, and surfaces was done.

After endoscopy completion admission of the patient for at least 48 hours before discharge, all patients were referred to the post-covid clinic in our hospital for risk stratification by chest (COVID-19) consultant on whether to continue DOACs use or not (case by case). A follow-up endoscopy after at least four weeks was done for most of the cases.

2.3.Calculation of sample size

The sample size calculation was performed using the EpI-Info 2002 software statistical package designed by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). The sample size was calculated based on the following considerations: the prevalence of bleeding in COVID-19 patients receiving intermediate or therapeutic doses of anticoagulants was 12.42% according to a previous study[15] with 4% confidence limit and 95% confidence level. At least 262 are needed. Therefore, we recruited 305 cases to overcome drop-out.

2.4.Statistical analysis

Statistical analysis was done using SPSS v26 (IBM et al., USA). Quantitative variables were presented as mean and standard deviation(SD). Qualitative variables(%) were presented as frequency and percentage.

3. Results

In this study, 447 patients were assessed for eligibility, and 142 patients did not meet the criteria in the study. All allocated patients were followed up and analyzed statistically .Figure 1.

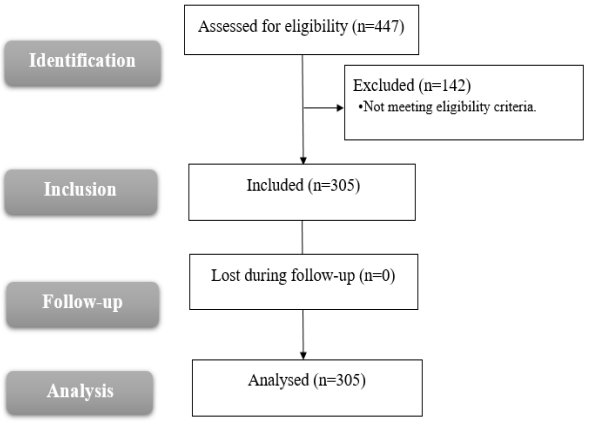

Figure 1.Strobe flowchart for studied patients

Our study was carried out on 305 patients, 99 (32.46%) females and 206 (67.54%) males. 200 patients presented with hematemesis, 75 patients presented with melena, and 30 patients presented with both hematemesis and melena.

As regards co-morbid conditions, 21.97% patients were obese, 10.82% patients were diabetes mellitus type 2, 8.20% patients were

hypertensive, 2.95% patients had osteoarthritis and 2.30% patients were asthmatics. Table 1

Table 1. Patient characteristics, co-morbid conditions, and clinical presentation of the studied patients

		N = 305
AGE (YEAR)	Mean ± SD	52.98± 8.4
	Range	27 - 86
SEX	Male	206 (67.54%)
	Female	99 (32.46%)
BMI (KG/M^2)	Mean ± SD	28.3 ± 3.8
	Range	23 - 37
CO-MORBID CONDITIONS	Obesity	67 (21.97%)
	Diabetes mellitus	33 (10.82%)
	Hypertension	25 (8.20%)
	Osteoarthritis	9 (2.95%)
	Bronchial asthma	7 (2.30%)
CLINICAL PRESENTATION	Hematemesis	200 (65.57%)
	Melena	75 (24.59%)
	HEMATEMESIS AND MELENA	30 (9.84%)

Data are presented as mean ± SD or frequency (%), BMI: Body mass index.

Significant anemia in most of our patients with decreased hemoglobin level (8.94±5.98). Normal mean levels as regards platelet count, D-dimer, kidney functions,and liver enzymes.Table 2

Table 2. Laboratory investigations of the studied patients

		N = 305
HB (GM/DL)	Mean ± SD	8.94±5.98
	Range	5-110
PLATELETS (CELL/MM^3)	Mean ± SD	199.85±85.22
	Range	10-1320
WBCS (X10^3/MM^3)	Mean ± SD	6.6±2.22
	Range	0.2-11.6
D DIMER (NG/ML)	Mean ± SD	245.5±160.76
	Range	22-2300
SERUM UREA (MG/DL)	Mean ± SD	38.97±9.32
	Range	4-76
SERUM CREATININE (MG/DL)	Mean ± SD	0.98±0.14
	Range	0.6-1.3
ALT (UNIT/L)	Mean ± SD	41.02±10.04
	Range	22-70
AST (UNIT/L)	Mean ± SD	46.15±12.05
	RANGE	0-78

Data are presented as mean ± SD, Hb: hemoglobin. WBC: white blood cells. ALT: alanine transaminase. AST: aspartate aminotransferase

DOAC used were Rivaroxaban 10 mg once daily in 150 (49.18%) patients, Apixaban 2.5 mg BID in131 (42.95%) patients, Apixaban 5 mg BID in 15 (4.92%) patients, Rivaroxaban 20 mg in 9 (2.95%) patients. The mean duration of bleeding following DOAC used was 31.77 ± 5.42 days, emergency blood transfusion was done in 76 (24.92%) patients. 68 (22.30%) patients used NSAIDs in the preceding week before the bleeding episode.Table 3

Table 3. DOAC used and daily dose, duration of bleeding following DOAC, emergency blood transfusion, and NSAIDs use in the preceding week before bleeding in the studied patients

		N =305
DOAC USED AND THE DAILY DOSE	Rivaroxaban 10 mg once	150 (49.18%)
	Apixaban 2.5 mg BID	131 (42.95%)
	Apixaban 5 mg BID	15 (4.92%)
	Rivaroxaban 20 mg	9 (2.95%)
DURATION OF BLEEDING (DAYS) FOLLOWING DOAC	Mean ± SD	31.77 ± 5.42
	Range	19 - 50
EMERGENCY BLOOD TRANSFUSION		76 (24.92%)
NSAIDS		68 (22.30%)

Data are presented as mean ± SD or frequency (%), DOAC: direct oral anticoagulants. NSAIDs: non-steroidal anti-inflammatory drugs. BID: two times a day.

The duration of bleeding and the need for emergency blood transfusion were insignificantly different among the different DOAC used in the studied patients. Table 4

Table 4. Relation between DOAC used and daily dose, duration of bleeding following DOAC, and

emergency blood transfusion in the studied patients

DOAC	RIVAROXABAN 10 MG ONCE(N =131)	APIXABAN 2.5 MG BID (N = 15)	APIXABAN 5 MG BID (N= 150)	RIVAROXABAN 20 MG (N=9)	P VALUE
DURATION OF BLEEDING FOLLOWING DOAC	31.19 ± 5.32	33.33 ± 6.30	32.27 ± 5.41	29.11 ± 4.31	0.102
EMERGENCY BLOOD TRANSFUSION	35 (23.33%)	35 (26.72%)	3 (20.0%)	3 (33.33%)	0.962

Data are presented as mean ± SD or frequency (%), DOAC: direct oral anticoagulants.

Variceal bleeding occurred in 162 patients; 125 (40.98%) patients presented with esophageal varices, 12 (3.93%) patients presented with gastric varices, and 25 (8.20%) patients presented with both esophageal and gastric varices. Non-variceal bleeding occurred in 143 patients; 53 (17.38%) patients presented with gastric ulcer, 33 (10.82%) patients presented with Duodenal ulcer, 36 (11.80%) patients presented with portal hypertensive gastropathy, 5 (1.64%) patients presented with Mallory Weiss tear (MWT), 7 (2.30%) patients presented with gastric antral vascular ectasia (GAVE), 5 (1.64%) patients presented with gastroesophageal reflux disease (GERD), 4 (1.31%) patients presented with bleeding gastric mass. Table 5

Table 5. Endoscopic findings in the studied patients

		N =305
ENDOSCOPIC FINDINGS	E. V	125 (40.98%)
	Gastric ulcer	53 (17.38%)
	PHG	36 (11.80%)
	Duodenal ulcer	33 (10.82%)
	EV+ GV	25 (8.20%)
	MWT	5 (1.64%)
	GV	12 (3.93%)
	GAVE	7 (2.30%)
	GERD	5 (1.64%)
	GASTRIC MASS	4 (1.31%)

Data are presented as frequency (%), GERD: gastroesophageal reflux disease, PHG: portal hypertensive gastropathy, GAVE: gastric antral vascular ectasia, MWT: Mallory-Weiss tear, E.V: esophageal varices G.V: gastric varices.

Endoscopic band ligation (EBL) was done in 100 (32.79%) patients, Argon plasma coagulation was done in 71 (23.28%) patients, diluted epinephrine injection was done in 42 (13.77%) patients, EBL plus cyanoacrylate injection was done in 25 (8.20%) patients, application of Hemoclips was done in 19 (6.23%) patients, Cyanoacrylate injection was done in 12 (3.93%) patients and Hemospray was applied in 11 (3.61%) patients. Table 6

Table 6. Endoscopic therapy in the studied patients

		N =305
ENDOSCOPIC THERAPY	EBL	100 (32.79%)
	Argon plasma coagulation	71 (23.28%)
	Diluted epinephrine injection	42 (13.77%)
	EBL + cyanoacrylate injection	25 (8.20%)
	Ethanolamine injection sclerotherapy	25 (8.20%)
	Hemoclips	19 (6.23%)
	Cyanoacrylate injection	12 (3.93%)
	HEMOSPRAY	11 (3.61%)

EBL: Endoscopic band ligation

The follow-up of every patient was done one month after the first episode of bleeding. 279 (91%) patients improved after the first endoscopic intervention, rebleeding occurred in 21 (7%) of patients while 5 (2%) of patients died due to different causes other than bleeding like sepsis and cardiopulmonary failure. 117 (38.4%) patients continued on DOAC after discharge. Table 7

Table 7. Follow-up of studied patients after one month

		N = 305
FOLLOW UP AFTER ONE MONTH	Improved	279 (91%)
	Rebleeding	21 (7%)
	DIED	5 (2%)

Data are presented as frequency (%).

4. Discussion

Anticoagulants are essential in managing

COVID-19 cases as COVID-19 is associated with higher arterial and venous thrombotic risks. Therefore, the American Society of Hematology recommended the use of thromboprophylaxis anticoagulants in COVID-19 cases and suggested using prophylactic-intensity over intermediate- or therapeutic-intensity anticoagulation forCOVID–19–related acute illness who do not have suspected or confirmed VTE. [16]

COVID-19 may invade the epithelium of the GI tract and could extend to infect the endothelial cells. [17]

Our results show a significantly decreased hemoglobin level (8.94±5.98) in most of our patients with normal levels of platelet count, D-dimer, kidney functions, and liver enzymes. The mean duration of bleeding following use was 31.77 ± 5.42 days, and emergency blood transfusion was done in 24.92% of patients. The duration of bleeding and the need for emergency blood transfusion were insignificantly different among the different DOACs used in the studied patients. These findings were consistent with those of Martin et al.[18], who included COVID-19 patients with upper GI bleeding. The patient showed a declined hemoglobin level of 7.5 g/dL with average platelet count and D-Dimer level. Blood transfusion occurred in 73% of the patients. In the same context, Zellmer et al.[19] enrolled 4128 COVID-19 patients to clarify the association between the occurrence of GI bleeding and comorbidities and medications. They observed that GI bleeding patients had hemoglobin drops with normal renal and liver functions. Also, they found that 80.6% of patients were on anticoagulants, 16.1% were administered NSAIDs, and 22.6%of % were administered both anticoagulation and anti-platelet agents. 58.1% of patients received blood transfusions.

Moreover, Rentsch et al.[20] demonstrated that DOAC usage among COVID-19 patients admitted to the hospital showed an insignificant increased risk of severe bleeding events.

The current endoscopic finding showed that variceal bleeding occurred in 162 patients; 40.98% of patients presented with esophageal varices,3.93% of patients presented with gastricvarices, and 8.20% of patients presented with both esophageal and gastric varices. Non-variceal bleeding occurred in 143 patients; 17.38% of patients presented with gastric ulcer; 11.8% of patients presented with portal hypertensive gastropathy that was consistent with Ashktorabet al.[21], who found that among 633 COVID-19 patients underwent endoscopic evaluation, the bleeding was localized in the upper GI tract in 66.0% of patients and the lower GI tract in 24.8%. The remaining 9.2% had unspecified GIB locations.

These results were different from Mauro et al.[22] found that peptic ulcerations were the most common finding (44% active ulcers and 22% diffuse erosive hemorrhagic gastritis), and only one patient developed variceal bleeding from gastroesophageal varices in UGIB in COVID-19 patients. The discrepant findings could be justified by different sample sizes and the fact that the Egyptian population has a high prevalence of liver diseases, including viral hepatitis infection and non-alcoholic fatty liver disease (NAFLD). [23]

Confirming our results, Nakamura et al.[24] enrolled 2894 consecutive COVID-19 patients, who identified the impact of primary bleeding on clinical outcomes and found that the most common bleeding site was the GI tract at 44%. In COVID-19 cases, gastric ulcers are the most common cause of GI tract bleeding.[25]

COVID-19 is associated with a higher risk of gastrointestinal bleeding, possibly due to the direct mucosal gastrointestinal damage caused by the virus, coagulopathy induced by inflammation, and thrombo-inflammation.[26] As the viral binding site of SARS-CoV-2 is angiotensin-converting enzyme 2 in the brush border of intestinal enterocytes, it can infect enteric cells with the highest expression.[27] In fact, thromboprophylaxis drugs are administered to the majority of admitted cases to the hospital, and this adds risk for the occurrence of bleeding. [28]

In our results, the endoscopic therapy revealed that the endoscopic band ligation (EBL) was carried out in 23.28% of patients, followed by argon plasma coagulation in 23.28% and diluted epinephrine injection in 13.77%. El Kassas et al.[11] also reported this in a case report, who performed esophagogastroduodenoscopy and revealed large, risky esophageal varices. Endoscopic band ligation was done with successful control of bleeding.

Moreover, Papanikolaou et al.[29] performed an upper gastrointestinal endoscopy on a COVID-19 patient and found that esophageal varices were actively bleeding; they performed band ligation endoscopy as a therapeutic endoscopy that resulted in adequate hemostasis.

A one-month follow-up period showed improvement in 91% of cases, rebleeding in 7%, and 5 2% of deaths.

Supporting our results, Mauro et al. [22] showed improvement in 78% of cases, rebleeding in 17% of cases, and 22% died in UGIB patients with COVID-19.

Moreover, Martin et al. [18] showed that in UGIB patients with COVID-19, there were improvements in 63.4% of cases, rebleeding in 12.2%, and 24.4% of cases died.

Although this research had several strengths,

including being a prospective study, the patients were followed up. Outcomes such as improvement, rebleeding, and death were evaluated; the study also had some limitations, including its small sample size, single-center setting, and the lack of a control group to determine risk factors for gastrointestinal bleeding in COVID-19 patients.

4. Conclusion

The endoscopic findings revealed that esophageal variceswere the most common bleeding site in post-COVID-19 patients, and the endoscopic band ligation intervention was the proper endoscopic intervention with 91% improvement. The risk of gastrointestinal bleeding after DOAC use should also be considered proper patient selection according to the risk-benefit ratio of value.

Disclosure

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