Blood thinners and gastrointestinal endoscopy

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Abstract

As the number of diagnostic and therapeutic gastrointestinal endoscopies is increasing, and there is an increase in number of patients taking blood thinners, we are seeing more and more patients on blood thinners prior to endoscopic procedures. Gastrointestinal bleeding or thromboembolism can occur in this category of patients in the perendoscopic period. To better manage these patients, endoscopists should have a clear concept about the various blood thinners in the market. Patients’ risk of thromboembolism off anticoagulation, and the risk of bleeding from endoscopic procedures should be assessed prior to endoscopy. The endoscopic procedure should be done when it is safe to do it.

Key words: Acute coronary syndrome; Gastrointestinal bleeding and endoscopy; Blood thinners; Antiplatelet agents and endoscopy; Gastrointestinal bleeding and endoscopy; Anticoagulation bridge before endoscopy; Anticoagulants and endoscopy

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Core tip: While patients on blood thinners undergoing endoscopic procedures are encountered in our clinical practice frequently, endoscopists need to be familiar with the various blood thinners and have a strategy to manage these patients efficiently. This article will discuss the various blood thinners including their mechanism and duration of action, and the current guidelines of performing gastrointestinal endoscopies when the patients are on those blood thinners.
hypercoagulable disorders[1]. Gastrointestinal tract is the most common site of significant bleeding in patients on blood thinners. Thousands of people per day and millions of people per year are having gastrointestinal endoscopies in the United States[2,3] and throughout the world. The various gastrointestinal endoscopic procedures performed are esophagogastroduodenoscopy, colonoscopy, endoscopic retrograde cholangiopancreatography (ERCP), flexible sigmoidoscopy, pouch/stoma endoscopy, enteroscopy (push, spiral, balloon assisted, i.e., single balloon or double balloon), endoscopic ultrasound (EUS - mediastinal, pancreatic, rectal), capsule endoscopy and capsule colonoscopy. All these procedures have diagnostic and therapeutic potentials except capsule endoscopy and capsule colonoscopy in which neither any diagnostic biopsy nor any intervention can be done. Blood thinners may potentiate the risk of bleeding during or after performing these procedures. In the last few years, new blood thinners have been introduced in the market. As safety is the most important concern before performing a procedure, endoscopists should be very familiar with the different blood thinners available in the market.

BLOOD THINNERS

Anti-platelet agents
These include irreversible cyclooxygenase inhibitor, adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, glycoprotein IIb/IIIa inhibitors and protease-activated receptor-1 (PAR-1) inhibitor.

Irreversible cyclooxygenase inhibitor
Aspirin: Low dose aspirin irreversibly inhibits platelet cyclooxygenase-1, thus decreasing production of prostaglandin H2 (PGH2) from arachidonic acid. As a result, production of thromboxane A2 (TXA2) derived from PGH2 is decreased. TXA2 is responsible for platelet aggregation and vasoconstriction. Low dose aspirin works as a weak antiplatelet agent. Aspirin is widely used in coronary artery disease, cerebrovascular disease and atrial fibrillation. Aspirin can be continued for low risk and high-risk elective procedures.

Adenosine diphosphate receptor inhibitors
They competitively inhibit ADP binding to ADP receptors on platelets, and thus prevent ADP mediated up-regulation of glycoprotein IIb/IIIa receptor, leading to inhibition of platelet aggregation. They include Clopidogrel (Plavix), Parasugrel (Effient), Ticagrelor (Brilinta) and Ticlopidine (Ticlid). Clopidogrel is widely used in acute coronary syndrome, post-coronary artery stenting, cerebrovascular accidents and peripheral vascular diseases. Parasugrel is used in acute coronary syndrome. It has rapid onset of action and more bleeding risk. Ticagrelor is used in acute coronary syndrome, post-myocardial infarction and post-coronary artery stenting. Ticlopidine is approved for the prevention of stroke when combined with aspirin, and also for the prevention of coronary artery thrombosis after coronary artery stenting. But because of its rare but serious side effect of neutropenia and thrombocytopenia, it is rarely used nowadays. These medications are thienopyridines which inhibit platelet aggregation by irreversibly binding to P2Y12 ADP receptors on platelets[4]. Clopidogrel, parasugrel and ticagrelor should be withheld for 5-7 d and ticlopidine for 10-14 d prior to any endoscopic procedures.

Phosphodiesterase inhibitors

Cilostazol (Pletal): It prevents platelets from sticking together to form clots and is a direct vasodilator. It reduces intermittent claudication in peripheral vascular diseases. Cilostazol should be withheld for 2 d prior to endoscopic procedures.

Dipyridamole: It inhibits phosphodiesterase and prevents adenosine reuptake into platelets, red blood cells and endothelial cells. As it prevents platelets aggregation, it is used to prevent clot formation after cardiac valve replacement, and also to prevent myocardial infarction and stroke. It should be withheld for 2 to 3 d before performing any endoscopic procedure.

Glycoprotein IIb/IIIa inhibitors
This group of medications blocks the receptor on the platelet for fibrinogen and von Willebrand factor and thus prevent cross-linking of platelets and platelet aggregation. They are intravenous drugs used in acute coronary syndrome and percutaneous coronary intervention. The 3 agents available in this group are tirofiban (Aggrastat) - a synthetic non-peptide with a plasma half-life of 1.5 to 2 h and 80% of platelet aggregation returns 4 h after stopping the medication, abciximab (ReoPro) - a murine-human chimeric antibody with a plasma half-life of 10 min and platelet function recovery over 48 h after discontinuing the medication, and Eptifibatide (Integrilin) - a synthetic peptide with a plasma half life of 2.5 h and 50% of platelet aggregation returns 4 h after stopping the medication[5]. Elective gastrointestinal procedures are not done while patients are on these medications. Urgent procedures should be on hold until recovery of platelet aggregation occurs.

PAR-1 inhibitor
Proteolytic activation of cell surface of PAR-1 by thrombin activates platelets. Selective inhibition of PAR-1 by Vorapaxar (Zontivity) leads to potent antiplatelet effect[6]. Vorapaxar has been approved as an adjunct to dual anti-platelet therapy to reduce myocardial infarction, cerebrovascular accidents, cardiovascular death and to use during revascularization procedures. It can cause moderate to severe bleeding including intracranial hemorrhage[7]. It is contraindicated in patients with transient ischemic attacks, stroke and intracerebral bleeding. Endoscopic procedures should be hold for about 2 wk as its duration of action is 5 to 13 d.
Anticoagulants
These include parenteral and oral agents. Parenteral agents include unfractionated heparin, low molecular heparin and fondaparinux. Oral agents include warfarin and novel oral anticoagulants (NOAC) which are oral direct factor Xa inhibitors and direct thrombin inhibitors.

Unfractionated heparin
Unfractionated heparin is an injectable blood thinner widely used in the prevention and treatment of deep venous thrombosis (DVT) and pulmonary embolism. It is also used in atrial fibrillation, acute coronary syndrome, indwelling peripheral or central venous catheters, hemodialysis/hemofiltration and extracorporeal membrane oxygenation (ECMO) circuit for extracorporeal life support. Heparin exerts its major anticoagulant effect by activating anti-thrombin III which inactivates thrombin and activated factor X (Factor Xa). Inactivation of thrombin inhibits formation of fibrin from fibrinogen and also inhibits thrombin-induced activation of platelets and factor V and VII[3]. The main side effect is bleeding. Other side effects include hyperkalemia, abnormal liver function test, heparin-induced thrombocytopenia (due to formation of IgG antibody against heparin-platelet factor 4 complex in the blood), osteoporosis and alopecia. The plasma half-life varies with the dose of heparin but is approximately 90 min. In case of intravenous administration of heparin, endoscopy should be held for 4 to 6 h and in case of subcutaneous administration of heparin, endoscopy should be held for 12 to 24 h after stopping heparin. The action of heparin can be reversed by protamine (1 mg of protamine can neutralize 100 units of heparin).

Low molecular weight heparins
Low molecular weight heparins (LMWH) are derived from fractionation of standard heparin so that each fragment is about one third the size of the original compound. As the number of long chains is reduced, there is less binding to thrombin. LMWH (containing majority of short chains) mainly works by inhibiting factor Xa without inactivating thrombin. Thus partial thromboplastin time (PTT), a measure of anti-thrombin activity of heparin can be reversed by protamine sulfate and rVIIa. The major side effect is bleeding. The duration of action of LMWH is 24 h, endoscopic procedure should be held for 12 to 24 h after stopping LMWH. The action of heparin can be reversed by protamine (1 mg of protamine can neutralize 100 units of heparin).

Fondaparinux (Arixtra)
Fondaparinux (Arixtra) is a specific inhibitor of factor Xa without any effect on thrombin or other clotting factors but it needs antithrombin III as a cofactor for inhibition of factor Xa. A fixed dose is given subcutaneously and does not require monitoring of PTT. It is used for the treatment of DVT with or without pulmonary embolism, and for the prevention of DVT in high-risk individuals who are immobilized or who have undergone abdominal or orthopedic surgery. As it has no affinity for PF-4 antigen, the chance of developing heparin-induced thrombocytopenia is very rare. Fondaparinux is eliminated mainly unchanged through the urine and the elimination half-life is 17 to 21 h. It should be discontinued 36 to 48 h prior to any high-risk endoscopic procedure. Fondaparinux activity can be reversed by protamine sulfate and rVIIa.

Warfarin
Warfarin is the most commonly used oral anticoagulant throughout the world. It is used in various clinical conditions like DVT, pulmonary embolism, atrial fibrillation, following cardiac valve replacement, following hip/knee surgery, to prevent stroke and myocardial infarction. It inhibits formation of vitamin K dependent clotting factors - II, VII, IX and X and natural anticoagulants Protein C and protein S by inhibiting C1 subunit of vitamin K epoxide reductase. The major side effect is bleeding. The duration of action of warfarin is 2 to 5 d. Endoscopy should be held for 5 d after stopping warfarin.

Oral direct factor Xa inhibitors
Oral direct factor Xa inhibitors are rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Savaysa). Factor X is activated by both extrinsic and intrinsic pathways. Unlike heparin and warfarin which inhibit multiple coagulation factors, they are specific for factor Xa. They have rapid onset of action (time to maximal effect: Rivaroxaban-2 to 4 h, Apixaban-1 to 3 h) with good oral bioavailability and they do not need any bridging therapy. Their plasma half-lives range from 8 to 15 h. They have both renal and fecal excretion. As a result they have less accumulation in the body in renal failure. Edoxaban should be stopped at least 24 h before any high-risk endoscopic procedure. Rivaroxaban and apixaban should be stopped 1 to 4 d, i.e., at least 2 half-lives before high-risk endoscopic procedures depending on the creatinine clearance. These medications are approved for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF), DVT and pulmonary embolism. In ENGAGE AF-TIMI 48 Trial[10], both high dose (60 mg/d) and low dose (30 mg/d) Edoxaban were found to be non-inferior to warfarin for the prevention of recurrent symptomatic thromboembolism. The annual rate of major gastrointestinal bleeding was higher with high dose Edoxaban than with warfarin (1.51% vs 1.23%) but lowest with low dose Edoxaban (0.82%). Although gastrointestinal bleeding risk (GIB) is similar in patients using warfarin and NOAC in the young and middle-aged
population, in the elderly (age > 75) population, there is increased risk of GIB in patients taking NOAC[11].

Direct thrombin inhibitors
Direct thrombin inhibitors are oral Dabigatran (Pradaxa) and subcutaneous Desirudin (Iprivask). Dabigatran is an oral anticoagulant which has been approved for: (1) the treatment of patients with DVT and pulmonary embolism (PE) after 5 to 10 d of parenteral anticoagulant; (2) the prevention of DVT and PE in patients who have been treated previously; and (3) the prevention of stroke and systemic embolism in patients with NVAF. Dabigatran was found to be non-inferior to warfarin in the treatment and prevention of DVT and PE but carried increased risk of bleeding[12] particularly gastrointestinal bleeding than the placebo group (5.3% vs 1.8%). Its anticoagulant activity can be assessed by Ecarin Clotting Time or dilute thrombin time. Dabigatran has a half life of 12-24 h. It should be stopped 2 to 6 d (i.e., at least for 4 half-lives) prior to high risk endoscopic procedures depending on the creatinine clearance. Desirudin has been approved for the prevention of DVT in patients after elective hip replacement surgery. As this medication is metabolized and excreted renally similar to Dabigatran, the dose is adjusted according to creatinine clearance. The anticoagulant activity can be monitored by aPTT. The terminal half-life is 2 h after subcutaneous administration. High-risk endoscopic procedures should be done 10 h after discontinuation of desirudin.

Thrombolytic agents
Thrombolytic agents are clot busters used in acute myocardial infarction, cerebral infarction and occasionally in massive pulmonary embolism. Thrombolytics have also been used as provocative agents to induce bleeding during endoscopic procedures, bleeding scan and angiogram to evaluate obscure gastrointestinal bleeding. The five thrombolytics currently available in the United States have different plasma half-lives: Streptokinase - 20 min, tissue plasminogen activator- 5 min, anistreplase - 2 h, retelase - 18 min and tenecteplase - 20 min. Five percent of patients on thrombolytics can have minor bleeding, 1% serious bleeding including intracranial hemorrhage. At the present time, there is no guideline about doing endoscopic procedures on patients who received thrombolytic therapy. In patients with acute myocardial infarction and overt upper gastrointestinal bleeding, upper endoscopy prior to cardiac catheterization has been advocated as platelet inhibition and anticoagulation are needed post percutaneous coronary intervention[14].

GUIDELINES
Before doing an elective endoscopic procedure for patients on blood thinners, we must evaluate whether the patient has high-risk or low-risk condition and whether it is a high-risk or low-risk endoscopic procedure.

Low-risk conditions
Low-risk conditions have low risk of thromboembolic events after temporary interruption of blood thinners (absolute risk less than 2 per 1000 patients). These include DVT, NVAF, biologic heart valve, mechanical heart valve in the aortic position[15].

High-risk conditions
High-risk conditions have high risk of thromboembolic events after temporary interruption of blood thinners (absolute risk more than 2 per 1000 patients). These include valvular atrial fibrillation (AF) or AF associated with other risk factors (prosthetic heart valve, congestive heart failure with ejection fraction of < 35%, history of thromboembolism, diabetes mellitus, hypertension or age > 75), coronary artery stenting - bare metal less than 1 mo, drug-eluting less than 12 mo, mechanical heart valve in the mitral position, mechanical heart valve in any position with history of thromboembolism, acute coronary artery syndrome, percutaneous coronary intervention without coronary artery stenting after myocardial infarction.

Low-risk procedures
In the absence of blood thinners, the risk of clinically significant bleeding is less than 1%[16]. These include diagnostic esophagogastroduodenoscopy, colonoscopy and flexible sigmoidoscopy with or without biopsy, Argon plasma coagulation, Barrett’s ablation, ERCP without sphincterotomy, EUS without FNA, push enteroscopy with or without biopsy, diagnostic balloon-assisted enteroscopy, capsule endoscopy and enteral stent placement without dilation (controversial).

High-risk procedures
The risk of clinically significant bleeding is more than 1% in the absence of blood thinners. These include polypectomy, treatment of varices, endoscopic hemostasis, percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, pneumatic balloon dilatation, pneumatic balloon dilatation for achalasia, endoscopic therapy of Zenker’s diverticulum, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic tumor ablation by any technique (esophagus, stomach, colon and rectum), therapeutic balloon-assisted enteroscopy (other than argon plasma coagulation), endoscopic sphincterotomy, ampullary resection, EUS with FNA, cystogastrostomy, cystoenterostomy, per-oral endoscopic myotomy[17].

Risk stratification
Aspirin and non-steroidal anti-inflammatory drugs are safe in both low-risk and high-risk procedures except EMR, ESD and ampullectomy.
**Low-risk endoscopic procedures irrespective of low-risk or high-risk condition**

If the patient is on antiplatelet agent or anticoagulant, it should be continued. In case of warfarin, the INR should be in therapeutic range. If the INR is supratherapeutic, warfarin dose should be adjusted to keep the INR in therapeutic range before doing the endoscopic procedure\[^18\]. The morning dose of NOAC should be missed on the day of the procedure.

**High-risk procedure but low-risk condition**

If the patient is on aspirin and clopidogrel, clopidogrel should be stopped 5 to 7 d prior to the procedure but aspirin should be continued. If the patient is on warfarin, it should be discontinued 5 d prior to the procedure. INR should be less than 1.5 prior to the procedure. Warfarin should be restarted after the procedure on the same day with the usual daily dose. Patient's INR should be rechecked one week after the procedure to make sure that the patient is getting enough anticoagulation.

NOAC should be discontinued 48 h prior to the procedure in patients with normal renal function. If the creatinine clearance is 30 to 50 mL/min, last dose of NOAC should be given 72 h prior to the procedure.

**High-risk procedure and high-risk condition**

If the patient is on aspirin and clopidogrel, clopidogrel should only be discontinued after discussion with the cardiologist taking care of the patient. Aspirin should be continued. As the risk of thromboembolism is always a concern, elective endoscopic procedure should be delayed. Clopidogrel should not be stopped in certain high-risk conditions such as within one month of placing of a bare metal coronary stent and within 12 mo of placing a drug-eluting coronary stent. After these periods, clopidogrel can be temporarily stopped 7 d prior to the endoscopic procedure and then can be restarted on the day after the procedure. If the patient is on warfarin, bridge therapy should be utilized. The risk of systemic thromboembolism must be taken into consideration against the risk of bleeding during bridge therapy.

Warfarin should be held 5 d prior to the procedure and LMWH should be started two days after discontinuing warfarin. On the night of the procedure, regular dose of warfarin should be started. LMWH should be started the following day and continued until therapeutic INR is achieved. NOAC are not used for high-risk conditions.

**Bleeding risk**

In patients with history of venous thromboembolism on warfarin, bridge therapy for invasive procedures was associated with increased risk of bleeding\[^19\].

**Thrombosis risk**

There is also increased risk of thrombosis in patients receiving LMWH for mechanical heart valve (Table 1).

**Emergency endoscopic procedures**

Frequently we encounter acute gastrointestinal bleeding in patients: (1) who are on antiplatelet or anticoagulant therapy for various reasons; (2) who had coronary artery stenting done recently; and (3) who have acute coronary syndrome (ACS): Unstable angina or acute myocardial infarction.

The risk of bleeding to death should be assessed against the risk of thromboembolism due to discontinuation of antiplatelet or anticoagulant therapy on an individual basis. Patients on antiplatelet therapy should be discussed with their cardiologists. In case of significant gastrointestinal bleeding, the antiplatelet agent should be stopped after discussing with the cardiologist, and platelet transfusion can be given. In case of baby aspirin induced peptic ulcer bleeding, aspirin should be continued and proton pump therapy should be started. As soon as endoscopic hemostasis is obtained, antiplatelet therapy should be resumed\[^20\].

The risk factors for GIB in patients on anticoagulant therapy are prior history of GIB, use of aspirin and supratherapeutic INR.

Anticoagulation therapy should be discontinued in patients with active gastrointestinal (GI) bleeding. If the patient is on warfarin and the bleeding is massive, rapid

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Table 1  Summary of recommendations for elective endoscopic procedure

| Low-risk conditions                                                                 | High-risk conditions                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Low-risk procedures**                                                              | **High-risk conditions**                                                               |
| Continue APA, warfarin and NOAC                                                    | Continue APA, warfarin and NOAC                                                      |
| Keep INR in therapeutic range in case of warfaran                                   | Keep INR in therapeutic range in case of warfaran                                     |
| Hold thienopyridines for 5 to 7 d before the procedure. Resume theonopyridine once hemostasis is obtained | Hold theonopyridines for 5 to 7 d before the procedure after discussion with the cardiologist. Resume theonopyridine once hemostasis is obtained |
| In case of dual APA, hold theonopyridines for 5 to 7 d before the procedure but continue aspirin | In case of dual APA, hold theonopyridines for 5 to 7 d before the procedure but continue aspirin |
| Hold warfarin 5 d before the procedure. Resume warfarin on the same day as the procedure | Delay endoscopic procedure if coronary artery stenting done and theonopyridines cannot be discontinued |
| Hold NOAC: Rivaroxaban 2 to 4 d, apixaban 2 to 4 d, edoxaban 1 d and dabigatran 2 to 6 d before the procedure depending on creatinine clearance. Resume NOAC when adequate hemostasis is obtained | If the patient is on warfarin, bridge therapy with LMWH |

APA: Antiplatelet agents; NOAC: Novel oral anticoagulants; LMWH: Low molecular weight heparins; INR: International normalized ratio.

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reversal of INR can be done with fresh frozen plasma (FFP), 4-factor prothrombin complex (PCC) containing factors II, VII, IX and X, or intravenous vitamin K. In case of mechanical heart valve and massive GI bleeding, FFP or PCC can be given but vitamin K should be avoided because of the risk of hypercoagulable state. Endoscopic therapy should be given in patients with active bleeding and INR < 2.5. In high-risk patients, heparin infusion should be started after endoscopic hemostasis. Hemodialysis should be done in case of dabigatran-induced massive GI bleeding.

Patients with active gastrointestinal bleeding with history of coronary artery stent placement - i.e., within one month of bare metal stenting and within one year of drug eluting stenting, should be discussed with the cardiologist. Clopidogrel should not be discontinued without permission from the cardiologist as there is high risk of coronary artery thrombosis and myocardial infarction. Discontinuation of clopidogrel should not exceed 5 d because of the risk of increased stent thrombosis.

Patients with ACS and GIB are unique group of patients who require close communication between the cardiologist and the gastroenterologist. This is a serious entity as ACS and GIB are independent risk factors for ischemic complications, higher morbidity and mortality. There are two distinct settings: (1) patients develop gastrointestinal bleeding first, then develop ACS. This group of patients have primary gastrointestinal lesions which have caused GIB. As GIB is the inciting event leading to ACS, endoscopic treatment would be more beneficial for this group of patients; and (2) patients develop ACS first, then develop gastrointestinal bleeding. This is the commoner entity as this group of patients receive antiplatelet and/or antithrombotic agents for their ACS, either treated conservatively or by PCI. One study showed 1.3% of patients developed GIB within 30 d of acute coronary syndrome; there was significantly increased incidence of stent thrombosis in the GIB group than non-GIB group (5.8% vs 2.4%). Predictors of post-ACS GIB were old age, female sex, smoking status, baseline anemia, diabetes mellitus, hypertension, heart failure, ST-segment elevation ≥ 1 mm, longer duration of blood thinner administration before angiogram. There was 8 fold increase in mortality when ACS patients developed GIB. Another study showed that patients with ACS who had also upper GIB had 30% mortality within 30 d of their ACS. Upper endoscopy can have procedural and anesthetic risk like hypotension, EKG changes, hypoxia and life threatening arrhythmia in the setting of ACS. One study done in a tertiary care center found upper endoscopy to be relatively safe in the diagnosis and management of upper GIB within 30 d of having myocardial infarction (Table 2).

**CONCLUSION**

Because a good number of blood thinners are available in the market, sound knowledge about these blood thinners is necessary. Anti-platelet agents, heparin and warfarin have been in our clinical practice for many years. NOAC introduced over the last few years are being increasingly used as they do not need Lab test monitoring like warfarin. Their onset of action is short and the duration of action depends on creatinine clearance. So serum creatinine and half-life of these medications should be considered in the perendoscopic period. Whether it is an elective case or an emergent case, an endoscopist should always evaluate high-risk and low-risk conditions and procedures, and bleeding and thrombotic risk. The main aim is success of the procedure maintaining safety of the patient.

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