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Pharmacological approach to iatrogenic bleeding during bronchoscopy: what do we know so far and where do we go from here?

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TO THE EDITOR:

Massive bleeding and mortality are exceedingly rare and occur mostly in therapeutic bronchoscopy.[1] In the diagnostic setting, endobronchial and especially transbronchial biopsies, as well as lung cryobiopsies, are the most problematic procedures.[1] Bleeding severity classification is crucial for management decisions.

Bleeding severity can be characterized according to the volume of fluid aspirated: it is usually accepted that bleeding < 50 mL is minor, bleeding of 50-100 mL is moderate, and bleeding > 100 mL is severe. Also, bleeding severity can be classified according to the intervention required to control the bleeding: moderate bleeding is defined as bleeding that requires wedging of the biopsied segment and/or endobronchial drug administration; and severe bleeding is defined as bleeding that requires additional interventions, such as temporary bronchial blocker placement or blood products administration. The latter proposal is less influenced by blood dilution with bronchial secretions and instilled products, and it is often considered easier and more reproducible.[2]

In a recently performed survey among respiratory specialists, nearly half of them were less than confident in managing acute bleeding and nearly all of them would be interested in further training.[3] Challenges in the management of iatrogenic hemorrhage are often related to insufficiently diverse clinical team training, since a systematic and multidisciplinary approach is required. In addition, availability of suitable resources such as rigid bronchoscopy, which can be safer and more efficient than flexible bronchoscopy, varies from institution to institution. Moreover, standardized recommendations are missing, including those regarding patients' hemorrhagic risk factors. Patients with uremia, thrombocytopenia, HIV/AIDS, solid organ transplant, hematological disorders, and severe pulmonary hypertension are reported to have an increased bleeding risk.[1,4] However, evidence is still lacking when several risk factors are present, and such evidence is crucial in an older population with a complex comorbid profile.[4] Regardless of careful evaluation for potential indicators of bleeding risk, about two thirds of patients with significant bleeding have normal coagulation and no identifiable risk factors.[2]

A lack of recommendations persists for drug discontinuation and pre-procedure management. Current data do not indicate a heightened risk of bleeding with the use of aspirin alone. For instance, Herth et al.[5] concluded that the use of this drug was not linked to increased probability of bleeding, and their proposal was to continue aspirin before bronchoscopy. Nonetheless, the absence of more data accentuates the need for careful decision making. Pathak et al.,[6] who summarized the literature, recommend discontinuing P2Y12-ADP receptor inhibitors 5-7 days before the procedure, discontinuing warfarin 5 days before the procedure, and monitoring the international normalized ratio. Some direct oral anticoagulants require to be discontinued for more than 48 h (Chart 1).[6] Larger studies are needed on several recent drugs, and there is a literature demand for validation of whether these practices are reliable.

Levels of systemic drug absorption through the endobronchial route remain mostly unevaluated. It is thought that more distal administration into the airway may lead to higher plasmatic absorption.

Endobronchial instillation of ice-cold saline is one of the oldest and most common practices. It can promote hemostasis by inducing vasoconstriction and by vascular tamponade. However, hypothermia may be paradoxically associated with an increased risk of bleeding, and there are no guidelines on recommended maximum safe doses.[7] After repeated instillation of 5-10 mL without a favorable outcome, other measures should be taken.

Some of the most relevant adrenoreceptors in the lungs are the beta2-adrenoreceptors, expressed on the airway smooth muscle whose activation causes bronchodilation, and the alpha1-adrenoreceptors, present on the small- and medium-sized pulmonary arteries whose stimulation leads to vasoconstriction. Examples of adrenergic drugs that selectively bind to alpha1-adrenoreceptors are phenylephrine and oxymetazoline. Adrenergic drugs can also be nonselective and bind to a combination of adrenergic receptors, such as adrenaline.[8] Vasoconstrictor drugs are widely employed, and, indeed, adrenaline has been the most extensively studied and widely used drug in this setting. However, adrenaline dosage and dilution vary widely in the literature, and adverse effects can arise with doses as low as 100 µg. The British Thoracic Society guidelines for bronchoscopy propose the instillation of 5-10 mL of adrenaline diluted to 1:10,000 (500-1,000 µg).[2] Life-threatening arrhythmia is one of the most troubling adverse effects, and it has been reported after the instillation of 5 mL of adrenaline diluted to 1:20,000 (200 µg).[1] Other side effects such as cerebral hemorrhage, hypertension, or myocardium ischemia may develop.[1] Adrenaline diluted in ice-cold saline is often used, mainly when potentially safer drugs are unavailable. Patient history should be carefully reviewed, and adrenaline

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Chart 1. Management of patients on anticoagulant therapy undergoing bronchoscopy.

Mechanism of action	Drug	Withhold time (prior to procedure)	Restart time (after procedure)	Reversal agent
Vitamin K-dependent antagonist	Warfarin[a]	Withhold drug 5 days prior to procedure, monitor INR	Restart drug 12-24 h after procedure	Vitamin K, four-factor PCC, three-factor PCC, or activated PCC
Direct thrombin inhibitor	Dabigatran	Withhold drug 1-2 days prior to procedure if CrCl ≥ 50 mL·min^{-1}; withhold drug 3-5 days prior to procedure if CrCl < 50 mL·min^{-1}	Restart drug 24 h after procedure if hemorrhagic risk is low; restart drug 48-72 h after procedure if hemorrhagic risk is high	Idarucizumab
Direct factor Xa inhibitor	Apixaban Edoxaban Rivaroxaban	Withhold drug 1-2 days prior to procedure; withhold apixaban 3 days prior to procedure if hemorrhagic risk is high	Restart drug 24 h after procedure if hemorrhagic risk is low; restart drug 48-72 h after procedure if hemorrhagic risk is high	Three- or four-factor PCC or activated PCC
Parenteral anticoagulant agent	Unfractionated heparin	Withhold drug 4-6 h prior to procedure	Restart drug 24 h after procedure	Protamine sulfate
	Enoxaparin Dalteparin	Withhold drug 24 h prior to procedure		

INR: international normalized ratio; PCC: prothrombin complex concentrate; and CrCl: creatinine clearance. [a]If spontaneous INR > 1.4 and/or platelets < 25,000, high-hemorrhagic-risk procedures are contraindicated. According to patient thrombotic risk and procedure hemorrhagic risk, consider bridging with enoxaparin.

use should be considered accordingly. Phenylephrine 0.5% and xylometazoline 0.1% have been increasingly employed as vasoconstrictor drugs to treat the nasal mucosa, despite lacking formal validation. In our center, the authors adopted the use of xylometazoline 0.1% (3 drops in 5-10 mL of ice-cold saline; maximum of 6 drops in two administrations).

Another drug that has become increasingly widespread is tranexamic acid (TXA), a synthetic antifibrinolytic agent that is a reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin from binding to and stabilizing the fibrin matrix.[9] Some authors underline the risk of TXA causing thrombotic events, as described for the intravenous route.[7] However, the efficacy of TXA in controlling bleeding from mucosal tissue has led to its endobronchial use.[9] Non-standardized but upright results have been reported with endobronchial administration of 20 mL of diluted TXA (TXA 500 mg/5 mL in 15 mL of ice-cold saline) up to a maximum of 3 doses, with a 1.5-min period of observation for hemostasis between administrations.[9] Lack of formal validation also applies to aminocaproic acid. The suggestion of 2 ampules of aminocaproic acid (each ampule 2.5 g/10 mL) in 50 mL of ice-cold saline, 5-10 mL in each administration, is commonly found.[10]

When these therapeutic options have been exhausted and a major hemorrhage is present, the approach will be determined by several variables, including the procedural protocols of the working place. Resuscitation equipment and qualified clinical staff are imperative. Structured knowledge of the best approach when preventive measures fail is critical. In addition, standardization and pharmacological validation of endobronchial drug administration are key for favorable outcomes.

AUTHOR CONTRIBUTIONS

AA, VC, and LF: study conception and design. AA, VC, DN, LF, and PD: data acquisition, analysis, and interpretation. AA, VC, DN, and LF: drafting of the manuscript. PD: critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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