Reversal of Anticoagulants in Critical Care

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ABSTRACT

There has seen an increase in anticoagulant consumption worldwide over the past few decades. With this widespread utilization of anticoagulants, clinicians are increasingly likely to encounter situations where anticoagulants would need to be withheld. This includes emergency and elective procedures or surgeries as well as major or minor bleeding as a direct result of over anticoagulation or consequent to other intercurrent illnesses such as sepsis or trauma with multiorgan failure, where the anticoagulant may contribute to coagulation abnormalities. Clinicians are required to have a thorough understanding of the indications for anticoagulant prescription, drug interactions and monitoring, indications and options of reversal of anticoagulation and management of bleeding in the situations described above. Once the acute process is managed, the ongoing need and timing of reinitiation of anticoagulation is also crucial. This article provides an overview on the indications for reversal of anticoagulation, the agents used for reversal and the timing of reinitiation of anticoagulants.

Keywords: Anticoagulant, Critical care, Direct thrombin inhibitors, Protamine, Reversal, Vitamin K antagonists

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INTRODUCTION

The past decade has seen an increase in anticoagulant consumption worldwide. In the United States alone, over 6 million patients who are on anticoagulants are at risk of complications from the same.[1] The reason for this is twofold. First, with increasing longevity, we are seeing an increasing number of patients presenting with cardioembolic strokes, which contributes to about 15–30% of strokes. Atrial fibrillation is a major risk factor for the same.[2,3] This has resulted in the use of anticoagulants in an attempt to prevent thrombosis and thromboembolism (venous thromboembolism and ischemic strokes), globally reported to be the foremost cause of morbidity and mortality.[4] Second, given the convenience (lack of the need of regular monitoring), limited drug interactions and proven efficacy in thrombosis reduction, direct oral anticoagulants (DOAC) are increasingly being prescribed instead of warfarin.[1] The inability to adjust dosing to optimal "therapeutic effect" may limit the ability to monitor for bleeding risk due to over anticoagulation.

With this widespread utilization of anticoagulants, clinicians are increasingly likely to encounter patients with major bleeding events.[5] Several randomized controlled trials over the past decade comparing different DOAC agents with warfarin have reported major bleeding complications with both agents.[5] A meta-analysis has shown that DOACs "significantly reduced the risk of major bleeding [relative risk (RR) 0.72, $p < 0.01$], fatal bleeding (RR 0.53, $p < 0.01$), intracranial bleeding (RR 0.43, $p < 0.01$), clinically relevant non-major bleeding (RR 0.78, $p < 0.01$), and total bleeding (RR 0.76, $p < 0.01$)" when compared with warfarin.[5] It has also been found that intracranial hemorrhage (ICH) was associated with a 4-fold increased risk of mortality compared with extra cranial major bleeds.[6]

There is hence an increased responsibility for the clinician to optimize care of these patients through careful prescribing, understanding drug interactions and monitoring, whenever possible, for over anticoagulation. This article will focus on indications for reversal of anticoagulation, the agents used for reversal and the timing of reinitiation of anticoagulants.

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HOW IS ANTICOAGULATION REVERSED?

Reversal of anticoagulation is done with pharmacological agents and/or blood products. Whilst it may appear that the clinical situation mandates reversal, it is important to assess if the anticoagulant is the cause of the bleed and/or is exacerbating the bleed. Two dimensions help in this process, namely pharmacokinetic properties of the anticoagulant and laboratory abnormalities. For example, in a patient with an acute bleed, who was on heparin or warfarin, a normal activated partial thromboplastin time (aPTT) or prothrombin time (PT)/International Normalized ratio (INR) and a time lapse of 4–5 half-lives since the last dose, there may not be a need for complete anticoagulant reversal. In these settings, it must also be kept in mind that thrombocytopenia and thrombocytopathy (e.g. drugs like aspirin, clopidogrel and systemic disease like uremia) can contribute to bleeding.

In a bleeding patient, it is useful to assess the level of anticoagulant activity.[7] The traditional tests PT/INR and aPTT are recommended for monitoring adequacy of warfarin and heparin anticoagulation. These tests are however not helpful in the assessment of the level of anticoagulation of newer anticoagulants (direct thrombin inhibitors (DTIs) and factor Xa inhibitors). Whilst DTIs and factor Xa inhibitors can prolong aPTT and PT respectively, normal results cannot be used to establish lack of anticoagulant activity. If adequacy of anticoagulation needs to be assessed, dilute thrombin time and anti-Xa levels (calibrated with the drug of interest) respectively are recommended. Routine monitoring

Table 1: Summary of anticoagulants and the agents used for reversal in major bleeding

Anticoagulant	Tests to pick up excess AC effect	Reversal agent and dose	Prothrombin Complex Concentrate	Role for Factor VIIa	Role for FFP
Vitamin K antagonists	PT/INR	PCC with simultaneous administration of Intravenous vitamin K 10 mg in 25–50 ml NS over 15–30 minutes	4 factor-PCC (4F-PCC) preferred to 3 factor PCC* and FFP	Off-label use for refractory bleeding; weigh risks of thromboembolism	Indicated only if 4F PCC not available
Unfractionated heparin (UFH)	APTT	Protamine sulfate 1 mg for every 100 units of UFH used within 2 hours of the bleed (Maximum single dose 50 mg to be infused at 5 mg/min slowly over 10 minutes)		Off label use for refractory bleeding; weigh risks of thromboembolism	Can be given if bleeding persists despite protamine
Low-molecular weight heparin (LMWH)	Anti-Xa assay	1 mg protamine sulfate for every 100 anti-Xa units (enoxaparin, 100 anti-Xa units = 1mg) in the first 8 hours after LMWH; 0.5 mg protamine sulfate for every 100 anti-Xa units if bleed 8 hours after LMWH	Not recommended		
Direct thrombin inhibitors	Thrombin time APTT[†]	IV Idarucizumab (2 doses of 2.5 g) for dabigatran; Activated charcoal if within 2 hours; Dialysis if prolonged thrombin time despite idarucizumab or if idarucizumab not available. Other DTIs have short half-life, hence cessation of infusion is sufficient		Off-label use for refractory bleeding; weigh risks of thromboembolism	Not indicated[13]
Factor Xa inhibitors	Anti-Xa assay PT/INR[‡]	First line 4F PCC at 50 IU/kg or andexanet alfa 400 mg IV bolus over 15–30 minutes followed by continuous infusion of 4 mg/min for 120 min Both should not be given together	First line 4F PCC at 50 IU/kg	Off-label use for refractory bleeding; weigh risks of thromboembolism	Not indicated

AC, anticoagulant; PCC, prothrombin complex concentrate; INR, international normalized ratio; PT, prothrombin time; FFP, fresh frozen plasma; * Dosing as follows: INR 2–4: 25 IU/kg; INR 4–6: 35 IU/kg; INR >6: 50 IU/kg; INR to be checked 30 min after administration and every 4 hours-repeat dose can be given if necessary; [†]prolonged APTT indicates excess anticoagulation, however normal APTT does not exclude anticoagulant effect; [‡]prolonged PT/INR indicates excess anticoagulation, however normal PT/INR does not exclude anticoagulant effect

of anticoagulant effect of DTIs and Factor Xa inhibitors is not advocated.

INDICATIONS FOR ANTICOAGULATION REVERSAL

Broadly, anticoagulant reversal is indicated in three clinical settings namely, (a) prior to an elective surgical or invasive procedure, (b) acute bleeding (major or minor), and (c) prior to an emergency surgery or invasive procedure.

Major bleeding as defined by the Control of Anticoagulation Subcommittee refers to either bleeding with hemodynamic compromise and/or bleeding in a critical anatomic site (intracranial, pericardial, intraspinal, intraocular, retroperitoneal, intra-articular, or intramuscular with compartment syndrome) and/or an acute drop in hemoglobin by more than 2 g/dL or the requirement of more than 2 units of blood or massive transfusion.[8] While reversal is important in the situations described above, the risk of subsequent thromboembolic events due to reversal, ranging from 7.2–12% within 30 days from the event, should also be kept in mind.[9,10] Thus the decision on when and how to restart anticoagulation following an episode of acute bleed is also important.

ANTICOAGULATION REVERSAL IN SPECIFIC CLINICAL SETTINGS

Major Bleed

In major and life-threatening bleeds, all anticoagulants must be discontinued and reversal agents must be administered if available. This should not delay fluid and blood resuscitation and local measures to control the bleeding whilst ensuring normothermia, normal acid base status and ionised calcium. In critical site bleeding, it is also important to liaise with the appropriate specialist for definitive management. Restrictive blood transfusions targeting Hemoglobin >7 g/dL (>8 g/dL in patients with ischemic heart disease),[11,12] platelet transfusion to maintain platelet counts >50000/mm³ and cryoprecipitate to maintain fibrinogen >100 mg/dL[13] are advised. In patients with poor response to platelet transfusion or uremia, there may be a role in targeting a hemoglobin level 9–10 g/dL to optimize interaction between platelets and endothelium.[14] A summary of the recommended methods of anticoagulant reversal is provided in Table 1. Specific agents are discussed below.

Vitamin K Antagonists

Vitamin K restores the hepatic carboxylation of vitamin K dependent coagulation factors. It is recommended that 10 mg of vitamin K is administered as an intravenous infusion in 25–50 mL of normal saline over 15–30 minutes.[15] This can be given even before PT/INR results are available because the risks associated with vitamin K are low and alternate anticoagulation can be started if required. Intravenous Vitamin K has a more predictable and rapid reduction in INR as compared with oral or subcutaneous preparations. Since vitamin K does not immediately correct the coagulation, it is recommended that clotting factors are simultaneously replenished.

Prothrombin complex concentrate (PCC) is recommended in patients with serious bleeding and INR >2. Four-factor PCC (containing factors II, VII, IX and X) is preferred over 3-factor PCC

(containing factors II, IX and X) in view of the more successful INR reversal, with less adverse events.[16] Usual PCC dose ranges from 25 to 50 units/kg depending on patient weight and INR (INR 2–4: 25 U/kg; INR 4–6: 35 U/kg and INR >6: 50 U/kg).[13] INR must be rechecked half an hour following PCC administration and every 4 hours subsequently.

Fresh frozen plasma (FFP) (initial dose 15–30 mL/kg for rapid reversal) may be given if PCC is not available or during massive transfusions for severe bleeding. Since this amounts to a large amount of plasma for correction, 10–15 mL/kg plasma has been used in some studies.[13] Since FFP comes with the added risks of volume overload and transfusion reactions, with less adequate hemostasis and slower reduction of INR when compared with PCC,[17,18] this is not the preferred choice. While there is evidence to suggest that recombinant activated factor VII (rFVIIa) can rapidly correct supratherapeutic INR,[19] it is not recommended for warfarin-associated bleeding because it does not supply all the vitamin K-dependent factors, has a short half-life, is costly and there is some evidence (limited) of thromboembolic events following administration.[20]

Heparin

Protamine sulfate is licensed for reversal of unfractionated heparin (UFH). It works by preventing the interaction of heparin with antithrombin. This is given as a slow intravenous bolus at a dose calculated from the number of units of UFH received in the last 2 hours, with 1 mg protamine sulfate neutralizing approximately 80–100 units of UFH (maximum single dose 50 mg to be infused at 5 mg/min slowly over 10 minutes).[21] It is important to accurately calculate the protamine requirement, as protamine by itself is an anticoagulant. It is important to anticipate and manage complications of protamine infusion (hypotension, pulmonary hypertension and anaphylactic reactions especially in individuals with previous protamine exposure, fish allergies and following vasectomy).

Whilst protamine is less effective at reversing anti-Xa activity of low-molecular weight heparin (LMWH) it is still recommended for reversal given the absence of alternatives and the report of benefit from retrospective studies.[22] The 8th edition of the American College of Chest Physicians (ACCP) guidelines recommend 1 mg protamine sulfate for every 100 anti-Xa units (for enoxaparin, 100 anti-Xa units equate to approximately 1 mg) in the first 8 hours after LMWH administration.[23] A repeat dose of 0.5 mg protamine for every 100 units can be given if bleeding persists or if the bleeding occurs 8 hours after the last dose of LMWH.[23]

Direct Thrombin Inhibitors

Given the short half-lives of argatroban ($t_{1/2}$ 45 minutes) and bivalirudin ($t_{1/2}$ 25 minutes), reversal can be achieved by stopping the infusion. Idarucizumab (an antibody fragment which mimics the structure of thrombin and binds to dabigatran with high affinity), at a dose of two 2.5 g aliquots, is licensed for rapid reversal of dabigatran in life threatening bleeding or emergency surgery.[24] The RE-VERSE AD study[25] found a 100% laboratory reversal and cessation of clinical bleeding within 4 hours. This should not be given to patients if the thrombin time is normal. There was a 6% risk of thrombotic complications postreversal of dabigatran activity.[25] If idarucizumab is not available, PCC or FFP can be used in addition to supportive measures and drug cessation. Hemodialysis has also been suggested in patients with high drug activity since dabigatran has minimal protein binding.[26]

Factor Xa Inhibitors

This includes the direct Xa inhibitors (e.g. Apixaban, Edoxaban, Rivaroxaban) and indirect Xa inhibitors (e.g. fondaparinaux). There is no licensed reversal agent. In the case of severe bleeding or emergency surgery, andexanet alfa[27] (binds and sequesters direct factor Xa inhibitors), at a dose of 400 mg IV bolus over 15–30 minutes followed by continuous infusion of 4 mg/min for 120 mins OR 4-factor PCC at 50 U/kg, can be considered for reversal. *Both should not be combined together*. Based on the limited trials, 4F-PCC at 50 U/kg is suggested over 25 U/kg in view of better control of bleeding.[28] In case these agents are not available, FFP can be given in the emergency setting. Given the prothrombotic effect of andexanet alfa and the absence of relationship between decreased factor Xa levels and hemostasis, andexanet is still not licensed for use.

There is limited data on reversal of Fondaparinaux. Whilst it has been shown that Vitamin K is not useful, the decision to use prohemostatic agents like activated PCC or rFVIIa must be weighed against the risk of bleeding. Experimental drugs under investigation for reversal of DTIs, factor Xa inhibitors and LMWH include Ciraparantag[29,21] and FXa[116L].[30]

Non-major Bleeding

The approach is largely dependent on clinical judgment and balancing the risks versus benefit of anticoagulant reversal at this point. The decision on withholding one to two doses of the anticoagulant and reversal depends on the thromboembolic risk of the patient, the site of the bleed (whether it can be controlled by local measures or not) and the need for hospitalisation. If it is determined that the patient need not be hospitalised or a procedure needed, the American College of Cardiology (ACC) Expert guidelines recommend continuing the oral anticoagulant.[13] Specifically for warfarin, low dose (5–10 mg) intravenous vitamin K administration can be considered. There is limited data on partial reversal of other anticoagulants in this setting.

No Bleeding with Evidence of Deranged Bleeding Parameters

It is advised that a couple of doses of the anticoagulant are withheld. There is no role of blood products or reversal agents in this situation. However, if the INR is >10 and the patient does not have clinically significant bleeding, warfarin should be withheld and 2.5–5 mg of oral vitamin K should be administered. This should reduce INR within 24–48 hours.[31] If INR is between 4.5–10, the 2012 ACCP and the 2018 American Society of Haematology (ASH) guidelines[31,32] suggest not to use vitamin K in this setting. Warfarin should be withheld; oral vitamin K 1 – 2.5 mg can be considered in patients with a high risk of bleeding and low thromboembolic risk. There is however no evidence of benefit in a recent meta-analysis.[33]

Elective Surgery and the Indication for Bridging Anticoagulation

There is a lack of high quality evidence to guide ideal practice for this common but difficult problem. Broadly, anticoagulant interruption is recommended. In patients where the risk of thromboembolism is high (stroke or venous thromboembolism in the past 3 months, mechanical heart valves, CHA_2DS_2VASc score >6 or CHAD score 5–6) as opposed to the bleeding risk, the clinician needs to first assess whether the surgery is indicated at that point of time.[34] If indicated, it is recommended that the interruption of the anticoagulation be kept to the minimum duration. There may be a role for bridging

anticoagulation with heparin (either unfractionated heparin or LMWH) in such patients. This however is controversial given that the periprocedural bleeding: thrombosis risk is much higher with bridging anticoagulation (10:1 versus 5:1 without bridging).[35] Additionally, the actual rate of peri-procedural thromboembolism for unbridged anticoagulant interruptions has been documented to be as low as 0.53%.[35]

IVC filter insertion is recommended in patients requiring emergency surgery with recent (within a month) venous thromboembolism who are likely to have a high bleeding risk with bridging anticoagulation.

Systemic Illness in a Critically Ill Patient on Anticoagulants

In critically ill patients with sepsis, following trauma, massive blood loss and massive transfusion or transfusion related coagulopathy, it may be difficult to ascertain the contribution of the anticoagulant and the systematic problem. Routine investigations like PT, APTT and fibrinogen assay may not be useful in this situation. Viscoelastic tests, namely thromboelastogram (TEG) and rotational thromboelastometry (ROTEM) may help in deciphering the aetiology of bleed - whether it is related to coagulation factors, platelets or fibrinolysis.[36] ROTEM additionally offers 4 tracings: INTEM that tests the intrinsic pathway similar to APTT; EXTEM tests the extrinsic pathway similar to PT; FIBTEM demonstrates the contribution of fibrinogen on clot strength; APTEM can help in picking up hyperfibrinolysis. ROTEM also offers optional tests like HEPTEM that can help uncover coagulopathy unrelated to heparin (by eliminating the effect of heparin with heparinise) and ECATEM that tests anticoagulant activity of direct thrombin inhibitors. Both TEG and ROTEM also assess the contribution of platelets in clot formation, but to assess platelet function, a platelet function analysis should be used. Deciphering such information will help in precision management of coagulation in these critically ill patients.

REINITIATION OF ANTICOAGULANTS

There is recent evidence to suggest that anticoagulant resumption with either warfarin or direct oral anticoagulants following a bleeding event has a lower risk of ischemic stroke than anticoagulant cessation.[37] The decision to restart anticoagulants must be reassessed weighing the risks versus benefit of doing so.

In conditions with a low risk of thromboembolism, the ACC expert guidelines[13] suggests stopping the anticoagulant. These conditions include paroxysmal atrial fibrillation with a low CHA_2DS_2VASc score <1 or conditions which required anticoagulation temporarily.

In patients with high thrombotic risk (mechanical valve prosthesis -mitral or aortic valve+/–AF or prior stroke within 6 months; AF with high CHA_2DS_2VASc SCORE ≥6 or CHAD score 5–6 +/– stroke or TIA within 3 months; unprovoked or recurrent venous thromboembolism within 3 months +/–active cancer; prior thromboembolism with anticoagulant interruption; left heart thrombus; left ventricular assist device),[13] there is an ongoing indication for anticoagulation. The clinician must evaluate the net benefit of restarting the anticoagulant and weigh the risks of rebleed against the risk of thromboembolism.

The clinician must also address reversible factors (concomitant antiplatelet therapy, renal insufficiency and drug interactions) that could have exacerbated the bleed.

TIMING OF RESTARTING ANTICOAGULANTS

Following an episode of major bleeding in patients with high thromboembolic risk, early anticoagulant reinitiation is recommended once hemostasis is achieved.[13] It is important to choose the right anticoagulant for the patient adjusting for organ function and drug interactions. It is also important to correct reversible factors such as vitamin K deficiency.

For patients with high re-bleeding risk (intracranial hemorrhage, inadequate and suboptimal hemostasis, lack of bleeding source identification, spontaneous onset of bleed) and high thromboembolic risk, unfractionated heparin infusion can be started within 1–3 days due to its short half-life and an available reversal agent if the patient rebleeds. Decisions following an intracranial hemorrhage are more challenging and need to be individualized. Amyloid angiopathy causing lobar hemorrhage, microbleeds and spontaneous intracranial hemorrhage (ICH) have a higher risk of rebleeding. The risks of hemorrhage expansion are highest in the first hours and days after ICH, while the risks of thromboembolism and recurrent ICH accumulate over time. There is a lack of consensus in this setting and minimal data on the optimal time, with suggested times ranging from 4 to 7 days[38] to 10–30 weeks.[39] Most experts have concluded that anticoagulation can be restarted at 7–14 days.[40]

The timing of restarting anticoagulation following an emergency surgery with adequate hemostasis depends on the post procedural bleeding risk. For procedures with low bleeding risks, ACC recommends restarting anticoagulation 24 hours after the procedure.[13] If the bleeding risk is higher, anticoagulation can be delayed for 48–72 hours.[41]

CONCLUSION

Bleeding complications related to overanticoagulation and emergent and elective indications for cessation of anticoagulant therapy are not uncommon in intensive care practice. An algorithmic approach would enable these situations to be managed appropriately. This process is more defined for conventional anticoagulants such as heparin and warfarin. The approach to and management of patients on newer anticoagulants is more challenging given the lack of ease of assessment of degree of anticoagulation as well as limited agents for reversal. More work is needed in this area.

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