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Management of bleeding in patients on direct oral anticoagulants in Sri Lanka

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Abstract

Direct oral anticoagulants (DOACs) are being used increasingly in Sri Lanka. However, the specific antidotes for the reversal of DOACs are not currently available in Sri Lanka. Although DOACs have a predictable dose response they may cause bleeding, including major bleeds such as intra cranial and gastrointestinal bleeds. Most of the available algorithms providing guidance for management of bleeding in patients on DOACs contain laboratory tests and therapeutic agents that are not available in Sri Lanka. Therefore, it is timely to have an evidence-based guide for managing patients who develop bleeding while on a DOAC in Sri Lanka.

Key words: direct oral anticoagulants, warfarin, bleeding risk

Introduction

DOACs act by directly inhibiting coagulation serine proteases. They are more convenient to use, and at least as safe and effective as vitamin K antagonists (VKA)[1,2]. Although DOACs are yet to be registered in Sri Lanka, physicians increasingly encounter patients who are prescribed these medications. The most frequently encountered DOACs are the direct thrombin inhibitor dabigatran and direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban. DOACs are more convenient to use than VKA because they have a predictable dose response, therefore, do not require routine monitoring and have fewer food and drug interactions[3]. However, unlike warfarin, they are approved only for specific indications and are superior or at least as effective as VKA in stroke prevention in non-valvular atrial fibrillation (NVAF), treatment and prophylaxis of venous thrombo-embolism (VTE)[4-9]. The use of rivaroxaban in combination with anti-platelets is licensed for secondary prevention of acute coronary syndrome (ACS) in the absence of atrial fibrillation (AF)[9]. Many clinical trials show DOACs are non-inferior to VKA and low molecular weight heparin (LMWH) in prophylaxis and treatment of cancer associated VTE[10-11].

When bleeding risk is considered, DOACs have less risk of intra cranial haemorrhage (ICH) than VKA but gastrointestinal (GI) bleeding risk is higher with rivaroxaban, dabigatran and edoxaban compared to warfarin[5-8]. DOACs may also cause major bleeds, most commonly GI followed by ICH[12]. Specific antidotes for DOACs such as idarucizumab for factor IIa inhibitors and adexanet alpha for factor Xa inhibitors have been approved for clinical use[2]. Controlling of bleeding associated with DOACs is challenging in Sri Lanka because of the unavailability of the specific antidotes and their prohibitive cost. A 100mg vial of Andexanet Alpha is about $2750 (a single dose is 400mg) and idarucizumab 5g kit is $3500 to 4200[13] (Table 1).

Monitoring of the anticoagulant effect of DOACs

Routine monitoring of anticoagulant effect is not recommended for patients on DOACs. Monitoring of drug levels are indicated in the following circumstances[1,14].

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Table 1. Characteristics of DOACs[2,4-8,13]

	Apixaban	*Edoxaban*	*Rivaroxaban*	*Dabigatran*
Target	Factor Xa	Factor Xa	Factor Xa	Factor IIa
Time to peak effect (hours)	1-3	1-2	2-4	1-3
Half-life (hours)	12	6 -10	5-9	12-17
Dosing regimen	Twice daily	Once daily	Once daily	Twice daily
Renal clearance (%)	25%	50%	33%	80%
Dosing in acute VTE treatment	10 mg BID for 7 days, then 5mg BID	60 mg OD after 5 days of parenteral anticoagulation	15 mg BID for 21 days, then 20 mg OD	150 mg BID after 5 days of parenteral anticoagulation
Prophylactic dose for VTE prevention	5 mg BID	60 mg OD	20 mg OD	150 mg BID

- Pre-operatively or prior to invasive procedures if drug has been taken within 24 hours
- If patient is bleeding
- Taken an overdose
- Renal impairment
- To establish the optimal dose in patients with extremes of body weight
- If the patient develops thrombosis while on treatment.

Quantitative assessment of drug levels using liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the gold standard to monitor drug levels[15]. However, due to the limited availability of LC-MS/MS, adaptations of more widely available coagulation tests are used to monitor coagulation activity of DOACs. Calibrated Xa assay for factor Xa inhibitors and modified diluted plasma thrombin time (dTT) or Ecarin clotting time (ECT) for factor IIa inhibitors are some of them. Qualitative tests such as prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) may give some indication of whether the anticoagulant effect is supra-therapeutic, therapeutic or sub-therapeutic. Dabigatran causes prolongation of APTT and TT and a normal TT indicates a very low level of dabigatran. Rivaroxiban and edoxaban cause prolongation of PT, but PT and APTT are usually insensitive to apixaban[1,15].

Management of bleeding in patients on DOACs

Management options depend on the type of anticoagulant, site and severity of bleeding. Initial non-pharmacological management is most important and is common to all types of anticoagulant associated bleeding. Specific pharmacological management depends on the type of DOAC and severity of bleeding[13,16].

1) Initial non-pharmacological measures[1,16].

- Stop the drug
- Document the time and dose of the last drug dose and other concomitant medications.
- Document presence of pre-existing renal or hepatic impairment and other comorbidities.
- Estimate the half-life (Table 1).
- Assess the source of bleeding.
- Request FBC, PT, APTT, TT, fibrinogen level, serum creatinine.
- If available, specific laboratory test to measure the anticoagulant effect of the drug: diluted TT for dabigatran and calibrated anti Xa assay for factor Xa inhibitors.
- Intravenous filuid resuscitation and red cell concentrate (RCC) transfusions to maintain haemodynamic stability.

- Mechanical compression to control bleeding. e.g. for superficial wounds, epistaxis.
- Endoscopic, radiological or surgical measures to control bleeding.

2) Adjunct treatment

Antifibrinolytics: Tranexamic acid and e-amino-caproic acid have not been specifically studied for their therapeutic effect in DOAC associated bleeding. They stabilize the clot by inhibiting fibrinolysis. Therefore, they can be considered in moderate to severe bleeding[1,17].

Desmopressin: Has not been specifically studied in DOACs associated bleeding. It increases the secretion of VWF from endothelial cells and increases plasma VWF and promotes haemostasis. Therefore, it can be considered in DOACs associated bleeding[1,17].

3) Specific treatment

3.1 Factor IIa inhibitors (Dabigatran)

If the patient presents within 2 hours of the last dose of dabigatran, activated charcoal is effective for prevention of further drug absorption. Dabigatran can be effectively cleared from plasma by haemodialysis, haemofiltration and charcoal haemoperfusion because of its low plasma protein binding ability[16].

Minor bleeds can effectively be managed with non-pharmacological measures. Major bleeds and minor bleeds not responding to non-pharmacological measures may need antidotes to reverse the effect of dabigatran[13,16]. Idarucizumab is the specific antidote for dabigatran. It is a humanized monoclonal anti-dabigatran antibody (dose 5mg IV). When idarucizumab is not available, the next option is activated prothrombin complex concentrate (aPCC) at a dose of 50 IU/Kg. Other available lesser effective options are recombinant factor VIIa (rFVIIa) and four factor or three factor PCC[2,13,16-19].

Idarucizumab is currently not available in Sri Lanka and aPCC is the available first option. If aPCC is not available rVIIa or 4 factor or 3 factor PCC can be used.

3.2 Factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban)

Minor bleeds can effectively be managed with non-pharmacological measures. Major bleeds and minor bleeds not responding to non-pharmacological methods need a reversal agent. Andexanet alpha is the specific antidote for factor Xa inhibitors, which is catalytically inactivated recombinant factor Xa. It binds and sequestrates factor Xa inhibitors. When andexanet alpha is not available the next option is four factor PCC. Other less effective options are rFVIIa, aPCC and fresh frozen plasma (FFP)[2,13,16-19].

In Sri Lanka the available first option is four factor PCC and if it's not available rFVIIa, aPCC or FFP can be used.

Peri-operative management of patients on DOACs

Treatment interruption is required prior surgery, usually 24-48 hours before surgery depending on renal function and the bleeding risk of surgery[20].

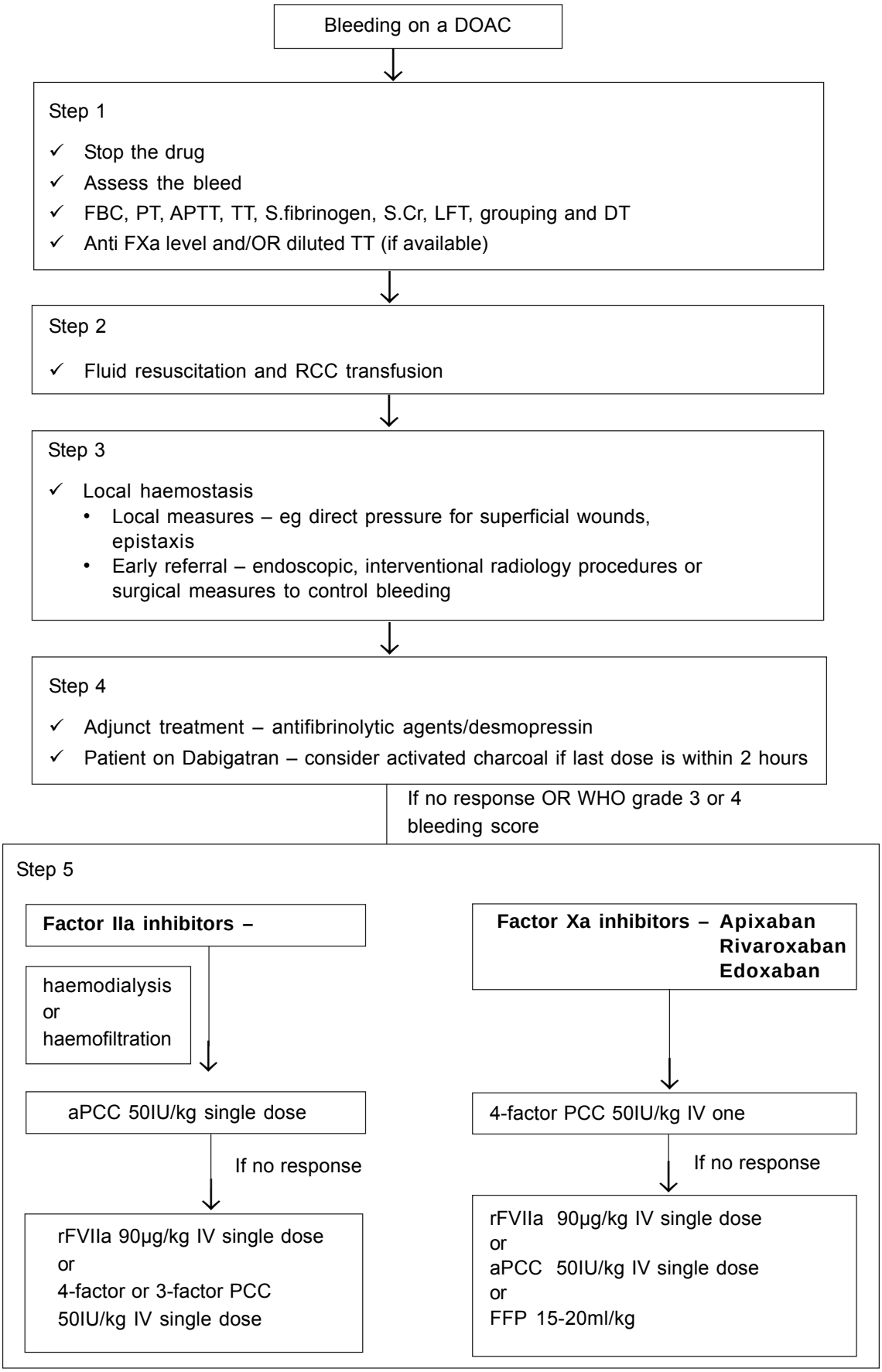
Table 2. Pre-operative interruption of DOACs

Drug	*Minor surgery*	*Major surgery*
Apixaban[1,18,19]	24 h	48 h
Edoxaban[1,18]	24 h	48 h
Rivaroxaban[18,19]	24 h	48 h
Dabigatran[1,18,19]		
CrCl >80 mL/min	24 h	48 h
CrCl 50-80 mL/min	36 h	72 h
CrCl 30-50 mL/min	48 h	96 h

If the patient needs an urgent invasive procedure or surgery it should be delayed for at least 12 hours after the last dose of DOAC, if possible. If it cannot be delayed, use of reversal agents is suggested. (refer step 5 of algorithm I).

DOACs can be restarted at a therapeutic dose 24 hours after "low bleeding risk" procedures and 48-72 hours after "high bleeding risk" procedures, if adequate haemostasis has been achieved. If the patient has high thromboembolic risk, starting a low dose of dabigatran (75mg bd), rivaroxaban (10mg bd), apixaban (2.5mg bd) or low molecular weight heparin (LMWH) 6-8 hours after surgery once haemostasis has been achieved can be considered[20,21].

Algorithm I – Treatment algorithm for bleeding in patients on DOACs in Sri Lanka



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