St George Renal Department – INTERNAL ONLY

HEPARIN PROTOCOL AND OTHER ANTI-COAGULANT MEDICATIONS ON HAEMODIALYIS

Summary

- Being on haemodialysis is a high risk for major bleeding including intracerebral bleeds.
- Patients on multiple anticoagulation medications are at even higher risk when they have renal failure
- Heparin and warfarin are anticoagulants that are not renally excreted and are thus useful anticoagulants for patients with renal failure.
- Multiple anticoagulants concurrently obviously increase bleeding risk and should be avoided unless absolutely necessary.
- Similarly anticoagulant plus one or more anti-platelet drugs also increase bleeding risk and should be avoided if clinically appropriate
- For patients with renal failure undergoing dialysis it is appropriate to reduce or withhold heparin doses with INR of 2-3 in patients taking warfarin (see "Considerations for pre-dialysis administration of Heparin" below).
- Anticoagulant should be used with caution or withheld in the presence of other bleeding risk factors:
    1. Thrombocytopenia (platelets < 50x109^/L);
    2. Severe/uncontrolled hypertension (see HTN management on HD Guideline);
    3. Intra-cranial haemorrhage / trauma/surgery/ tumour;
    4. Known acquired or congenital bleeding disorder/coagulopathy;
    5. Severe liver disease;
    6. Unstable patients with frequent falls.
- Heparin dose must be adjusted or may need to be withheld if INR at therapeutic level.
- Appropriate dosing and use of anticoagulants are recommended and where applicable should be checked with existing guidelines (see also Table 1.).

Background

Overlapping therapeutic INR (2 -3) and therapeutic heparin for a few days are usually safe in patients with normal renal function and are used frequently in management of deep vein thrombosis (DVT) and pulmonary embolus (PE). However in patients with renal failure undergoing dialysis it may be better to be cautious by reducing heparin doses with INR of 2 -3 in patients taking warfarin. According to Phelan et al 2011, there is already a high risk of major bleeding events in haemodialysis patients, irrespective of oral anticoagulants. However, when a patient is receiving more than one type of anticoagulant and/or antiplatelet drug, the risk of bleeding increases (Holden, Harman et al. 2008). Particular cautions should be observed for patients with uncontrolled or difficult to control hypertension. This protocol has been instigated as a result of adverse incidents involving patients who are on warfarin and heparin.

Purpose

It is presumed that administering heparin pre-dialysis to patients who are already on warfarin therapy can be a major risk factor for intracranial haemorrhage and other bleeding incidents. Therefore, this protocol outlines a list of factors to consider before administering heparin to patients who are currently on Warfarin therapy.

Considerations for pre-dialysis administration of Heparin

1. For patients with renal failure undergoing dialysis it is appropriate to reduce heparin doses with therapeutic INR of 2-3 in patients taking warfarin.
2. For patients receiving warfarin, standard oral anticoagulation with an INR between 2 and 3 it may be insufficient to prevent clotting during haemodialysis (*Anticoagulation Guidelines for Chronic and Acute Hemodialysis Patients, 2012*).
3. Give low dose heparin 500 load and 500 infusion per hour if INR is in either the therapeutic or sub-therapeutic level, considering normal therapeutic levels are between 2-3 unless otherwise indicated or if the patient is a known clotter.
4. Do not give heparin if patient is on clexane or fragmin and the INR is in therapeutic level.
5. Monitor INR weekly.

6. INR result should be acquired urgently and Registrar to be informed consequently to determine if there is a need to change warfarin dose.
7. Careful consideration should be given for those patients with uncontrolled hypertension (see protocol). In high risk patients this should be withheld.
8. For reversal of heparin in over-heparinised patients see ***protamine sulphate*** protocol.

Other considerations:

Warfarin, antiplatelet drugs and their interactions

Patients who are on warfarin therapy may sometimes be prescribed antiplatelet drugs like aspirin, thienopyridines (Ticlopidine and Clopidogrel), NSAIDS, COX -2 Inhibitors, dypiridamole, and/or IIb/IIIa receptor inhibitors (Abciximab, Eptifiban and Tirofiban) may also increase the risks of bleeding (Ho, 2002). Warfarin and heparin are both anticoagulant drugs; therefore heparin may also interact with antiplatelet dugs. Further formulation of guidelines regarding warfarin interaction with other drugs is advised.

Consideration of other factors affecting bleeding

This protocol is specifically attempting to target the use of heparin, warfarin and other anticoagulant drugs. There is no established evidence based literature focusing on anticoagulation use in dialysis and guidelines like these still do not guarantee that strict implementation of the protocol will prevent bleeding incidents in haemodialysis patients. In view of this fact the observation of outcomes (decreased bleeding rates, increased bleeding rates and/or dialyser clotting events) is highly advised. The results and experience of this guideline will help to identify the effectiveness of this protocol. Indications, dosing and targets of antiocogaulation are outlined in Table 1 (Fischer 2007).

Table 1. Anticoagulation during intermittent haemodialysis (Fischer 2007)

	Indication	**Dose**	**Comment**
***Unfractionated heparin* (*UFH*)**			
Standard heparin	Patient with normal bleeding risk	Initial loading: 50 IU/kg MD: 500 to 1500 IU/hr	Target ACT: 80% above baseline, depending on dialyzer used
Low heparin (with maintenance dose)	Patient with increased bleeding risk	Initial loading 10 to 25 IU/kg MD: 250 to 500 IU/hr	Target ACT: 40% above baseline in venous line
Very low heparin (without loading or maintenance dose)	Patient with very high bleeding risk or active bleeding	Rinse dialyzer with 5000 to 20,000 IU of heparin, flush system with 0.5 to 2 L of saline. Intermittently rinse with normal saline.	Target ACT: no change from baseline. Keep blood flow ≥250 mL/min
***Low-molecular-weight heparin* (*LMWH*)**			
	Improvement of lipids possibly: less osteoporosis, less pruritus, less hair loss, less blood transfusions compared with UFH		Monitoring requires measurement of anti-factor Xa-activity in venous line (aPTT and ACT are unreliable)
Dosing of selected drugs (according to the manufacturers' information)			
Dalteparin		*In patients with a low bleeding risk:* either 85 anti-Xa-IU/kg as bolus (HD up to 5 hr) or initial bolus 30 to 35 IU/kg; MD: 10 to 15 IU/kg/hr (target anti-Xa-level: ≥0.5 IU/mL) *In patient with a high bleeding risk:* initial bolus 5 to 10 IU/kg; MD: 4 to 5 IU/kg/hr (target anti-Xa-level: 0.2 to 0.3 max. 0.4 IU/mL)	
Enoxaparin		100 anti-Xa-IU/kg as single bolus (if clots are formed: repeat 50 to 100 anti-Xa-IU/kg)	
		In patients with a high bleeding risk: 50 anti-Xa-IU/kg	

	Indication	Dose	Comment
		with use of double lumen catheter 75 anti-Xa-IU/kg with use of single lumen catheter	
Nadroparin		*With a normal bleeding risk and dialysis up to 4 hr:* <50 kg, 2850 anti-Xa-IU as single bolus 50 to 69 kg, 3800 anti-Xa-IU as single bolus > 70 kg, 5700 anti-Xa-IU as single bolus	
Tinzaparin		4500 IU as single bolus into arterial line increase by 500 IU for next HD, if clots visible; decrease by 500 IU for next HD, if prolonged bleeding after HD at arterio-venous fistula Rinse system with 750U	
Heparinoid substance			
Danaparoid	In HIT type II	Bolus weight adjusted Before 1st HD Before 2nd HD Before 3rd and following HD treatments: measure anti-factor Xa-level; target in venous line: up to 0.5 to 0.8 IU/mL, adjust dose accordingly: anti-Xa<0.3: anti-Xa 0.3 to 0.35: anti-Xa>0.35	<55 kg 2500 IU 2000 IU 2000 IU 2000 IU 1500 IU >55 kg 3750 IU 3750 IU 3000 IU 2500 IU 2000 IU
Direct thrombin inhibitors			
Hirudin Lepirudin	In HIT type II	Dose applies to high-flux-dialyzer: 1st HD: bolus: 0.1 mg/kg; for subsequent HDs dose depends on aPTT before HD: bolus: 0.05 to 0.1 mg/kg	High risk of bleeding complications; no antidote available; target hirudin levels: 0.5 to 0.8 µg/mL target aPTT 50 to 75 s
Argatroban	In HIT type II	250 µg/kg loading dose before HD MD: 1.7 to 3.3 µg/kg × min (in normal liver function)	Target aPTT: 1.5 to 3 × mean of normal range
Citrate	In patients with high bleeding risk	3 mmol citrate/L blood flow (e.g., 50 mmol/hr at a blood flow of 250 mL/min) Ca^{2+}-infusion: blood flow into venous line	Target ACT: 200 to 250 s in venous line use no calcium and low sodium in dialysate adjust according to target >1 mmol/L ionized Ca^{2+} in arterial line

ACT=activated clotting time; aPTT=activated partial thromboplastin time; HIT=heparin-induced thrombocytopenia; MD=maintenance dose

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