

Anticoagulation In Haemodialysis

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Abstract: Anticoagulation in hemodialysis is targeted to prevent activation of coagulation cascade during the procedure. Adequate anticoagulation requires basic knowledge of principles of haemostasis and the pharmacotherapeutics of the various drugs available. Commonly used anticoagulant is unfractionated heparin, followed by low-molecular-weight heparin preparations. Danaparoid, lepirudin, and argatroban are currently being used for alternative anticoagulation, all of which have specific advantages and disadvantages. Strategies for avoiding exposure to heparin are applied for patients at bleeding risk, alternatives include regional citrate anticoagulation. The aim is to provide safe and effective dialysis.

INTRODUCTION

Anticoagulation is an important component of the dialysis prescription. Exposure of patients blood to tubing's, drip chambers, headers, potting compounds and dialysis membranes predisposes to blood clotting in the circuit. Thrombus formation in the extracorporeal circuit can cause occlusion & malfunction ultimately leading to discontinuation of therapy. If no anticoagulation is used 5-10% of dialysers may clot resulting in loss of approximately 100-150 ml of blood. Anticoagulation is targeted to prevent activation of the coagulation cascade during dialysis.

MECHANISMS OF CLOTTING

Clotting in the extracorporeal circuit occurs as a result of activation of platelets and coagulation cascade. Activation of leukocytes¹ and platelets² leads to release of lipid-rich blebs from leukocyte cell membrane and microparticles of platelet surface membrane. These particles are potent sources of tissue factor³ which through the tenase and pro-thrombinase complexes initiates the generation of thrombin⁴ resulting ultimately in fibrin formation. Fibrin along with activated platelets is deposited on the dialyzer capillary surface resulting in clot formation.

Interaction of plasma with the dialyser membrane is determined by the composition of the membrane, charge and surface area. Various factors like slow blood flow rate, high ultrafiltration rate, high haematocrit, access recirculation, intradialytic blood product transfusion etc also contribute to thrombogenesis. In the arterial and venous bubble traps slow blood flow / stasis, the interface of air and blood and turbulences in the bubble trap are known to activate the coagulation cascade.

HEPARIN

Heparin is the most commonly used anticoagulant as it is easy to administer, has a short half life and low cost. Unfractionated heparin (UFH) preparations constitute a mixture of anionic glucosaminoglycans of molecular size varying from 5-40 kDa. Heparin acts indirectly on the coagulation system by binding to antithrombin III ("heparin-binding factor I") and enhances its activity 1000 to 4000-fold. Antithrombin inactivates thrombin, factor Xa, and to a lesser extent factors IXa, XIa, and XIIa. At high doses, heparin also binds to "heparin-binding factor II" and inhibits the generation of thrombin.

UFH has a rapid onset of action (3-5 min), and a half-life between 0.5 h and 2.0 h in patients receiving dialysis. UFH is metabolized by hepatic and vascular endothelial heparinases, in a dose dependent manner. Half-life can be modified by nonspecific binding to the endothelium, leukocytes and plasma proteins.⁵ UFH is highly charged and therefore nonspecific

binding to plastic tubing and dialyzer membrane surfaces can occur altering its pharmacokinetics. As per the European best-practice guidelines heparin is infused an initial loading dose of 50 IU/kg into the arterial access needle. The maintenance dose of heparin is 500 to 1500 IU/hr, given via constant infusion into the arterial line.⁶ Alternatively, the maintenance dose can be given as repeated bolus injection. This maintenance infusion is stopped 30-60 min before the end of treatment to reduce bleeding times from fistula needle sites. Dosing of UFH can be monitored at the bedside aiming for an activated coagulation time (ACT) of 140-180 s (80% above baseline), or in the laboratory by targeting an activated partial thromboplastin time ratio (aPTTr) of 1.5-2.5.

Side effects of heparin are increased bleeding risk, worsening of osteoporosis, dyslipidemia, pruritus, hyperkalemia and thrombocytopenia. Bleeding caused by excessive heparin administration can be reversed with protamine, at a dose of 1 mg per 1,000 IU heparin. Rarely, heparin administration can cause profound hypotension, in cases of contamination with negatively charged molecules like chondroitin sulfate.

Within the first 2 to 3 days of heparin therapy, direct heparin-induced degranulation of platelets can result in a modest reduction in platelet count (<100,000/mL). This is categorized as HIT type I. Platelet count increases subsequently even though heparin use is continued. HIT type II which is an immune-mediated disease may present from 4 to 10 days after initiating heparin therapy. There is antibody formation against the complex of heparin and platelet factor 4 ("HIT antibodies"). If HIT is suspected, all heparin use has to be stopped, even before laboratory test results are available confirming the presence of antibodies. In HIT, platelet consumption owing to the disease process & presents as venous and arterial thromboembolism instead of bleeding complications.

Even in patients at high risk for bleeding complications, UFH still is the most frequently used agent for anticoagulation, although in modified regimen. In "low heparin" intermittent HD, the extracorporeal circuit is rinsed with 2500 to 5000 IU of heparin mixed in at least 2 L saline. A low-maintenance dose of heparin is used in order to maintain the systemic ACT no higher than 40% above baseline. If the bleeding risk is extremely high (e.g., in patients at risk for intracranial bleeding, pericarditis, recent surgery), maintenance heparin is completely avoided. In addition short treatment time of 2-3 hr, a high blood flow (>250 mL/min), repeated rinsing of the extracorporeal system with saline (25-150 mL every 15-30 min) is required. This protocol is frequently called "heparin-free dialysis." Alternative approaches include (a) administering a single bolus dose, and only giving an additional second small bolus (~50% original load) if a thrombus forms in the dialyzer or venous air detector, aiming for an activated coagulation time of 120 s (40% above baseline) and/or an aPTTr of 1.5-2.0.13 (b)

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omit the bolus dose, and simply administer an infusion of 15 IU/kg per h.⁷

LMWH

LMWHs are produced by chemical or enzymatic cleavage of UFH to smaller size, ~5 kDa. LMWHs contain the key pentasaccharide motif, but are not long enough to bind both ATIII and thrombin (factor IIa), and therefore various LMWHs have different actions in terms of their anti-IIa activity compared with blocking factor Xa activation. This is measured as the relative ratio of anti-Xa to anti-IIa activity. Advantages of LMWHs include higher bioavailability, less nonspecific binding to the endothelium, plasma proteins and platelets. LMWHs have a more rapid onset of action and cause less leukocyte and platelet activation^{8,9} and less fibrin deposition on dialyzer surfaces.¹⁰

Additional benefits of LMWH include improved lipid profile, reduced hyperkalemia, reduced risk of osteoporosis and lower incidence of heparin-induced thrombocytopenia type II. As LMWHs are predominantly cleared by the kidneys, half-lives are increased in patients receiving dialysis. For a 4 hour dialysis session a dose of 10000 – 15000 aXaICU is adequate with little or no prolongation of APTT. Bedside test for monitoring are not routinely available. In patients with hemorrhage attributable to LMWHs, a bolus of protamine might not be as effective in reversing bleeding as it is with UFH, particularly in patients given LMWHs that have a high anti-Xa to anti-IIa activity ratio. Factor VIIa concentrates might be required in patients who cannot be managed conservatively and do not respond to protamine. As LMWHs are derived from UFH, patients might develop allergic reactions and hypotensive reactions attributable to bradykinin production, particularly in cases of chondroitin sulfate contamination.

HEPARINOID

Danaparoid a heparinoid of low molecular weight (5.5 kDa), a mixture of 84% heparan sulfate, 12% dermatan sulfate and 4% chondroitin sulfate, is the recommended anticoagulant for patients with heparin-induced thrombocytopenia. It acts by binding to ATIII and heparin co-factor II. Danaparoid reduces the binding of platelet factor 4 (PF4) to platelets, and disrupts immune complexes that contain PF4, thus prevent activation of platelets by HIT antibodies.¹¹ It has low cross reactivity with HIT antibodies. Danaparoid has a prolonged half-life of ~30 h in patients receiving dialysis, therefore monitoring and adjustment of dose is based on the anti-Xa activity before the start of the subsequent dialysis session. In adult practice a single bolus is administered (3,750 IU, reduced to 2,500 IU in patients <55 kg) and then 2,500 IU is given before the subsequent dialysis (2,000 IU if <55 kg). Thereafter the dose is adjusted on the basis of the anti-Xa activity before dialysis, aiming for a value of <0.2 IU/ml and no visible signs of clotting in the circuit with an intradialytic anti-Xa activity of 0.4–0.6 IU/ml.¹² No antidote is available, and fresh frozen plasma or factor VIIa concentrate might be required. Fondaparinux is a synthetic pentasaccharide that binds to the key heparin binding site on ATIII & exerts high anti-Xa activity. Its major advantage is the lack of cross reactivity with HIT antibodies. Its half-life is markedly increased in patients receiving dialysis. Fondaparinux, and idraparinux are currently not approved for hemodialysis.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors bind to and block thrombin, the final key enzyme within the coagulation process. Lepirudin is a recombinant hirudin preparation approved for use in patients with HIT. Lepirudin is mainly eliminated by the kidneys and its half-life is markedly prolonged in renal failure making it difficult to use in patients with renal failure or on dialysis.^{13,14,15} Monitoring of therapy is frequently performed by measuring aPTT (target range 1.5–2.5 of normal). Disadvantages include absence of an antidote; factor VIIa or FFP may be required in patients in

whom bleeding occurs.

Argatroban is a potent thrombin inhibitor derived from arginine that reversibly binds to the catalytic site of thrombin. It is being approved as an alternative anticoagulant for HIT in the United States, Canada, and a number of European countries. It does not cross-react with HIT antibodies. In contrast to hirudin, argatroban is metabolized primarily by the liver, and its half-life is only moderately extended in patients with renal insufficiency.¹⁶ For hemodialysis, a combination of an initial bolus of 250 µg/kg with an infusion starting at 2 µg/kg per min, or 6–15 mg/h, and titrated to achieve an aPTT of 2.0–2.5. To prevent excessive bleeding from fistula needle sites, the infusion should be stopped 20–30 min before the end of the dialysis session. Substantially reduced doses are required for patients with liver disease.

REGIONAL ANTICOAGULATION

Regional heparinization can be used to prevent extracorporeal circuit thrombogenesis and minimising systemic anticoagulation, but it is labor-intensive and error prone.^{17,18} In this technique heparin is administered @ 500 to 750 U/hr into the arterial line (often with an initial 500-U bolus at the initiation of dialysis) and by the simultaneous administration of protamine into the venous line. ACT from the arterial and venous lines is monitored to maintain the ACT for the patient at baseline while the ACT in the dialysis circuit is prolonged 10 seconds or longer with adjustments of the heparin and protamine infusion rates accordingly. Additional protamine is infused at the end of dialysis to prevent a rebound bleeding risk.^{19,20}

A variant of regional anticoagulation includes the use of sodium citrate administered in the arterial line to bind calcium, an important co-factor in the coagulation cascade, with dialysate containing no calcium thus inhibiting coagulation of the circuit. Ability of the blood to clot adequately is restored by use of a calcium infusion administered via the venous line. Advantages of regional citrate anticoagulation are blood flow rates do not have to be high and less incidence of clotting. The disadvantages are need for two infusions and frequent testing for plasma ionized calcium levels. Increased plasma bicarbonate generation from sodium citrate is possible requiring caution. This technique is therefore not widely used for intermittent dialysis but is more popular in CRRT. An alternative approach has been to develop a dialysate with citrate replacing some of the acetate (Citrasate®; Advanced Renal Technologies, Bellevue, Washington, USA; containing 1.5 mmol/l calcium and 0.8 mmol/l citrate).²¹ This citrate-containing dialysate does not require additional calcium replacement, and by reducing dialyzer membrane fouling has been reported to improve dialyzer clearances.²² This type of dialysate can be used as part of a heparin free regimen.

FUTURE

Newer options include serine protease inhibitors like Gabexate mesilate, nafamostat mesilate which inhibit thrombin, factor Xa and factor XIIIa, but is not dependent on ATIII for these effects.²³ PGI₂, and its analog epoprostenol, are potent antiplatelet agents that block cyclic AMP. Advantages as compared to UFH include a reduced generation of platelet microthrombi during hemodialysis resulting in less membrane fouling and increased dialyzer efficiency.^{24,25,26,27} Other prostanoids, PGE₁ (alprostadil), PGE₂ and PGD also have antiplatelet effects and can be used as anticoagulants.

CONCLUSION

To conclude, in order to achieve adequate anticoagulation during the dialysis session without increasing the risk of systemic bleeding and to overcome situations of immune-mediated thrombocytopenia, a detailed knowledge and understanding of the mechanisms of coagulation & properties of the various agents available at our disposal is essential. Individualised

anticoagulation strategies are essential for adequate dialysis.

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LITERATURE REVIEW

Elevated Preoperative Phosphorus Levels Are an Independent Risk Factor for Cardiovascular Mortality.

Jan-Peter van Kuijk, Willem-Jan Flu, Michel Chonchol et al. *Am J Nephrol* 2010;32:163-168

Serum phosphorus levels have been associated with adverse long-term outcome in several populations, however, no prior studies evaluated short-term postoperative outcome. The present study evaluated the predictive value of phosphorus levels on 30-day outcome after vascular surgery. The study included patients scheduled for major vascular surgery (aortic aneurysm repair, lower extremity revascularization or carotid surgery), divided into four quartiles based on the preoperative fasting phosphorus level. The endpoints of the analyses were all-cause and cardiovascular mortality during the first 30 postoperative days and during long-term follow-up (median 3.6 years, interquartile range 1.8–8.0).

Prior to surgery, 1,798 patients were categorized into the following quartiles: <2.9 mg/dl (n = 459), 2.9–3.4 mg/dl (n = 456), 3.4–3.8 mg/dl (n = 444) and >3.8 mg/dl (n = 439), respectively. During the first 30 postoperative days, 81 (4.5%) patients died of which 66 (81%) secondary to a cardiovascular cause. In multivariate analyses, an independent association was observed between phosphorus level >3.8 mg/dl and all-cause (OR 2.53, 95% CI 1.2–5.4) or cardiovascular mortality (OR 2.37, 95% CI 1.1–5.7). Baseline serum phosphorus >3.8 mg/dl was also significantly associated with long-term all-cause mortality (HR 1.38, 95% CI 1.1–1.7).

Conclusions: Preoperative elevated serum phosphorus demonstrated an independent relationship with the occurrence of all-cause and cardiovascular mortality during the first 30 days after major vascular surgery. In addition, an elevated serum phosphorus was independently associated with long-term mortality. Use of these simple assessment tools and practice of these effective interventions by general medical and healthcare practitioners will go a long way in addressing the rising tobacco epidemic in India and making general healthcare more comprehensive.

LITERATURE REVIEW

Primary IgA nephropathy in north India: is it different?

Neha Mittal, Kusum Joshi, Swapnil Rane, Ritambhara Nada, Vinay Sakhujia; *Postgrad Med J* 2012;88:15-20

Immunoglobulin A (IgA) nephropathy is the most common glomerulonephritis worldwide, but has a variable geographic distribution. The bulk of the disease burden is borne by Asian countries. However, its exact prevalence or clinicopathologic spectrum in India is not well documented.

This cross sectional study analysed the renal biopsy findings and clinical features at presentation in 66 patients of primary IgA nephropathy diagnosed over a period of 2 years (2007–2008). The results were compared with studies from other centres in the country and elsewhere.

IgA nephropathy comprised 8.1% of all native kidney biopsies. The mean age of the patients was 29.9 years with a male:female ratio of 4.4:1. Most patients presented with renal failure and a significant percentage (23%) also had nephrotic range proteinuria. Renal biopsies were classified by the Haas classification and were further scored by the MEST scoring system of the Oxford classification. By Haas classification, 41 cases (62%) showed advanced sclerotic lesions of class V. Active crescents (cellular or fibrocellular) were seen in 42% of cases, and 26% of cases showed endocapillary proliferation. Serum creatinine values were highest in the presence of proliferative lesions. MEST scoring of the Oxford classification was not applicable in approximately 18% of cases because of the presence of advanced sclerotic lesions. On immunofluorescence, the majority of the cases showed both mesangial and membranous positivity for IgA antisera. Electron microscopy revealed para-mesangial location of immune complex deposition in the majority of the cases. It also showed glomerular basement membrane abnormalities in two cases.

Conclusion Comparison of clinical and pathological features revealed that this disease presents as an advanced disease in much younger individuals in this study compared to other studies. Elucidation of the underlying factors may have immense therapeutic implications.