Published in final edited form as:
Semin Dial. 2010 ; 23(5): 510–515. doi:10.1111/j.1525-139X.2010.00770.x.

Unfractionated Heparin for Hemodialysis: Still the Best Option

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Abstract

Unfractionated heparin (UFH) is the anticoagulant of choice for most maintenance hemodialysis units in the United States. Low molecular weight heparin (LMWH) is the norm in Western Europe, but is not approved for this indication in the United States. UFH is likely to remain the agent of choice in the United States because of its relative ease of use, safety, and low cost. Coating tubing and dialyzers with heparin is now possible, but systemic anticoagulation with heparin is usually still required. The additional cost of this innovation does not yet justify its use. Side effects of both UFH and LMWH include heparin-induced thrombocytopenia, hypertriglyceridemia, and hyperkalemia. It is uncertain whether osteoporosis is an important side effect, as vitamin D deficiency, secondary hyperparathyroidism, age, and debility are confounding factors. When UFH poses a risk or its use is contraindicated, e.g., after development of heparin-induced thrombocytopenia, the use of direct thrombin inhibitors, regional citrate anticoagulation, citrate dialysate, and heparin-free dialysis may be appropriate.

Anticoagulation techniques for hemodialysis in the United States rely almost exclusively on unfractionated heparin (UFH) and have changed little over the past several decades. During hemodialysis, the clotting cascade may be activated when blood components (e.g., proteins, platelets) contact dialysis tubing, the drip chamber, or the dialyzer. At one time, monitoring anticoagulation effect of heparin with the activated clotting time (ACT) was in vogue, but has fallen out of favor because of its relative complexity, difficulty with standardization, and the general acceptance that it added little to the safety of the anticoagulation procedure. Plasma anti-Xa activity can be used to assess the anticoagulation effect of either unfractionated heparin (UFH) or low molecular weight heparin (LMWH), but it is not a rapid turnaround test and is unsuitable for routine use in the dialysis unit.

Standard Heparin Anticoagulation

In practice, there is no "standard" dosing for heparin (Table 1). Rather there are several choices that can be tailored to meet individual patient needs. Usual options are bolus and continuous heparin or an initial bolus followed by subsequent intermittent boluses. Continuous therapy usually begins with a bolus followed by a continuous infusion that is carried to the end of therapy for patients with catheters, or discontinued one hour prior to completion in patients with grafts and fistulas in order to avoid prolonged bleeding. Alternatively, bolus therapy (25–30 IU/Kg) at the beginning of the dialysis procedure is followed by a lower dose every hour (500–2000 U), with the last dose given no later than one hour prior to completion. Many variations on this technique can be adopted by dialysis

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Conflicts of Interest
None declared.

personnel depending on whether the greater concern is dialyzer clotting or postdialysis bleeding from a fistula or graft. Heparin dose for bolus and infusion is empiric, but pharmacodynamic modeling can be used effectively to choose the initial heparin bolus and subsequent infusion rate (1). This technique was demonstrated to increase dialyzer reuse. However, this study also demonstrated that the control heparin group and modeled heparin group were not significantly different in calculated bolus and infusion doses, and there was considerable interpatient heparin dose variability. In the current dialysis era where economic incentives to reuse dialyzers have declined, minor dialyzer clotting is no longer an important issue.

Unfractionated Heparin Versus Low Molecular Weight Heparin for Dialysis

In the United States, LMWH is not approved for use in dialysis; in Western Europe, LMWH is the norm. The perceived advantages of UFH are a long history of safe use, low cost, and rapid dissipation of the anticoagulation effect at the end of the procedure. Continuous infusion of UFH at doses achieving 0.3–0.7 IU/ml of anti-Xa activity during the dialysis session had a first-order elimination half-life of 54 minutes (2). By 90 minutes postdialysis, anti-Xa activity fell to <0.1 IU/ml, a level where the risk of bleeding is low.

On the other hand, duration of the anticoagulation effect is prolonged following a bolus injection of LMWH enoxaparin with anti-Xa activity levels of 0.4 IU/ml 10 hours postdialysis, with a persistent elevation of >0.1 IU/ml at 24 hours (3). Purported benefits of LMWH for outpatient hemodialysis are reduced dialyzer clotting, reduced bleeding, reduced cost, and no requirement for routine clinical monitoring (4). Unlike UFH, however, there is no available antidote to reverse the anticoagulation effect of LMWH in the event of uncontrollable bleeding.

A survey of 54 intensive care units in 23 countries confirmed the overall safety of UFH in managing 1006 intensive care unit patients requiring continuous renal replacement therapy (CRRT) for acute kidney injury (5). This survey (B.E.S.T Kidney) noted that 33% of patients were treated without anticoagulation, 42.9% received UFH, 9% were managed with regional citrate, 6.1% nafamostat mesilate, and 4.4% received LMWH. Incidence of bleeding was higher with LMWH compared to UFH, 11.4% vs. 2.3%, $p < 0.0083$.

Heparin-Free Dialysis

For patients with a bleeding disorder, heparin-free dialysis is often required and poses little risk other than dialyzer clotting that occurs in approximately 5– 7% of cases (6–8). For patients with acute kidney injury and attendant bleeding risk, heparin-free CRRT is the choice for up to a third of patients (5). Frequent dialyzer clotting is the accepted downside result of this choice of therapy. This technique may be performed with or without periodic saline bolus flushes to wash fibrin strands into the drip chamber. However, at least in the case of patients undergoing dialysis with low-dose daltaparin, saline flushes do not prevent dialyzer clotting (9).

Citrate Dialysate

A dialysate using low-dose citric acid instead of acetic acid as the acidifying agent may allow a heparin-free or reduced heparin dose dialysis (10). An improvement in the efficiency of dialysis, as demonstrated by a significantly higher eKt/V urea, was an unanticipated side benefit and might be explained by less dialyzer clotting from the dual anticoagulation effects of Ca^{2+} chelation by citrate and heparin. The much higher cost of citrate dialysate currently makes this an unattractive option for regular use.

Anticoagulant Coating of Dialyzers

As an alternative to heparin-free dialysis, the extracorporeal circuit and dialyzer can be coated with either UFH or LMWH in a fashion similar to that in cardiopulmonary bypass. Anticoagulation effect appears to occur at extracorporeal surfaces with little of the heparin coat being released systemically. When compared with systemic anticoagulation with heparin, there is no difference in the formation of d-dimers or p-selectin release, measures of hypercoagulability and platelet activation, respectively (11). Lavaud et al. (12) successfully dialyzed nonuremic sheep and, later, 32 patients (2590 dialysis sessions) with heparin-flushed AN69 ST dialyzers whose negative surface charge was neutralized by a surface treatment (ST) with a layer of polyethyleneimine. In a 6-month patient study, heparin-flushed membranes permitted a 50% reduction in the standard UFH and LMHW doses. The feasibility of producing a 50% reduction in heparin dose with heparin-flushed AN69 ST membranes was shown again in a 6-month study comparing this technique to nonheparin-binding dialyzers subjected to full-heparin dosing (13). In a subgroup of 66 dialysis sessions using heparin-flushed AN69 ST dialyzers alone, without systemic anticoagulation with heparin, only one episode of massive clotting occurred, but patchy dialyzer clotting was noted in 17 instances (12).

However, this technique of heparin-flushed AN69 ST dialysis without systemic anticoagulation with heparin in high-risk patients was inferior to two forms of regional citrate anticoagulation (3 meq/l Ca^{2+} or 0 meq/l Ca^{2+} dialysate) using premature dialyzer clotting that terminated dialysis as the primary outcome (14); it occurred in 39%, 13%, and 0% ($p < 0.005$) of treatments, respectively. Concerns that hold back greater acceptance of heparin-coated dialyzers include additional technician time required to prime dialyzers with heparin and their failure to prevent clotting consistently without addition of at least low doses of heparin.

Other Anticoagulation Options

Direct thrombin inhibitors, primarily argatroban, are useful for patients with HIT, or where heparin is ineffective because of inherited or acquired antithrombin deficiency (15,16). Regional citrate dialysis is used primarily in the ICU setting for patients with short-term bleeding risks. Drawbacks included a more complex setup and the need for regular laboratory monitoring of ionized calcium during the procedure. Despite its increased complexity, it can be adopted for patients receiving long-term hemodialysis (17).

Adverse Effects of Heparin

Heparin-induced osteoporosis is a clinically important issue when it is used long term for the prevention of venous thrombosis and treatment of pulmonary embolism during pregnancy (18,19) (Table 2). LMWH appears to reduce or eliminate this complication (20,21). However, there are no convincing and unambiguous data that intermittent exposure to heparin during dialysis for end-stage renal disease (ESRD) leads to osteoporosis, as these patients are at risk for bone disease for many reasons including older age, diabetes mellitus, physical inactivity, vitamin D deficiency, and secondary hyperparathyroidism.

Hyperlipidemia

Heparin has been implicated in the dyslipidemia of ESRD. The dyslipidemia that characterizes patients on hemodialysis differs from that in the general population. The predominant abnormalities in these patients are hypertriglyceridemia and low HDL cholesterol (22); total cholesterol and LDL tend to be normal or reduced. Disappointing, but consistent with this lipid profile in hemodialysis patients, are two randomized controlled

trials in dialysis patient that failed to show a mortality benefit of statin therapy (23,24). The role of these abnormalities in causation of cardiovascular disease in chronic kidney disease is far from clear. It is possible that hypertriglyceridemia is an important abnormality favoring the development of atherosclerotic cardiovascular disease in this population (25–27). Hypertriglyceridemia is the likely result of both increased production and decreased clearance. Plasma triglycerides are cleared by lipoprotein lipase, an enzyme located in the endothelium; its activity is reduced in chronic renal failure as a consequence of uremia-induced endothelial dysfunction (28). Administration of heparin during dialysis, either unfractionated or LMWH, further aggravates this process by releasing and depleting stores of endothelium-bound lipoprotein lipase with a resultant rise in plasma triglycerides late in dialysis (29). Reports of a more favorable triglyceride profile in dialysis patients using LMWH are inconsistent, with some showing benefit (30), while others do not (29,31,32). It is unknown whether anticoagulation techniques that do not rely on heparin are capable of mitigating the hypertriglyceridemia seen in hemodialysis patients. This is a topic worthy of future study.

Hyperkalemia

Both unfractionated and low molecular weight heparin may cause a rise in serum potassium concentration. Hyperkalemia appears to be mediated by an effect of heparin on aldosterone involving several pathways including suppression of aldosterone synthesis by zona glomerulosa cells in adrenal cortex, reduction in number of aldosterone receptors on glomerulosa cells, and ultimately a reduction in zona glomerulosa cell number (33). While aldosterone's renal effects may be absent or minimal in dialysis patients, an extrarenal effect on potassium balance is likely. For patients on chronic hemodialysis, heparin use is intermittent and its effect on potassium balance is rarely of clinical significance. However, a suppressive effect on aldosterone can be demonstrated. In a 2- week crossover study involving 12 chronic hemodialysis patients, predialysis plasma potassium following 2 weeks of dialysis with unfractionated heparin was significantly higher than after LMWH, 5.7 ± 0.8 vs. 5.2 ± 0.7 mm, $p < 0.01$ (34). However, LMWH also alters potassium homeostasis. In 416 non-dialysis inpatients treated with LMWH, by day six, serum potassium had risen from 4.2 ± 0.5 to 4.5 ± 0.5 mmol/l, $p < 0.0001$ (35). Only 2.4% of patients developed hyperkalemia, i.e., a serum potassium concentration>5.5 mmol/l.

Thus, while the anticoagulant effect of unfractionated heparin is gone within a few hours and with LMWH within 10–15 hours, the effect of both on the potassium–aldosterone system is prolonged. Fortunately, clinically significant heparin-related hyperkalemia is rarely a problem for the regularly dialyzed patient; it could pose a problem for patients who are poorly adherent to the treatment schedule.

Allergic Reactions to Heparin

Immediate-type hypersensitivity reactions (Type I) may follow heparin administration and can be confused with generalized systemic reactions sometimes associated with the initiation of dialysis (36–38). The hypersensitivity that develops to standard heparin and cross-reactivity with low molecular weight heparin and to heparinoids can pose a serious clinical problem. Alternative anticoagulants like the recombinant direct thrombin inhibitor hirudin may be used, but instances of cross-reactivity with heparin may still occur (39).

Heparin-Induced Thrombocytopenia (HIT)

This topic is reviewed extensively in a recent publication that specifically targets kidney patients (40). HIT occurs in up to 10% of patients exposed to heparin and is characterized by increased clotting resulting from heparin- induced platelet activation. In a survey of 10,564

maintenance hemodialysis patients in the United Kingdom, the prevalence of HIT was 0.26 per 100 patients and only 17% of these had complications related to the disorder (41). Clotting may occur in both the arterial and venous circulations. The disorder is typically discovered 5–10 days following exposure to unfractionated heparin and is characterized by a modest drop in platelet count and variable occurrence of a clotting event, e.g., pulmonary embolism, venous thrombosis, limb artery thrombosis, mesenteric arterial occlusion, or skin necrosis at heparin injection sites. Venous thromboembolism predominates over arterial events in a 4:1 ratio (42). Arterial disorders, e.g., recent vascular surgery or extensive atherosclerosis, are factors that seem to predispose to arterial thrombosis. Venous limb gangrene is a particularly devastating complication of HIT that may occur when warfarin is substituted too early as the anticoagulant. This complication is thought to result from a disturbance in the balance between coagulation and anticoagulation factors in the blood; warfarin induces a reduction in protein C, a natural anticoagulant that appears to synergize with the hypercoagulable state produced by HIT. When severe, amputation of the extremity may be required.

The drop in platelet count is typically 30–50% below baseline and rarely reduced to the low levels seen with other drug-induced thrombocytopenias. Heparin-induced thrombocytopenia results from a platelet-activating IgG antibody directed at a platelet factor 4-heparin complex. When heparin is withdrawn, platelet counts typically recover to baseline within 2 weeks. The immediate clinical response for the physician is to remove all heparin from the patient's environment, including heparin locks in permanent vascular access devices and peripheral intravenous lines. LMWH should not be used as an alternative to treat HIT as cross-reactivity to heparin–platelet factor 4 may occur.

Anticoagulation alternatives are available for patients who develop HIT including direct thrombin inhibitors, regional citrate dialysis, and citrate dialysate (17,41). The primary disincentive for using most of these alternatives is the expense, and for regional citrate dialysis, additional setup and monitoring is required. Citrate dialysate, in which a small amount of citric acid is substituted for acetic acid as the acidifying agent, is placed in the A concentrate at the start of dialysis, but cost is as much as 20 times higher than standard concentrate and for this reason, it will likely be restricted to acute dialysis in ICU settings and for chronic hemodialysis patients with HIT. Golper (43) has suggested some innovations that might bring down the cost differential between standard and citrate dialysate, potentially allowing routine use of heparin-free dialysis in the chronic hemodialysis population. Successful rechallenge with UFH in hemodialysis patients after HIT antibodies have disappeared is reported, but caution is still advised in this situation (44).

Diagnosis of HIT

The diagnosis of HIT must combine clinical assessment with laboratory studies. Antiplatelet factor 4 immunoassays are very sensitive and when negative, rule out HIT with a high degree of confidence (45,46). However, the antiplatelet factor 4-heparin immunoassay may be positive in the absence of clinical HIT. For this reason, these tests should only be performed when clinical suspicion for disease is high. The 4T clinical scoring system developed by Warkentin (47) is a useful tool that enhances the predictive value of laboratory studies. The components of 4T scoring system include (i) the degree of thrombocytopenia, (ii) the timing of the fall in platelets, (iii) the occurrence of thrombosis or other sequelae, and (iv) lack of other causes for thrombocytopenia. A graded scale with 0–2 points given for each measure results in a scoring grade of 0–3 for low probability of HIT, 4–5 for intermediate probability, and 6–8 for high probability of HIT (46,47). A low-probability 4T score combined with negative immunoassay testing rules out the presence of HIT with near

100% accuracy (46,48). A low probability 4T score alone may approach this level of certitude.

Since making this diagnosis has significant clinical and economic consequences, it is prudent to insist upon the presence of a higher immunoassay titer, ≥1.2 O.D. units, than the usual cutoff value of ≥0.4 O.D. units used to define a positive test. The higher titer agrees well with the gold standard ^{14}C-serotonin release assay (40). More difficult to understand are reports of adverse consequences occurring in patients with antibodies to the platelet factor 4–heparin complex in the absence of HIT. In a group of unselected, asymptomatic hemodialysis patient without evidence of HIT receiving UFH anticoagulation, the presence of progressively more specific testing for antibodies to the platelet factor 4-heparin complex was associated in a multivariate model with a significant increase in risk of death over the span of the 2.5-year study (49). How these antibodies were related to mortality was unclear, but raised the question of whether another form of anticoagulation might lead to better survival.

In summary, UFH is likely to remain the anticoagulant of choice for hemodialysis patients in the United States. Its proven history of safe, flexible, and low cost use are its most attractive features. While interpatient dosing requirements can vary widely, for an otherwise stable patient, the dose is predictable over time. When these patients are at risk for bleeding (e.g., following surgery or a gastrointestinal bleeding episode) heparin-free dialysis can be used, accepting the likelihood that dialyzer clotting will be increased. Other alternatives to UFH include LMWH (not approved for dialysis use in the United States), heparin-coated dialyzers, direct thrombin inhibitors, regional citrate dialysis, and citrate dialysate. The last three modalities are useful in patients who develop heparin-induced thrombocytopenia where all contact with heparin or heparinoid products must be eliminated.

Acknowledgments

This work was supported by the University of Texas South-western Medical Center O'Brien Kidney Research Core Center (P30DK079328).

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TABLE 1

Anticoagulation options for hemodialysis

	Advantages	Disadvantages
Heparin (UFH)	Safety, rapid dissipation of anticoagulation effect, low cost	Short half-life requiring continuous infusion and/or repeated boluses, HIT
Low Molecular Weight Heparin (LMWH)	Single injection, monitoring not required	Long half-life, risk of bleeding 10–15 hours after procedure, no reversal antidote, HIT, cost, not approved for this use in United States
Heparin-coated dialyzer	No or reduced systemic heparinization (UFH or LMWH)	Increased setup time, increased dialyzer clotting, HIT, cost
Direct thrombin inhibitors argatroban	Rapid acting, hepatic metabolism, short elimination half-life, alternative to heparin in patient with HIT	Activated clotting time (ACT) monitoring required, cost
Regional citrate	Reduced risk of bleeding, alternative to heparin in patient with HIT	Procedural complexity, increased laboratory monitoring, primarily an inpatient procedure, cost
Citrate dialysate alone, or with low-dose heparin	Minimal systemic anticoagulation, reduced risk of bleeding, increased Kt/V, alternative to heparin in patient with HIT	Dialyzer clotting without small dose of systemic heparin, cost
Heparin free ± saline boluses	Reduced risk of bleeding	Dialyzer clotting with increased materials cost

TABLE 2

Adverse effects of heparin

	Comment
Osteoporosis	Proven for continuous use (e.g., DVT treatment in pregnancy) in non-CKD patient; unknown if intermittent use for hemodialysis aggravates the other causes of ESRD bone disease
Hyperlipidemia	Heparin (UFH and LMWH) releases and depletes endothelium-bound lipoprotein lipase causing hypertriglyceridemia
Aldosterone suppression	Promotesmodest interdialytic rise in serum potassium concentration, UFH > LMWH. Not a clinical issue for otherwise stable patient
Allergic reaction	Immediate hypersensitivity (Type I) to heparin can be confused with other systemic reactions (e.g., to dialyzer)
Heparin-induced thrombocytopenia (HIT)	Antibody-mediated (Type II) reaction leading to platelet activation with arterial and venous thrombosis