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Efficacy and safety of low-dose heparin in hemodialysis

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Abstract

Introduction: The dose of unfractionated heparin (UFH) administered during hemodialysis (HD) varies widely. This prospective study evaluated the safety and efficacy of UFH dose de-escalation.

Methods: Sixty-six prevalent patients on HD receiving UFH per standard-dose protocol (load dose [LD] 50–75 units/kg, maintenance dose [MD] 500–1000 units/hour) had heparin prescription converted to low-dose protocol (start LD 15 units/kg and MD 500 units/hour; dose adjusted in small increments based on assessments of extracorporeal blood circuit). Coagulation parameters, dialysis adequacy, dialyzer clotting, anemia management, and dialyzer reuse rates were compared based on the heparin protocol.

Findings: Mean(SD) UFH dose per HD session, before and after protocol conversion, was 6178(2644) and 2913(1116) units, respectively ($P < 0.0001$). This corresponded to LD 52.1(16.6) units/kg and MD 615(207) units/hour with standard-dose protocol, and LD 18.3(6.5) units/kg and MD 505(27) units/hour with low-dose protocol ($P < 0.0001$). Mid and postdialysis aPTT was 55.3(31.2) and 35.1(7.8) seconds before, and 37.3(12.9) and 31.5(5.3) seconds after conversion ($P = 0.007$ and 0.003, respectively); no significant changes in D-dimer levels occurred. Low-dose UFH was associated with a small increase in URR and spKt/V (73.0 and 1.54) compared with dialysis clearance on standard-dose UFH (71.2 and 1.48, respectively, $P = 0.02$). Weekly dose of ESA decreased by 2388 units postconversion ($P = 0.03$), while hemoglobin levels and the weekly dose of intravenous iron did not change ($P = 0.16$ and 0.78). A small rise in the rate of moderate dialyzer clotting at the end of HD was noted with low-dose UFH (5.7% vs. 7.5%, $P = 0.002$); the rate of severe dialyzer clotting events did not change ($P = 0.91$). No change in the dialyzer reuse rate was noted (18.5 vs. 17.0 treatments, $P = 0.26$).

Discussion: Low-dose heparinization did not compromise dialysis adequacy and permitted ESA dose reduction. Our findings suggest that in prevalent patients on HD, UFH dose of 15–20 units/kg loading and 500 units/hour maintenance was medically safe and effective.

Key words: Anemia, dialyzer, erythropoietin, hemodialysis, heparin

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INTRODUCTION

Systemic anticoagulation during hemodialysis (HD) reduces the risk of extracorporeal circuit clotting. Decades of medical experience with unfractionated heparin (UFH) and safety profile enhanced by its short half-life made UFH the most common anticoagulant employed for HD.[1] Little research has been done to delineate the lowest optimal dose of UFH for HD. Historically, UFH was recommended

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at a dose sufficient to achieve a rise in activated partial thromboplastin time (aPTT) or whole blood activated clotting time (ACT) of 1.5–2 times baseline values.[2–6] Over time, establishing UFH doses based on measurements of aPTT or ACT became impractical. Using artificial neural networks and nonlinear mixed effects modeling, two equations were proposed for UFH dose calculation: (a) Loading dose (IU) = $1600 + 10 \times (W - 76) - 300 \times Fd - 100 \times Fs$; and (b) Infusion Rate (IU/h) = 1750, where W is patient's weight in kg, Fd indicates the presence (Fd = 1) or absence (Fd = 0) of diabetes, and Fs denotes whether the patient is (Fs = 1) or is not (Fs = 0) a smoker.[7] Variable biological activity of UFH and nonspecific electrostatic binding of UFH to the endothelium, leukocytes, plasma proteins, dialyzer tubing, and capillary membrane surfaces in the extracorporeal circuit contributed to the failure of pharmacokinetic algorithms to predict UFH dosages and improve anticoagulation regimes.[8,9] As a result, most nephrologists and centers prescribe empirical doses of UFH. Loading boluses between 25 and 75 IU/kg are typically administered, followed by maintenance infusions of 500–1500 IU/hour stopped 30–60 minutes prior to cessation of HD. In other centers, two boluses of UFH are given: a larger dose at dialysis initiation, and a second smaller dose midway through HD treatment.

Given the broad range of UFH dosing, side effects and costs associated with heparin, along with a paucity of outcomes data, studies exploring the lowest dose of UFH that can safely be administered during HD are warranted. This study prospectively examined the effects of de-escalated UFH dose on HD adequacy, extracorporeal dialysis circuit thrombosis, anemia management, and dialyzer reuse rates in a cohort of prevalent dialysis patients with end-stage renal disease (ESRD) treated with a contemporary HD prescription.

MATERIALS AND METHODS

Patient selection

Prevalent patients receiving in-center HD at nine Wake Forest Outpatient Dialysis facilities in northwestern North Carolina were screened for participation. Eligibility criteria included age $\geq$18 years and receipt of standard-dose UFH. Patients were enrolled in the study between September 4, 2014 and October 30, 2015. Exclusion criteria included patients who were not receiving heparin, were already on a modified dose of UFH where conversion to low-dose heparin would have changed total heparin dose per HD session by <20%, were receiving warfarin, or had a history of frequent clotting of the extracorporeal circuit. The study was approved by the Wake Forest School of Medicine Institutional Review Board and written informed consent was obtained from each participant.

Heparin protocols

The study was performed in two stages. Initially, patients received UFH for HD according to standard WFOPD protocols or as prescribed by their nephrologist. At study initiation, two standard-dose heparin protocols were in use at WFOPD: high-dose heparin (load dose [LD] 75 units/kg, maintenance dose [MD] 800–1000 units/hour), and tight-dose heparin (LD 40 units/kg, MD 500–800 units/hour). In the second stage of the study, the heparin dose was converted to low-dose protocol (LD 15 units/kg, MD 500 units/hour). During the study, nursing staff contacted the principal investigator in the event of early signs of extracorporeal circuit clotting or noticeable drops in the dialyzer reuse rate. In these instances, UFH dose was titrated in small increments up to 25 units/kg LD and/or up to 800 units/hour MD.

Dialysis procedure

Patients received HD treatments 3–4 times per week using Asahi high-flux polysulfone-based hollow fiber gamma-ray sterilized (APS 21R, APS 18R, APS 15R) or Fresenius high-flux polysulfone-based hollow fiber electron beam sterilized (F200NR, F180NR) dialyzers. WFOPD standard procedures include priming dialysis circuits with 1 L of 0.9% saline solution prior to each HD session and using citric acid-based dialysate (Citrapure®; Rockwell Medical, Wixom, MI, USA). The HD prescription (blood and dialysate flow rates, dialyzer size, and type, ultrafiltration [UF] rate and treatment duration) were tailored by the patient's nephrologist to achieve target single pool urea Kt/V (spKt/V) and urea reduction rate (URR). Medications administered during dialysis (erythropoietin stimulating agents [ESA], intravenous iron, active vitamin D analogues) were dosed according to WFOPD treatment protocols or as ordered by the patient's nephrologist.

Measurements and data collection

An electronic database was used to gather information on age, sex, race, dialysis vintage, ESRD etiology, presence of diabetes mellitus, and prescription of antiplatelet medications (aspirin and clopidogrel) at study initiation. For each study stage, the type of HD vascular access (arteriovenous fistula [AVF], arteriovenous graft [AVG], and tunneled central venous catheter [TCVC]), dialysis prescription, and

laboratory data (average of the monthly spKt/V, URR, hemoglobin, ferritin, transferrin saturation, calcium, phosphorus, and intact parathyroid hormone [PTH]) were recorded. The average weekly ESA (epoetin or darbepoetin alfa) and average weekly intravenous iron doses (iron sucrose or sodium ferric gluconate) were calculated for each study stage. For uniformity, milligrams of darbepoetin were converted to units of epoetin using darbepoetin alfa mg: epoetin alfa unit ratio 1:250. Total red blood cell (RBC) transfusion events were recorded in each study stage. Coagulation parameters (activated partial thromboplastin time [aPTT] and D-dimer) were obtained in a subset of participants during each study stage using blood drawn from the extracorporeal arterial line pre-dialysis, mid-dialysis (120 minutes into the HD treatment), and postdialysis.

Dialyzer clotting assessment and reuse processing

WFOPD dialysis nurses record the condition of the dialyzer fibers, arterial header and venous header at the end of each HD session. Clotting at the completion of each treatment is rated as none (all fibers appear white and header surface clean), slight (<10% of fibers appear pink or red, and/or distinct red ring at the dialyzer wall), moderate (≥10% of fibers appear pink or red, and/or significant clots present on the surface), and severe (≥75% of fibers appear pink or red, and/or dialyzer completely covered with clots). The highest level of clotting that involved either the dialyzer fibers or the dialyzer headers were recorded for each HD session. All dialyzers were processed for reuse using the Renatron® PA 100 Series Dialyzer Reprocessing Station with Selectable Programs (for Standard, High Efficiency and High Flux Dialyzers) and 1% germicide solution. According to WFOPD protocol, dialyzers are rejected if they fail the volume or pressure tests, have a residual total cell volume <80% of original, have severe fiber clotting following dialysis (see below), or major clotting requiring interruption of the HD treatment, exhibit blood leakage, or are esthetically unacceptable.

Statistical analysis

Descriptive statistics, including means, standard deviations, and medians for continuous measures and frequencies and proportions for categorical data, were calculated. Since the same patients were evaluated before and after UFH dose conversion, each participant served as his/her own control. With this design, the tests were based on changes in primary and secondary outcomes over a period of 4 months in each study stage. The primary outcomes included dialysis adequacy (assessed as delivered URR and spKt/V) and the incidence of dialyzer clotting. Dialyzer clotting events (none, slight, moderate, or severe) were computed in each patient as the percentage of each type of clotting event considering the total number of HD sessions before and after heparin dose conversion. The average of the complete counts of dialyzer reuse per patient in each study stage was recorded. Secondary prespecified outcomes included anemia management and dialyzer reuse rate. To assess statistical significance, paired t-tests were used to assess the mean change in each outcome. The hypothesis is that the change is not different from 0 (no change); P values <0.05 were considered statistically significant.

Table 1 Baseline characteristics of study participants

Variable	N (%) or mean (SD), median
Age (years)	61.7 (13.3), 61.5
Sex (female)	25 (38%)
Race	
Black	44 (67%)
White	21 (32%)
Dialysis vintage (years)	4.4 (3.6), 3.5
Diabetes mellitus	31 (47%)
ESRD etiology	
Diabetic nephropathy	25 (38%)
Hypertension	19 (29%)
Other	22 (33%)
Medications	
Aspirin	28 (42%)
Clopidogrel	4 (6%)
Aspirin and Clopidogrel	4 (6%)

Data presented as number of patients (percentage) for categorical variables and mean (SD), median for continuous variables. ESRD = end-stage renal disease.

RESULTS

Patient and HD treatment characteristics

Sixty-six prevalent patients on HD were included in this study. Baseline demographic and clinical characteristics are shown in Table 1. Mean (SD) age was 61.7 (13.3) years, dialysis vintage 4.4 (3.6) years, 31 (47%) patients had diabetes, and 36 (55%) were taking antiplatelet medications (aspirin and/or clopidogrel). Dialysis treatment parameters before and after heparin dose conversion are displayed in Table 2; there were no significant differences

Table 2 Hemodialysis parameters before and after heparin dose conversion

Parameter	Before heparin dose conversion	After heparin dose conversion
HD frequency per week	3.0 (0.3)	3.0 (0.2)
HD duration per session, min	222 (25.2)	224 (23.3)
Total number of HD sessions, per study stage	55.2 (15.5)	51.0 (10.2)
Dialysis Access		
AVF	45 (68%)	51 (77%)
AVG	5 (8%)	7 (11%)
TCVC	16 (24%)	8 (12%)
Blood flow rate, mL/min	395 (56)	403 (50)
Dialysate flow rate, mL/min	673 (99)	701 (85)
Ultrafiltration rate, mL/kg/min	11.9 (4.3)	12.4 (4.4)

Data presented as number of patients (percentage) for categorical variables and mean (SD), median for continuous variables. HD = hemodialysis; AVF = arteriovenous fistula; AVG = arteriovenous graft; TCVC = tunneled central venous catheter.

in HD frequency and duration, blood flow rate, dialysate flow rate, and ultrafiltration rate. The distribution of vascular access used for HD at the beginning of each study stage is shown in Table 2; AVF was the main form of vascular access, used in 45 (68%) and 51 (77%) of patients before and after UFH protocol conversion, respectively.

Heparin dose

At the study enrollment, the UFH dose per HD session was LF 52.1 (16.6) units/kg and MD 615 (207) units/hour for MD (Table 3). At the time of heparin dose conversion, the initial LD was 15 units/kg and the initial MD was 500 units/hour. Within 3 weeks of conversion to low-dose UFH, early signs of extracorporeal circuit clotting were observed in two patients and there was a perceived decrease in dialyzer reuse rate in three other patients. For these patients, the LD was titrated to 25 units/kg and the MD was increased to 800 units/hour. No further signs of circuit clotting or appreciable reductions in dialyzer reuse were reported for the remainder of the study. At study completion, the UFH dose per HD session was LD 18.3 (6.5) units/kg and MD 505 (27) units/hour (Table 3).

Coagulation parameters

Coagulation parameters (aPTT and D-dimer) were measured in 33 participants 1 month before and 1 month after UFH dose conversion. A significant decrease in aPTT checked mid-dialysis (120 minutes into HD treatment) and postdialysis was noted with low-dose heparin (mid-dialysis aPTT before and after UFH dose conversion 55.3 [31.2] and 37.3 [12.9] seconds, respectively, $P = 0.007$; postdialysis aPTT before and after UFH dose conversion 35.1 [7.8] and 31.5 [5.3] seconds, respectively, $P = 0.003$). D-Dimer levels obtained pre and postdialysis did not change significantly between study stages ($P = 0.25$ and 0.10, respectively) (Table 4).

Table 3 Heparin dose and anemia management before and after heparin dose conversion

Medication, mean (SD)	Before heparin dose conversion	After heparin dose conversion	P value
UFH dose, per HD treatment			
LD, units/kg	52.1 (16.6)	18.3 (6.5)	<0.0001
LD, units	4492 (2156)	1605 (991)	<0.0001
MD, units/hour	615 (207)	505 (27)	<0.0001
MD, units	1688 (707)	1360 (221)	<0.0001
Total UFH dose (LD + MD), units	6178 (2644)	2913 (1116)	<0.0001
Anemia management, dose per week			
ESA, units	8953 (10169)	6565 (6584)	0.03
Intravenous iron, mg	121 (393)	51 (94)	0.16

UFH = unfractionated heparin; LD = load dose; MD = maintenance dose; ESA = erythropoietin stimulating agent. Dose conversion darbepoetin alfa mg: epoetin alfa units ratio 1:250.

Table 4 Coagulation parameters before and after heparin dose conversion

Parameter, mean (SD)		Before heparin dose conversion	After heparin dose conversion	P value
aPTT, sec	Pre-dialysis	31.1 (3.1)	30.4 (3.9)	0.15
	Mid-dialysis	55.3 (31.2)	37.3 (12.9)	0.007
	Post-dialysis	35.1 (7.8)	31.5 (5.3)	0.003
D-Dimer, mg/L	Pre-dialysis	1.98 (1.83)	2.36 (2.43)	0.25
	Post-dialysis	1.89 (1.70)	2.40 (2.56)	0.10

aPTT = activated partial thromboplastin time; Mid-HD = mid-dialysis aPPT collected 120 minutes into HD treatment.

Primary outcomes

Dialysis adequacy

Patients were observed for 55.2 (15.5) HD treatment sessions prior to UFH dose conversion and 51.0 (10.2) treatment sessions after UFH dose conversion. Markers of dialysis adequacy improved following conversion to low-dose heparin: URR before and after UFH dose conversion was 71.2 (6.7) and 73.0 (5.8), respectively (P = 0.02), and spKt/V was 1.48 (0.8) and 1.54 (0.26), respectively (P = 0.02) (Table 5). Small changes in total carbon dioxide and calcium levels were noted, while levels of serum potassium, phosphorus, and intact PTH levels did not change significantly (Table 5).

Dialyzer clotting

The rate of dialyzer clotting, calculated as percentage of each type of clotting event of the total number of HD sessions for each patient during each study stage, is presented in Table 6. At the end of each HD treatment, the dialyzer appeared to have evidence of moderate clotting more often with low-dose UFH protocol than with standard-dose UFH protocol (7.5% vs. 5.7%, P = 0.02). The frequency of slight and severe dialyzer clotting was not different between the low-dose and standard-dose UFH (P = 0.13 and 0.91, respectively). No abrupt HD treatment interruptions due to circuit clotting occurred in either study stage.

Secondary outcomes

Anemia management

Laboratory parameters pertaining to anemia management (ferritin, transferrin saturation, hemoglobin) were collected. Mean (SD) dose of ESA and intravenous iron administered weekly before and after UFH dose conversion were calculated and compared. Small changes in ferritin levels were noted (773 [336] ng/mL before and 865 [366] ng/mL after UFH dose conversion, P = 0.03), while levels of transferrin saturation and hemoglobin did not change significantly (Table 5). On average, the weekly dose of ESA decreased by 2388 units after heparin dose conversion (P = 0.03); no significant change was noted in the weekly dose of intravenous iron (P = 0.16) (Table 3). Two participants required RBC transfusion (total 2 units packed RBCs) in the first stage of the study before heparin conversion; no RBC transfusions were performed in the second stage of the study after heparin dose conversion.

Table 5 Laboratory parameters before and after heparin dose conversion

Parameter, mean (SD)	Before heparin dose conversion	After heparin dose conversion	P Value
URR	71.2 (6.7)	73.0 (5.8)	0.02
spKt/V	1.48 (0.8)	1.54 (0.26)	0.02
Potassium, mEq/L	4.6 (0.5)	4.5 (0.5)	0.13
Total CO2, mEq/L	24.3 (1.9)	23.7 (1.8)	0.008
Hemoglobin, g/dL	10.9 (1.0)	10.9 (0.9)	0.78
Ferritin, ng/mL	773 (336)	865 (366)	0.03
Transferrin saturation, %	31.1 (9.1)	30.7 (9.7)	0.72
Platelets, cells/mcL × 1000	206 (52.4)	210 (56)	0.42
Calcium, mg/dL	9.2 (0.7)	9.0 (0.6)	0.04
Phosphorus, mg/dL	5.4 (1.2)	5.2 (1.2)	0.08
Intact PTH, pg/mL	495 (317)	502 (324)	0.78

URR = urea reduction rate; spKt/V = single pool Kt/V; PTH = parathyroid hormone.

Table 6 Dialyzer clotting and reuse rates before and after heparin dose conversion

Outcome	Before heparin dose conversion	After heparin dose conversion	P value
Dialyzer clotting[a]			
No clotting	10.8%	10.5%	0.64
Slight clotting	82.4%	80.9%	0.13
Moderate clotting	5.7%	7.5%	0.002
Severe clotting	1.1%	1.1%	0.91
Dialyzer reuse[b]	18.5 (11.1)	17.0 (10.3)	0.26

[a]Outcome assessed as percentage of each type of clotting events out of total number of HD sessions per patient.
[b]Outcome assessed as complete count of dialyzer ruse per patient, mean (SD).

Dialyzer reuse

We calculated the mean (SD) highest count of dialyzer reuse per patient and compared between the two UFH dose protocols. During standard-dose UFH protocol, the highest dialyzer reuse count was 18.5 (11.1). Following conversion to low-dose UFH protocol, the highest dialyzer reuse count was 17.0 (10.3), P = 0.26 (Table 6).

DISCUSSION

In a contemporary cohort of prevalent patients on HD, 50% reductions (range 28%–75%) in UFH dose administered with HD did not compromise uremic solute clearance and enabled significant reductions in ESA dosage. These outcomes occurred in spite of an elevation in the frequency of moderate dialyzer clotting noted at the end of HD sessions. Other outcomes, including hemoglobin level, weekly dose of intravenous iron, and markers of bone-mineral metabolism did not change with low-dose UFH.

Heparin is widely used for anticoagulation during HD in the United States; however, scant data are available to optimize dosing. Due to marked inter and intrapatient variability in response to heparin, [10,11] pharmacodynamic models to determine individual heparin dose using serial measurement of coagulation times, computer software to solve complex equations, and computer-controlled heparin infusion pumps to achieve and maintain a desired ACT have been explored; their implementation proved to be time consuming and expensive.[2,4,12,13] Simpler methods of prescribing UFH, such as based on body weight alone, were proposed and adopted in clinical practice.[7,14,15] Still, marked differences exist in UFH dosing with HD between dialysis providers and nephrologists. Patients on chronic HD are exposed to UFH doses ranging from no heparin (in those at high risk of bleeding) to upward of 12,000 units per HD session. This equates to total annual doses of 250,000–1,500,000 units of UFH in a given patient. Besides the financial cost of UFH in HD, heparin is associated with potentially severe complications including gastrointestinal bleeding, cerebral hemorrhage, subdural hematoma, retroperitoneal hemorrhage, heparin induced thrombocytopenia, and rarely anaphylaxis.[14–16] Chronic heparin exposure can also cause osteoporosis, hypertriglyceridemia, and increases the risk of hyperkalemia. In addition, heparin administration has been associated with a reduction in tissue factor plasma levels and release of tissue factor pathway inhibitor.[17] This basic observation could signify risk for accelerated atherosclerosis and coronary artery calcification, because high tissue factor pathway inhibitor concentrations are independently associated with cardiovascular disease.[18–20]

Targeting a lower aPTT or ACT with UFH might confer similar dialysis efficacy at lower cost and with fewer heparin-related complications. A number of small studies examined reduced-dose UFH (LD 20 units/kg followed by MD 1000–1500 units/hour) to increase the ACT by 20%–50%; results suggested similar dialysis adequacy with unchanged rates of extracorporeal thrombosis using several different dialyzer membranes.[21–24] In addition, the procedure of HD has changed since these initial studies; a contemporary HD prescription includes high-flux dialyzers, high blood flow rates, low thrombogenicity extracorporeal tubing, and low thrombogenicity dialysate.[25] Leveraging recent technological advances in HD, the present study evaluated lower doses of UFH than previously assessed. Average UFH LD of 18.3 units/kg, followed by MD of 505 units/hour were administered. After conversion to low-dose UFH, dialysis adequacy parameters remained within the optimal range, without significant changes in the HD prescription. Although this finding might seem surprising given the increased frequency of moderate dialyzer clotting noted at the end of treatments, it is likely that the low-dose UFH used in this study was sufficient to confer adequate solute clearance with the modern-day HD treatments. Another important

finding in this study was that the weekly dose of ESA decreased by an average of 25% after the reduction in UFH dose; similar hemoglobin levels and intravenous iron dosing were present. This could relate to decreased bleeding from the vascular access at dialysis termination or decreased rates of occult bleeding from the gastrointestinal tract.

In our study, there was a small decline in dialyzer reuse rate that did not reach statistical significance. This result may not have achieved statistical significance due to the small sample and/or short follow-up. Previous studies detected a rise in dialyzer reuse rates following small increases in UFH dose.[12] Smith et al. developed a pharmacodynamics model for HD heparin dosing to predict the UFH dose that would yield a 150% rise in the intradialytic whole-blood ACT (compared to ACT pre-dialysis).[2,12] This model was applied by Ouseph et al. in 22 patients on chronic HD; the UFH LD was reduced from 2382 (628) to 2425 (908) units and the MD from 1398 (367) to 1393 (532) units/hour. This lead to an increase in dialyzer reuse rates (11 [8] to 18 [12] reuses, $P = 0.003$) and a small but significant decline in hematocrit (35.2% [2.6%] to 34.7% [1.8%], $P = 0.008$) over 3 months before and 3 months after UFH dose change.[12] In the present study, we observed a nonsignificant 10% reduction in the rate of dialyzer reuse. This result was not unexpected given the higher incidence of moderate dialyzer clotting seen with low doses of UFH. However, the effects seen on dialyzer clotting were not of clinical significance, given no episodes of dialysis treatment interruption, blood transfusion, or changes dialysis adequacy seen with low-dose UFH protocol. It is probable that "fine-tuning" of heparin doses exercised in this study after UFH dose conversion (see Methods) improved the outcomes and led to reduced dialyzer failure during reprocessing. UFH doses were each time slightly increased at the earliest sign of dialyzer header clotting or a trend toward potential reductions in dialyzer reuse. Preemptive dose adjustment is akin to usual UFH dose management in HD, based on visual inspection of the dialyzer header and venous air detector chamber for clots, bleeding, or other complications. This likely optimized dosing of UFH, avoiding significant reductions in dialyzer reuse while maintaining lower heparin dosing.

This study had some limitations. Despite being the largest contemporary analysis of the effects of low-dose heparin with HD to date, the study population size was relatively small. Although UFH dose reduction did not impair the clearance of small molecules, effects on middle molecule clearance were not evaluated. The study was not powered to evaluate clinical consequences of heparin dose reduction, including effects on gastrointestinal, and CNS bleeding; future larger prospective studies will be necessary to evaluate these and other important outcomes.

In conclusion, in this study, UFH dose de-escalation in prevalent patients on HD was accompanied by equivalent uremic solute clearance and modest ESA dose reduction. These results suggest that a medically safe and effective UFH dose prescription for HD is 15–20 units/kg loading followed by 500 units/hour; these doses can be titrated upwards at early signs of circuit clotting.

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