Heparin-free renal replacement therapy for chronic hemodialyzed patients at high risk for bleeding: a comparison of on-line predilution hemodiafiltration with conventional hemodialysis

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Abstract

Background: In chronic hemodialysis patients with high risk of bleeding, optimal anticoagulation of the extracorporeal circuit is challenging. Heparin-free hemodialysis (HD) with heparin-coated AN69ST dialyzer is now considered as a good option and recommended by experts. Predilutional hemodiafiltration (HDF) may represent also a feasible alternative but has been poorly investigated. In this study, our aim was to evaluate the performance of on-line automated predilution heparin-free HDF as compared to conventional heparin-free HD with a heparin-coated membrane.

Methods: We prospectively studied chronic hemodialysis patients at high risk of bleeding consecutively admitted to hospital who underwent heparin-free renal replacement therapy (RRT) in our nephrology department. During 1 year, we routinely used heparin-free HD and on-line HDF in these settings. By using a propensity score, we compared HDF to HD regarding to session failure and efficiency.

Results: One hundred and seventy-nine patients were included in the study. Clotting phenomena necessitating premature termination of RRT sessions were encountered in 19% of them. After propensity score matching, the comparison of 77 HD and 77 HDF sessions showed no significant differences in duration of the sessions and in dialyzer clotting. By multivariate analysis, a blood flow less than 250 mL/min and recent surgery were the only parameters associated with extracorporeal circuit thrombosis.

Conclusion: Heparin-free on-line predilutional HDF is a safe and effective technique for chronic hemodialysis patients with increased bleeding risk. The use of an automatic substitution volume that avoids filters hemoconcentration and of a blood flow above 250 mL/min strongly contribute to the observed performance. Further studies are, however, intended to confirm these results.

Key words: Bleeding risk, chronic hemodialysis, hemodiafiltration, heparin-free hemodiafiltration, heparin-free hemodialysis

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INTRODUCTION

During hemodialysis, the extracorporeal circuit (ECC) triggers clotting through activation of coagulation factors by blood-membrane contact and changes in the rheological conditions.[1] Though substantial improvements have been made in dialyzer membranes and ECC biocompatibility, effective anticoagulation is still required to prevent ECC clotting.[2,3] Hemodialysis patients are generally believed to have an elevated bleeding risk related to an acquired defect of primary hemostasis caused by platelet dysfunction and altered platelet-vessel wall interaction.[4] They have also numerous disease-related clotting abnormalities and concomitant therapies including antiplatelet agents, vitamin K antagonists which could increase the risk of bleeding. Moreover, several pathologies and circumstances such as post-surgical period that often occur during hospitalization amplify the risk of bleeding.[5] Thus, effective systemic anticoagulation during renal replacement therapy (RRT) may reduce clotting risk but may also increase bleeding risk whereas inadequate anticoagulation may result in circuit clotting.[6] To face this problem, several strategies were investigated including heparin-free RRT which remains the most recommended and used alternative in patients with high risk of bleeding.[2] Heparin-free hemodialysis (HD) is a safe and efficient strategy that was used for more than 25 years in patients with high bleeding risk.[7–11] Several dialysis procedures have been evaluated but they are non-standardized and none of them have shown full efficacy in controlled studies.[12,13] As a consequence, a coated-heparin membrane has been developed but showed equivocal results.[14,15] Hemodiafiltration (HDF) performed with a predilutional mode has also been proposed but again led to controversial results.[13,16] Yet, the best management of heparin-free RRT for chronic hemodialysis patients at risk of bleeding remains under scrutiny. Studies comparing different techniques and procedures in these settings are scarce.[13,17] At the best of our knowledge, the effect of predilution free-heparin HDF associated to an automatic controlled substitution has never been studied. We aimed therefore to assess in this study the usefulness of heparin-free automatic predilution HDF sessions as compared to HD sessions using coated-heparin dialyzers.

MATERIALS AND METHODS

The procedures were in accord with the committee on human experimentation of our institution. The institutional Review Board approved the study and waived the need for informed consent. This observational prospective study was carried out from May 2013 to May 2014 at the Nephrology Department of Montpellier University Hospital (France). Whenever admitted to the hospital, chronic hemodialysis patients underwent their RRT in the hemodialysis unit of this department in the exception of those requiring intensive care.

Patients, aged more than 18 years, on regular dialysis treatment for more than 3 months and hospitalized in our institution for an acute disease were eligible for inclusion in the study. All patients studied were on regular hemodialysis, mostly on ambulatory dialysis centers. Whenever an acute complication occurred or a surgical procedure need to be or was performed, the chronic hemodialyzed patient was hospitalized and RRT was underwent in our dialysis unit.

Those who underwent heparin-free RRT sessions that lasted at least 180 minutes were included. If an included patient underwent more than 1 heparin-free dialysis session during the study period, data of subsequent sessions were collected but solely the first heparin-free session was used for analysis and comparison. All the included patients have an a priori effective vascular access including a fistula or a double-lumen catheter. However, single-needle dialysis was possible for patients with difficult blood vessel access. According to the medical prescription, a patient could benefit from HDF and HD during his hospitalization. Patients receiving curative and oral anticoagulant treatments during the interdialytic period have been excluded. Bleeding risks were defined and classified into 4 different categories, modified from Lohr and Swartz[18]: (1) very high risk: active bleeding at time of dialysis; (2) high risk: active bleeding stopped for less than 3 days or surgery or trauma within the previous 3 days; preoperative dialysis (3) moderate risk: active bleeding stopped for more than 3 days but less than 7 days, surgery or trauma within the previous 3 to 7 days, uremic pericarditis or pleuritis; invasive procedure or intravascular intervention (4) low risk: greater than 7 days after active bleeding, surgery, trauma, ischemic stroke at risk of hemorrhagic transformation.

Heparin-free RRT procedure was used in hospitalized patients who had a contraindication to the use of systemic heparinization because of a bleeding risk or allergy to heparin. The procedure included no systemic heparin use at the beginning and during sessions. EEC priming was usually performed with heparinized fluid washed out by unheparinized fluid, or only with unheparinized fluid in case of severe heparin-induced thrombocytopenia. Blood transfusions were allowed during RRT sessions. We routinely used 2 dialysis modalities: standard HD procedure with a heparin-coated membrane or on-line predilution

HDF with a high-performance membrane associated with an automatic substitution fluid. HD and HDF sessions were performed using a Fresenius 5008 dialysis machine (Fresenius Medical Care, Bad Homburg, Germany) using an ultrapure bicarbonate dialysate. The prescribed blood flow was above 300 mL/min and the prescribed dialysate flow was set at 500 mL/min. The hemodialyzer was a 1.65 m^2 heparin-coated AN69ST dialyzer (Nephral 400ST [1.65m^2], Gambro Corporation AB, Lund, Sweden). At the beginning of each hemodialysis session, ECC was primed with 2 liters of saline containing 10.000 IU heparin as recommended. The hemodiafilter was a 1.8 m^2 Polysulfone hollow fibre dialyser (FX 800 [1.8m^2], Fresenius Medical Care, Bad Homburg, Germany). Infusate flow rate was automatized using the *Autosub* system (Fresenius Medical Care, Bad Homburg, Germany). *Autosub* technical advances allowed automatic prescription of substitution volume rate according to hematocrit and total protein values (blood viscosity). In *Autosub* mode, the HDF monitor will run automatically the session targeting to adjust substitution volume while keeping transmembrane pressure in a safe range.

Demographic data included age, gender, cause of chronic kidney disease, comorbidities, and Charlson score. Causes for admission to the hospital and indications of heparin-free RRT sessions were collected. Treatments administered to the patients during the interdialytic period were recorded, particularly antiplatelet agents and heparin dose if any. Biological data were collected before each RRT session. For each RRT session, we collected effective session duration and blood flow, venous pressure and its increase above 50% from baseline. RRT sessions efficacy was assessed by ionic dialysance (OCM system, Fresenius Medical Care, Bad Homburg, Germany).[19] For HDF sessions, dialyzed blood volume and substitution volume were also collected. Episodes of heparin-free RRT session failure, defined as ECC clotting or coagulated filter necessitating cessation of RRT and blood restitution to the patient, were recorded. Blood restitution was performed by the nurse in charge of the session who evaluated and classified its quality into: good, medium, or poor. Adverse events occurring during the following 2 days after the studied dialysis session were also recorded.

We compared the efficiency and the safety of 2 heparin-free RRT modalities, AN69ST coated-heparin membrane HD and Polysulfone membrane on-line predilution HDF, routinely used in our institution. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile ranges ($IQ_{25–75}$) and categorical values were expressed in absolute and relative frequencies. To minimize bias by indication, HD patients were matched to HDF patients according to their propensity score at baseline. The propensity score of receiving HDF was assessed using a multivariable logistic regression analysis with HDF treatment as the dependent variable. The a priori selected variables were age greater than 65 years; Charlson comorbidity index greater than 6; use of catheter as vascular access; single-needle dialysis; invasive procedure. Comparison between groups was made using unpaired t test or Wilcoxon-Mann-Whitney test for continuous variables according to the Gaussian distribution and chi-square or Fisher exact test for categorical variables. RRT failure assessed by elapsed session time was compared between groups using the Kaplan-Meier method (log-rank test). The propensity score for each patient (based on the probability of HDF initiation) was then included in univariate and multivariate logistic regression analysis of factors related to heparin-free session failure. We considered $P < 0.05$ as significant. SPSS version 18.0 (IBM Corp., Armonk, NY, USA) was used to perform statistics and Graphpad Prim version 5.00 (GraphPad Software, San Diego, CA, USA) to perform the figure.

RESULTS

Cohort characteristics

During the period of the study, 3165 RRT sessions were performed in 1089 chronic HD patients hospitalized for various reasons in different departments of the University Hospital of Montpellier. Among them, 179 subjects have received heparin-free RRT sessions (99 HD and 80 HDF sessions). The patients admitted in Intensive Care Unit have not been taken into account in the analysis. Main characteristics of the heparin-free HD population before matching are displayed in Table 1. Patients were mainly males (66%) with a mean age of 66 ± 14 years and exhibited a high comorbidity as reflected by the median Charlson index score: 7 [6–9]. Concomitant medications, contraindications to heparin use, hemorrhage risk, and biological variables measured before the first heparin-free RRT session of each patient are summarized in Table 1. Seventy-two patients (40.2%) were treated with aspirin or clopidogrel and 22 (12.3%) received a combination therapy of aspirin and clopidogrel. Sixty-five patients (36.3%) received subcutaneous heparin treatment for the prevention of thromboembolic events. The patients treated with oral anticoagulant were excluded. Ninety-seven patients (54.2%) displayed a moderate or low hemorrhage risk

Table 1 Characteristics of the population (n = 179 patients) before the propensity score-matched analysis

Age, years, mean ± ST	66 ± 14
Male sex, n (%)	119 (66)
Dry weight, Kg, moy ± SD	66.6 ± 16.7
Body mass index, kg/m^2, median [IQ$_{25–75}$]	22.7 [19.8–26.2]
Vascular access	
Arteriovenous fistula	109 (60.9)
Tunneled double lumen venous jugular catheter (Canaud)	66 (36.9)
Arteriovenous graft	4 (2.2)
Primary renal disease, n (%)	
Diabetic nephropathy	45 (25.1)
Vascular nephropathy	31 (17.3)
Glomerulonephritis	34 (19)
Polycystic kidney disease	13 (7.3)
ANCA vasculitis	11 (6.1)
Tubulo-interstitial nephritis	30 (16.8)
Unknown cause	15 (8.4)
Charlson comorbidity index, median [IQ$_{25–75}$]	7 [6–9]
Main comorbidities, n (%)	
Coronary heart disease	80 (44.7)
Heart failure	33 (18.4)
Peripheral artery disease	73 (40.8)
Diabetes mellitus	69 (38.5)
Cancer/hematologic malignancy	31 (17.3)
Hepatic disease	25 (14)
Stroke	23 (12.8)
Chronic obstructive pulmonary disease	28 (15.6)
Dementia	11 (6.1)
Duration of dialysis therapy, months, median [IQ$_{25–75}$]	41 [9–11]
Causes of hospitalization, n (%)	
Surgery	75 (50.3)
• Orthopedic	29 (16.2)
• Digestive	11 (6.1)
• Urological	11 (6.1)
• ENT	6 (3.4)
• Cardiac	8 (4.5)
• Vascular	6 (3.4)
• Other surgery: thoracic, neurological	4 (2.2)
Invasive procedure	56 (31.3)
• Biopsy	14 (7.8)
• Draining abscesses (percutaneous)	7 (3.9)
• Pacemaker or defibrillator placement	5 (2.8)
• Chronic dialysis catheter insertion	7 (3.9)
• Arteriography or arterial embolization	9 (5)
• Diagnostic coronary angiography	8 (3.9)
• Colonoscopy	4 (2.2)
• Transcatheter aortic valve insertion	2 (1.1)
Gastrointestinal bleeding, hematuria or hemoptysis	15 (8.4)
Trauma or hematoma without surgery	8 (4.5)
Ischemic or hemorrhagic stroke	10 (5.6)
Heparin-induced thrombocytopenia	3 (1.7)
Pericarditis or endocarditis	4 (2.2)
Miscellaneous	8 (4.5)
Hemorrhage risk according to Lohr and Schwab definition, n (%)	
Low risk	56 (31.3)
Moderate risk	41 (22.9)
High risk	66 (36.9)
Very high risk, active bleeding	16 (8.9)
Renal replacement therapy modality (first session)	
Conventional hemodialysis	99 (55.3)
Hemodiafiltration	80 (44.7)
Concomitant medications, n (%)	
Antiplatelet agents	94 (52.5)
• One antiplatelet therapy (aspirin or clopidogrel)	72 (40.2)
• Dual antiplatelet therapy (aspirin + clopidogrel)	22 (12.3)
Low dose of heparin (prevention of venous thrombosis)	65 (36.3)
Blood laboratory values before RRT sessions	
Hemoglobin, g/dL, mean ± SD	10.2 ± 1.7
Platelet, 10^9/L, median [IQ$_{25–75}$]	219.5 [162.5–273]
Prothrombin time, %, median [IQ$_{25–75}$]	90.5 [81–100]
Activated cephalin time, ratio, median [IQ$_{25–75}$]	1 [0.93–1.1]
C-reactive protein, mg/L, median [IQ$_{25–75}$]	31.6 [9.8–89]
Fibrinogen, g/L, mean ± SD	5.5 ± 1.5

One hundred and seventy-nine patients underwent at least 1 heparin free renal replacement therapy session in our dialysis department during the study duration. The patients were hospitalized in different surgical or medical departments of the hospital.

ENT = ear, nose, and throat; IQ = interquartile range; SD = standard deviation.

according to the Lohr and Schwab grading system. In only 15 patients (8.4%), heparin-free RRT was performed because of an active bleeding. Main reasons for avoiding systemic heparin during RRT were a perioperative management in 75 patients (50.3%) and for an invasive procedure in 56 patients (31.3%).

Characteristics of the heparin-free RRT sessions

Main characteristics of the 179 consecutives heparin-free RRT sessions are summarized in Table 2. Mean effective duration for RRT sessions was 206 ± 36 minutes with a mean time prescription of 216 ± 27 minutes. RRT was prematurely stopped in 41 sessions (22.9%): 27 (15.1%) for clotting prevention, 7 (3.9%) for massive ECC clotting, and 7 (3.9%) for other reasons than coagulation problems (poor tolerance or technical problem) (Table 2). Of note, ultrafiltration was performed in sequential mode in 6 RRT sessions (3 in each modality): ultrafiltration (1 hour) followed or preceded 3 hours of HD/HDF. A severe bleeding episode occurred in 2 patients, one after HD and the other after HDF. A blood transfusion support of 7 packed red blood cells was necessary in 4 patients within 48 hours after RRT session (2 HD sessions and 2 HDF sessions). One patient experienced a hemorrhagic shock caused by surgery of a femoral fracture and died 13 days after a preoperative heparin-free HD session.

Propensity score-matched analysis

After performing propensity score matching, 77 patients were matched in each group. Patient's characteristics are shown in Table 3. Patient's baseline characteristics and RRT parameters of the 2 groups were similar (Tables 3 and 4). As expected, the heparin priming dosage was higher in the HD group. Although the prescribed blood flow was different between HD and HDF sessions, the real blood flow was similar between the 2 modalities. It is noteworthy that blood and dialysate flows were above 300 mL/min and 500 mL/min, respectively, in both modalities. No differences were found in RRT duration, failure or efficiency. Instantaneous urea nitrogen blood clearance was higher in HDF but the difference was not statistically significant (Kt/V: 1.28 ± 0.3 versus 1.20 ± 0.31; P = 0.083). A similar rate of heparin-free RRT failure due to circuit and filter clotting was observed with both HD and HDF modalities. However, blood restitution was considered significantly better by the nurses after HD as compared to HDF sessions.

Table 2 Main characteristics of the 179 consecutives heparin-free renal replacement therapy sessions

RRT modality and dialyzer	
Conventional hemodialysis, polyacrylonitrile (AN69), Nephral 400 ST, n (%)	99 (55.3)
Hemodiafiltration, Polysulfone, FX 800, n (%)	80 (44.7)
Renal replacement therapy prescription	
Prescribed duration, min, mean ± SD	216 ± 27
Prescribed blood flow, mL/min, mean ± SD	366 ± 46
Prescribed dialysate flow, mL/min, mean ± SD	506 ± 48
Heparin priming, IU, mean ± SD	7709 ± 2662
Predilution on-line hemodiafiltration, *Autosub* (n = 80)	
Substitution volume, L/session, mean ±SD	33 ± 12.74
Substitution rate, mL/min, mean ± SD	160 ± 51
Duration of renal replacement therapy	
Effective, mean ± SD, min	206 ± 36
Prescribed duration, %, mean ± SD	95.5 ± 12.6
Session completed, n (%)	138 (77.1)
RRT characteristics, mean ± SD	
Real mean blood flow, mL/min	342 ± 63
Mean venous pressure, mmHg	181 ± 41
Ultrafiltration rate (except substitution), mL/min/kg, mean ± SD,	0.11 ± 0.072
RRT efficiency	
Treated blood volume, L, mean ± SD	66.7 ± 18.35
Kt/V, ionic dialysance (OCM), mean ± SD	1.23 ± 0.32
Weight gain, kg, median $IQ_{25–75}$	1.5 [0.6–2.4]
Intradialytic symptomatic hypotension, n (%)	20 (11.2)
Cessation of RRT, n (%)	
Other reasons than coagulation problems	7 (3.9)
To prevent ECC coagulation	27 (15.1)
Complete ECC coagulation, n (%)	7 (3.9)
Heparin-free RRT failure, n (%)	34 (19)
Restitution quality (n = 172), n (%)	
Good	18 (10.5)
Middling	80 (46.5)
Poor	59 (34.3)
Undocumented	15 (8.7)
Venous chamber coagulation (n = 172), n (%)	22 (12.8)
Intradialytic blood transfusion, n (%)	6 (3.3)

Heparin-free failure was defined as total ECC clotting or occlusion of dialyzer rendering dialysis impossible or premature restitution to prevent ECC clotting. Weight gain = dry weight − weight on the day of dialysis session.

ECC = extra corporeal circulation; IQ = interquartile; IU = international unit; OCM = Online Clearance Monitoring (Fresenius); RRT = renal replacement therapy; SD = standard deviation;

Table 3 Comparison by propensity score analysis of hemodialysis and predilutional hemodiafiltration: patients' characteristics

	HD, n = 77	HDF, n = 77	P
Characteristics			
Age, years, mean ± SD	68.7 ± 12.5	64.6 ± 14.7	0.06
Age > 65 years, n (%)	50 (64.9)	43 (55.8)	0.32
Male, n (%)	51 (66.2)	52 (67.5)	1
Duration of dialysis therapy, months, median [$IQ_{25–75}$]	44.6 [12–130]	50 [14–112.5]	0.72
Dry weight, kg, mean ± SD	66.8 ± 18	67.3 ± 16	0.6
Body mass index, kg/m^2, mean ± SD	23.4 ± 5.7	23.6 ± 4.9	0.56
Comorbidities			
Charlson comorbidity index	7 [6–9]	8 [5–9]	0.74
Coronary heart disease	36 (46.7)	39 (50.6)	0.75
Heart failure	15 (19.5)	17 (22.1)	0.84
Peripheral artery disease	28 (36.4)	38 (49.4)	0.14
Diabetes mellitus	30 (39)	28 (36.4)	0.87
Cancer/hematologic malignancy	13 (16.9)	14 (18.2)	1
Hepatic disease	13 (16.9)	11 (14.3)	0.82
Stroke	11 (14.3)	10 (13)	1
Chronic obstructive pulmonary disease	13 (16.9)	13 (16.9)	1
Dementia	7 (9.1)	4 (5.2)	0.53
Vascular access, n (%)			
Chronic catheter use	24 (31.2)	24 (31.2)	1
Arteriovenous fistula or venous graft	53 (68.8)	53 (68.8)	—
Causes of hospitalization, n (%)			
Surgery	37 (48)	32 (41.6)	0.52
Invasive procedure	18 (23.4)	24 (31.1)	0.37
Gastrointestinal bleeding, hematuria or hemoptysis	4 (5.2)	9 (11.7)	0.25
Trauma without surgery	2 (2.6)	4 (5.2)	0.68
Stroke	6 (7.8)	4 (5.2)	0.75
Endocarditis or pericarditis	1 (1.3)	1 (1.3)	1
Other	7 (9.1)	3 (3.9)	0.33
Concomitant medications, n (%)			
Antiplatelet agent	42 (54.5)	42 (54.5)	1
Preventive heparin dose	31 (40.3)	31 (40.3)	1
Blood laboratory values before RRT sessions, mean ± SD or median [$IQ_{25–75}$]			
Hemoglobin, g/dL	10.1 ± 1.7	10.3 ± 1.7	0.45
Platelet, $10^9/L$	209 [159.5–265.5]	221.5 [173–301]	0.23
Prothrombin time, %	89 [82–98.5]	91.2 [79–98.5]	0.98
Activated cephalin time, ratio	1.02 [0.93–1.12]	0.98 [0.93–1.11]	0.27
Activated cephalin time, s	28.9 [27–33.1]	28.5 [26.5–30.6]	0.30
C-reactive protein, mg/L	33 [8.4–87.6]	44 [10–107]	0.45
Fibrinogen, g/L	5.5 ± 1.4	5.5 ± 1.6	0.99

The following variables were used in the regression model to derive the propensity score for each patient: age greater than 65 years; Charlson comorbidity index greater than 6; use of catheter as vascular access; single-needle dialysis; admission for invasive procedure.
HD = hemodialysis; HDF = hemodiafiltration; SD = standard deviation.

We observed a similar rate of sessions without ECC clotting or without premature blood restitution along 240 minutes of treatment with HD and HDF as reflected by Kaplan-Meier curves (Log-rank, chi-square = 0.004812, P = 0.9447) (Figure 1). Dialyzer lifespan was similar with the 2 modalities. ECC survival reached 89.6% and 89.5% after 180 minutes of treatment, and 77.3% and 74.5% after 240 minutes of treatment with predilution HDF and HD, respectively.

We performed univariate and multivariate logistic regression with propensity score (based on the probability of HDF initiation) for each subject included (n = 179) to

Table 4 Comparison by propensity score analysis of hemodialysis and predilutional hemodiafiltration: renal replacement therapy parameters

	HD, n = 77	HDF, n = 77	P
Dialyzer			
Polyacrylonitrile (Nephral 400ST)	77 (100)	0	—
Polysulfone (FX 800)	0	77 (100)	—
Renal replacement therapy prescription			
Prescribed duration, min, mean ± SD	219 ± 26	215 ± 28	0.37
Prescribed blood flow, mL/min, mean ± SD	362 ± 45	377 ± 38	*0.033*
Prescribed dialysate flow, mL/min, mean ± SD	504 ± 53	509 ± 49	0.27
Heparin priming, IU, mean ± SD	9675 ± 1240	5195 ± 1709	*<0.0001*
Duration of renal replacement therapy			
Effective, min, mean ± SD	207 ± 37	207 ± 35	0.76
Prescribed duration, %, mean ± SD	94.8 ± 13.6	96.5 ± 11.8	0.3
Session completed, n (%)	62 (80.5)	64 (83.1)	0.83
Weight gain, kg, mean ± SD	1.763 ± 1.445	1.788 ± 1.614	0.89
Dialysis characteristics			
Real mean blood flow, mL/min, mean ± SD	347 ± 53	353.5 ± 54.5	0.37
Mean venous pressure, mmHg, mean ± SD	177 ± 40	183 ± 41	0.41
UF rate (except substitution), mL/min/kg, mean ± SD	0.1162 ± 0.066	0.1135 ± 0.079	0.54
Single-needle RRT, n (%)	1 (1.3)	1 (1.3)	—
Dialysis efficiency, mean ± SD			
Treated blood volume, L	69.6 ± 18.5	65.6 ± 16.3	0.16
Kt/V, ionic dialysance (OCM)	1.2 ± 0.31	1.28 ± 0.3	0.083
Predilution on-line HDF, mean ± SD			
Substitution volume, L/session	—	33.7 ± 12.3	—
Substitution rate, mL/min	—	163 ± 49	—
Intradialytic symptomatic hypotension, n (%)	8 (10.4)	9 (11.7)	1
Increase venous pressure > 50%, n (%)	14 (18.2)	15 (19.5)	1
Venous bubble trap thrombosis, n (%)	11 (14.3)	8 (10.4)	0.62
Premature termination			
Other reasons than coagulation problems, n (%)	2 (2.6)	3 (3.9)	1
To prevent ECC coagulation, n (%)	13 (16.9)	11 (14.3)	0.82
ECC total clotting, n (%)	3 (3.9)	4 (5.2)	1
Heparin-free RRT failure, n (%)	16 (20.8)	15 (19.5)	1
Restitution quality			0.018
Good, n (%)	13 (16.9)	2 (2.6)	
Middling, n (%)	35 (45.5)	35 (45.5)	
Poor, n (%)	24 (31.2)	35 (45.5)	
Undocumented, n (%)	5 (6.5)	5 (6.5)	
Blood transfusion, n (%)	3 (3.9)	3 (3.9)	1

The following variables were used in the regression model to derive the propensity score for each patient: age greater than 65 years; Charlson comorbidity index greater than 6; use of catheter as vascular access; single-needle dialysis; admission for invasive procedure. Weight gain = dry weight − weight on the day of dialysis session.
ECC = extra corporeal circuit; HDF = hemodiafiltration; HD = hemodialysis; RRT = renal replacement therapy; SD = standard deviation; UF = ultrafiltration.

identity predictive factors of ECC thrombosis. By logistic regression analyses, we found that low blood flow rate and postoperative period were the 2 independent risk factors for clotting (failure of heparin-free RRT session) (Table 5). RRT modality was not associated with a failure of the heparin-free session in both univariate and multivariate analysis.

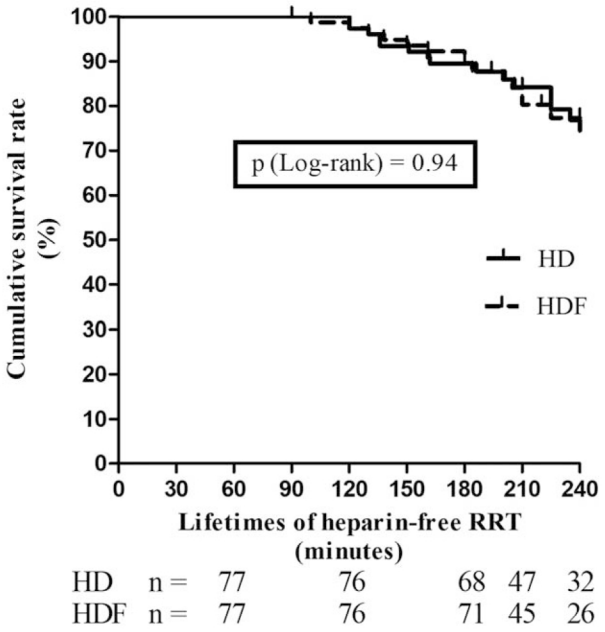

Figure 1 Risk of premature cessation of heparin-free replacement therapy along time period of sessions according to the renal replacement modality: conventional hemodialysis (HD) and on-line predilution hemodiafiltration (HDF). Log-Rank test, chi-square = 0.004812, P = 0.9447. One hundred and forty-four patients matched by propensity score analysis: 77 HD and 77 HDF patients.

DISCUSSION

In this cohort study of chronic hemodialysis patients at increased risk of bleeding, we routinely used 2 modalities of heparin-free RRT sessions: HD and predilutional HDF. We confirmed the safety and the effectiveness of these techniques since 77.1% of all sessions were completed and only 3.9% of them interrupted for massive clotting. When compared to heparin-free HD with heparin-coated AN69 dialyzer, on-line automatic predilution HDF was equally feasible, safe, and efficient. Low blood flow rate and postoperative period were found to be independent risk factors for clotting or premature termination of sessions whereas RRT modality (HD or HDF) has no influence.

Hemodialysis without heparin has long been used in maintenance dialysis patients with bleeding risk.[7,9] A major side effect is the occurrence of bloodline clotting which reduces the delivered dialysis dose and generates blood loss.[2] The additional use of periodic saline rinse have improved ECC survival[16] but it was shown in some studies that it increases coagulation markers and premature restitution frequency.[17,20,21] Also, saline flushes if not associated to additional ultrafiltration rate may lead to hypervolemia. Continuous saline infusion prevented ECC clotting more efficiently than intermittent saline flushes.[22] Yet, whatever saline rinse is used, the workload for the nurses is substantially increased. A possible alternative is represented by the use of heparin-coated membrane, a material that has the ability to bind heparin in its surface providing predominantly a local anticoagulation effect.[23] Results were, however, equivocal; circuit coagulation was reported with a frequency varying from 5 to 50% and early termination of dialysis session from 5% to 7%.[13–15,17,24,25] We routinely used a modified polyacrylonitrile membrane (AN69ST) for HD sessions. We deplored bloodlines clotting in only 3.9% of all HD sessions as did Keller and colleagues[26] in their prospective study of 296 heparin-free HD sessions. Notably, premature sessions termination was much lower in our cohort (19%) as compared to their study (47%).[26] Several factors may have contributed to the performance of heparin-free dialysis in our patients: a high proportion of patients with antiplatelet therapy,[27] a wide spread use of prophylactic subcutaneous heparin, a prescribed sessions duration less than 240 minutes and a median hemoglobin level at 9.8g/dL that may prevent filter clotting.[8] Moreover, the high nurses to patients ratio in our dialysis unit permitted a close intradialytic monitoring that allowed complete blood restitution before clotting.

Table 5 Multivariate analysis of factors related to free-heparin renal replacement therapy sessions failure

Multivariate logistic regression analysis showing predictors for heparin-free RRT failure			
	Hazard ratio	95% CI	P
HD versus HDF	0.89	0.4–1.98	0.77
Recent surgery	7.05	2.84–17.51	<0.001
Mean blood flow < 250 mL/min	7.8	1.62–37.67	0.01

The propensity score for each patient based on the probability of HDF initiation was included in the univariate and multivariate logistic regression analysis of factors related to heparin-free RRT failure. Heparin-free RRT failure was defined as total ECC clotting or occlusion of dialyzer rendering RRT impossible or premature restitution to prevent ECC clotting. Propensity score for HDF prescription include: age > 65 years old, catheter use, Charlson index > 6, invasive procedure, single-needle dialysis).
CI = confidence interval; ECC = extra corporeal circuit; HDF = hemodiafiltration; HD = hemodialysis; HR = hazard ratio; RRT = renal replacement therapy; UF = ultrafiltration.

On-line predilution heparin-free HDF was also described for more than 20 years ago as a feasible technique in bleeding risky patients.[28] Our main concern in this study was to evaluate this modality in such a population and to compare its efficacy to that of HD with heparin-coated membrane. We observed a similar rate of RRT failures with both modalities and improved clearances by predilutional HDF (without significance). Heparin-free-heparin HD is known to do not affect delivered dialysis dose,[11,27,29] our work strongly suggests that HDF modality would provide the same or even better performance, as measured by kt/V. Actually, we used a predilution HDF mode because it would significantly increase the hemofilter survival rate by the preservation of a filtration fraction less than 25% at the contrary of post-dilutional mode.[30] We also did not use a fixed predilution substitution flow mainly at 200 mL/min which may lead to an increased risk of ECC thrombosis.[31,32] When the substitution flow rate is elevated, high flow may become turbulent in the dialyzer promoting platelet activation and excessive blood dilution may inhibit anticoagulant factors. Consequently, current recommendations are the use of low flow substitution rate varying from 25 to 75 mL/min.[33] We then used an automated substitution mode which applies medical prescription with an individual adaptation according to blood viscosity and hemoconcentration during the session. Using the *Autosub* automated substitution, we reached an average substitution rate at 160 ± 51 mL/min without any significant adverse effect on circuits' thrombosis. Moreover, the use of Polysulfone membranes with large area and high permeability rather than AN69ST membranes in our HDF sessions did not jeopardize filters survival. In fact, the comparison of these 2 types of highly biocompatible synthetic membranes did not show any significant difference in ECC thrombotic risk.[14,25,34,35] Thus, we did not experience an over-clotting risk with predilutional HDF as compared to HD in our bleed risky patients unlike the Hepzero study.[13] A blood flow rate maintained above 250 mL/min—a mean blood flow rate at 342 ± 63 mL/min in our study—may explain our results with both free-heparin HD and HDF sessions.[8,15] However, blood restitution quality was considered worse after HDF than after HD sessions. Nonetheless, we found predilutional HDF modality easier and better than HD with saline infusion because of less logistic burden for nurses and no additional risk of intradialytic events. Dialysis for patients bleeding or at risk for bleeding requires special modalities of treatment that are difficult to perform without potential side effects. In the free-heparin RRT cohort, to prevent the risk of ECC clotting, the dialysis duration was shorter than usual duration (around 210 minutes in the cohort versus 240 minutes usually). This strategy induced a decrease in the delivered dialysis dose evaluated by Kt/V(urea). Short dialysis duration is inadequate for maintenance chronic dialysis program but this short treatment time was probably not relevant because of its transitory nature.

In case of contraindication of systemic anticoagulation, several alternatives exist including regional protamine or citrate anticoagulation besides heparin-free RRT with and without saline flushes and AN69 ST membrane. Regional citrate anticoagulation has become more popular during the last years and represents the most promising option. However, it should be performed by an experienced medical and paramedical team and necessitates a close monitoring of ions and acid-base metabolism. Its use on a routine practice remains very limited especially during HDF.[21,36,37] Technical improvements including the use of citrate enriched dialysate have been developed or are in development but are not yet validated.[38] A recent use of vitamin E-coated dialyzer showed high failure of heparin-free HD sessions and would not represent an alternative to heparin-coated membrane for patients with heparin-induced thrombocytopenia.[15]

Our study has several limitations. First, it was a non-randomized single-center study. We therefore analyzed only the first session of each patient and used a propensity score mimicking a randomized study. Second, the conventional strategy of saline flushes which would serve as a control despite its many limitations[20] has not been tested in this study. Third, we evaluate the performance of RRT modalities mainly through ECC clotting and sessions termination but not through thrombogenicity markers. Last, the evaluation of blood restitution quality was not standardized and venous bubble trap was not specifically assessed.

In conclusion, automated predilution substitution free-heparin HDF was a safe and effective strategy for chronic hemodialysis patients with a bleeding risk and offered the same performance and security than free-heparin-coated membrane HD. A blood flow maintained above 250 mL/min was necessary to secure circuits survival. Further studies are, however, required to confirm our observations.

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