ORIGINAL ARTICLE

Hemodialysis without anticoagulation: Less clotting in conventional hemodialysis than in predilution hemodiafiltration

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Abstract

Introduction: Hemodialysis patients with contraindication to systemic anticoagulation require a heparin-free hemodialysis technique. Among several alternatives to heparin, predilution hemodiafiltration (HDF) is often used, albeit without any confirmation of its effectiveness.

Methods: Patients hospitalized in a nephrology ICU and hemodialysed for stage 5 CKD or AKI and with contraindication to systemic anticoagulation were randomized to either standard HD with a polysulfone membrane, or to predilution HDF with the same membrane. Coagulation activation was evaluated clinically by the need for premature termination and by the measurement of D-dimers.

Findings: Two hundred dialysis sessions were performed in 155 patients. Survival curves showed better circuit survival in HD ($P = 0.046$). In HD, 12% of sessions were interrupted for coagulation versus 23% in predilution HDF ($P = 0.04$).

Discussion: Predilution HDF was associated with more premature clotting than conventional HD without improvement in dialysis duration or performance epuration indices. When aiming for a 4-hour duration session, conventional heparin-free hemodialysis can be safely proposed in most patients with high bleeding risk.

Keywords: Hemodialysis, predilution hemodiafiltration, anticoagulation, trial

INTRODUCTION

During hemodialysis, coagulation is activated when the blood comes in contact with the artificial dialysis membrane; as a result, anticoagulation is often required to achieve an adequate 240-minute duration.[1] Current practice consists in the intravenous administration of low-molecular-weight heparin or alternatively unfractionated heparin. However, heparin administration is responsible for systemic anticoagulation, which may put at risk some patients with active bleeding or with a high bleeding risk. In these patients, many alternative options have been proposed including saline flushes and regional citrate anticoagulation. Regional anticoagulation with citrate is highly effective but requires citrate and calcium infusions and is, therefore, more complex to monitor.[2,3] Citrate dialysates without calcium have also been advocated but still require a calcium infusate.[4,5] Alternatively, and for many years, heparin-free hemodialysis has consisted in periodic saline flushes to rinse the extracorporeal circuit.[6,7] However, this technique is time-consuming for the nurses and may induce fluid overload. Although poorly documented, this method has been recommended

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until recently by European guidelines. More recently, it has been suggested that predilution hemodiafiltration (HDF) could replace saline flushes by continuously rinsing the circuit without fluid overload given that the infusion fluid is eliminated in the effluent.[8] This technique has gained widespread acceptance and is now increasingly used when anticoagulation is contraindicated.[9] There are some data, however, indicating that saline flushes and convective techniques may promote coagulation.[10,11] In light of these controversies, the present study was undertaken to assess the effectiveness of predilution HDF as compared with heparin-free hemodialysis in a cohort of patients with high bleeding risk.

PATIENTS AND METHODS

Study design

This prospective randomized, open trial was conducted in the Nephrology department of the University Hospital of Strasbourg between October 2014 and September 2017.

Patients

Included patients were hospitalized in the Nephrology Intensive Care Unit of the University Hospital of Strasbourg. All patients received oral and written information and signed an informed consent form. The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki and its revisions.

In order to be included, patients had to provide informed consent, should be 18 years of age or older, scheduled for a 4-hour hemodialysis session, and have a contraindication for systemic anticoagulation. Patients requiring systemic anticoagulation for other reason than hemodialysis were excluded. Antiplatelet agents used on a regular basis were maintained throughout the study.

Hemodialysis procedures

Patients were randomized using a computerized predetermined sequence to receive either an HD session or a predilution HDF session. If a second session without anticoagulation was required, the patient received the alternative technique in a crossover design. A maximum of two sessions per patient were analyzed in the study.

Hemodialysis sessions were performed with the Fresenius 4008 and 5008 therapy systems.

A polysulfone hollow fiber dialyser (FX100, Fresenius Medical Care, Bad Hamburg, Germany) and a citrate dialysate (Citrasate, Hemotech, Toulouse, France) were used for all sessions. The dialyser was rinsed as recommended by the manufacturer in the absence of heparin.

The initial blood flow rate was prescribed by the nephrologist and subsequently decreased by the nurse according to the vascular access conditions. The mean blood flow rate was calculated by dividing the total blood volume treated by the duration time.

The dialysate flow rate was kept constant at 500 ml/min. Dialysate composition was prescribed by the nephrologist and remained unchanged throughout the study (potassium 3.0 mmol/l; calcium 1.5 mmol/l; sodium 130–140 mmol/l; bicarbonate 31–33 mmol/l; citrate 0.80 mmol/l; magnesium 0.50 mmol/l).

For predilution HDF sessions, the convective flow rate was set at 50 ml/min in predilution mode. No anticoagulation was administered for either HD or preHDF. When clotting occurred within the extracorporeal circuit, departmental policy consisted in terminating the session and beginning another whenever necessary. Under no circumstances were saline flushes or change in dialyser or lines performed during the session.

Data collection

The following data were collected anonymously: demographic data (gender, age, height, weight), renal anamnestic data (acute or chronic kidney disease, vascular access), medical history (contraindication for anticoagulation, diabetes, thromboembolic diseases, antiplatelet agents), biological data (hemoglobin, platelet count, white blood cell [WBC] count, C-reactive protein [CRP], serum albumin, D-dimers, prothrombin ratio, APTT ratio, fibrinogen) and data from the dialysis procedure (effective length and premature termination), minimal blood pump flow, total blood volume treated, mean blood flow, mean ultrafiltration rate, final relative blood volume (RBV), blood pump stops, recirculation, hypotension, online KT or KT/V and mean dialysance). Mean ultrafiltration rate was calculated by dividing the effective total ultrafiltration by the effective length; mean blood flow was calculated by dividing the total blood volume treated by the effective length while mean dialysance was calculated by dividing KT by the effective length or by multiplying KT/V by V (Watson formula) and subsequently dividing by the effective length.

Statistical analyses

Subjects and hemodialysis sessions data are presented as mean and standard deviation for quantitative variables and were compared with the Student test when following a normal distribution or with the Mann–Whitney test for

non-normally distributed data. Qualitative data are presented as number and percentage for each modality and compared with the χ^2 test.

The primary objective was to compare the extracorporeal circuit thrombosis-free survival between hemodialysis and HDF without any anticoagulation. Survival was analyzed by constructing Kaplan–Meier survival curves, which were compared with the Log-rank test. Circuit thrombosis was also analyzed by the percentages of sessions interrupted before the scheduled ending and compared using the χ^2 test. Coagulation was defined by complete or partial clotting of the extracorporeal circuit or by a rising venous pressure above 50% of the initial value indicating premature termination.

The secondary objective was to compare the level of D-Dimers between the two groups in order to assess coagulation activation in the extracorporeal circuit. D-Dimers were measured in the arterial line at the beginning of the session and in the venous line downstream of the dialyser membrane at the third hour so as to avoid the lack of data due to premature termination of certain sessions. D-dimer values obtained at the third hour were compared with the Mann–Whitney test owing to a non-Gaussian distribution, while the proportion of patients with doubling D-dimers was compared with the χ^2 test.

Since patients having undergone only one session could also be included, the two groups may not be totally comparable despite the randomization. A multivariate Cox regression was thus performed to adjust for other factors potentially involved in blood coagulation during hemodialysis: acute or chronic kidney disease, catheter use, blood flow rate, ultrafiltration rate, perdialytic hypotension episodes, inflammation markers, hemoglobin, platelets, and fibrinogen. All of the above analyses were also performed in the small cohort of patients, who were included with 2 sessions with the two compared techniques.

Differences were considered significant, if the corresponding *P*-value was <0.05. All statistical analyses were performed using the Stata 13.1 software (StataCorp LP, Texas).

RESULTS

One hundred and fifty-five patients were included and underwent 200 hemodialysis sessions. Characteristics of the patients as well as of the dialysis sessions are detailed in Tables 1 and 2, respectively. Briefly, patients were mostly dialysed for stage 5 chronic kidney disease (78.1%) and had a permanent vascular access (71%). Contraindications for anticoagulation included active bleeding in 17 cases (11%), in association with surgery in 109 cases (70.3%) and in particular kidney transplantation in 67 cases (43.2%). Among the other 28 (18.1%) contraindications, kidney biopsy accounted for 14 cases (9.0%). Characteristics of the HD and predilution HDF groups were comparable except for the final RBV, which was slightly although statistically significantly lower in the HD group despite a comparable or even lower ultrafiltration rate.

Table 1 Characteristics of the 155 study patients

Characteristics	Values
Male gender, *n* (%)	100 (64.5)
Age, years	57 ± 16
Weight, kg	77 ± 18
BMI, kg/m^2	26.9 ± 5.7
Diabetes, *n* (%)	38 (24.5)
AKI, *n* (%)	34 (21.9)
CKD, *n* (%)	121 (78.1)
Vascular access, *n* (%)	
Catheter	45 (29.0)
AVF or Graft	110 (71.0)
Contraindications for anticoagulation, *n* (%)	
Active bleeding	17 (11.0)
Preoperative period	53 (34.2)
Postoperative period	56 (36.1)
Others	29 (18.7)
Thromboembolic history or predisposition, *n* (%)	27 (17.4)
Diabetes, *n* (%)	38 (24.5)

AKI = acute kidney injury; AVF = arteriovenous fistula; BMI = body mass index; CKD = chronic kidney disease.

Kaplan–Meier survival curves showed a significantly better thrombosis-free survival of the dialysis filter in the HD group ($P = 0.046$) (Figure 1).

Effective median duration time was not significantly different in HD and predilution HDF groups; however, there were less sessions interrupted due to coagulation before the scheduled termination in the HD group (12.0% vs. 23.0%, $P = 0.04$) (Table 3). Interruption for purposes other than coagulation was comparable in the two groups.

In multivariate analysis, risk factors significantly associated with premature clotting were end-stage kidney disease and catheter use, while predilution HDF was not significantly associated with premature clotting (Table 4).

Biological markers of coagulation activation did not differ between the two groups, whether for D-dimers measured at the third hour or in terms of the proportion of sessions with a doubling concentration of D-dimers between the two groups (Table 3).

Forty-five included patients were dialysed with the two different techniques (90 sessions). Among the latter, 4 (8.9%) had premature clotting during HD and 11 (24.4%) during predilution HDF ($P = 0.048$). The

Table 2 Characteristics of the hemodialysis sessions

	Overall(n = 200)	HD(n = 100)	preHDF(n = 100)	P[a]
Male gender, n (%)	128 (64)	59 (59.0)	69 (69)	0.14
AKI, n (%)	48 (24)	26 (26.0)	22 (22)	0.51
Catheter, n (%)	61 (30.5)	30 (30)	31 (31)	0.88
Dialysate composition				
K, mmol/L	3 ± 0	3 ± 0	3 ± 0	NA
Ca, mmol/L	1.5 ± 0.02	1.5 ± 0.03	1.5 ± 0	0.32
Na, mmol/L	136 ± 1.7	136 ± 1.7	136 ± 1.8	0.53
HCO3, mmol/L	31 ± 0.24	31 ± 0.2	31 ± 0.3	0.56
Dialysate flow, mL/min	500 ± 0	500 + 0	500 ± 0	NA
Minimal BF, mL/min	331 ± 61	329 ± 61	333 ± 61	0.67
Mean BF, mL/min	313 ± 58	313 ± 57	312 ± 60	0.90
Mean dialysance, mL/min	222 ± 39	218 ± 38	226 ± 39	0.33
Recirculation, %	14 ± 15	13 ± 10	15 ± 20	0.91
Ultrafiltration rate, mL/h	396 ± 867	339 ± 250	451 ± 1199	0.86
Final RBV, %	91.8 ± 5.6	90.7 ± 5.8	92.7 ± 5.3	0.03
Blood pump stops, n (%)	49 (26.1)	24 (25.3)	25 (26.9)	0.80
Hypotension, n (%)	20 (10.6)	13 (13.7)	7 (7.5)	0.17
Leucocytes, 10^9/L	9.2 ± 4.4	9.5 ± 4.8	8.9 ± 4.0	0.43
Hemoglobin, g/dL	9.5 ± 1.7	9.4 ± 1.6	9.5 ± 1.8	0.73
Platelets, 10^9/L	182 ± 93	182 ± 90	182 ± 97	0.91
Prothrombin ratio, %	81 ± 15	81 ± 16	80 ± 15	0.37
APTT ratio	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.98
Fibrinogen, g/L	4.1 ± 2.4	4.1 ± 3.2	4.1 ± 1.3	0.09
Initial D-Dimers, µg/L	2706 ± 3410	2482 ± 3162	2921 ± 3635	0.56
CRP, mg/L	54.6 ± 85.3	51.1 ± 87.1	58.1 ± 83.7	0.70
Albumin, g/L	34.0 ± 4.7	34.2 ± 4.7	33.8 + 4.8	0.57

[a]Comparison between HD and preHDF groups. Values are constant and identical.
AKI = acute kidney injury; APTT = activated partial thromboplastin time; BF = blood flow; CRP = C-reactive protein; HD = hemodialysis; NA: not applicable; preHDF = predilution hemodiafiltration; RBV = relative blood volume; UF = ultrafiltration.

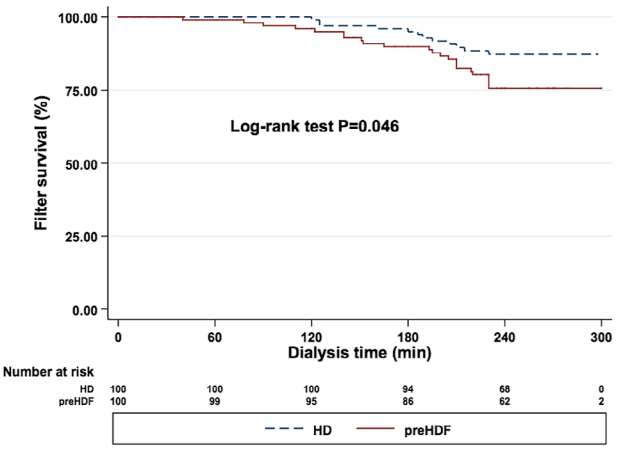

Figure 1 Kaplan–Meier curves of filter survival. HD: Hemodialysis; preHDF: predilution hemodiafiltration; Twelve sessions lasted more than 240 minutes, 7 in the preHDF group, and 5 in the HD group; none exhibited clotting and two reached 300 minutes. [Color figure can be viewed at wileyonlinelibrary.com]

survival curves for these 90 sessions were very similar to those presented in Figure 1 (Supporting Information Figure 1). In multivariate analysis, risk factors associated with premature clotting in this selected subgroup were predilution HDF and high WBC count (Table 4).

DISCUSSION

Despite its increasingly widespread use as an anticoagulation-free hemodialysis technique,[9] the present study results demonstrate that predilution HDF was not only ineffective on dialysis duration but also potentially harmful by causing more premature interruptions because of clotting.

However, when performing a multivariate Cox regression to adjust for other factors possibly associated with increased clotting during hemodialysis, the latter raised conflicting results. In the analysis of the whole cohort, which included many patients undergoing only one dialysis session, predilution HDF was found not to be associated with premature clotting, as opposed to chronic

Table 3 Details of clotting results

	HD (n = 100)	preHDF (n = 100)	P
Effective sessions duration, min	228 ± 31	221 ± 41	0.53
Sessions interrupted for coagulation, n (%)	12 (12.0)	23 (23.0)	0.04
Shortened dialysis time due to clotting, min	7.4 ± 2.4	15.5 ± 3.9	0.04
Time to clotting, min	178.4 ± 10.9	172.6 ± 11.5	0.83
Sessions interrupted for other reasons, n (%)	13 (13.0)	9 (9.0)	0.37
D-dimers at H3, μg/L	6991 ± 7052	6873 ± 6996	0.84
Doubling D-dimers, n (%)	35 (45.5)	34 (44.2)	0.87

HD = hemodialysis; H3 = third hour of hemodialysis; preHDF = predilution hemodiafiltration.

kidney disease and catheter use. This finding points to the fact that despite the randomization, the patients were not totally comparable in the two groups and that catheter use and chronic kidney disease are potent procoagulant factors. Conversely, when restricting the multivariate Cox regression analysis to the subgroup of patients who underwent a session with each technique, patient characteristics were much more comparable, and predilution HDF was confirmed as a procoagulant factor.

Anticoagulation-free HD and predilution HDF have not been rigorously compared until now. Brunot *et al*. recently published an uncontrolled comparative study of HD and predilution HDF in patients at bleeding risk and found no advantage or disadvantage of predilution HDF over HD in terms of coagulation.[12] However, in their study, the authors used different dialysers in each of the two dialysis modalities, and therefore did not only compare HD and predilution HDF but also the properties of the membranes. The difference between the two groups may also have moreover been blunted since many patients received antiplatelet agents and/or preventive subcutaneous heparin and, secondly, the prescribed session durations only lasted 180 (or more) minutes (vs. 240 minutes or more in the present study), whereas clotting is usually observed after the third hour. Despite the above, only 80% of sessions reached the prescribed time without coagulation in their study.

In the randomized HepZero study, HD with a heparin-grafted membrane was compared to saline flushes or predilution HDF.[9] As the dialysis membranes were intrinsically different, it is difficult to draw any firm conclusion although predilution HDF in this latter study was seemingly associated with more premature clotting than HD with the HeprAN membrane. Of note, the results of the predilution HDF group compared poorly with those of the present study. Indeed, in the HepZero study, only 40% of the predilution HDF sessions completed the 4 hours without any intervention as opposed to 74.5% in the present study. In addition, the heparin-grafted membrane group completed the 4-hour sessions without any intervention in only 68.5% of cases. Hence, both experimental and conventional groups of the present study showed much better results than those observed in the HepZero study.

Table 4 Multivariate analysis of risk factors for premature clotting

	For all sessions (N = 200)			For paired sessions only (n = 90)		
Parameter	HR	95%CI	P	HR	95%CI	P
Predilution HDF	1.99	0.86–4.59	0.11	6.1	1.09–33.80	0.04
AKI	0.23	0.06–0.89	0.03	0.09	0.01–1.47	0.09
Catheter	3.55	1.21–10.44	0.02	6.67	0.51–87.96	0.15
Ultrafiltration rate	1.0	0.99–1.01	0.32	1.00	0.99–1.01	0.10
Mean blood flow rate	0.99	0.99–1.00	0.16	1.00	1.00–1.01	0.85
Hypotensive episodes	1.86	0.59–5.82	0.29	4.77	0.94–24.25	0.29
CRP	1.00	0.99–1.01	0.20	1.00	0.99–1.01	0.94
Leucocytes	1.10	1.00–1.20	0.06	1.23	1.02–1.49	0.03
Hemoglobin	1.23	0.95–1.59	0.12	0.82	0.49–1.36	0.44
Platelets	1.00	1.00–1.01	0.46	1.00	0.99–1.01	0.50
Fibrinogen	0.91	0.76–1.09	0.30	0.94	0.67–1.32	0.73

AKI = acute kidney injury; CRP = C-reactive protein; HDF = hemodiafiltration.

The theoretical rationale for predilution HDF was the expectation that the infused dialysate would rinse the dialyser in a continuous mode without fluid overload. Indeed, as coagulation is initiated in the dialyser, it would thus seem advantageous to rinse the membrane and avoid adhesion of cells and proteins involved in blood coagulation.[1] However, the study of Sagedal *et al*. and other studies suggest that intermittent saline flushes may actually promote clotting in the extracorporeal circuit.[10,13,14] Guery *et al*. also found that intermittent saline flushes did not confer any benefit in preventing extracorporeal circuit thrombosis and, furthermore, that continuous saline infusion did not perform better compared to heparin-coated membranes.[15] Earlier, Klingel *et al*. showed that convective techniques (both hemodiafiltration and hemofiltration in predilution mode) were associated with greater levels of D-dimers and thrombin-antithrombin complexes (representing putative markers of coagulation activation) than hemodialysis.[11] Likewise, in continuous renal replacement therapy, the meta-analysis conducted by Brain *et al*. also suggests that purely convective techniques such as continuous veno-venous hemodiafiltration (CVVH) are associated with shorter filter life span than techniques containing diffusive flux (CVVHD and CVVHDF).[16]

Saline flushes and predilution induce two fundamental changes in the extracorporeal circuit, firstly, hemodilution upstream of the dialysis membrane and secondly, enhancement of convective flux across the dialysis membrane. In the 1990s, hemodilution with saline was shown to be responsible for a hypercoagulable state by an unresolved mechanism.[17,18] Although this phenomenon has not been specifically demonstrated, the enhanced convective flux may also promote coagulation by increasing the adhesion of proteins and cells to the dialysis membrane as well as increasing shear stress.[19] This hypothesis is reinforced by unpublished observations from our group that higher convective flux (150 ml/min) in predilution mode is associated with greater coagulation than low or moderate convective fluxes (20 or 80 ml/min).

In the present study, we used a dialysate containing citrate at very low concentration. This likely would not have influenced the results since (i) the same dialysate was used for both modalities and (ii) certain other studies have demonstrated that citrate-containing dialysate does not significantly reduce clotting in the extracorporeal circuit.[20–22]

In addition to the clotting issue, predilution HDF may provide some benefit over HD by increasing the clearance of the middle molecules; however, the convective flux in our study was probably not sufficiently high to achieve a significant effect and, moreover, the positive effect of increased clearance may be blunted by the premature clotting. As shown by the ionic dialysance, the diffusive epuration of the small solutes was comparable between the two techniques.

The present study has certain limitations. First, the study may be biased by the lack of blinding, although blinding in this setting would be unrealistic. For many years, the standard practice in our department has been predilution HDF for patients contraindicated for anticoagulation; it is thus possible that nurses may have expected more extracorporeal circuit clotting during hemodialysis compared to predilution HDF. However, this bias would have reduced the difference between the techniques rather than explaining this difference. Second, most patients included in the study were in intensive care settings and exhibited mild inflammatory syndrome (mean CRP 54 mg/l). This specific procoagulant profile may cast some question as to the extrapolation of our findings to chronic ambulatory hemodialysed patients. However, most dialysis patients with a high bleeding risk also present with AKI or in a perioperative setting and exhibit an inflammatory syndrome, an observation which reinforces the relevance of our findings.

In conclusion, the present study results demonstrate that predilution HDF, which is increasingly used as an anticoagulation-free dialysis technique in patients with high bleeding risk, paradoxically increased premature clotting as compared to conventional hemodialysis with a polysulfone membrane. Our conclusions apply to patients with acute inflammation, which represent a large proportion of patients requiring dialysis in a postoperative setting. Although these results will require external validation in similar cohorts, the present findings may currently have important implications for daily practice.

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CONFLICT OF INTEREST

None of the authors had any conflict of interestin relation to this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supporting Information Figure 1 Kaplan–Meier curves of filter survival for paired sessions only HD: Hemodialysis; preHDF: predilution hemodiafiltration;