

Evaluation of coagulation and anti-Xa factor when using a heparin-coated AN69ST® dialyser

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ABSTRACT

Background: Haemodialysis systems are potentially thrombogenic, so anticoagulation is routinely used. Its prescription involves certain risks, despite which the recommendations regarding dosage are still based on very disparate criteria. **Methods:** We performed a randomised, crossed pilot study. Six patients underwent six sessions of post-dilution haemodiafiltration with a polysulfone HF80® dialyser and standard anticoagulation with nadroparin, and six sessions with heparin-coated polyacrylonitrile AN69ST® membrane without the administration of systemic anticoagulation therapy. The coagulation level of the dialyser and extracorporeal circuit was evaluated every hour using a visual scale along with variation in clotting parameters such as anti-Xa factor. Our primary objective was to assess anti-Xa activity in the absence of differences in the rate of massive coagulation between the two groups. **Results:** No complete or grade 4 dialyser clotting occurred in any of the 36 sessions with either dialyser. Partial clotting of the dialyser occurred below 25% (grade 1-2) in 32 (88.9%) AN69ST® sessions and 35 (97.2%) sessions using the standard dialyser, and partial clotting surpassed 25% (grade 3-4) in 4 (11.1%) AN69ST® sessions and 1 (2.8%) dialysis session with heparin. Arterial chamber blood clotting did not surpass 25% (grade 3 and 4) in any of the studied sessions, and venous chamber coagulation occurred in only 1 (2.8%) session with the usual dialyser and in 3 (8.4%) sessions with the AN69ST®, with no significant differences between the two dialysers. The activated partial thromboplastin time at two hours showed differences between the two techniques in correlation with the administration of low molecular weight heparin (33.3±2.7s with polysulfone and 27.5±2.3s in

AN69ST®; $P < 0.05$), which remained significant at the end of the session (29.8±2.1s with polysulfone and 27.2±1.8s with AN69ST®; $P < 0.05$). Anti-Xa factor activity reached a maximum at two hours after the administration of nadroparin, with differences between the two dialysers (0.46±0.13IU/ml in dialysis with polysulfone and 0.04±0.04IU/ml with AN69ST®; $P < 0.05$), and levels decreased after 4 hours (0.17±0.12IU/ml in dialysis with polysulfone and 0.02±0.03IU/ml in AN69ST®; $P < 0.05$). One patient on dialysis with AN69ST® had an adverse reaction in the form of generalised pruritus and was excluded from the study, by withdrawing consent for participation in the first session. **Conclusion:** We demonstrate the low thrombogenicity of the AN69ST® dialyser, allowing for post-dilution haemodiafiltration sessions without systemic anticoagulation therapy and without increasing the frequency of severe coagulation events as compared to the HF80® dialyser with nadroparin, with a lower associated risk of bleeding by not modifying anti-Xa factor activity.

Keywords: *Anti-Xa. Coagulation. Heparin. Haemodialysis. Haemodialysis membrane.*

Valoración del grado de coagulación y del factor anti-Xa al introducir el dializador AN69ST® con heparina impregnada

RESUMEN

Introducción: Los sistemas de hemodiálisis tienen capacidad trombogénica, por lo que se utiliza de forma rutinaria la anticoagulación. Su prescripción no se encuentra exenta de riesgos, a pesar de lo cual las recomendaciones respecto a la dosis pautaada siguen basándose en criterios muy diversos. **Métodos:** Se realizó un estudio experimental aleatorizado y cruzado. Seis pacientes realizaron seis sesiones de hemodiafiltración posdilución con el dializador de polisulfona HF80® y

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anticoagulación habitual con nadroparina, y seis sesiones con el dializador AN69ST® de poliacrilonitrilo con una cubierta de heparina sin el uso de anticoagulación sistémica. Evaluamos cada hora el grado de coagulación del dializador y del circuito extracorpóreo mediante una escala visual y las variaciones en los parámetros de coagulación, entre los que se incluyó el factor anti-Xa. Nuestro objetivo primario fue valorar las variaciones en la actividad del factor anti-Xa en ausencia de diferencias en la tasa de coagulación masiva entre los dos grupos. **Resultados:** No se coaguló el dializador de forma completa o grado 4 en ninguna de las 36 sesiones realizadas con cada dializador. Se produjo una coagulación parcial del dializador inferior del 25% (grado 1-2) en 32 (88,9%) sesiones con AN69ST® y 35 (97,2%) con el dializador habitual, y superior del 25% (grado 3-4) en 4 (11,1%) sesiones con AN69ST® y en 1 (2,8%) sesión con el dializador con heparina. La coagulación del atrapaburbujas arterial no fue superior al 25% (grados 3 y 4) en ninguna de las sesiones estudiadas, y la cámara venosa en sólo 1 (2,8%) sesión con el dializador habitual y 3 (8,4%) con AN69ST® sin diferencias entre los dos dializadores. El valor del tiempo de tromboplastina parcial activada presentó diferencias a las dos horas entre ambas técnicas, relacionadas con la administración de la heparina de bajo peso molecular ($33,3 \pm 2,7$ s con polisulfona y $27,5 \pm 2,3$ s en AN69ST®, $p < 0,05$), que continuaron siendo significativas al finalizar la sesión ($29,8 \pm 2,1$ s con polisulfona y $27,2 \pm 1,8$ s con AN69ST®, $p < 0,05$). La actividad del factor anti-Xa fue máxima dos horas después de la administración de nadroparina, con diferencias entre ambos dializadores ($0,46 \pm 0,13$ UI/ml en diálisis con polisulfona y $0,04 \pm 0,04$ UI/ml con AN69ST®, $p < 0,005$), para ir descendiendo en la determinación de las 4 horas ($0,17 \pm 0,12$ UI/ml en diálisis con polisulfona y $0,02 \pm 0,03$ UI/ml en AN69ST®, $p < 0,05$). Un paciente fue excluido del estudio al presentar una reacción adversa caracterizada por prurito generalizado con el dializador AN69ST®, motivo por el que retiró en la primera sesión el consentimiento. **Conclusión:** Demostramos la baja trombogenicidad del dializador AN69ST® de forma que permite realizar sesiones de hemodiafiltración posdilución sin necesidad de anticoagulación sistémica, y sin aumentar la frecuencia de eventos de coagulación grave en comparación con el dializador HF80® junto a nadroparina y con menor riesgo de sangrado al no modificar la actividad del factor anti-Xa.

Palabras clave: Factor anti-Xa. Coagulación. Heparina. Hemodiálisis. Membrana de hemodiálisis.

INTRODUCTION

Haemodialysis (HD) systems increase biocompatibility, but we have yet to be able to produce laminar flow which completely avoids system coagulation. The needles, lines,

chambers, and membranes of the dialyser have a thrombogenic capacity, which necessitates anticoagulants in order to maintain the patency of the extracorporeal circuit.

During dialysis sessions in which anticoagulants are not administered, 5% of cases produce a notable coagulation of the dialyser,¹ which translates into a loss of 150ml of blood occupying the lines and dialyser. For this reason, anticoagulation treatment is administered routinely in patients with no risk of haemorrhage, although substantial disparity exists regarding the criteria used for prescribing it.

Traditionally, unfractionated sodium heparin has been used for this purpose. The anti-coagulation properties of this compound are based on the conformational change of antithrombin III and the inactivation of coagulation factors, above all Xa. The effects of administering sodium heparin are immediate, with a half-life of 30 minutes to 2 hours. It is generally administered in boluses, a continuous drip, or through regional heparinisation, and is associated with secondary side effects such as haemorrhage due to excess doses, thrombocytopenia mediated by IgG-heparin immunocomplexes, and thrombocytopenia-associated thrombosis. Other undesirable effects that can appear include hypersensitivity, cutaneous necrosis, and osteoporosis.²

Low-molecular weight heparin (LMWH) provides an alternative for anticoagulation therapy. This drug is obtained by degrading the original heparin molecule into fractions of 4-6kDa. LMWH is used for its lower associated risk of bleeding, since it does not produce an anti-thrombin response. However, it does inhibit Xa, XIIa, and kallikrein, without producing any effect on thrombin, IX, or XI. The half-life of LMWH is longer than normal heparin, which allows for a single dose administered at the start of dialysis that is expressed in anti-Xa units. Although this drug is more expensive, it has fewer secondary side effects on platelet aggregation and thus produces fewer issues with bleeding. The European Best Practice guidelines recommend LMWH as the anticoagulant of choice for dialysis.³

Several different factors can increase the tendency of the circuit for coagulation, such as low blood flow, elevated haematocrit, and high rate of ultrafiltration; in addition, technical errors are an important cause of system coagulations. Isolated clots normally form during HD sessions using routine heparinisation. During the HD session, we can visually monitor signs of coagulation in the dialyser and circuit, such that, depending on the overall aspect of the fibres, we can adjust the anticoagulation dose for the following dialysis session. Laboratory analyses can also aid in assessing the coagulation state of the patient, but not of the circuit. We can measure the number of platelets and bleeding time, which serve to assess primary haemostasis and platelet function. Activated partial thromboplastin time (APTT) measures intrinsic coagulation

activity and facilitates an effective control of unfractionated heparin levels. Finally, activated anti-Xa factor is a more sensitive test that allows for controlling coagulation during the use of LMWH.⁴

In the majority of HD units, these measurements are not normally made. The recommendations regarding dosage are based on body weight, comorbidities, bleeding, and type of HD.^{5,6} In patients with a high risk of haemorrhage, it is preferable to use HD without anticoagulation therapy, although the use of polyacrylonitrile dialysers with heparin coating is currently being introduced as an alternative method. The AN69ST[®] membrane design incorporates a polyethylenimine polymer that neutralises polyanionic groups, conferring the capacity for fixing heparin to the surface of the membrane through electric potentials. The AN69ST[®] membrane with heparinisation during the predialysis cleaning phase has low thrombogenicity and does not require saline solution flushes during its use on heparin-free HD. These haemocompatibility results show that the use of this type of membrane is safe and does not increase the risk of massive coagulation for the dialyser and extracorporeal circuit.⁷⁻¹⁰

We designed a study in patients on a haemodiafiltration (HDF) programme using AN69ST[®] dialysers without systemic anticoagulation therapy, with the goal of evaluating the variation in patient coagulation parameters, including anti-Xa factor levels; we evaluated the level of coagulation in the dialyser and extracorporeal circuit every hour using a visual scale. Our primary objective was to determine whether differences existed in anti-Xa levels in the absence of differences in terms of massive coagulation between the two groups.

MATERIAL AND METHOD

We carried out an experimental, randomised, crossed study including six patients with stage-5 chronic kidney disease on a periodic HD programme for at least six months before. We performed six consecutive sessions of post-dilution HDF using a high-permeability HF80[®] polyethersulfone filter (1.89m²) and anticoagulation using standard doses of intravenous nadroparin. In addition, six sessions were administered using AN69ST[®] dialysers using heparin-coated polyacrylonitrile membranes (2.2m²) without systemic anticoagulation therapy.

Patients and the order of treatment sessions were randomised. All patients signed an informed consent. The study was approved by the healthcare bioethics committee of the Castellon General Hospital.

Patients were selected based on the following inclusion criteria: age >18 years, with haemodynamic stability and a

life expectancy longer than the predicted duration of the study. Each patient received dialysis treatment three times per week, and had serum albumin levels >3g/dl and haematocrit >30%. We also established the following exclusion criteria: active systemic infectious or inflammatory disease, uncured cancer, haemostasis disorders, or oral anticoagulant treatment at the time of the study. No patients were allowed to receive blood or blood derivative transfusions during the week prior to the study, during the study, or one week afterwards.

We included patients with native arteriovenous fistulas or prosthetic fistulas. We also attempted to minimise the differences in blood flow rates in each patient between types of HD. During the study period, neither the duration of HD sessions nor the type of solution used was modified, and the same conventional post-dilution or on-line HDF was used with programmed convection rates. We used the same dialyser during each period and the same anticoagulation dose during the normal dialyser period.

Prior to starting each dialysis session, the extracorporeal circuit was purged with 2l heparinised solution at 5000IU/l. Every hour, 100ml of saline solution was infused in order to observe the coagulation level of the dialyser and bubble trap.

On the sixth session, in each of the periods, we determined haemogram values in order to evaluate platelet count and haemostasis: prothrombin time, Quick index, APTT, and fibrinogen, and we also measured anti-Xa factor levels. The laboratory analyses were collected at the start of HD, after 2 hours, after ending the session, and prior to the following dialysis session or 44 hours later. We also measured plasma concentrations of urea, creatinine, glucose, sodium, potassium, calcium, phosphorous, total protein, albumin, uric acid, and C-reactive protein at the start of HD and at the end of each session.

The dosage for dialysis sessions was measured using the following formulas:

$$\text{Kt/V second generation Daugirdas: } \text{Kt/V} = -\text{Ln} \left(\frac{[\text{C}_2/\text{C}_1]}{1 - [0.008 * \text{T}]} \right) + (4 - 3.5 * [\text{C}_2/\text{C}_1]) * \text{UF/final weight.}$$

$$\text{Kt/V corrected for rebound: } \text{Kt/V}_r = \text{Kt/V} * (1 - [0.6/\text{T}]) + 0.03$$

Samples were sent for processing to the haematology laboratory at the Castellon General Hospital.

Samples were extracted for laboratory analyses after each session from 20-25ml of blood taken from the arterial branch after slowing the arterial pump to a flow of 50ml/min during one minute, according to the standard department protocols.

We evaluated circuit coagulation every hour using a photographic visual scale with 4 different coagulation levels in the arterial and venous bubble traps:

1 = normal.

2 = fibrous ring.

3 = clot formation.

4 = system coagulated.

The dialyser was inspected every hour until the end of each dialysis session:

1 = normal.

2 = less than 25% of capillaries coagulated.

3 = 25-50% of capillaries coagulated.

4 = dialyser completely coagulated.

Statistical analysis

Prior to the study, we calculated the optimal sample size in order to achieve a statistical power of 80% and a 95% confidence interval for paired samples. The sample size was calculated by comparing the two means for anti-Xa factor obtained in studies from the medical literature.^{6,10} We also estimated the standard deviation of the mean at 0.1, based on previous studies. We defined Epsilon, which is the minimal difference between means that is considered of practical importance, at 0.2. We estimated that 4 patients would be needed, and taking into account the possible loss of 15% of the study sample, 2 more patients were added.

The risk of moderate or severe coagulation events with systemic heparinisation was defined as 5% of sessions, with a noninferiority margin of 10%.^{6,11,12} The unilateral α risk was 0.95. The number of sessions required (result) was 58. The possible loss of patients was estimated at 15%.

All statistical analyses were performed using SPSS software, version 11.5.

We used the Kolmogorov-Smirnov test to evaluate whether the study variables adhered to a normal distribution. For two-sample parametric variables, we used paired Student's *t*-tests, and ANOVA tests for cases of more than two comparisons. For two-sample variables that did not adhere to a normal distribution, we used the Wilcoxon non-parametric test for paired samples, and repeated measures tests for cases of more than two comparisons. We also used χ^2 test and

Fisher's exact test of inference for proportions in categorical variables. We evaluated the bivariate relationship using a linear regression analysis, and calculated Pearson's correlation coefficients in order to evaluate goodness of fit.

We considered a *P*-value <.05 to be statistically significant.

Ethical considerations

This study was carried out in accordance with the recommendations of the Helsinki Declaration of 1964, for the orientation of performing biomedical research in human subjects.

RESULTS

The demographic characteristics of the patients included in our study are described in Table 1.

We used systemic anticoagulation therapy only during sessions involving a conventional dialyser. The mean dose of nadroparin was 2500±547.7IU (38.5±8.2IU/kg).

In our study, we did not observe differences in the distribution of coagulation levels between the two types of dialysers. No cases of complete or level 4 coagulation (>50% of the fibres in the dialyser coagulated) were observed in any of the 36 sessions using a conventional

Table 1. Demographic characteristics of the study population

Patients	6
Age (years)	67.7±16.7
Sex (males/females)	4/2 (66.6/33.3%)
Aetiology of renal failure	
Glomerulonephritis	3
Nephroangiosclerosis	1
Interstitial nephropathy	1
Adult polycystic kidney disease	1
Median time on dialysis (months)	61.5 (17-120)
Weight	65.3±6.8
Body mass index	24.1±3.19
Patients taking anti-platelet drugs	4
Erythropoietin (dose in UI)	8667±6890

dialyser or the 36 sessions involving the AN69ST® system. Partial coagulation less than 25% (level 1-2) was observed in 32 (88.9%) of sessions using the AN69ST® system, and 35 (97.2%) sessions using the conventional dialyser, and greater than 25% (level 3) in 4 (11.1%) sessions without heparin and 1 (2.8%) session with the dialyser using heparin (Table 2).

Coagulation in the arterial bubble trap did not surpass 25% (levels 3 and 4) in any of the dialysis sessions, and this value was surpassed in the venous chamber in only one (2.8%)

session using the conventional dialyser and in three (8.4%) sessions using the AN69ST®. There were no significant differences between the two dialysers.

The APTT value after two hours was significantly different between the two techniques, and was correlated with the administration of LMWH (33.3±2.7s with polysulfone and 27.5±2.3s with AN69ST®; $P<.05$), and these differences continued to be significant at the end of the session (29.8±2.1s with polysulfone and 27.2±1.8s with AN69ST®; $P<.05$) (Table 3).

Table 2. Technical characteristics of dialysis sessions

	Normal dialyser	AN69ST®	P
Number of HDF sessions	36 (24 on-line/12 conventional)	36 (24 on-line/12 conventional)	ns
Duration of session	245.5±22.6	245.5±22.6	ns
Infusion volume	17.4±7.7	17.8±7.7	ns
Dialyser	HF80®	Evodial®	
Heparin	2500±547.7	0	
Heparin/weight	38.5±8.2	0	
Blood flow (ml/min)	372±46.6	369.3±40.0	ns
Dialysate flow	780.0±27.7	783.3±25.8	ns
Programmed ultrafiltration	2700±335	2900±237	ns
Predialysis BP (mm Hg)	111±18 / 60±14	117±13 / 59±13	ns
Post-dialysis BP (mm Hg)	102±15 / 55±12	108±16 / 55±9	ns
Number of severe cases of hypotension	0	1	ns
Venous pressure after 4 h (mm Hg)	159.2	163.7	ns
Circuit coagulation			
After 3 hours	Level 1: 22 (61.1%)	Level 1: 18 (50%)	ns
	Level 2: 14 (38.8%)	Level 2: 16 (44.4%)	ns
	Level 3: 0	Level 3: 2 (5.6%)	ns
	Level 4: 0	Level 4: 0	ns
End of session	Level 1: 18 (50%)	Level 1: 17 (47.2%)	ns
	Level 2: 7 (47.2%)	Level 2: 16 (44.4%)	ns
	Level 3: 1 (2.8%)	Level 3: 3 (8.3%)	ns
	Level 4: 0	Level 4: 0	ns
Dialyser coagulation			
After 3 hours	Level 1: 25 (69.4%)	Level 1: 12 (33.3%)	P<.005
	Level 2: 10 (27.7%)	Level 2: 22 (61.1%)	P<.05
	Level 3: 1 (2.8%)	Level 3: 2 (5.6%)	ns
	Level 4: 0	Level 4: 0	ns
End of session	Level 1: 14 (38.8%)	Level 1: 6 (16.7%)	P<.05
	Level 2: 21 (58.3%)	Level 2: 26 (72.2%)	ns
	Level 3: 1 (2.8%)	Level 3: 4 (11.1%)	ns
	Level 4: 0	Level 4: 0	ns

HDF: haemodiafiltration; ns: not significant; BP: blood pressure.

Table 3. Patient results (coagulation and dialysis efficacy parameters)

	Normal dialyser	AN69ST®	P
Haemoglobin (g/dl)	10.7±1.3	11.0±1.6	ns
Haematocrit (%)	33.2±4.8	34.2±5.8	ns
Platelets (thousands of cells/μl)	269.2±105.9	287.3±116.3	ns
PT (seconds)			
At start	12.0±1.7	12.2±1.1	ns
After 2 hours	11.8±1.8	12.3±0.8	ns
At end	12.4±0.5	11.9±0.7	ns
APTT (seconds)			
At start	29.9±6.5	28.8±2.6	ns
After 2 hours	33.3±2.7	27.5±2.3	P<.05
At end	29.8±2.1	27.2±1.8	P<.05
Fibrinogen (mg/dl)			
At start	467.5 ±167.0	451.8±148.3	ns
After 2 hours	529.8±179.6	456.2±205.7	ns
At end	529.5±138.6	570.6±203.3	ns
Anti-Xa (IU/ml)			
At start	0.017±0.040	0.042±0.065	ns
After 2 hours	0.456±0.132	0.040±0.039	P<.005
At end	0.168±0.121	0.018±0.026	P<.05
KtV	1.94±0.51	1.97±0.70	ns
KtV corrected for rebound	1.68±0.45	1.71±0.61	ns
PRU	78.4±9.4	77.4±12.8	ns
TAC urea	41.2±22.7	45.14±18.9	ns

PRU: percent reduction in urea; TAC: time averaged concentration of urea; PT: prothrombin time; APTT: activated partial thromboplastin time.

The anti-Xa factor value reached a maximum two hours after administering LMWH, with statistically significant differences between the two dialysers (0.46±0.13IU/ml in dialysis with nadroparin and 0.04±0.04IU/ml in AN69ST®; *P*<.005), and then decreased after 4 hours (0.17±0.12IU/ml in dialysis with nadroparin and 0.02±0.03IU/ml in AN69ST®; *P*<.05) for both modalities. A positive relationship was established between APTT and anti-Xa factor (regression equation: $y=27.9+7.58x$; $r=0.44$) (Figure 1).

The mean Kt/V value was similar for the two different treatments.

One patient on the AN69ST® dialyser developed abrupt hypotension with loss of consciousness. One patient on the AN69ST® dialyser was excluded from the study due to an adverse reaction in the form of generalised pruritus, for which the patient retracted the informed consent after the first session. Another patient developed nausea and general discomfort 15 minutes after starting a session

using the AN69ST® dialyser, which was resolved with metoclopramide, and no further incidents occurred.

DISCUSSION

The type of dialyser and form of HD used are determining factors in the parameters of thrombogenicity present during dialysis sessions. The dialyser provides the largest surface area exposed to the blood. Flow control and circuit pressures are other factors that can be modified to minimise the activation of the coagulation pathway. In our study, we demonstrated a low thrombogenicity of the polyacrylonitrile AN69ST® dialyser, without needing anticoagulation therapy. The results were similar to those observed using a conventional high-permeability polysulfone dialyser with anticoagulation therapy in the form of LMWH using post-dilution HDF. This modality favours haemoconcentration throughout the dialyser capillaries, since the replacement infusion volume comes after ultrafiltration. These results are possible due to the presence of polyethylenimine as the

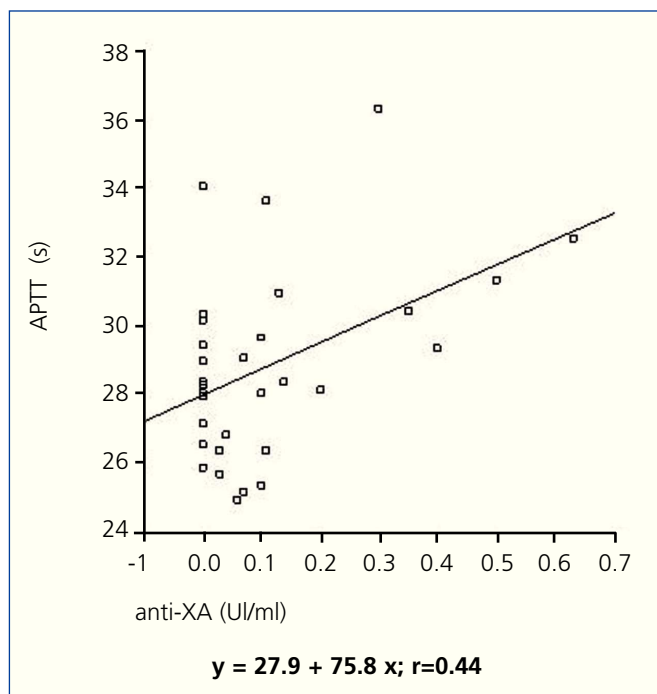


Figure 1. Association between APTT and anti-Xa factor during the 4 hours of treatment.

APTT: activated partial thromboplastin time.

polymer that covers and neutralises the negative charge of the polyacrylonitrile, allowing for the binding of unfractionated heparin molecules. The modifications made to the surface, along with the heparin coating, increase the biocompatibility of the dialyser membrane.¹³⁻¹⁵ This membrane pre-treatment minimises the binding of molecules involved in the contact activation of the intrinsic coagulation pathway.

Neither the dialyser nor the rest of the extracorporeal circuit were completely coagulated in any of the 36 sessions performed using the conventional dialyser or the AN69ST[®]. These findings are in accordance with previously published results, which situate the rate of complete system coagulation at 0.5%-2% of sessions.^{9,16} In sheep models, HD sessions were administered using the AN69ST[®] dialyser with heparin coating and without systemic anticoagulation therapy, with no system coagulation produced during 6-hour sessions. Under these same conditions, massive circuit coagulation was produced after 90 minutes using the AN69[®] dialyser without heparin coating.¹⁰ Studies in humans using the AN69ST[®] dialyser require an optimum level of sodium heparin (2000-3000IU), administered intermittently; with this prescription, partial coagulation was observed in 5/39 sessions using 2000IU heparin and 2/150 sessions with 3000IU heparin ($P < .008$). As regards the need for LMWH, 20mg of enoxaparin were administered, and no episodes of system coagulation were observed in the 30 sessions administered. When the dose was reduced to 10mg, partial coagulation was produced in 7/29 sessions.¹⁰

The experience gained using the AN69ST[®] dialyser without heparin and with adequate supervision resulted in only 1 case of massive system coagulation and 17 cases of partial or >25% coagulation in a sample of 66 sessions.¹⁰ Prior to the dialysis sessions, both groups were primed with a heparinised solution, such that the heparin would impregnate the membrane surface and maintain its anticoagulant effects during the session, without requiring systemic heparin administration. In a randomised crossed sample of 54 patients on HD without heparin, 6% of sessions were interrupted due to complete coagulation of the dialysers. A total of 9% of the sessions were with AN69ST[®], and 13% with polysulfone developed partial circuit coagulation, with a persistent increase in venous pressure.¹¹ Upon comparing the AN69ST[®] dialyser with another polysulfone dialyser using a visual scale, in patients in which the anticoagulation therapy had been decreased by 50%, no differences were observed in coagulation in the venous bubble trap.¹⁵

Anticoagulation therapy in HD implies a risk for active bleeding in dialysis patients, both as a new condition and in terms of worsening pre-existing issues. Standard systemic heparinisation has been associated with a risk of haemorrhagic complications that can occur in as many as 26% of all sessions.¹⁷ Several different alternatives have been used in patients with a high risk of bleeding. Intermittent flushes with saline solution do not appear to improve the visual signs of circuit coagulation or intravascular coagulating activity parameters in stable patients.¹⁸ It is used in 90% of patients in intensive care units, with only 2% of cases developing complete circuit coagulation.¹⁶ Regional heparinisation or small controlled doses of heparin have been used in different studies involving patients with a high risk of bleeding.¹⁹ Using the AN69ST[®] dialyser allows for reducing the dose of unfractionated heparin administered in HD by 50%, without increasing the risk of circuit coagulation.⁷

In our study, we observed a positive relationship between APTT and anti-Xa factor levels. Both values increased two hours after starting heparin administration. Anti-Xa values remained stable during the entire session with the AN69ST[®] dialyser, whereas in sessions with systemic heparinisation, these levels increased, reaching values that avoid circuit coagulation but that alter the coagulation state of the patient. In the last two hours, levels decreased, but remained above normal at the end of the HD session. Specific haemostasis values have been defined that reduce the risk of circuit coagulation. APTT must be maintained >40s and anti-Xa factor >0.2mIU/ml, based on the results from visual inspection of the dialyser and chambers.¹⁰ In sessions with nadroparin, despite using doses of 38.5 ± 8.2 IU/kg, anti-Xa levels remained close to 0.2 at the end of the HD session, which implies a risk of haemorrhage that is not reflected in the value of APTT, which decreased to levels similar to those at the start of the session.

Other studies using the AN69ST[®] have encountered various factors that serve as measures of thrombogenicity during the HD session, such as prothrombin fragment 1+2 as a marker for the vascular formation of thrombin, thrombin-antithrombin III complexes, or B-thromboglobulin as a marker for platelet activation.¹⁸

CONCLUSIONS

In our study, we demonstrated a low thrombogenicity of the AN69ST[®] dialyser, such that we were able to perform sessions of post-dilution HDF without requiring systemic anticoagulation, without increasing the frequency of severe coagulation events, and with a lower risk of bleeding by not modifying the anti-Xa factor.

Conflicts of interest

The authors state that they have no potential conflicts of interest related to the contents of this article.

REFERENCES

- Sanders PW, Taylor H. Hemodialysis without anticoagulation. *Am J Kidney Dis* 1985;5(1):32-5.
- Fort J, Piera L. Anticoagulación y fibrinólisis. En: Jofre R, et al. (eds). *Tratado de hemodiálisis*. 2.ª ed. Barcelona; Editorial Jims; 2006. p. 201-11.
- European Best Practice Guidelines for Haemodialysis (Part 1). *Nephrol Dial Transplant* 2002;17 Suppl 7:64-6.
- Frank RD, Brandenburg VM, Lanzmich R, Floege J. Factor Xa-activates whole blood clotting time (XA-ACT) for bedside monitoring of dalteparin anticoagulation during hemodialysis. *Nephrol Dial Transplant* 2004;19:1552-8.
- Sagedal S, Hartmann A, Sundstrom K, Bjornsen S, Fauchald P, Brosstad F. A single dose of dalteparin effectively prevents clotting during hemodialysis. *Nephrol Dial Transplant* 1999;14:1943-7.
- Herrero-Calvo JA, González-Parra E, Pérez-García R, Tornero-Molina F, en representación del Grupo de estudio español sobre anticoagulación en hemodiálisis. Estudio español sobre anticoagulación en hemodiálisis. *Nefrología* 2012;32(2):143-52.
- Chanard J, Lavaud S, Maheut H, Kazes I, Vitry F, Rieu P. The clinical evaluation of low-dose heparin in haemodialysis: a prospective study using the heparin-coated AN69ST[®] membrane. *Nephrol Dial Transplant* 2008;123:2003-9.
- Leblanc M, Lafrance JP, Renald A. Dialyzer fiber bundle volumen during hemodialysis using large-surface dialyzers. *ASAIO J* 2006;52(6):646-51.
- Lavaud S, Paris B, Maheut H, Randoux C, Renaux JL, Rieu P, et al. Assessment of the heparin-binding AN69 ST hemodialysis membrane: II. Clinical studies without heparin administration. *ASAIO J* 2005;51(4):348-51.
- Lavaud S, Canivet E, Wuillai A, Maheut H, Randoux JM, Bonnet JM, et al. Optimal anticoagulation strategy in haemodialysis with heparin coated polyacrylonitrile membrane. *Nephrol Dial Transplant* 2003;18:2097-104.
- Brunet P, Frances J, Vacher-Coponat H, Jaubert D, Lebrun G, Gondouin B, et al. Hemodialysis without heparin: a randomized, controlled, crossover study of two dialysis membranes (AN69ST and polysulfone F60). *Int J Artif Organs* 2011;34(12):1165-71.
- Swartz RD. Hemorrhage during high-risk hemodialysis using controlled heparinization. *Nephron* 1981;28(2):65-9.
- Briel RC, Zielke E, Zwirner M. Untersuchungen zur korrelation der anti-faktor-Xa-aktivität von niedermolekularem heparin (fragmin) und der aktivierten vollblutgerinnungszeit im aC-tester. *Ärztl Lab* 1987;33:237-40.
- Schulz W, Deuber HJ, Gunthner R, Ohrisch G, Eichhorn M, Werthmann G. Aktueller stand des einsetzes von niedermolekularem heparin in der hä modialyse-therapie. *Nieren- u Hochdruckkrankheiten* 1995;24:187-97.
- Sagedal S, Witczak BJ, Osnes K, Hartmann A, Os I, Eikvar L, et al. A heparin-coated dialysis filter (AN69 ST) does not reduce clotting during hemodialysis when compared to a conventional polysulfone filter (Fx8). *Blood Purif* 2011;32(3):151-5.
- Schwab SJ, Onorato JJ, Sharar LR, Dennis PA. Hemodialysis without anticoagulation. One-year prospective trial in hospitalized patients at risk for bleeding. *Am J Med* 1987;83(3):405-10.
- Maher JF, Lapierre L. Regional heparinization for hemodialysis. *N Engl J Med* 1963;268:451-6.
- Sagedal S, Hartmann A, Osnes K, Bjornsen S, Torremocha J, Fauchald P, et al. Intermittent saline flushes during hemodialysis do not alleviate coagulation and clot formation in stable patients receiving reduced dosis of dateparin. *Nephrol Dial Transplant* 2006;21:444-9.
- Romao JE, Fadil MA. Haemodialysis without anticoagulant: haemostasis parameters, fibrinogen kinetic, and dialysis efficiency. *Nephrol Dial Transplant* 1997;12:106-10.