Background. The AN69 ST haemodialysis membrane, a new membrane resulting from coating polyethyleneimine upon the polyacrylonitrile surface, binds heparin. In patients at risk of bleeding, a pilot study has demonstrated the efficient anticoagulant effect of this heparin-coated membrane.

Study design. In chronic haemodialyzed patients, we evaluated whether this anticoagulant effect can be validated in a controlled, prospective, open study. Pragmatically, we tested the hypothesis of no difference of the massive clotting rate in two groups of patients haemodialyzed either with 50% reduced standard doses of nonfractionated heparin using the heparin-coated AN69 ST or with a full dose of heparin (100%) using another type of dialysis membrane that does not bind heparin. Secondary objectives included evaluation of partial clotting, changes in haemoglobin levels, erythropoietin consumption and dialyzer performances.

Results. One hundred and eighty-four patients were elected and 170 finally included in an 18-month follow-up study. They were allocated to one of the two arms of the study. In the heparin-reduced group (n = 85, mean age: 73 ± 11 years), 12 472 sessions were performed after priming the AN69 ST dialyzer with 2 L of heparinized saline (5000 IU/L heparin) and using 50% reduced doses of previously administered heparin. In the control group with standard heparin (n = 85, mean age: 74 ± 13 years), 14 154 sessions were analysed (NS), and mean heparin doses were 2718 ± 1388 and 4800 ± 1564 IU per session, respectively (P < 0.001). In the heparin-reduced group, massive clotting occurred in 1.4 per 1000 sessions, whereas it occurred in 1.6 per 1000 sessions in the standard heparin group (P < 0.05). Mild to moderate partial clotting in the venous drip chamber and in the dialyzer was evaluated in a subset of patients, on a visual scale. It was more frequent in the experimental group than in the control group (P < 0.001). Platelets, haemoglobin levels, erythropoietin needs and dialyzer performances remained unchanged in both groups.

The global mean death rate was 16.8% per year and did not differ significantly between groups.

Conclusion. The use of the heparin-coated AN69 ST membrane allows a 50% reduction of standard doses of nonfractionated heparin administration for routine haemodialysis without increasing the risk of massive clotting of the extracorporeal circuit. This result needs confirmation since massive clotting questions clinical practice and is team dependent.

Keywords: AN69 ST dialysis membrane; dialysis anticoagulation; haemodialysis; heparin-coated membrane

Introduction

In haemodialysis, optimal anticoagulation of the extracorporeal circuit remains a controversial issue for standard practice [1]. ‘Optimal’ doses of heparin, the universal anticoagulant in use, vary among centres. Changes in activated partial thromboplastin time (APTT) and anti-Xa activity are generally used to assess and control efficient anticoagulation; however, sophisticated and expensive analyses of coagulation cannot adequately predict risk of clotting [2,3]. In all haemodialyzed patients, and more specifically in patients considered at risk of bleeding, the advantages of heparin reduction are counterbalanced by risk of clotting of the extracorporeal circuit. Their uraemic condition increases risk of bleeding [4,5], in addition to age-related factors, cardiac arrhythmias treated with oral anticoagulant and atherosclerotic vascular disease with risk of plaque rupture. For example, it is recommended in the patient with cholesterol crystal embolism for avoiding anticoagulation in order to limit arterial wall dissection. Similarly, it is considered that heparin administration increases risk of retinal bleeding in patients with diabetic retinopathy. Guidelines for the prevention of clotting, in haemodialyzed patient with elevated risk of bleeding, have recommended strategies that combine avoidance of anticoagulant with regular saline flushing or regional citrate anticoagulation, while regional heparinization using protamin should be avoided because...
of a rebound anti-coagulation effect [6,7]. Besides its anti-coagulant effects, heparin alters lipoprotein metabolism by decreasing endothelial lipoprotein lipase activity [8], contributing to uraemic hypertriglyceridaemia and accelerated atherosclerosis, and contributes to uraemic bone osteodystrophy [9].

Intrinsically, the extracorporeal circuit triggers clotting through activation of coagulation factors by blood-membrane contact and changes in the rheological conditions associated with its geometry [10]. The design of the circuit cannot be easily modified, nevertheless, a circuit without a bubble air trap chamber on the venous line has been tested [11], without avoiding risk of air embolism. A pragmatic solution to lessen the thrombogenic effect of the circuit could be the use of a more haemocompatible membrane allowing drastic reduction of heparin requirements. Recent advances in this field have been achieved; heparin can be grafted over a dialysis membrane surface rendering the membrane more haemocompatible [12–16]. The design of the dialysis membrane in use, the routine anticoagulation protocol consisted in the administration of nonfractionated heparin at a total dose of 75–100 IU/kg body weight per session. A bolus of 3000–5000 IU heparin was administered at the start of the session, followed by a second bolus of the same dose, at the second hour. The patients were considered stable on haemodialysis without acute cardiovascular complication for up to 3 months before inclusion. Patients with active vasculitis or cancer were not included. The absence of vascular access dysfunction, evaluated by the Transonic \textregistered technique (Meditor, France), was mandatory.

The goal of the present clinical study was to demonstrate the effectiveness of the heparin-coated AN69 ST membrane in conducting haemodialysis with reduced doses of systemic heparin. We postulated that risk of clotting could be equivalent in a group of patients haemodialyzed with the heparin-coated AN69 ST membrane and 50% reduction of systemic heparin as compared with patients on non-AN69 ST highly permeable membranes that do not bind heparin and standard doses of heparin.

**Table 1.** General characteristics of the patients at inclusion

<table>
<thead>
<tr>
<th>Groups of haemodialysis</th>
<th>50% heparin reduced</th>
<th>Heparin standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis membrane</td>
<td>Heparin-coated AN69 ST</td>
<td>Polysulfone ($n = 30$), PMMA ($n = 37$), cellulose acetate ($n = 18$)</td>
</tr>
<tr>
<td>Patients ($n$)</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Female/male ($n$)</td>
<td>39/46</td>
<td>39/46</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73 ± 11</td>
<td>74 ± 13</td>
</tr>
<tr>
<td>Chronic glomerulonephritis ($n$)</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Nephroangiosclerosis ($n$)</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes ($n$)</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Chronic interstitial nephritis ($n$)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Polycystic renal disease ($n$)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Not determined ($n$)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>32.8 ± 55.0</td>
<td>30.1 ± 48.2</td>
</tr>
<tr>
<td>Dry body weight (kg)</td>
<td>68 ± 15</td>
<td>68 ± 15</td>
</tr>
<tr>
<td>Kt/V (urea)</td>
<td>1.26 ± 0.18</td>
<td>1.29 ± 0.40</td>
</tr>
<tr>
<td>Platelets (per mm$^3$)</td>
<td>228 000 ± 46 000</td>
<td>212 000 ± 62 000</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>109.8 ± 15.1</td>
<td>111.6 ± 13.0</td>
</tr>
<tr>
<td>EPO$^a$ (IU/kg/week)</td>
<td>118 [0–536]</td>
<td>107 [0–517]</td>
</tr>
<tr>
<td>CRP$^a$ (mg/L)</td>
<td>9 [3–287]</td>
<td>9 [1–590]</td>
</tr>
<tr>
<td>Ionic conductance (mSiemens)</td>
<td>165 ± 17</td>
<td>172 ± 17</td>
</tr>
</tbody>
</table>

Variables were not significantly different between groups. Kt/V was calculated according to a single-pool model. Doses of EPO are for hr-EPO α or equivalent.

$^a$Median [min-max].

**Patients and method**

**Patients**

All the patients chronically haemodialyzed in the dialysis unit were enrolled in the study. Application of exclusion criteria, as listed below, resulted in a population of 185 patients. They were included in a controlled prospective, open study that was conducted from February 2005 to August 2006. The study was approved by the ethical committee, according to French regulations. All patients provided informed consent.

Prior to inclusion, patients were regularly haemodialyzed for 4 to 6 h per session, three times per week, in order to maintain a Kt/V for urea higher than 1.2. The arterial blood flow rate was comprised between 250 and 350 mL/min and modulated according to cardiovascular stability. Whatever the dialysis membrane in use, the routine anticoagulation protocol consisted in the administration of nonfractionated heparin at a total dose of 75–100 IU/kg body weight per session. A bolus of 3000–5000 IU heparin was administered at the start of the session, followed by a second bolus of the same dose, at the second hour. The patients were considered stable on haemodialysis without acute cardiovascular complication for up to 3 months before inclusion. Patients with active vasculitis or cancer were not included. The absence of vascular access dysfunction, evaluated by the Transonic \textregistered technique (Meditor, France), was mandatory. The patients did not take oral anticoagulant, but aspirin or antiplatelet drugs were allowed. Continuous follow-up was recorded using Hemadialyse \textregistered software (Gambro, France). Demographic data are summarized in Table 1.

**Protocol**

The protocol (Figure 1) was designed to test the anticoagulant effect of the heparin-coated AN69 ST membrane allowing reduction of systemic doses of heparin [16]. It is a general policy in our centre to allocate dialysers randomly to each patient starting chronic haemodialysis. Dialyzers are provided on a weekly basis, in the following proportion: AN69 ST: 50%, polysulfone: 30%, polymethylmethacrylate (PMMA): 15% and cellulose triacetate: 5%.
Haemodialysis with a heparin-coated membrane

Fig. 1. General presentation of the trial testing the effects of heparin reduction in haemodialysis using the heparin-coated AN69 ST membrane. The primary outcome was ‘massive clotting of the extracorporeal circuit’ in an intention-to-treat analysis.

Ninety-three stable patients haemodialyzed with AN69 ST were included in the experimental arm of the protocol (group 1). They were paired with 92 patients haemodialyzed with a non-AN69 ST highly permeable membrane, on dialysis vintage (±1 year difference), sex and age (±2 years difference) constituting the control arm (group 2).

The principal outcome was quoted ‘massive clotting’ of the extracorporeal circuit, resulting in premature ending of a session and, eventually, replacement of the dialyzer and blood lines. Massive clotting could result, in some cases, from insufficient supervision of the session. When circular clotting was observed in the venous bubble trap chamber, the decision to stop the session was considered. In some instances the sharp increase of blood pressure in the venous line due to worsening of clotting in the bubble trap chamber led to blood restitution to the patient in order to avoid massive clotting and blood spoliation. When it occurred, such an event was quoted as equivalent of massive clotting.

The experimental arm tested a 50% reduction of the dose of nonfractionated heparin previously used for standard haemodialysis. In this group, the AN69 ST membrane (Nephral ST or Crystal ST, Gambro-Hospal, Meyzieux, France) was only used and primed with 2 L of heparinized saline (5000 IU/L heparin) for 10 min at about 150 mL/min, whatever the membrane surface (1400 to 2000 m²). The control arm included patients on regular haemodialysis with any highly permeable membrane excluding the AN69 ST, and standard doses of heparin (polysulfone: 45 patients; polymethylmetacrylate: 25 patients; cellulose acetate: 15 patients). The priming procedure used 2 L of saline without heparin for rinsing the circuit. In the case of bleeding associated with intercurrent complication, systemic heparin administration was avoided. As previously documented using the heparin-coated AN69 ST membrane [17], heparin-free dialysis may be conducted in such patients; consequently they remained included in the study. Conversely, in the absence of sufficient safety with heparin-free dialysis using other synthetic or cellulosic membrane, patients of group 2 with bleeding complications were excluded from the study. In the case of vascular access dysfunction complicating the course of dialysis, the affected patient was temporarily withdrawn from the protocol until baseline conditions were restored.

Haemodialysis sessions were carefully monitored. Hourly visual inspection of the venous drip chamber allowed clotting scoring, especially looking at the blood surface in contact with air; grading (0) was for normal or near normal appearance and (++) for partial clotting. In the case of occurrence of partial clotting, the blood level was lowered in the bubble trap chamber and the formation of a new ring of clotting, beneath the previous one, was carefully followed. At the end of the session, clotting in the dialyzer was similarly staged by visual inspection. Iterative pictures of the bubble trap chamber and a picture of the dialyzer at the end of the session were blindly evaluated during the first month of the protocol. Scoring was established by two independent investigators.

Blood cells count and coagulation tests were performed once a month. They included measurement of APTT and anti-Xa activity in the venous line, at the 180th min of the session. CRP was measured twice per year. All biology was measured using commercially available reactants. In a subset of 20 patients, dialysis efficiency was monitored online by means of ionic clearance measurement [18,19] using the Diascan® monitor (Gambro-Hospal, Meyzieux, France). Values shown in Tables 1 and 2 are the mean (±SD) of 10 measurements per patient obtained respectively during the first and last months of the study.

Statistics

Statistical analysis was performed using SAS v8.0®. To test the equivalence hypothesis we considered from previous pilot studies [20] that risk of ‘massive clotting’ was in the range of 4.2 per 1000 sessions with full-dose heparin and 4.5 per 1000 with the AN69 ST and reduced doses of heparin, from 0 to 50% of the standard dose. Consequently, the sample size estimated to document a delta no more than 0.5 per 1000 sessions, a risk α of 0.05 and a power of 80% requires 10 519 sessions per arm. Data were expressed as mean ± SD or median and range for quantitative data. Analysis was conducted with intention to treat. To evaluate difference, the Student t-test was performed when distribution was normal. Otherwise, the Mann–Whitney test was performed. Qualitative variables were expressed as number or percentage. The χ² test was performed for comparative analysis. Time to massive coagulation was assessed using the Kaplan–Meier method. Comparison between groups used the log-rank test. Significant threshold was considered at P < 0.05.

Results

One hundred and eighty-five patients were enrolled in the pre-inclusion phase of the study, but 170 definitively included. The initial drop out of 15 patients, 7 in group 1 and 8 in group 2, observed during the 3-month pre-inclusion period, was due to intermittent complications such as thrombosis of vascular access or arrhythmia requiring oral
Massive clotting (per 1000 sessions) 1.4 1.6

Patients (CRPα (mg/L) 8 [2–159] 10 [1–310]

Haemoglobin (g/L) 110.2 ± 14.8

Erythropoietina (IU/kg/week) 125 [0–482] 112 [0–386]

Ionic conductance (mSiemens) 168 ± 5.4

Time of massive clotting after inclusion (m) 6.9 ± 5.4

Moderate clotting in the drip chamber (n/sessions) 145/240 (60%)†

Patchy clotting in the dialyzer (n/sessions) 46/240 (19%)†

Platelets (per mm³) 236 000 ± 58 000

Haemoglobin (g/L) 110.2 ± 14.8

Erythropoietina* (IU/kg/week) 125 [0–482]

CRP* (mg/L) 8 [2–159]

Ionic conductance (mSiemens) 168 ± 15

Careful evaluation of partial clotting in the venous drip chamber and in the dialyzer at the end of the session was made in a restricted number of haemodialysis sessions, as indicated in the text. Partial clotting was significantly increased using reduced doses of heparin with the heparin-coated AN69 ST membrane when compared to standard doses of heparin with a non-heparin-coated membrane. Haemoglobin levels, doses of EPO and the ionic conductance rate were measured at the end of the study. Comparison between groups: *P < 0.001, †P < 0.05; otherwise, variables were not significantly different.

<table>
<thead>
<tr>
<th>Type of membrane</th>
<th>Patients (n)</th>
<th>Sessions (n)</th>
<th>Dose of heparin (per session)</th>
<th>Massive clotting (n)</th>
<th>Massive clotting (per 1000 sessions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysulfone</td>
<td>45</td>
<td>7 540</td>
<td>4620 ± 1430</td>
<td>14</td>
<td>1.8</td>
</tr>
<tr>
<td>PMMA</td>
<td>25</td>
<td>4 040</td>
<td>5000 ± 1900</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>CTA</td>
<td>15</td>
<td>2 574</td>
<td>4870 ± 1470</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>14 154</td>
<td>4800 ± 1555</td>
<td>23</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Variables between subgroups were not significantly different.

<table>
<thead>
<tr>
<th>Groups of patients</th>
<th>50% heparin-reduced</th>
<th>Standard heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis membrane</td>
<td>Heparin-coated AN69 ST</td>
<td>Other membrane</td>
</tr>
<tr>
<td>Heparin dose (IU/session)</td>
<td>2718 ± 1388</td>
<td>4800 ± 1555</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Death (n)</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Sessions (n)</td>
<td>12 472</td>
<td>14 154</td>
</tr>
<tr>
<td>Massive clotting (n sessions)</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Massive clotting (per 1000 sessions)</td>
<td>1.4</td>
<td>1.6*</td>
</tr>
</tbody>
</table>

Massive clotting occurred in both groups. It was not time dependent since its mean time occurrence after inclusion in the protocol was 6.9 ± 5.4 [median 7.5 (extremes 1–18)] months in group 1 and 8.2 ± 4.3 [median 9.0 (extremes 4–16)] months in group 2 (P < 0.001). Massive clotting was observed in 17 patients and in 23 patients in groups 1 and 2, respectively (NS).

There were 9/17 and 13/23 events due to ‘massive clotting equivalents’ where blood of the extracorporeal circuit was returned to the patient, avoiding blood spoliation. Expressed per 1000 sessions, an equivalence of the massive coagulation rate between the two groups was observed: 1.4 ± 1.6 for groups 1 and 2, respectively. Moreover, this slight but significant (P < 0.05) difference was observed at the expense of the standard heparinization protocol. This difference was not associated with the prescription of aspirin or antiplatelet drugs in 10 patients in group 1 and 12 in group 2 (NS).

Either by direct evaluation or by analysis of pictures, it was not possible to find a clearcut distinction between low and high clotting intensity in dialyzers that was, by consensus, quoted as ‘patchy clotting’ in the dialyzer and ‘moderate clotting’ in the venous drip chamber. Grade (+) clotting in the venous drip chamber (60% versus 11%) and in the dialyzer (19% versus 5%) were significantly more frequent (P < 0.001) in the heparin-reduced group than in the control group.

Massive clotting occurred in both groups. It was not time dependent since its mean time occurrence after inclusion in the protocol was 6.9 ± 5.4 [median 7.5 (extremes 1–18)] months in group 1 and 8.2 ± 4.3 [median 9.0 (extremes 4–16)] months in group 2 (NS).
the 180th min of dialysis, in the venous blood. As expected, of group 2, APTT and anti-Xa activity were measured at 3 weeks.

and were transiently excluded from the protocol for 1 to by either transcutaneous endoluminal dilatation or surgery, AN69 ST, patients were

Table 4. Heparin dose reduction with the heparin-coated AN69 ST membrane and massive clotting in the extracorporeal circuit

<table>
<thead>
<tr>
<th>Doses of heparin (IU/session)</th>
<th>N patients</th>
<th>N sessions</th>
<th>N massive clotting</th>
<th>Incidence per 1000 sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>1140</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>1000</td>
<td>11</td>
<td>1326</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>2000</td>
<td>13</td>
<td>1956</td>
<td>5</td>
<td>2.6</td>
</tr>
<tr>
<td>3000</td>
<td>23</td>
<td>3048</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>≥ 4000</td>
<td>30</td>
<td>5002</td>
<td>6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Incidence of sessions complicated by massive clotting was calculated for 1000 sessions in the group of patients allocated to 50% heparin reduction using the heparin-coated AN69 ST haemodialyzer. In the table is included the subgroup of patients who did not receive any systemic administration of heparin because of the intercurrent complication considered at high risk of bleeding. In comparison, patients haemodialyzed with 100% heparin doses using the other dialysis membrane had an incidence of massive clotting of 1.6 per 1000 sessions.

3–18) months in group 2 (NS). The proportion of massive clotting versus time in the protocol, calculated according to the Kaplan–Meier method, was not statistically different between the two groups (Figure 2).

In order to further define the relationship between clotting and the anticoagulant effect of the heparin-coated AN69 ST, patients were a posteriori stratified according to the dose of heparin they received. As seen in Table 4, a similar incidence of massive clotting was observed, whatever the dose in use. Heparin administration ranging from 1000 to over 4000 IU per session was associated with massive clotting in 1.2 to 2.6 sessions per 1000 sessions (NS). A small group of eight patients became at risk of bleeding during the study and heparin was withheld during prolonged periods. With 0 dose heparin, incidence of massive clotting was 1.8 per 1000 sessions.

During the study, 12/85 and 15/85 patients in groups 1 and 2, respectively, (NS), required repair of vascular access by either transcutaneous endoluminal dilatation or surgery, and were transiently excluded from the protocol for 1 to 3 weeks.

In a subgroup of 207 sessions of group 1 and 198 sessions of group 2, APTT and anti-Xa activity were measured at the 180th min of dialysis, in the venous blood. As expected, significant differences ($P < 0.001$) were found between the experimental and the control groups: 41 ± 6 s versus 70 ± 18 s and 0.29 ± 0.10 IU/mL versus 0.56 ± 0.16 IU/mL for APTT and anti-Xa activity, respectively. Platelet levels, as measured monthly from arterial sampling, did not change significantly throughout the study.

Baseline haemoglobin concentration (109.8 ± 15.1 g/L in group 1 and 111.6 ± 13.0 g/L in group 2) did not change significantly at the end of the study (110.2 ± 14.8 g/L in group 1 and 112.4 ± 12.5 g/L in group 2) and doses of EPO did not change significantly in either group throughout the study. In any case of massive clotting blood transfusion was prescribed. Ionic clearance, as well as urea clearance, remained constant in both groups, indicating that membrane permeability for small molecules did not change using heparin reduction with the heparin-coated AN69 ST membrane. Similarly, plasma triglycerides and total cholesterol were in the same range throughout the study (data not shown).

**Discussion**

We postulated that decreasing the standard dose of heparin delivered during a dialysis session could increase risk of clotting of the extracorporeal circuit. However, using a membrane coated with heparin may lessen the need of systemic heparin administration without increasing such a risk. Pilot studies have documented that the AN69 ST membrane fulfilled this goal [17,20]. The present controlled, prospective, open study validates such an anticoagulant property in a large series of chronically haemodialyzed patients. More precisely, the use of both the heparin-coated AN69 ST membrane and 50% reduced doses of intravenously heparin did not increase risk of massive clotting observed in a control group of patients haemodialyzed with standard doses of heparin (100%) and dialysis membranes that are unable to bind heparin.

The design of the intention-to-treat study, which was performed in one centre, could have introduced a bias in patient selection, since randomization for membrane allocation was performed before starting the protocol. However, membrane allocation was carefully checked and maintained throughout the study and patients on AN69 ST were carefully matched with control patients. In Table 1, baseline characteristics of the groups were not significantly different, including prescription of aspirin or antiplatelet drugs. Patients were censored in the case of death or prescription of anticoagulant treatment with either low-molecular weight heparin or anti-vitamin K. A limitation of the study could be some lack of statistical power, since the number of sessions to be performed in each group was calculated from estimates of pilot studies. In these studies, as indicated in Statistics, massive clotting occurred more frequently than observed in the present trial. The only explanation we propose is improvement of supervision care due to larger experience in holding the membranes.

At bedside, clotting in the extracorporeal circuit was carefully investigated. Massive clotting was a rough criteria indicating inadequate anticoagulation and in some instances, insufficient dialysis supervision. In the case of
circular clotting in the bubble trap chamber, even without an increase of venous pressure, it was possible to return blood to the patient, sparing some 200 mL of blood contained in the dead space of the circuit. This procedure, considered as equivalent of massive clotting, occurred in nearly 40% of the cases quoted ‘massive clotting’. Incidence of massive clotting was slightly (and significantly) higher in the control group than in the heparin-reduced group: 1.4 and 1.0 per 1000 sessions, respectively ($P < 0.05$). These results fulfill the working hypothesis of the anticoagulant effect of the heparin-coated AN69 ST membrane. Priming the membrane with heparinized saline allows an optimal binding of heparin of some 1200 IU per square metre and heparin shedding is <15% [14].

Evaluation of partial clotting of the circuit can be made throughout the session at the level of the venous bubble trap chamber, whereas clotting in the dialyzer has to be made at the end of the session and may require opening of the dialyzer box. This explains why grading cannot be easily reproduced. A recent study evaluating fibre bundle volume during haemodialysis with Nephral ST dialyzers equipped with the AN69 ST membrane, under the condition of heparin-free haemodialysis, tight heparinization and large doses of heparin, documented the absence of any significant variation between groups [21]. In the present study, partial clotting was evaluated using a set of pictures in a restricted number of sessions in patients starting the protocol (Table 3). A full dose of heparin prevented significant partial clotting as compared with the heparin-reduced group, underlying the effect of membrane-independent hot spots of clotting all along the circuit: changes in tubular section inducing changes of the blood flux rate and disturbed blood rheology, and contact with air in the bubble trap chamber [10].

It was possible to sustain heparin-free haemodialysis for a long period of time in eight patients at risk of bleeding due to surgery or clinical complications, such as rupture of an atherosclerotic arterial plaque inducing cholesterol crystal embolism. In the absence of systemic heparin administration, the massive clotting incidence rate was 1.8 per 1000 sessions, a value similar to that observed in standard haemodialysis. These results confirm results obtained in short pilot studies [17,20]. The use of the heparinized membrane represents an obvious advantage in patients at risk of bleeding.

Predictability of clotting in haemodialysis is not well assessed by the measurement of APPT and anti-Xa activity. In group 1, at the 180th min of dialysis, at least 1 h before the end of the session, these parameters were in the so-called normal range, at risk of clotting. On the contrary, in group 2, biological values in the range of efficient anticoagulation were associated with clotting. Risk of clotting could be evaluated more precisely in measuring generation of free thrombin, as reflected by plasma thrombin–antithrombin (TAT) complex concentration, for example. In a previous study [17] we demonstrated that the heparin-coated AN69 ST membrane delayed significantly the increase of TAT complex levels during a session, when compared to the effects of the mother, and was no longer available for the chronic haemodialysis AN69 membrane, under similar systemic heparin administration. This indicates that heparin is acting inside the protein layer that coats the polygel membrane and that the local anticoagulant effect associated with heparin binding lasts at least a few hours [16,22,23]. This also indicates that there is no late significant heparin shedding from the membrane, as previously documented [16].

Haemoglobin concentration as well as doses of EPO did not change significantly during the study. This indicates that incipient blood spoliation due to increased clotting in the circuit, which could have been associated with insufficient heparin administration, did not occur. These results are also in accordance with the constancy of membrane permeability, as measured by ionic clearance, which did not change significantly in either group, throughout the study.

It was demonstrated that the AN69 ST membrane binds nonfractionated and low-molecular weight heparins [16]. This property, which is associated with the free cationic residues of the polyethyleneimine polymer that lays the surface of the polyacrylonitrile matrix [24], allows heparin binding. At the membrane surface, heparin can interact with coagulation proteins such as ATIII and thrombin. Presently, at bedside, the easy way for coating the AN69 ST membrane with heparin is to use 2 L of heparinized saline (5000 IU/L of heparin) for priming the dialyzer at a rate of 150 mL/min. Manufacturing ready-to-use heparin-coated membranes seems feasible and should improve safety of dialysis.

A heparin-binding membrane has been sought for years with unreliable results. For example, secondary grafting of heparin on a cellulosic membrane, through bridging with polyethylene glycol, has been extensively tested in the field of cardiopulmonary surgery, but does not seem to be suitable for long-term regular haemodialysis [25]. Dialyzers containing diethylaminoethyl-cellulose membranes bind heparin and may allow heparin-free dialysis [14]. However, at bedside, they were not as successful as expected.

In summary, we have validated on a long-term basis results of pilot studies that demonstrated the anticoagulant properties of the heparin-coated AN69 ST dialysis membrane. Using this heparin-coated membrane with 50% reduction of the standard dose of heparin the risk of massive clotting of the extracorporeal circuit was not increased, nor was there any blood loss or reduction in dialysis efficiency. As risk of massive clotting depends on careful supervision of the session and training of the team, and cannot be avoided due to the constraints of the extracorporeal circulation, further studies are required to fully demonstrate the anticoagulant effect of the heparin-coated AN69 ST membrane.

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