Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Chapter 7

Nadroparin versus dalteparin anticoagulation in high-volume, continuous venovenous hemofiltration: A double-blind, randomized, crossover study

Anne-Cornélie J.M. de Pont, Heleen M. Oudemans-van Straaten, Klaas J. Rozendaal and Durk F. Zandstra

Chapter 7

Abstract

Background
To prevent thrombogenesis in the extracorporeal circuit during hemofiltration, several anticoagulant regimens have been proposed. We chose low molecular weight heparins because of their good antithrombotic activity and reduced risk of bleeding in comparison with unfractionated heparin. The first aim of this study was to compare circuit survival times using bioequivalent doses of two different low molecular weight heparins: dalteparin and nadroparin. The second aim of this study was to evaluate other factors influencing circuit survival times.

Methods and results
Thirty-two critically ill patients with renal failure were treated with postdilutional high-volume continuous venovenous hemofiltration with a standard blood flow rate of 200 ml/min and an ultrafiltrate volume of 100 l in 24 h. A highly permeable, large-surface cellulose triacetate membrane was used. Anticoagulation with anti-Xa bioequivalent doses of nadroparin and dalteparin was administered in the extracorporeal line before the filter. Blood was sampled for determination of coagulation variables before, at 0.5, 2, 4, 6, and 12 h and at the end of the hemofiltration run. Anti-Xa peak activity, time of anti-Xa peak activity, area under the curve for 0–3 h and circuit survival time were not significantly different using nadroparin or dalteparin. When analyzing the patients according to the length of circuit survival time, no relationship among anti-Xa peak activity, area under the curve for 0–3 h, and circuit survival time was found. However, there was a strong trend toward a negative correlation between baseline platelet count and circuit survival time ($r^2=0.11; p=0.07$). Mean blood urea nitrogen decreased from 81.0 ± 31.9 to 41.1 ± 21.2 mg/dl ($p<0.01$) and mean creatinine decreased from 3.4 ± 1.8 to 1.9 ± 1.2 mg/dl ($p<0.01$). There were no clinically important bleeding complications.

Conclusions
Nadroparin and dalteparin are bioequivalent with respect to their anti-Xa activities. Using either drug, we did not find a difference in circuit survival time during high-volume continuous venovenous hemofiltration. No relationship between anti-Xa activity and circuit survival time could be found. However, there was a strong trend toward a negative correlation between baseline platelet count and circuit survival time. This suggests that during high-volume, continuous venovenous hemofiltration, patients with a higher baseline platelet count might need a different anticoagulation regimen to obtain longer circuit survival times.
Introduction

Continuous venovenous hemofiltration is used in intensive care medicine as a method of renal replacement and blood purification in patients with multiple organ dysfunction syndrome. The advantages of continuous hemofiltration over hemodialysis include a greater cardiovascular stability [1] and the possibility of extracting cytokines and other middle molecules from the circulation of patients with sepsis and multiple organ dysfunction syndrome [2,3]. A powerful beneficial effect of high-volume, continuous venovenous hemofiltration (HV-CVVH) on hemodynamics was first demonstrated by Grootendorst et al. [4,5] in an animal model of septic shock. In a recent article, Bellomo et al. [6] reported an impressive decrease in the inotropic requirement in patients with septic shock treated by HV-CVVH (6 l/h) compared with standard CVVH (1 l/h). Multiple organ dysfunction syndrome usually develops as a result of a systemic inflammatory response syndrome, after a wide variety of insults, such as trauma, cardiovascular surgery, or cardiogenic or hemorrhagic shock [7]. In our experience, systemic inflammatory response syndrome arising from these insults represents the same clinical response as the septic shock response arising from infection. Consequently, each patient with systemic inflammatory response syndrome could potentially benefit from HV-CVVH.

To prevent clotting in the extracorporeal circuit, several anticoagulation regimens have been proposed: unfragmented heparin, low molecular weight heparin, prostacyclin, citrate, serine-esterase inhibitors, saline flushes, and regional anticoagulation. We chose low molecular weight heparins because of their good antithrombotic activity and reduced risk of bleeding in comparison with unfragmented heparin [8,9]. The biological activity of low molecular weight heparins is generally quantified by the extent of factor Xa inhibition. However, the correlation between anti-Xa activity and efficacy of anticoagulation is questionable [10-12]. Therefore, anti-Xa bioequivalence does not implicate equal clinical efficacy. Until 1995, we used dalteparin to prevent clotting in the extracorporeal circuit. In 1995, we switched to nadroparin because of its lower price and proven efficacy during hemodialysis [13-14]. However, mean filter survival times seemed shorter using nadroparin. One aim of the present study was to compare filter survival times during HV-CVVH in patients with normal coagulation variables, using anti-Xa bioequivalent doses of dalteparin and nadroparin. A second aim was to evaluate other factors influencing filter survival time.
Chapter 7

Materials and methods

Patients
The study was approved and the need for informed consent was waived by our institutional review board. Patients with an indication for HV-CVVH were eligible for the study. Indications for HV-CVVH were renal failure, associated with volume overload, uremia, acidosis, or sepsis. Exclusion criteria were the intravenous use of heparin or low-molecular weight heparin 12 h before the start of the study and/or manifest bleeding or manifest clotting disorder (defined by a prothrombin time (PT) of >=20 s and/or an activated partial thromboplastin time (APTT) of >=60 s).

Study Design
Before the first HV-CVVH run, patients were randomized by our hospital pharmacist to receive either dalteparin (Pharmacia & Upjohn, Woerden, The Netherlands) or nadroparin (Sanofi Winthrop, Maassluis, The Netherlands). Patients and investigators were blinded for the study medication used. Patients eligible for a second hemofiltration run after an interval of at least 12 h received the other study medication in a crossover fashion. Each patient was only studied once on each study medication. Patients in the crossover study served as their own control. Coagulation variables and filter survival times were compared for the two study medications used. Second, to analyze which factors are related to filter survival time, all patients were divided into two groups according to the filter survival time of their first HV-CVVH run. Group 1 had a filter survival time of more than the median of 18 h, and group 2 had a filter survival time of <18 h. Coagulation variables were compared between groups.

Hemofiltration Procedure
Vascular access was obtained by insertion of a double-lumen polyurethane catheter (Circle C, Neostar, Atlanta, GA) into a large vein (femoral, subclavian, or internal jugular vein). Hemofiltration was performed using a hemoprocessor (40020 GS, Sartorius GmbH, Göttingen, Germany) and a highly permeable cellulose triacetate membrane with a filtration surface of 1.9 m² (Nipro hemofilter, UF 205, Nissho, Osaka, Japan) (Figure 1). The standard blood flow rate was 200 ml/min and substitution fluid was added after the hemofilter (postdilution). On the ultrafiltration side of the hemofilter, a constant negative pressure of 75 mmHg was applied by means of an ultrafiltrate pump, resulting in a filtration fraction gradually declining from 50% to 25%. The aim of each HV-CVVH run was to exchange 100 l in -24 h (4 l/h). This volume was calculated to reach an ultrafiltration volume similar to the one used by Grootendorst et al. [4,5] in their animal model of HV-CVVH (0.8 l/kg). In humans with a mean body weight of 70 kg, ~50 l would have to be ultrafiltrated to reach an equivalent volume. We selected intermittent 24 h
sessions, interrupted by a rest period of >=12 h, to make a more efficient use of the available hemofiltration machines. To achieve a mean ultrafiltration rate of 50 l/day, this resulted in intermittent hemofiltration sessions of 100 l/2 days. The HV-CVVH run was stopped when a total of 100 l had been ultrafiltrated or when clotting in the hemofilter had occurred.

Figure 1. High-volume, continuous venovenous hemofiltration circuit. AC, anticoagulation; HF, hemofilter; BT, bubble trap; B, blood pump; U, ultrafiltrate pump; S, substitution pump; WE, warming element; UF, ultrafiltrate; SF, substitution fluid.

Anticoagulant Administration
Dalteparin has an average molecular weight of 4000–6000 daltons and a specific anticoagulant activity of 160 anti-Xa IU/mg [8]. Nadroparin has an average molecular weight of 4500 daltons and a specific anticoagulant activity of 200 anti-Xa Institut Choay-U (IC-U)/mg (equivalent to 82 anti-Xa IU/mg) [14]. The extracorporeal circuit was primed for 15 min with a continuous infusion of either 400 IU of dalteparin or 1000 IC-U of nadroparin (equivalent to 410 IU). Anticoagulants were administered in the extracorporeal line before the filter. Patients received a loading dose of either 2000 IU of dalteparin or 5000 IC-U nadroparin (equivalent to 2050 IU). After this, anticoagulation was maintained by continuous infusion of either 320 IU of dalteparin/h or 800 IC-U of nadroparin/h (equivalent to 328 IU/h).
Laboratory Assays
Blood was drawn in citrate for determination of the anti-Xa activity at baseline, 0.5, 2, 4, 6, and 12 h after starting and at the end of the HV-CVVH run. Citrated plasma was frozen at -20°C (-4.0°F) for later determination of the anti-Xa activity using a chromogenic substrate (Spectrolyse Heparin, Biopool, Burlington ON, Canada). Platelet counts, PT, and APTT were determined at baseline, after 6 h, and at the end of the HV-CVVH run. Hemoglobin, blood urea nitrogen, and creatinine were measured before and after the HV-CVVH run.

Statistical Analysis
Data are reported as mean ± SD. For the crossover part of the study, data were analyzed using the Student’s t-test for paired variables. An effect of treatment order was sought using analysis of variance and the Student’s t-test. A p<0.05 was considered statistically significant. In addition, a 95% confidence interval of the observed difference was calculated.

For the analysis of factors influencing filter survival time, first-order analysis of variance was used. Means were compared using the Student’s t-test for independent variables. In addition, linear regression for continuous variables was performed.

Results
Patient Characteristics
Thirty-two critically ill patients with renal failure were enrolled in the study. Their characteristics are shown in Table 1. Fourteen patients received a second HV-CVVH run. Two of these patients were excluded from the crossover study because of protocol violations: one patient received the wrong medication, and in one patient, the hemofiltration procedure was terminated for a computed tomography scan. The 12 patients included in the crossover study were ten males and two females, mean age 69.5 ± 10.6 yrs, mean body weight 83 ± 12 kg, and mean Acute Physiology and Chronic Health Evaluation II score 25 ± 4. Four of these patients had a first-run filter survival time of >18 h; eight patients had a first-run filter survival time of <18 h (not significant).

Eighteen patients had a single HV-CVVH run: in 14 patients, renal function recovered, and four patients died before the second HV-CVVH run could take place, attributable to causes unrelated to the HV-CVVH treatment (three from multiple organ failure and one from septic shock). In total, 12 of the 32 patients died, but none of the deaths was related to the HV-CVVH procedure (six from multiple organ failure, two from intestinal ischemia, two from respiratory failure, one from septic shock, and one from upper gastrointestinal bleeding).
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>21</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>31</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>12</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>1</td>
</tr>
<tr>
<td>Mean body weight (kg ± SD)</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>27 ± 7</td>
</tr>
</tbody>
</table>

APACHE, Acute Physiology and Chronic Health Evaluation.

Crossover Study

Anti-Xa peak activity, time of anti-Xa peak activity, area under the plasma concentration vs time curve for 0-3 h and filter survival time were not significantly different using nadroparin or dalteparin. Mean PT, mean APTT and baseline platelet count also were not significantly different (Table 2). Treatment order did not influence filter survival time (F=0.16; p=0.70).

Table 2. Crossover study; coagulation variables and filter survival time

<table>
<thead>
<tr>
<th>Coagulation variable</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of anti-Xa_max (h)</td>
<td>0.5 ± 0</td>
<td>0.63 ± 0.43</td>
<td>-0.15–0.40</td>
<td>.34</td>
</tr>
<tr>
<td>AUC0-3</td>
<td>1.06 ± 0.35</td>
<td>1.10 ± 0.44</td>
<td>-0.29–0.38</td>
<td>.80</td>
</tr>
<tr>
<td>Mean PT (s)</td>
<td>14.9 ± 1.3</td>
<td>15.8 ± 2.4</td>
<td>-0.79–2.44</td>
<td>.30</td>
</tr>
<tr>
<td>Mean APTT (s)</td>
<td>41.4 ± 8.3</td>
<td>44.2 ± 9.5</td>
<td>-4.8–10.5</td>
<td>.45</td>
</tr>
<tr>
<td>Baseline platelet count (x 10^9/l)</td>
<td>167 ± 114</td>
<td>163 ± 138</td>
<td>-110–104</td>
<td>.95</td>
</tr>
<tr>
<td>Filter survival time (h)</td>
<td>15.0 ± 9.9</td>
<td>15.4 ± 7.4</td>
<td>-7.0–7.8</td>
<td>.92</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval for difference; anti-Xa_max, maximum level of factor Xa inhibition; AUC0-3, area under the plasma concentration vs time curve for 0-3 h; PT prothrombin time; APTT, activated partial thromboplastin time.
Analysis of Factors Related to Filter Survival Time

All 32 patients were analyzed on an intention-to-treat basis. The filter survival time during the first HV-CVVH run varied from 3 to 32 h, with a median of 18 h. During this first run, 16 patients had a filter survival time of more than the median of 18 h (group 1; mean filter survival time, 24.1 ± 3.0 h), and 16 patients had a filter survival time of less than the median of 18 h (group 2; mean filter survival time, 11.2 ± 4.5 h). The characteristics of these two subgroups of patients are shown in Table 3. There was no significant difference in anti-Xa peak activity, area under the curve for 0-3 h, mean PT, or mean APTT between these two groups (Table 3). However, there was a strong trend toward a negative correlation between baseline platelet count and filter survival time (r²=0.11; p=0.07) (Figure 2). In both groups, the mean platelet count decreased throughout hemofiltration: from 102 ± 57 x 10⁹/l to 92 ± 54 x 10⁹/l in group 1 (not significant) and from 155 ± 119 x 10⁹/l to 131 ± 101 x 10⁹/l in group 2 (p<0.01).

Table 3. Analysis of factors related to the filter survival time of the first high-volume, continuous venovenous hemofiltration run

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Men/women</td>
<td>9/7</td>
<td>12/4*</td>
</tr>
<tr>
<td>Mean age (yr ± SD)</td>
<td>71 ± 9</td>
<td>67 ± 11</td>
</tr>
<tr>
<td>Mean body weight (kg ± SD)</td>
<td>75 ± 10</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>APACHE II score (mean ± SD)</td>
<td>26 ± 8</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Nadroparin/Dalteparin</td>
<td>6/10</td>
<td>10/6</td>
</tr>
<tr>
<td>Anti-Xaₘₐₓ (IU/ml)</td>
<td>0.50 ± 0.18</td>
<td>0.52 ± 0.20</td>
</tr>
<tr>
<td>AUC₀₋₃</td>
<td>1.18 ± 0.51</td>
<td>1.13 ± 0.56</td>
</tr>
<tr>
<td>Mean PT (s)</td>
<td>16.3 ± 2.1</td>
<td>17.5 ± 2.5</td>
</tr>
<tr>
<td>Mean APTT (s)</td>
<td>46.3 ± 10.8</td>
<td>46.9 ± 12.9</td>
</tr>
<tr>
<td>Baseline platelet count (x10⁹/l)</td>
<td>102 ± 56</td>
<td>155 ± 119</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval for difference; APACHE, Acute Physiology and Chronic Health Evaluation; Anti-Xaₘₐₓ, maximum level of factor Xa inhibition; AUC₀₋₃, area under the plasma concentration vs time curve for 0-3 h; PT, prothrombin time; APTT, activated partial thromboplastin time. *p=0.046
Metabolic control
In all patients, mean blood urea nitrogen decreased from 81.0 ± 31.9 to 41.1 ± 21.2 mg/dl (29.4 ± 11.1 to 14.7 ± 7.6 mmol/l; p<0.01), averaging a decrease of 2.8 ± 2.4 mg/dl/h (1.0 ± 0.9 mmol/l/h). Blood urea nitrogen decrease/h was higher in patients with a filter survival time of <18 h (3.5 ± 3.5 vs 2.2 ± 1.1 mg/dl/h; 1.3 ± 1.2 vs 0.8 ± 0.4 mmol/l/h), reflecting the decrease in filter permeability over time. Mean creatinine decreased in all patients from 3.4 ± 1.8 to 1.9 ± 1.2 mg/dl (304 ± 160 to 172 ± 108 μmol/l; p<0.01) averaging a decrease of 0.12 ± 0.14 mg/dl/h (10.2 ± 12.1 μmol/l/h). As with the decrease in blood urea nitrogen, the decrease in creatinine/h was higher in patients with a filter survival time of <18 h: 0.2 ± 0.2 vs 0.1 ± 0.0 mg/dl/h (15.5 ± 19.3 vs 6.5 ± 2.6 μmol/l/h).

Complications
No major bleeding complications and no thromboembolic complications were documented. We observed no significant differences in clinical bleeding between the two anticoagulation regimens. Two patients experienced an episode of gastrointestinal bleeding using nadroparin, whereas one patient had an increase in chest tube blood drainage using dalteparin. Neither of these bleeding episodes was clinically important. There were no differences in demand for packed red blood cells between the two anticoagulation regimens (0.7 ± 0.9 vs 0.3 ± 0.7 units), and hemoglobin remained unchanged throughout the study. A low-baseline platelet count was not associated with increased bleeding episodes.
Discussion

The best regimen to prevent clotting in the extracorporeal circuit during continuous venovenous hemofiltration remains to be found. Although low molecular weight heparins have been reported to be an effective and safe form of anticoagulation during hemodialysis [15,16], reports on their efficacy during continuous venovenous hemofiltration are scarce and lack reproducibility. Moreover, the dose-effect relationship is unclear, and the value of anti-Xa activity as a monitoring variable is questionable [17].

In the present study, we tried to find an explanation for the high-frequency rate of premature filter clotting we experienced using nadroparin in postdilutional HV-CVVH. We demonstrated that this highly premature clotting frequency rate could not be attributed to a difference in pharmacokinetics between nadroparin and dalteparin. In fact, nadroparin and dalteparin had the same rate and extent of bioavailability as described by their maximum anti-Xa concentration, time for appearance of anti-Xa activity, and area under the plasma concentration vs time curve. Thus, they proved to be bioequivalent with respect to their anti-Xa activities, according to the guidelines of the Commission of the European Communities [18].

When we analyzed the factors influencing filter survival time, we found no relationship between anti-Xa activity and filter survival time. This confirms the finding of Journois et al. [17], who clearly demonstrated the absence of a relationship between anti-Xa activity and hemofilter performance as expressed by the membrane permeability index in postdilutional continuous venovenous hemofiltration.

We found a strong trend toward a negative correlation between baseline platelet count and filter survival time. This confirms the reports of two retrospective studies that patients with a higher baseline platelet count require more heparin to reach the same filter survival time [19,20], which could be attributable to the higher concentration of platelet factor 4. The fact that platelet activation plays a central role in filter clotting is supported by the finding that filter survival time can be prolonged by adding prostacyclin to the current anticoagulation regime [17, 21]. However, filter clotting cannot entirely be prevented by adding prostacyclin.

The high-frequency rate of premature filter clotting in postdilutional HV-CVVH with a highly permeable filter might be related to the higher blood flow velocity and the higher viscosity near the end of the hemofilter, resulting in a more turbulent flow and higher shear stress on the platelets than in low-volume hemofiltration. In postdilutional hemofiltration, at the ultrafiltration rate we used (100 l/24 h), the hematocrit at the end of the hemofilter may rise by as much as 50%. The mean filter survival time we found (16.9 ± 7.9 h) was significantly shorter than the one reported by Martin et al. [19] (24.7 ± 13.2 h), using low-dose standard heparin and postdilution. This is probably the result of the lower blood flow rate they used (100-150 ml/min), reducing the effect of
turbulence and shear stress on the platelets. However, our mean filter survival time was similar to the one found by Langenecker et al. [21] (14.3 ± 3 h), using a flow rate of >150 ml/min, standard heparin and predilution. This suggests that blood velocity may play a more important role than blood viscosity. By using HV-CVVH with low-molecular weight anticoagulation, we achieved an excellent metabolic control without experiencing clinically important bleeding complications.

In summary, the current prospectively randomized, crossover study shows that nadroparin and dalteparin are bioequivalent with respect to their anti-Xa activities. By using either drug, we did not find a difference in filter survival time during high-volume, continuous venovenous hemofiltration. Moreover, this study adds to the reports that platelets play an important role in the initiation of hemofilter clotting during continuous venovenous hemofiltration. Methods to overcome this problem may include heparin coating of membranes and tubing [22] and the use of pharmacologic agents capable of interfering in platelet activation by shear stress [23]. Further studies are needed to determine the efficacy and safety of these methods.
References


