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Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study

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Abstract *Objective:* The purpose of this study was to evaluate the efficacy and safety of the low molecular weight heparin enoxaparin as anticoagulant in continuous veno-venous hemofiltration (CVVH) compared with unfractionated heparin. *Design:* Prospective randomized controlled crossover study. *Setting:* Medical and Surgical Intensive Care Unit of a University Hospital. *Patients:* Forty consecutive adult medical and surgical ICU patients with normal anticoagulation parameters requiring CVVH. *Intervention:* CVVH was performed with pre-filter fluid replacement at 2500 ml/h and blood flow rates of 180 ml/min. Heparin-treated patients received an initial pre-filter bolus of 30 IU/kg and a maintenance infusion at 7 units/kg h^{-1}, titrated to achieve a systemic activated partial thromboplastin time (aPTT) of 40–45 s. Enoxaparin-treated patients received an initial pre-filter bolus of 0.15 mg/kg and a maintenance infusion starting at 0.05 mg/kg h^{-1}, which was subsequently adjusted to maintain systemic anti-factor Xa activity (anti-Xa) at 0.25–0.30 IU/ml. Each patient received both regimens in a crossover design. Maximum treatment duration for each set was 72 h. *Results:* Patients included had a mean APACHE II score of 22 (10–35). Thirty-seven patients completed both study arms. Mean filter life span was 21.7 h (± 16.9 h) for heparin and 30.6 h (± 25.3) for enoxaparin ($p = 0.017$, ANOVA for repeated measures). One major bleeding episode occurred during heparin as well as during enoxaparin treatment. Cost analysis showed average daily costs of 270 and 240 € for heparin and enoxaparin, respectively. *Conclusion:* Enoxaparin can be safely used for anticoagulation during CVVH resulting in higher filter lifespan compared with unfractionated heparin.

Keywords anticoagulation · CVVH · renal replacement therapy · costs · safety · unfractionated heparin · low molecular weight heparin · filter life span · Enoxaparin

Introduction

Continuous veno-venous hemofiltration (CVVH) has become the method of choice for renal replacement therapy in the critically ill. Since the efficacy of this form of therapy depends on running time of the system, anticoagulation has become a major issue.

Throughout Europe unfractionated heparin is the major anticoagulant used because of its low initial cost, ease of administration, simple monitoring and reversibility with protamine [1, 2]. Unfractionated heparin (UFH) is a mixture of heparin molecules ranging from 5–30 kDa and acts by a 1000-fold potentiation of antithrombin (AT) equally inhibiting factors Xa and thrombin (IIa); however,

heparin binds non-specifically to drugs, cells, and proteins. Major side effects of UFH include systemic bleeding, hypoaldosteronism, effects on serum lipids, and development of heparin-induced thrombocytopenia (HIT) [3, 4].

On the other hand, low molecular weight heparins (LMWH) exhibit a higher anti-Xa:anti-IIa activity than UFH, ranging from 4:1 to 2:1. LMWH exhibit lower AT affinity, less platelet activation, less inactivation by platelet factor 4 (PF4) and less binding to plasma proteins resulting in higher and more constant bioavailability [3]. When used as anticoagulant in chronic hemodialysis LMWH are associated with reduced bleeding [5–7] and less influence on serum lipids [8, 9]. Frequency of HIT appears lower with LMWH as compared with UFH [4]. Despite these advantages over UFH, data regarding the use of LMWH in continuous renal replacement therapy (CRRT) are very limited [10–12].

The aim of this prospective, randomized controlled crossover trial was to compare efficacy, safety, and cost efficiency of the LMWH enoxaparin in comparison with unfractionated heparin in CVVH. The primary outcome was filter survival and the secondary outcome data were costs and bleeding events. The preliminary results of the study were presented at the 17th annual Congress of ESICM [13].

Patients and methods

Patient selection

This study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all patients. For incompetent patients informed consent was waived by the Ethics Committee and an "ex-post" information of patients about their participation in the study was required according to Austrian Law [14].

Adult surgical and medical ICU patients with an indication for CVVH were eligible for the study. Indications for CVVH were acute renal failure, persistent oliguria, severe acidosis, and septic shock with renal impairment. Exclusion criteria were intravenous use of heparin or enoxaparin within 12 h before start of the study, manifest bleeding or manifest clotting disorder as defined by PT (quick) $< 50\%$, INR > 1.8, activated partial thromboplastin time aPTT > 45 s, platelet count $< 50 \times 10^9$/l, known hypersensitivity for heparins or expected/scheduled surgery or intervention requiring interruption of CVVH within the next 72 h.

Hemofiltration procedure

The CVVH was performed using BM 25 hemofiltration machines (Edwards Lifesciences, Irvine, Calif.) with pre-filter fluid replacement adjusted at 2500 ml/h and blood flow rates of 180 ml/min.

Vascular access was obtained via a 11.5-F/CH double-lumen catheter (Mahurkar, Tyco/Healthcare Kendall, Mansfield, Massachusetts) introduced either into the right internal jugular or femoral vein. To avoid variations due to vascular access, site, and type of catheter were not allowed to be changed between treatment arms.

A bicarbonate based solution was used as substitution fluid (multiBIC, Fresenius Medical Care, Bad Homburg, Germany) Polysulfone high efficiency hollow fiber hemofilters (PSHF 1200 Edwards Lifesciences, Irvine, Calif.) were primed with 1 l of normal saline containing anticoagulant (5000 IU heparin or 25 mg enoxaparin, respectively). Anticoagulation was administered continuously via a perfusor in a pre-filter fashion. Heparin-treated patients received an initial pre-filter bolus of 30 IU/kg and a maintenance infusion at 7 units/kg h^{-1}, titrated to achieve a systemic activated partial thromboplastin time (aPTT) of 40–45 s. Enoxaparin-treated patients received an initial pre-filter bolus of 0.15 mg/kg (1 mg = 100 IU anti-factor Xa equivalent) and a maintenance infusion starting at 0.05 mg/kg h^{-1}, which was subsequently adjusted to maintain systemic anti-factor Xa activity (anti-Xa) at 0.25–0.30 IU/ml. Peak levels 4 h after subcutaneous injection of LMWH between 0.1 and 0.4 IU/ml are recommended for primary prophylaxis [15, 16] and levels > 0.5 IU/ml are recommended for intermittent hemodialysis [17]. Coagulation tests were performed in blood samples drawn at baseline, 0.5, 1, 2, 4, 12, 24, and 48 h after initiation and at the end of CVVH. Coagulation tests within the first 4 h were used for calculations of the AUC. First adjustment of anticoagulant dose was recommended on basis of the anticoagulation test obtained at 2 h and followed by subsequent time points. Hemofilter life span was measured from the time of commencement to the time of an increase of the transmembranous pressure (TMP) above 350 mmHg or spontaneous failure (clotting). Maximum treatment duration for each set was 72 h.

Study design

This prospective randomized controlled cross-over trial was designed to detect a 50 % increase in filter survival time with a beta error of 20% ($\beta = 0.2$) according to the previously observed mean filter survival of 18 h ($\pm$ 14 SD) using heparin as anticoagulant in our ICU. Based on this calculation 40 patients were required (including 4 dropouts).

Before initiation of CVVH patients were randomized by a statistician (H.U.) to receive either unfractionated heparin (A) or enoxaparin (B) for the first run (Fig. 1). Patients eligible for a second hemofiltration run after an interval of at least 12 h received the other medication in a crossover fashion. If treatment was required within

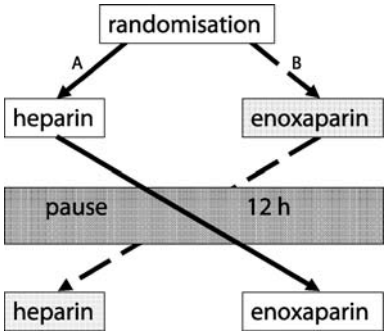

Fig. 1 Study design. The study was designed as a randomized controlled trial using a crossover design. Every patient was treated with both forms of anticoagulation. Randomization to either arm *A* or *B* decided the order of anticoagulation. A wash-out time of 12 h was applied between each anticoagulation cycle

this interval, CVVH without anticoagulation was allowed per protocol. Each patient was only studied once. Filter survival times and coagulation variables were compared for the two study medications used.

Laboratory assays

Hemostatic parameters were determined by routine laboratory methods. Prothrombin time (PT) was determined using a clot assay (ThromborelS, Dade Behring, Marburg, Germany). The activated partial thromboplastin time (aPTT) was determined via clot assay (Pathromtin SL, Dade Behring, Marburg, Germany). Anti-Xa activity was determined using a chromogenic substrate (Hyphen BioMed, Neuville-sur-Oise, France). D-dimer levels were determined with a latex-enhanced turbidimetric test for the quantitative determination of cross-linked fibrin degradation products containing D-dimer in human plasma using a Dade Behring Coagulation Analyzer. Total blood count determination was done automated on Sysmex NE 7000 hematology analyzer.

Safety monitoring

To insure maximal patient safety close observation of coagulation parameters was performed. Any significant reduction of platelet count (> 50%) within 24 h raising clinical suspicion of possible heparin-induced thrombocytopenia (HIT) [18] was investigated in terms of present heparin-PF 4 antibodies (ELISA test).

Major bleeding was defined as a clinically significant hemorrhage (i.e., serum hemoglobin reduction of more than 1 mg/dl day^{-1}) requiring substitution of packed red blood cells, and bleeding causing a reduction of less than 1 mg/dl day^{-1} of serum hemoglobin was deemed minor.

Cost analysis

The average daily costs of CVVH (see Table 1), in Euro (€), were calculated from the following values: (a) daily costs independent from filter run times (i.e., substitution fluids, bags); (b) the "per-set" costs for disposables (filters, lines, syringes, saline bags, priming solutions) multiplied by the numbers of sets required in 24 h based on average filter-run times of each group; and (c) costs for anticoagulant testing (aPTT or anti-FXa, determined twice daily) and for each anticoagulant derived from average daily dose. Cost of labor, equipment, and vascular access were not included.

Statistical analysis

The SPSS 11.0. software package (SPSS, Chicago, Ill.) was used for statistical analysis. Results are given as mean ± SD. Filter run times were compared using a two-way ANOVA for repeated measurements adjusting for the order of treatment. For better illustration filter survival was shown as Kaplan-Meier plot. Intention-to-treat as well as per-protocol analysis were performed. The same ANOVA model was used to compare anti Xa or aPTT levels over time followed by post-hoc Tukey's multiple comparison tests. Baseline coagulation parameters were compared using paired Student's *t*-test. Correlations between variables were assessed using Pearson's correlation coefficient. Al-

Table 1 Comparison costs (€) for UFH and enoxaparin as anticoagulation for CVVH

	Heparin	Enoxaparin
Sets (filters) per day	1.11	0.78
Costs per set (filter, lines, priming solutions, disposals)	120.22 €	120.22 €
Mean anticoagulant dose per day	14,160 IU	86.4 mg
Costs anticoagulants per 100 IU UFH/1 mg LMWH	0.06 €	0.17 €
Daily costs (€)		
Set (= filter) associated costs	132.96	94.29
Anticoagulants	8.50	14.69
Anticoagulation tests (aPTT/ aXa; two tests/24 h)	4.50	7
Replacement fluid and disposal bags (UF rate = 2.5 l/h)	124.20	124.20
Total cost per day	270.16	240.18

though filter run times were slightly right skewed distributed, application of Kolmogorov-Smirnov test showed that measurements fulfilled approximately normal distribution; however, non-parametric testing using a Wilcoxon test was applied to confirm the results of the ANOVA model for the primary endpoint. A p-value of < 0.05 was considered significant.

Results

Patient characteristics

Forty critically ill patients with renal failure were enrolled in the study between October 2001 and July 2004 (Table 2). This enrollment period was required because of restrictive criteria with respect to coagulation parameters excluding many patients treated in our unit (i.e., hematological or liver disease, DIC). A total of 37 patients completed both study arms. None of these patients required an additional CVVH treatment between treatment arms. In one patient CVVH was discontinued after having finished the heparin arm because of clinical improvement obviating further hemofiltration. One patient showed a major bleeding episode during UFH cycle (= second run, anti-Xa 0.17 IU/ml, aPTT 51, PT 65%, platelets 64,000) precluding further anticoagulation. One patient showed major bleeding from central venous catheter exit site in the enoxaparin study arm (= second run, anti-Xa 0.35 IU/ml, aPTT 37 s, PT 69%, platelets 37,000). In this patient CVVH was continued without anticoagulation, and he died 4 days later secondary to intractable septic shock with multiple organ failure.

Crossover study

Baseline values of the studied coagulation parameters (aPTT, PT, AT III, fibrinogen, anti-Xa, thrombocyte count, D-dimer levels) were not significantly different at the beginning of the crossover study for either enoxaparin or UFH (Table 3).

Primary end point (filter life)

Per-protocol analysis

In the per-protocol analysis ($n = 37$) only those patients were included who completed both treatment arms, i.e., heparin and enoxaparin. Filter life was significantly longer during anticoagulation with enoxaparin compared with heparin resulting in a mean filter life of 21.7 ± 17.4 h for heparin and 30.6 ± 25.1 h for enoxaparin, respectively ($p = 0.017$, ANOVA for repeated measurements). Applying non-parametric testing (Wilcoxon test) also showed a significant difference [$p = 0.035$, median filter life (IQR): 15.5 h (8.9–31.9) for heparin, 24 h (6.9–50.8) for enoxaparin].

Intention-to-treat analysis

To perform an intention-to-treat analysis ($n = 40$) missing filter run times of the second run were replaced by the patient-specific value of the first run (lost observation carried forward). As in the per-protocol analysis, filter life was significantly higher during anticoagulation with enoxaparin (filter life: 23.5 ± 18.9 h for heparin

Table 2 Patient characteristics

Patient characteristics		Diagnosis on admission	No. of patients
Men	26	Sepsis	17
Women	14	Acute respiratory failure	9
Age (years) ± SD (range)	57 ± 16 (25-93)	Post-operative acute renal failure	5
Body weight (kg)	77.2 ± 18	Acute heart failure	3
APACHE II	22 ± 6	CPR	3
SAPS II	48 ± 2	Other	3
No. of patients on catecholamines	19		

Table 3 Initial coagulation parameters at the beginning of each treatment

	Heparin ($n = 40$)	Enoxaparin ($n = 40$)	Significance (p)
aPTT (s)	41.82 (± 2.32)	42.25 (± 2.41)	0.996
PT (%)	79.94 (± 2.7)	81.77 (± 2.5)	0.719
Anti-Xa (IU/ml)	0.14 (± 0.21)	0.13 (± 0.10)	0.379
Thrombocytes (per milliliter)	158,918 (± 17,257)	160,971 (± 18,884)	0.866
Antithrombin (%)	79.03 (± 3.88)	79.44 (± 3.9)	0.878
Fibrinogen (mg/dl)	527 (± 33)	548 (± 36)	0.653
D-dimer (mg/dl)	1066.35 (± 266)	1211.57 (± 210.6)	0.297

and 31.8 ± 25.2 h for enoxaparin; $p = 0.019$, ANOVA for repeated measurements). Applying non-parametric testing (Wilcoxon test) also showed significant difference [$p = 0.035$, median filter life (IQR): 17.0 h (9.5–32.5 h) for heparin, 24.0 h (7.1–51.6 h) for enoxaparin].

Data are also shown as Kaplan-Meier curve for filter survival (Fig. 2). Order of treatment did not influence filter survival time ($p = 0.287$, two-way ANOVA for repeated measurements). We could not find any significant correlation between peak or steady-state aPTT or anti-Xa levels and filter survival. During anticoagulation with enoxaparin mean areas under the curve for the first 4 h (AUC_{0-4h}) were 0.727 ± 0.594 and 0.933 ± 0.634 IU h/ml for systemic and post-filter anti-Xa, respectively. $AUCs_{0-4h}$ and filter survival did not show any correlation. Average anti-Xa levels determined during CRRT showed values between 0.20 and 0.35 IU/ml (Fig. 3). Postfilter anti-Xa were consistently higher (0.27–0.42 IU/ml; $p < 0.001$, two-way ANOVA). Both systemic and post filter anti-Xa values tended to be higher at later time points (≥ 12 h) than at the beginning of CRRT ($p < 0.05$, Tukey's multiple comparison test; Fig. 3A). No other coagulation parameter (aPTT, PT, fibrinogen, AT III, D-Dimer, platelet count) appeared to have an influence on filter survival.

During anticoagulation with UFH (Fig. 4) post-filter aPTT were significantly higher than systemic values (two-way ANOVA, $p = 0.0059$ and 0.0046). Systemic aPTT levels were significantly higher 0.5 h than at 12 h after start of CVVH, post-filter aPTT levels showed a significant difference between 0.5 and 4, 12, and 24 h ($p < 0.05$, Tukey's multiple comparison test). Systemic and post-filter anti-Xa were not found to be statistically different (two-way ANOVA) during treatment with UFH.

Both in the UFH and the enoxaparin group maintenance dose had to be increased significantly within the first 12 h to reach respective aPTT or anti-Xa target values (Figs. 3B, 4C).

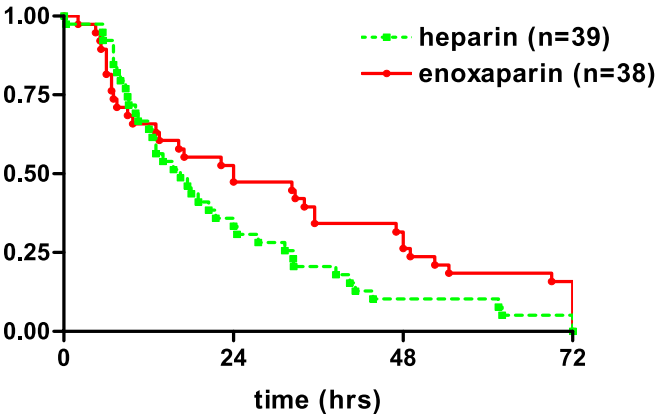

Fig. 2 Kaplan–Meier plot of filter survival during heparin and enoxaparin anticoagulation in CVVH ($p = 0.035$, ANOVA for repeated measurements)

Secondary outcomes

No significant change in platelets was found during the two anticoagulation regimens, the average change in platelet count (10^9/l) during one course of CVVH being 1.038 ± 32.807 for heparin and 1.143 ± 40.858 for enoxaparin ($p = 0.539$). The mean steady-state dose was 590 ± 46 IU/h for heparin and 3.6 ± 0.2 mg/h for enoxaparin. No case of HIT occurred in either study group.

One patient showed minor bleeding from a previous surgical intervention, which persisted in both study arms. As reported above, one major bleeding occurred under heparin and enoxaparin, respectively. Anticoagulant infusion was stopped in each case.

Cost analysis

The total daily costs of CVVH were 270.16 € during anticoagulation with heparin and 240,14 € during anticoagulation with enoxaparin (based on per-protocol

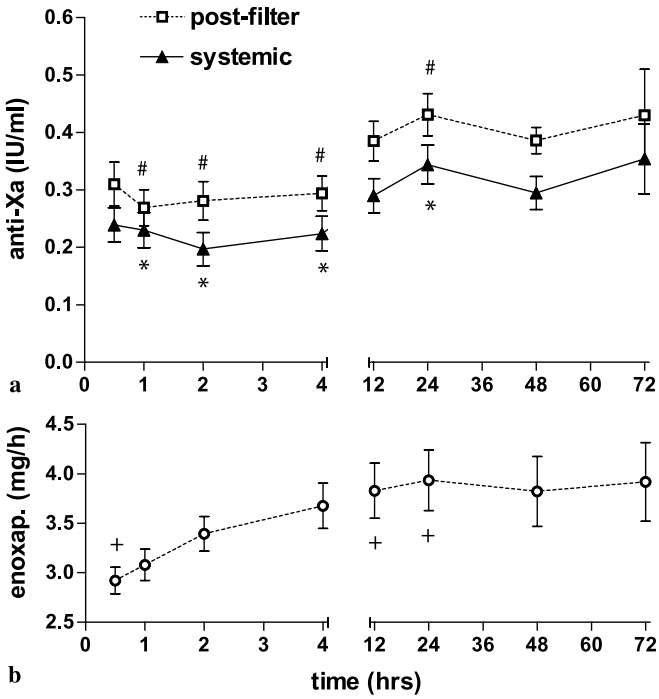

Fig. 3 **a** Average systemic and post-filter anti-Xa levels during CVVH using enoxaparin anticoagulation. Systemic and post-filter anti-Xa were significantly different (two-way ANOVA, $p = 0.0008$ and 0.0005). *Asterisk:* systemic anti-Xa levels 24 h after start of CVVH were significantly different from levels 1, 2, and 4 h after start ($p < 0.05$, Tukey's multiple comparison test). *Hatch symbol:* post-filter anti-Xa levels 24 h after start of CVVH were significantly different from levels 1, 2, and 4 h after start ($p < 0.05$, Tukey's multiple comparison test). **b** Average enoxaparin dose during CVVH. *Plus sign:* significant difference at 12 and 24 h compared with 0.5 h (ANOVA, $p < 0.05$, Tukey's multiple comparison test)

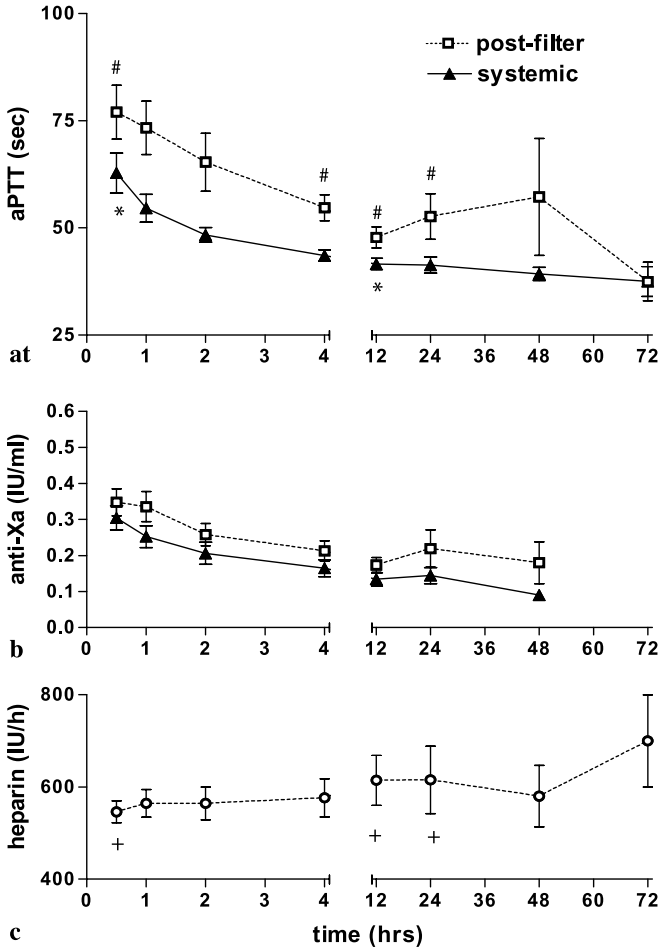

Fig. 4 Average systemic and post-filter aPTT (**a**) and anti-Xa levels (**b**) during CVVH using unfractioned heparin anticoagulation. Systemic and post-filter aPTT were significantly different (two-way ANOVA, $p = 0.0059$ and 0.0046). *Asterisk:* Systemic aPTT levels 24 h after start of CVVH were significantly different from levels 0.5 h after start ($p < 0.05$, Tukey's multiple comparison test). *Hatch symbol:* post-filter aPTT levels 4, 12, and 24 h after start of CVVH were significantly different from levels 0.5 and 2 h after start ($p < 0.05$, Tukey's multiple comparison test). **b** Systemic and post-filter anti-Xa were not significantly different (two-way ANOVA). **c** Average heparin dose during CVVH. *Plus sign:* significant difference at 12 and 24 h compared with 0.5 h (ANOVA, $p < 0.05$, Tukey's multiple comparison test)

analysis; Table 1). Due to the longer filter survival, lower costs of anticoagulation with enoxaparin occurred despite the repeated determination of anti-Xa, the latter being an important cost factor (3.5 € for one anti-Xa determination).

Discussion

This is the first study to directly compare UFH and enoxaparin continuously infused into the extracorporeal circuit during CVVH in critically ill patients. In our randomized, controlled crossover study we could show that the LMWH, enoxaparin, is a valuable alternative to unfractionated heparin for anticoagulation during CVVH resulting in significantly longer filter survival times without increasing bleeding complications.

There are only a few studies which examine the use of LMWH as an alternative to UFH for CRRT. Reeves and co-workers [12] found that dalteparin provided identical filter life in CVVHDF, and comparable safety, but increased total daily cost compared with heparin by approximately 20%. In contrast to that study, we found significantly longer filter survival when using enoxaparin resulting in even lower daily costs than in the heparin group. The observed discrepancy may be explained by several factors. Firstly, Reeves and co-workers [12] administered LMWH doses which were about twice as high as the doses applied in our study and they did not monitor anticoagulation in the dalteparin group. The anticoagulatory effect achieved by a fixed dose of dalteparin may vary in ICU patients depending on the severity of illness as demonstrated in two studies investigating daily subcutaneous administration of enoxaparin or certoparin [19, 20]. Secondly, heparin was given to achieve aPTT between 60 and 80 s by Reeves and co-workers [12], which is currently recommended for full anticoagulation. Since the degree of anticoagulation during CRRT puts the patient at higher risk of bleeding [21], we generally use lower levels of anticoagulation aiming at an aPTT between 40 and 45 s which may result in shorter filter survival times. Nevertheless, our observed hemofilter survival times were reasonable and comparable with those reported by other groups using heparin [11, 22–25]. When applying lower doses different anticoagulatory properties of UFH and LMWH may become apparent which are not discernible during full anticoagulation. In this context it must be noted that by infusing anticoagulants into the extracorporeal system we could achieve post-filter levels which were significantly higher than systemic antiXa or aPTT levels in our patients, thus providing significant anticoagulation for the system without putting the patient at enhanced risk for bleeding. Finally, LMWHs differ substantially regarding their molecular weight, distribution volumes, anti-Xa: anti-IIa activity ratio as well as fibrinolytic properties. Therefore, effects observed in our study may be specific for enoxaparin and not generalizable for all LMWHs.

By using continuous infusion of enoxaparin we achieved reliable anti-Xa levels. Although these levels tended to be higher at later time points of CVVH, we could not establish a significant correlation between anti-Xa levels and filter survival. This finding is confirmed by another publication which describes the effects of different LMWHs (nadroparin and dalteparin) in CVVH [11]. Despite higher anti-Xa $AUC_{(0–3h)}$ the resulting median filter survival of 18 h was lower than in our study. Al-

though loading dose was higher in de Pont's study [11], maintenance dose was slightly lower (about 320 IU/h vs. 360 in our study). The lower circuit survival reported by de Pont and co-workers may partially be explained by the higher filtrate fraction associated with higher ultrafiltrate flow and postdilution [11].

In our study standard coagulation parameters, such as PT, aPTT, fibrinogen, and thrombocyte count, did not show any influence on filter survival as reported in previous studies [11, 12]. Although systemic aPTT remained well within the targeted range of 40–45 s filter run times were significantly lower during anticoagulation with heparin. As expected by the lower ratio of anti-Xa:anti-IIa activity (1:1 as compared with 3.8:1 with enoxaparin) anticoagulation with UFH in our study resulted in consistently lower anti-Xa levels compared with enoxaparin. It may be speculated whether the determination of anti-Xa levels could be more relevant for anticoagulation with low-dose heparin in CRRT, although this assumption must be proved in a separate study.

A major concern with LMWH in the setting of reduced glomerular filtration rate is their potential accumulation and increased risk of hemorrhage, especially when given in continuous fashion [26]. Some studies support dosage adjustments in patients with renal disease, whereas others do not [27–29]. The product labeling of enoxaparin has recently been changed to include a dosage reduction for patients with renal insufficiency (Lovenox [package insert] (2003) Aventis Pharmaceuticals). A review of the influence of renal function on anti-factor Xa activity of LMWH came to the following conclusions [30]: (a) most well-designed studies demonstrate increased anti-factor Xa activity in patients with diminished renal function; (b) the pharmacokinetic effect of impaired renal function may differ among LMWHs; and (c) there is not a single creatinine clearance cutoff value that correlates with an increased risk of bleeding for all LMWH preparations.

In our study, accumulation of enoxaparin did not occur as determined by repeated measurements of anti-Xa levels. Although there was a trend toward higher anti-Xa activity beyond 12 h after start of CVVH, this resulted from dose adjustments of enoxaparin infusion to stay within the targeted range of 0.25–0.30 IU/ml. It is a concern that regardless of measured anti-Xa activity, at least three studies indicate that there are more bleeding events in patients with renal impairment receiving enoxaparin [31–33]; however, enhanced tendency to bleeding in patients with renal insufficiency is observed also with UFH [34] and even without use of any anticoagulant [35, 36]. Incidence of major and minor bleeding events was low and comparable for both enoxaparin and UFH in our study, possibly, because our anti-Xa values were similar to the recommended peak target range determined 4 h after subcutaneous enoxaparin administration (i.e., 0.1–0.4 IU/ml) when applying enoxaparin as antithrombotic prophylaxis [15, 16].

A major advantage of LMWH over UFH is the lower incidence of heparin-induced thrombocytopenia, a rare but potentially fatal condition, observed with prolonged administration of heparins [37]. In our study, we were not confronted with this entity, probably because of its low incidence and the short application period secondary to the design of our study including only the first two runs of CVVH in each patient. Nevertheless, given the large numbers of patients on heparin prophylaxis, even a low incidence of HIT may represent a significant, detrimental effect on patient outcomes. A recent meta-analysis confirmed that the absolute risk for HIT, though generally low, is significantly higher with UFH as compared with LMW heparins (2.6 and 0.2%, respectively) [37].

Our study has several limitations. Firstly, the number of patients included may be considered relatively low; however, comprising 40 patients, the present study still is the largest randomized controlled study comparing LMWH and UFH for CVVH. Furthermore, use of a crossover design improves the strength of our findings. Secondly, we generally used relatively low target values of anticoagulation achieving mean filter life spans between 22 and 31 h. Compared with studies applying high-dose anticoagulation regimens, our filter life spans may be considered relatively short; however, mean filter survival in studies using heparins generally range from 15 to 50 h [38–40]. Thirdly, in order to avoid both under- and overdosing of enoxaparin, anti-Xa measurements were performed. This assay may not be available in smaller hospitals and results in significant costs. Furthermore, to be able to adjust anticoagulation to the respective monitoring parameters aPTT or anti-Xa, we could not perform the study in a blinded design; however, adjustments of anticoagulation rates were guided strictly by the predefined protocol. Finally, cost analysis is based on the actual costs charged in our institution and may not reflect the situation in other hospitals. Nevertheless, the significant prolongation of filter lifespan may result in even more pronounced cost savings because the labor (nursing, staff) involved in setting up a new run was not included in our calculations.

Conclusion

In conclusion, our study shows that LMWH enoxaparin is a valuable and safe alternative to UFH to keep the extracorporeal circuit open during CVVH in critically ill patients, resulting in longer filter survival times, and lower cost, without showing higher incidence of bleeding complications. Determination of anti-Xa levels aiming at 0.25–0.35 IU/ml may be recommended to avoid both enoxaparin over- and under-dosage.

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