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Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: Erwin Otero Garcés, Josué Almeida Victorino, Fernando Saldanha Thomé, Liane Marise Röhsig, Estela Dornelles, Marcelo Louzada, Jonhatas Stifft, Felipe de Holanda & Francisco Veríssimo Veronese (2010) Enoxaparin versus unfractioned heparin as anticoagulant for continuous venovenous hemodialysis: a randomized open-label trial, Renal Failure, 32:3, 320-327, DOI: 10.3109/08860221003606281

To link to this article: https://doi.org/10.3109/08860221003606281

Published online: 06 Apr 2010.

Renal Failure, 32, 320–327, 2010

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.3109/08860221003606281

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CLINICAL STUDY

Enoxaparin versus unfractioned heparin as anticoagulant for continuous venovenous hemodialysis: a randomized open-label trial

Erwin Otero Garcés[1,2], Josué Almeida Victorino[3], Fernando Saldanha Thomé[1,2], Liane Marise Röhsig[4], Estela Dornelles[2], Marcelo Louzada[2], Jonhatas Stifft[2], Felipe de Holanda[2] and Francisco Veríssimo Veronese[1,2]

[1] *Graduate Program in Medical Sciences: Nephrology, Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil*

[2] *Nephrology Division, Hospital de Clínicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil*

[3] *Intensive Care Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil*

[4] *Medical Cryobiology Unit, Hematology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil*

ABSTRACT

Aim: In this study we aimed to compare the efficacy and safety of enoxaparin with unfractioned heparin (UFH) as anticoagulant for continuous venovenous hemodialysis (CVVHD). Methods: An open-label randomized controlled trial was carried out in an intensive care unit (ICU) where 40 patients with acute renal failure (ARF) who needed continuous renal replacement therapy were randomized to receive UFH (n = 21) or enoxaparin (n = 19). Coagulation parameters were evaluated, and antithrombotic activity of UFH was measured by activated partial thromboplastin time (aPTT) and for enoxaparin by anti-factor Xa activity. Primary outcomes were thrombosis of the extracorporeal circuit and bleeding, classified as major or minor. Results: Minor bleeding episodes were observed only in patients anticoagulated with enoxaparin (26 vs. 0%, p = 0.018). Comparing patients with or without bleeding after 24 hours of therapy, the level of anticoagulation tended to be higher (anti-factor Xa: 1.62 vs. 1.13 IU/mL, p = 0.09) and the platelet count to be lower [107 ± 53 vs. 229 ± 84 ($\times 10^3/\mu L$), p = 0.09] in patients who bled, but without statistical difference. Filter life span of enoxaparin and UFH groups was similar (43 ± 15 vs. 52 ± 18 hr, p = 0.10), as well as the proportion of circuit clotting. Conclusion: Weight-unadjusted enoxaparin in patients with ARF in CVVHD was associated with an increased rate of bleeding, a finding that addresses the need to adjust drug dose and to monitor anti-factor Xa activity during dialysis. No benefit to prolong dialysis circuit survival was found with enoxaparin. In patients who do not present contraindication for systemic anticoagulation, UFH remains an effective and low-cost option.

Keywords: anticoagulation; continuous venovenous hemodialysis; unfractioned heparin; low-molecular-weight heparin

Received 23 September 2009; revised 12 November 2009; accepted 13 December 2009
Correspondence: Francisco Veríssimo Veronese, Nephrology Division, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Sala 2030, Porto Alegre 90035-003, Rio Grande do Sul, Brazil; tel: +55 51 21018295; fax: +55 51 21018121; E-mail: fveronese@hcpa.ufrgs.br

INTRODUCTION

Acute renal failure (ARF) is a prevalent condition in intensive care units (ICUs). A multinational, multicenter study described a prevalence of ARF of 5.7%, with 72.5% of the patients needing dialytic support, most of the time a continuous renal replacement therapy (CRRT).[1]

CRRTs are preferred in critically ill patients due to a better hemodynamic tolerance, making possible removal of large fluid volumes.[2,3] Anticoagulation is routinely used in CRRT but is not mandatory, as these methods can be performed without anticoagulation. However, circuit survival time will be shorter.[4]

Unfractioned heparin (UFH) is the most widely used anticoagulant.[5] Theoretical advantages are its low-cost, short half-life, easy reversion of its effect with protamine, and easy monitoring by the activated partial thromboplastin time (aPTT).[6]

Recent studies in patients with end-stage renal disease suggest that low-molecular-weight heparins (LMWHs) are as effective as UFH in maintaining

dialyzer permeability.[7] Because of their more predictable pharmacokinetics, there would be no need for laboratory tests to monitor antithrombotic activity.[8]

However, in severe renal failure the half-life of the LMWH is prolonged[9] and their use has been associated with severe bleeding.[10] This might suggest the need to monitor its anticoagulant effect by plasma anti-factor Xa activity.[11] Another important aspect is the lack of an effective antagonist to reverse the anticoagulant effect of LMWH, since protamine has only partial action.[12]

In this randomized open trial we compared LMWH with UFH in the anticoagulation of continuous venovenous hemodialysis (CVVHD), administered to critically ill patients with ARF. Primary outcomes assessed were bleeding and clotting of the extracorporeal dialysis circuit.

MATERIALS AND METHODS

Study design

Randomized open-label trial with critically ill patients with ARF requiring CRRT were admitted to ICU.

Patients

Adult medical or surgical patients admitted to a general ICU at Hospital de Clínicas de Porto Alegre (HCPA) who presented ARF and were submitted to CRRT were selected from January 2001 to December 2006. A total of 9700 patients were admitted to ICU during this period, of whom 776 (8%) had ARF with indication for dialysis. Most patients (613, 79%) had either a contraindication to anticoagulation (active bleeding or at high risk of bleeding, platelet count $<100 \times 10^3/\mu L$, or presence of disseminated intravascular coagulation) and were dialyzed by CRRT with trisodium citrate, or were dialyzed by intermittent or extended hemodialysis. One hundred and sixty-three (21%) patients had indication for CRRT with heparin, but 109 met exclusion criteria. These were age under 18 years, chronic renal insufficiency prior to hospitalization in ICU, patients who had already been submitted to dialysis, pregnancy, patients who were on chronic use of anticoagulants or who had received any anticoagulant in the last 48 hours, those with immediate need for invasive interventions or surgery in the 24 hours following the prescription of CRRT, and family refusal to sign the informed consent form. At the end, 54 patients were included in the study and were randomized to UFH or enoxaparin.

This study was approved by the Ethics in Research Committee of HCPA, registered at the Institutional Review Board (IRB) number 00000921.

Renal replacement therapy

CVVHD was performed in all patients. A 12 Fr double-lumen catheter 20 or 24 cm in length was inserted into one of the central veins (90% femoral, 10% internal jugular). CVVHD was performed in FAD 100 machines (B. Braun, Melsugen, Germany). Dialysis prescription consisted of a blood pump flow kept at 150 mL/min, a lactate solution as dialysate at 1000 mL/hr, and an ultrafiltration rate that was adjusted according to clinical indication. The polysulfone hollow-fiber dialyzer (F-8 Fresenius Medical Care™, Bad Homburg, Germany) was used in all patients. Catheter placement and CVVHD prescription, as well as adjustments during dialytic therapy, were carried out by the treating nephrologist who was not involved in the study.

Randomization and intervention

Randomization was carried out by specific software (Program for Epidemiologists – PEPI version 3.0). Patients were randomized for one of the two groups: enoxaparin (Clexane®, Sanofi-Aventis, Paris, France) or UFH (Liquemine®, Roche, Basel, Switzerland).

Patients randomized for UFH received an initial bolus of 5000 UI followed by a continuous infusion at 5–10 UI/kg/hr. The dose was adjusted according to the level of aPTT which was done every 8 hours, with a therapeutic goal at 1.5–2.0 times the reference value, that is, between 60 and 75 seconds. Patients in the enoxaparin group received intravenous enoxaparin at a dose of 40 mg every 12 hours (~0.5–0.7 mg/kg/12 hr), which is the recommended adjusted dose for patients with severe renal insufficiency.[7,13,14] The antithrombotic effect of enoxaparin was measured through plasma levels of anti-factor Xa activity, but this analysis was made retrospectively. Therapeutic levels of anti-factor Xa was defined as 0.5–1.0 UI/mL.[15] Levels below 0.5 UI/mL were considered insufficient for effective anticoagulation and levels above 1.0 UI/mL were considered excessive anticoagulation. Anti-factor Xa activity was measured by a chromogenic assay according to the manufacturer (STA Rotachrom® Heparin 8, Diagnostica Stago, Asnières, France),[16] with a detection limit of 0.01 UI/mL. Quality control of the technique was performed using plasma controls containing predetermined levels of LMWH (STA® Quality LMWH, Diagnostica Stago).

A second-dose step of anticoagulation was permitted in the following situations: (a) UFH: if aPTT was more than 1.5 times the control value or minor bleeding occurred, then the dose was reduced by 50%; if circuit venous pressure increased to >100 mmHg or clots were found in circuit lines/filter, dose was increased by 50%; (b) Enoxaparin: if there was minor bleeding, dose was reduced by 50%; if circuit venous pressure increased to >100 mmHg or clots were found

in circuit lines/filter, dose was increased by 50%. For both UFH and enoxaparin, if oozing or bleeding persisted after 12 hours of reducing the dose, anticoagulation was stopped and the dialysis circuit was flushed with saline.

Anticoagulation protocol had a minimal duration of 24 hours and a maximum duration of 72 hours, when the extracorporeal circuit was changed in accordance to guidelines of the Committee for Infection Control of HCPA.

Laboratory tests

Biochemical and hematological parameters, including coagulation tests (platelets, prothrombin time, aPTT, fibrinogen, D-dimers), were prospectively recorded every 24 hours of CVVHD. Anti-factor Xa activity was measured at three time points: 24, 48, and 72 hours after initiation of CVVHD. Blood samples were collected 2 hours after the intravenous administration of enoxaparin, according to manufacturer's instructions,[16] and plasma was separated and frozen at −20°C. Measurements were done in retrospect. The UFH group worked as a control group as UFH also interferes on factor Xa in the coagulation cascade, although to a lesser extent.[6,15]

The urea equilibration coefficient (UEC): [(ultrafiltrate urea/arterial urea) × 100] was measured every 24 hours; when this index is lower than 0.6 indicating a severe reduction in the depuration of small molecules, it is a good predictor of filter clotting.[17]

Outcomes

Obstruction of the extracorporeal dialysis circuit was defined by the following criteria: presence of extensive blood clots in the filter, air-bubble detector and/or in the circuit lines, venous pressure persistently above 150 mmHg, and UEC equal or lower than 0.6.[7,13,17] Filter life span was measured in hours and recorded at the end of CVVHD procedure. Major bleeding was defined as a fatal hemorrhagic event, bleeding in a critical organ such as intracranial, intra-abdominal or pulmonary, or the need for transfusion of two or more units of packed red blood cells. Minor bleeding was defined as other clinically manifested hemorrhage of a lesser magnitude not occurring in such critical areas.

Statistical analysis

Sample size was determined to detect a 25% increase in the prevalence of the primary outcome – bleeding – based on a previously occurrence of bleeding in 25% of ARF patients that used enoxaparin as anticoagulant for CRRT in our center. Considering a beta error of 20% and study power of 80%, 40 patients were required to be included in this study.

Descriptive statistics were presented as percentage for qualitative data, and as mean ± SD or median and percentiles 25th and 75th for continuous variables. Chi-square test was used to compare categorical variables. Unpaired *t*-test and nonparametric Mann–Whitney test were employed for the analysis of symmetric and asymmetrical distributions, respectively. Data were processed and analyzed with SPSS software for Windows, version 12.0. Significance level was established at $p < 0.05$.

RESULTS

Fifty-four patients were initially randomized. After randomization, 14 patients (8 from UFH and 6 from enoxaparin group) were excluded according to study protocol, because they did not complete 24 hours of treatment. The main reasons for these exclusions were never related to the dialysis procedure (occurrence of major bleeding or circuit thrombosis) but to clinical decision by the intensive care team to withdrawn CVVHD, because of severe hemodynamic instability or the need for investigations outside ICU, or to patient death. Forty patients were included in the final analysis, of which 19 were randomized to enoxaparin and 21 patients to the UFH protocol.

There was no significant difference between the two groups in demographic, clinical, and baseline laboratory characteristics (Table 1). Coagulation parameters, proportion of patients with sepsis, and disease severity as measured by APACHE II at ICU entry were similar. Although aPTT was more prolonged in UFH group, this difference was not statistically significant.

Filter clotting occurred in 10 patients, 5 in each group. Five patients from enoxaparin group had minor bleeding and anticoagulation was stopped. Eight patients (1 from enoxaparin and 7 from UFH group) finished the CVVHD protocol at 72 hours. Seven patients died, and in the remaining 10 patients the reasons for dialysis withdrawal were urgent surgery ($n = 3$), urgent investigations outside ICU ($n = 5$), clinical decision by the intensive care team to withdraw CVVHD ($n = 2$).

At 24 hours of dialytic therapy, there was no significant difference between LMWH and UFH groups in coagulation parameters (Table 2). As expected, a trend toward a higher level of aPTT was found in UFH group, expressing the specific effect of UFH on intrinsic pathway of the coagulation cascade (62.4 ± 28 vs. 89.1 ± 50 seconds, $p = 0.06$).

At 48 hours of dialytic therapy, 21 (52.5%) patients remained on CVVHD. A significantly higher prothrombin time (PT) was observed in patients with enoxaparin

TABLE 1. Baseline clinical characteristics and coagulation parameters of the patient population.

	UFH (n = 21)	LMWH (n = 19)	p
Age (years)[a]	54.2 ± 19[a]	60.5 ± 14	0.26
Males, n (%)	8 (38)	7 (37)	1.00
Ischemic/multifactorial ARF[b] (%)	29/71	42/58	0.51
Blood urea nitrogen (mg/dL)	72 ± 32	65 ± 34	0.49
Serum creatinine (mg/dL)	3.2 ± 1.6	3.1 ± 1.1	0.87
Platelets (10^3/μL)	279 ± 121	267 ± 131	0.77
PT (%)	64.2 ± 14.9	65.1 ± 23	0.89
aPTT (seconds)	54.4 ± 44.0	44.0 ± 12.8	0.06
Use of anti-platelet aggregation drugs, n (%)	3 (14.3)	1 (5.3)	0.63
Use of vasopressors, n (%)	16 (78)	14 (75)	0.85
Presence of sepsis (%)	85.7	94.7	0.60
APACHE II at ICU entry	24.4 ± 7.0	22.1 ± 8.4	0.33

Notes: UFH, unfractioned heparin; LMWH, low-molecular weight heparin; PT, prothrombin time; aPTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy.
[a]Mean ± SD.
[b]Cause of acute renal failure: ischemic or multifactorial.

(77.3 ± 11.3 vs. 56.1 ± 20%, p = 0.014). Other coagulation parameters such as fibrinogen and D-dimers did not differ between the two groups, as shown in Table 2.

Minor bleeding occurred in patients who were anticoagulated with enoxaparin (26 vs. 0%, p = 0.018). These bleeding episodes consisted of oozing or frank hemorrhage clinically detected in mucosal of the mouth or nose, or around the tracheal tube, arterial lines, venous catheters, and in postoperative wounds. No patient in both groups had a major hemorrhagic event. The proportion of changes in anticoagulant dose – most of the time to decrease the dose – did not differ in UFH and enoxaparin groups (33 vs. 26%, p = 0.21).

The proportion of patients in the enoxaparin and UFH groups with thrombocytopenia was similar: at 24 hours 21 vs. 25% (p = 1.00) and at 48 hours 10 vs. 25% (p = 0.59), respectively. UEC was <0.6 in less than 10% of the HDVVC procedures in both groups, and had no correlation with the other parameters which indicated obstruction of the dialysis circuit.

At 72 hours, only 8 (20%) patients were still on dialysis. Functional survival of the CVVHD circuit was similar in LMWH and UFH groups, with a filter life span of 43 ± 15 vs. 52 ± 18 hours, respectively (p = 0.10). Excluding patients whose outcome was not associated with thrombosis, circuit clotting occurred in average after 50 ± 13 vs. 39 ± 14 hours in patients who were anticoagulated with enoxaparin (n = 5, 26%) and UFH (n = 5, 24%), respectively (p = 0.21).

In a secondary analysis, patients were stratified according to the presence or absence of clinical bleeding. All patients who bled were from the LMWH group (n = 5, 26%), as shown in Table 3. These patients were significantly younger (46.4 ± 14.1 vs. 65 ± 11.7 years, p = 0.008) in comparison with those who did not bleed, however APACHE II score was not different when comparing patients with and without bleeding (27.8 ± 4.7 vs. 29.5 ± 6.2, respectively; p = 0.59). At 24 hours of dialysis, platelet count and other coagulation parameters, including anti-factor Xa level, were not statistically different either (Table 3).

TABLE 2. Coagulation parameters during CVVHD in enoxaparin and UFH groups.

	24 hours			48 hours		
	LMWH (n = 19)	UFH (n = 21)	p	LMWH (n = 10)	UFH (n = 11)	p
Platelets (10^3/μL)	178 ± 83[a]	199 ± 124	0.51	204 ± 91	156 ± 85	0.21
PT (%)	63.8 ± 18.0	57.5 ± 11.7	0.31	77.3 ± 11.3	56.1 ± 20.0	0.014
aPTT (seconds)	62.4 ± 28.6	89.1 ± 50.4	0.06	59.5 ± 29.1	74.0 ± 30.5	0.29
Fibrinogen (mg/dL)	477 ± 200	479 ± 193	0.97	521 ± 180	490 ± 156	0.66
D-dimers[b]	1.19 ± 0.6	2.13 ± 1.1	0.89	2.12 ± 1.1	3.07 ± 1.79	0.39
Anti-factor Xa[c] (IU/mL)	0.62 (0.28–1.00)[d]	0.13 (0.04–0.38)	<0.001	1.15 (0.87–1.54)	0.12 (0.02–0.31)	0.001

Notes: UFH, unfractioned heparin; LMWH, low-molecular-weight heparin; PT, prothrombin time; aPTT, activated partial thromboplastin time.
[a]Mean ± SD.
[b]D-dimers: <5 μg/dL.
[c]Therapeutic reference values according to manufacturer – UFH: 0.15–0.30 IU/mL and LMWH: 0.5–1.2 IU/mL.[17]
[d]Median and interquartile range.

TABLE 3. Clinical and laboratory variables in patients with or without bleeding anticoagulated with enoxaparin in CVVHD.

	24 hours			48 hours		
	With bleeding (n = 3)	Without bleeding (n = 16)	p	With bleeding (n = 2)	Without bleeding (n = 8)	p
Age (years)[a]	46.4 ± 14.1	65 ± 11.7	0.008	52.0 ± 15.4	59.9 ± 19.7	0.60
APACHE II[b]	23.4 ± 6.3	23.2 ± 8.0	0.95	23.7 ± 6.1	22.6 ± 9.6	0.68
Platelets (10^3/μL)	127 ± 56	196 ± 84	0.11	107 ± 53	229 ± 84	0.09
aTTP (seconds)	57.4 ± 16.2	63.9 ± 13	0.70	66 ± 33	57.4 ± 30	0.74
PT (%)	63.2 ± 29.0	63.9 ± 31.8	0.94	96.5 ± 44.9	72.5 ± 36.7	0.002
Anti-factor Xa[c] (IU/mL)	0.60 (0.35–1.64)	0.62 (0.18–1.02)	0.72	1.62 (1.54–1.69)	1.13 (0.52–1.23)	0.09
LMWH dose (mg/kg/dose)	0.73 ± 0.18	0.62 ± 0.11	0.15	0.76 ± 0.15	0.66 ± 0.13	0.21

Notes: LMWH, low-molecular-weight heparin; PT, prothrombin time; aTTP, activated partial thromboplastin time.
[a]Mean ± SD.
[b]Measured at ICU entry.
[c]Median and interquartile range.

It is important to highlight that enoxaparin doses were calculated according to estimated body weight (not current weight) and renal function, and did not differ in patients with and without bleeding (0.73 ± 0.18 vs. 0.62 ± 0.11 mg/kg, respectively; p = 0.15). After 48 hours of dialysis, a lower platelet count was observed in patients with bleeding, but this difference did not reach statistical significance. At this time point of CVVHD, anti-factor Xa activity tended to be increased in patients who bled (1.62 [1.54–1.69] IU/mL vs. 1.13 [0.52–1.23] IU/mL, p = 0.09). However, the small number of patients that reached 48 hours of CVVHD therapy prevents a more accurate analysis of these data.

Considering the level of anticoagulation in patients who received enoxaparin, no association was found between a low anti-factor Xa activity and the occurrence of circuit clotting, as well as between excessive anti-factor Xa activity and bleeding, both in LMWH and UFH groups.

DISCUSSION

CRRT has been widely used in critical ill patients with ARF and hemodynamic instability, but these methods require an anticoagulation strategy in order to prevent thrombosis of the extracorporeal circuit.[4,5,18] Patients admitted to ICU, however, present an increased risk of bleeding associated with multiple organ dysfunction syndrome and its consequences, disseminated intravascular coagulation, thrombocytopenia, hepatic failure, and uremia.[19]

Several anticoagulant drugs have been employed in CRRT, such as UFH, LMWH, trisodium citrate, prostacyclin among others.[4,20,21] A theoretical limitation to the use of both UFH and LMWH in critically ill patients is driven by the low levels of antithrombin III that occur in sepsis thus reducing their therapeutic effectiveness, particularly in the case of UFH whose main mechanism of action is the high affinity to and activation of antithrombin III.[22,23] This can contribute to a shorter filter survival even when UFH anticoagulation level seems to be adequate, as indicated by targeted aPTT measurements.[24]

Reported advantages of LMWH over other anticoagulants are easier administration (intermittent doses) due to their low affinity to plasma proteins, endothelial cells, and macrophages, larger bioavailability and a more predictable therapeutic effect not requiring laboratory monitoring of their antithrombotic activity.[6,11,15] Moreover, in the critically ill patient who often presents thrombocytopenia,[20] LMWH interfere less on platelet factor-4 (PF-4) that induces heparin-associated thrombocytopenia, thus reducing the incidence of this complication, a frequent finding with UFH.[25–27] However, available evidence supports the potential for enoxaparin accumulation and increased risk of bleeding in severe renal insufficiency (creatinine clearance of 30 mL/min or less), in the obese and in elderly patients, and careful monitoring is now recommended for LMWH anticoagulation through target levels of anti-factor Xa activity.[28,29] Another important limitation to the use of LMWH has been their high cost in relation to UFH.[7,30]

LMWH has been more widely tested in chronic hemodialysis[7,31,32] with few clinical trials assessing their efficacy and safety in CRRT. Some were randomized and controlled, but in general these studies involved a small number of patients.[8,24,30,33,34] Three

of these trials compared dalteparin with UFH.[25,31] In other study nadroparin was compared to dalteparin,[33] and one uncontrolled trial investigated the efficacy and safety of enoxaparin in slow continuous hemodialysis.[8] In this latter study, neither thrombocytopenia nor bleeding was reported in association with enoxaparin. Joannidis et al.[35] in a controlled randomized crossover trial studying 37 patients in continuous venovenous hemofiltration, reported that enoxaparin as compared to UFH resulted in a significantly longer filter survival without increasing bleeding complications, but in this study enoxaparin dose was adjusted according to anti-Xa levels targeted at 0.25–0.30 IU/mL.

In our study the efficacy and safety of enoxaparin was compared to UFH, the standard for anticoagulation in CVVHD. No major bleeding occurred, but 26% of the patients in the enoxaparin group had minor bleeding episodes. This finding differs from the report by Reeves et al.[30] and by Joannidis et al.[35] who found no difference in the prevalence of hemorrhagic complications between the two methods of anticoagulation.

We argue that bleeding with LMWH could not be explained by differences in coagulation parameters, platelet level, severity of disease, prevalence of sepsis, or use of drugs that interfere in coagulation, because those parameters did not differ between the two groups at baseline. Patients who used enoxaparin and presented bleeding were younger than those who did not bleed, differently from previous reports where risk of bleeding with LMWH was higher in older people.[36,37] We have to consider that severity of disease was higher in the subgroup that had bleeding, yet it was not detected clinically by APACHE II score.

A tendency to higher levels of anti-factor Xa activity at 48 hours of CVVHD in patients who bled is probably related to accumulation due to impaired elimination of enoxaparin by impeded glomerular filtration, as this drug is mainly cleared by the kidneys.[9,15] As discussed above, in patients with renal failure the half-life of LMWH is prolonged, which might induce a state of excessive anticoagulation with increased risk of hemorrhagic events.[10,28,29,38,39] Another point to consider is that few amounts of LMWH are removed by the dialyzer during continuous dialysis. This hypothesis is supported by Singer et al.,[24] who measured LMWH concentration and anti-factor Xa in plasma and in ultrafiltrate, showing that removal of LMWH by the dialysis filter was insignificant, which could result in drug accumulation.

Because bleeding episodes occurred after the first 24 hours of fixed doses of enoxaparin not adjusted for patient weight, it probably accumulated during CVVHD. This may be aggravated by the negative weight variation that occurs in severely ill patients.[40] In this context, it is important to emphasize the need to adjust LMWH dose in patients on CRRT based on anti-Xa activity, because with target levels of anti-Xa the incidence of bleeding complications decreases as reported by several authors.[11,15,28–30,33–35,39] This was addressed by Lim et al. in a recent meta-analysis[29], showing that major bleeding was increased when standard doses of enoxaparin were used but did not increase with empirically adjusted doses. Even though enoxaparin dose was reduced on account of severe renal insufficiency, we recognize as a limitation of our study the use of enoxaparin in fixed doses of 40 mg not adjusted for patient weight, without monitoring and targeting the level of anti-factor Xa perhaps at less than 0.9 IU/mL. Unfortunately, in our center we could not measure anti-factor Xa prospectively due to logistic and economic reasons.

Another point to consider is the need to test a continuous infusion of enoxaparin instead of fixed doses, as reported in other studies.[24,35] Perhaps a more steady plasmatic level of the drug could affect less the activity of factor Xa and the coagulation cascade, resulting in a lower rate of bleeding.

At 48 hours of CVVHD, platelet count and proportion of patients with thrombocytopenia were similar between enoxaparin and UFH groups in accordance with the data reported by Reeves et al.[30] Nevertheless, in patients who presented bleeding, platelet levels tended to be lower. It is probable that thrombocytopenia in this context was associated more with severity of disease (sepsis and multiple organ dysfunction syndrome) than to an autoimmune effect induced by enoxaparin (heparin-induced thrombocytopenia), because it occurred earlier than 4 days and was not accompanied by thromboembolic events.[6,41]

Filter survival did not differ between the two methods. Reeves et al.[30] compared dalteparin with UFH in patients submitted to continuous venovenous hemodiafiltration, reporting a filter life span of 46.8 versus 51.7 hours for dalteparin and UFH, respectively, which is very similar to what was found in this study. In another study,[35] enoxaparin was associated with a longer filter life span as compared to UFH (30.6 ± 25.3 vs. 21.7 ± 16.9 hours, $p = 0.017$).

Some studies have shown that levels of anti-factor Xa lower than 0.5 IU/mL are clearly associated with the development of thrombosis due to insufficient anticoagulation.[34,42] In our study we did not find an association between low anti-factor Xa activity and thrombosis of dialysis circuit, both in enoxaparin and in UFH groups, although the number of patients remaining at 48 and 72 hours of CVVHD was too small, which is another limitation of our study.

In conclusion, the use of enoxaparin in fixed doses (not weight-adjusted) resulted in drug accumulation

and increased the rate of bleeding in these critically ill patients requiring CRRT, without having an impact in prolonging circuit survival. A lower and weight-adjusted dose of enoxaparin, given as a continuous infusion, should be tested in another LMWH protocol for CRRT. In patients with renal insufficiency who do not present contraindication for systemic anticoagulation, UFH may still be an effective and low-cost option.

Acknowledgments

The authors thank Daniela Benzano for her expert technical assistance and Research Fund of Hospital de Clínicas de Porto Alegre (FIPE) for the financial support.

Declaration of interest: All authors declare no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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