Audit of safety and quality of the use of enoxaparin for anticoagulation in continuous renal replacement therapy

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ABSTRACT

Objective: To evaluate the safety and efficacy of enoxaparin for anticoagulation during continuous renal replacement therapy (CRRT).

Design: Six-month prospective audit on filter life, anti-Xa activity and bleeding complications among patients undergoing continuous venovenous haemodiafiltration with 1.5 mg/kg enoxaparin per 24 hours. The audit was conducted between June and December 2009.

Results: Thirteen patients were included. The median overall filter survival time was 22 hours (range, 2–176 hours). Two patients experienced minor bleeding events, but there were no major bleeding events. Systemic activity of enoxaparin was demonstrated, with a significant rise in median anti-Xa activity between assays before and during filtration (0.00 [range, 0.00–0.13] v 0.31 [range, 0.07–1.26] anti-Xa U/mL; $P = 0.03$).

Conclusions: Enoxaparin at 1.5 mg/kg/24 h appears to be effective for circuit anticoagulation in CRRT and provides significant systemic anticoagulation. Further research is required to evaluate its safety, particularly in the absence of routine anti-Xa monitoring.

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Continuous renal replacement therapy (CRRT) is frequently employed in critical illness for the treatment of acute renal failure, particularly in instances complicated by hypervolaemia, hyperkalaemia or acidosis.[1,2] Anticoagulation in CRRT is routinely used to prevent extracorporeal circuit clotting while minimising systemic bleeding complications. Numerous methods for circuit anticoagulation exist, including infusions of unfractionated heparin, low-molecular-weight heparin (LMWH) and regional citrate.[2] Patients at high risk of bleeding may be managed with no anticoagulation,[3] or a combination of heparin and protamine in an attempt to regionally anticoagulate the circuit alone.

Compared with unfractionated heparin, LMWHs have been shown to have equivalent or superior filter lives and comparable overall cost. In a study comparing unfractionated heparin with fixed-dose dalteparin, Reeves and colleagues demonstrated no significant difference in filter life or bleeding complication rate.[4] However, cost per day was 10% higher with dalteparin. In a crossover study, Joannidis and colleagues compared a titrated dose of enoxaparin (to achieve anti-Xa activity of 0.25–0.30 anti-Xa units/mL [U/mL]) against unfractionated heparin.[5] They demonstrated superior filter survival time (30.6 v 21.7 hours; $P = 0.02$) and reduced daily cost with enoxaparin.

There are few data regarding the optimal dosage of enoxaparin for circuit anticoagulation and the role of anti-Xa activity monitoring in CRRT. Current recommendations for routine anti-Xa monitoring in CRRT[2] are based on scant evidence, with several studies failing to demonstrate a correlation between anti-Xa activity and filter survival.

Furthermore, there is little information on the systemic anticoagulation that results from enoxaparin use in the filter circuit, and this leads to uncertainty about appropriate venous thromboembolism prophylaxis in such patients. Although the pharmacokinetics of LMWH are generally more predictable than those of unfractionated heparin,[6] its elimination is predominantly renal, and therefore less predictable and less well understood in acute renal failure and CRRT. Enoxaparin was shown to cross both acrylonitrile and polysulfone filter membranes during CRRT in both in-vitro and in-vivo settings in one study.[7] However, this finding was not supported by a second in-vivo study.[8]

In our intensive care unit, the current policy for circuit anticoagulation is a continuous infusion of 1.5 mg/kg patient weight of enoxaparin per 24 hours, administered into the pre-filter limb of the circuit, without routine anti-Xa activity monitoring. Our audit evaluated the safety and quality of this protocol.

Methods

Our study was designed as a prospective audit. Consecutive adult patients undergoing CRRT with enoxaparin as the anticoagulant over a period of 6 months in the Royal Melbourne Hospital ICU were included in the study. There were no exclusion criteria.

Patients underwent continuous venovenous haemodiafiltration (CVVHDF) using the Prismaflex System with the Prismaflex ST100 set (AN69 acrylonitrile and sodium methallyl sulfonate copolymer membrane) (Gambro, Lund, Sweden), via either femoral or internal jugular two-lumen 10 Ga

haemodialysis catheters (Arrow Medical Supply, Libertyville, Ill, USA). A blood flow rate of 200 mL/min with 1800 mL/h pre-blood pump dilution was used in all cases.

During the data collection process, all patient data were de-identified. Age, sex, weight, APACHE (Acute Physiology and Chronic Health Evaluation) II score,[9] APACHE III diagnostic category[10] on admission, ICU length of stay and indication for CRRT were recorded. The times of each episode of filtration and of clotting and bleeding events were also recorded. Anti-Xa activity was tested before, during and after filtration, provided there were samples available from routine clinical testing suitable for such testing. It was also noted whether any other anticoagulation was administered within 24 hours of CRRT. Bleeding was reported if it was described in the patient record, and was classified as major if intervention (transfusion or surgery) was required.

No alteration was made to patient management due to involvement in the study.

Table 1. Characteristics of 13 patients with acute renal failure included in our study*

Characteristic	No. of patients
Age in years, median (range)	67 (30–85)
Male sex, *n*	9
Weight in kg, median (range)	79 (52–120)
APACHE II score,[9] median (range)	22 (18–35)
ICU length of stay in days, median (range)	5 (2–15)
APACHE III diagnostic category,[10] *n*	
Cardiovascular	6
Respiratory	2
Sepsis	2
Neurological	1
Other	2
Indication for CRRT, *n*†	
Acidosis	8
Hypervolaemia	5
Hyperkalaemia	3
Uraemia (urea > 30 mmol/L)	3

APACHE = Acute Physiology and Chronic Health Evaluation. CRRT = continuous renal replacement therapy. ICU = intensive care unit. * Data represent number of patients, except where otherwise specified. † More than one indication for CRRT could apply per patient. ◆

Table 2. Filter life and anti-Xa levels recorded for each patient during the study

Patient no.	Filter survival, h*	Before CRRT	During CRRT		After CRRT	
		Anti-Xa, U/mL	Hours after commencement	Anti-Xa, U/mL	Hours after cessation	Anti-Xa, U/mL
1	30	na	7.2	0.17	na	
			28.3	0.19		
2†	21	na	10.4	0.36	24.3	0.15
			34.1	0.18		
3	34	na	13.3	0.03	14.0	0.01
			27.0	0.10		
4†	34	0.10	3.3	0.21	18.5	0.07
			29.7	0.37		
5†	16	0.13	5.7	0.44	14.6	0.72
			26.8	0.32		
			51.4	0.65		
			80.7	0.11		
6	22	na	4.7	0.31	na	
7	26	0.00	17.2	0.62	na	
8	19	na	5.7	0.83	9.7	0.49
9	176	0.00	51.2	0.48	na	
			63.2	0.58		
			86.5	1.05		
			111.0	0.44		
			133.0	0.66		
			172.3	0.10		
			181.0	0.46		
			212.5	0.77		
			229.3	0.57		
10	2	0.00	17.8	0.15	49.7	0.12
			47.5	0.50		
			55.3	0.55		
			64.3	0.59		
			94.8	0.15		
11†‡	47	0.00	10.3	1.02	10.6	0.89
			35.5	1.50		
12‡	11	0.00	4.1	0.25	na	
13	4	na	10.0	0.10	35.4	0.10
			34.6	0.12		
			92.2	0.10		
			110.8	0.22		

CRRT = continuous renal replacement therapy. na = not applicable. * Filter survival was defined as duration of filtration until first clotting episode or termination of filtration. † Patients 2, 4, 5 and 11 also received subcutaneous enoxaparin as prophylaxis for deep vein thrombosis (40 mg for patients 2, 4 and 5; 20 mg for patient 11) within 24 hours of commencing filtration. ‡ Patients 11 and 12 suffered minor bleeding events (as described in the text). ◆

Statistical methods

Filter survival was determined as the filtration time to the first clotting episode (cessation of filtration due to rising transmembrane pressures and/or visible clot in the filter), or termination of filtration if clotting was not reported.

Systemic anti-Xa levels before, during and after CRRT were recorded, and the median, range and interquartile range calculated. Because of the small sample size, the Wilcoxon signed-rank test (PASW Statistics package, SPSS, Chicago, Ill, USA) was applied to determine whether significant differences existed between anti-Xa levels before, during and after CRRT for the cohort.

Ethics approval

Our study was conducted as a quality assurance audit. As such, no change was made to patient management, and no additional blood sampling was performed. Our hospital's human research ethics committee waived the need for informed consent.

Results

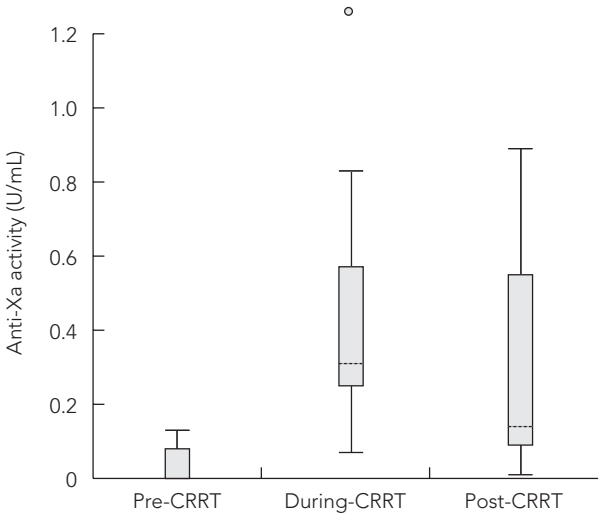
Thirteen critically ill patients with renal failure met the inclusion criteria and were enrolled in our audit between June and December 2009 (Table 1). A total of 67 patients underwent CRRT during this period.

The median filter survival time was 22 hours (range, 2–176 hours) (Table 2). Systemic anti-Xa activity was tested before commencement of CRRT in seven of 13 patients. All patients had anti-Xa levels assayed during CRRT, and eight had anti-Xa levels assayed after cessation of CRRT (Figure 1 and Table 2). Some patients had more than one anti-Xa assay during treatment. The times after commencement at which anti-Xa activity was first measured were not controlled, and ranged from 3.3 to 51.4 hours. There was a significant increase in anti-Xa levels from before CRRT (median, 0.00 U/mL; range, 0.00–0.13 U/mL) to during CRRT (median, 0.31 U/mL; range, 0.07–1.26 U/mL) ($P = 0.03$), but there was no significant difference between anti-Xa activity before and after CRRT or between anti-Xa activity during and after CRRT.

Several enrolled patients received anticoagulation within 24 hours of CRRT, other than that employed for CRRT. Subcutaneous heparin was administered in one case, and subcutaneous enoxaparin in a further four cases. One patient received heparin as circuit anticoagulation before changing to enoxaparin.

Minor bleeding events were reported in two patients. One suffered minor haemoptysis, macroscopic haematuria and minor ooze at the vascular catheter site. The other patient had a small blood clot suctioned via the endotracheal tube. Neither patient received transfusion or surgical intervention.

Figure 1. Box-and-whisker plot of anti-Xa activity before CRRT, during CRRT (median for each patient) and after CRRT



The box represents the interquartile range (IQR), with the median represented by a dotted line. The whiskers show the range, with circles for outliers (defined as more than 1.5 × IQR either side of the box). A significant rise was observed between pre-CRRT and during-CRRT levels ($P = 0.03$).

CRRT = continuous renal replacement therapy.

Discussion

The study evaluated our current unit protocol for anticoagulation for CVVHDF in 13 patients. The small sample size limits what can be deduced from the data. However, our filter life and bleeding outcomes were comparable to those previously described in similar populations.

The increase in anti-Xa levels during CRRT compared with before CRRT provides evidence that variable degrees of systemic anticoagulation occur as a result of enoxaparin anticoagulation for CRRT. This observation concurs with the results of a study by Reeves et al,[4] in which the mean anti-Xa activity in the dalteparin group was 0.49 U/mL (SE, 0.07 U/mL).

Two of our patients suffered bleeding events — both minor, and occurring at sites of instrumentation. One of these patients had the highest anti-Xa level observed in our study, but the other had only a modest anti-Xa level compared with the cohort.

Anti-Xa activity varied widely between patients and even within patients. Three patients became anticoagulated to a degree that would be considered in the range for therapy for thromboembolic disease,[11] as an unintended consequence of the use of enoxaparin to prevent filter clotting. This suggests that routine testing of anti-Xa levels may be indicated. Fortunately, no patient suffered a severe bleeding event.

Interpretation of anti-Xa activity after CRRT is difficult for several reasons. Patients had only a single anti-Xa level measurement after CRRT, and variability in the results, as well as timing of anti-Xa levels after cessation of CRRT, makes it difficult to assess the rate of decline in anti-Xa activity.

Our study was limited by its small sample size, and because of the audit nature of the study, the timing of anti-Xa levels relative to the onset and cessation of filtration was not controlled. Many other factors with the ability to affect filter life were also not controlled. Patients also often had interruptions to CRRT for reasons other than clotting, which limited assessment of the efficacy of enoxaparin for preventing circuit clotting. A larger prospective controlled study is required to address these limitations, with anti-Xa levels obtained before CRRT and at predetermined intervals after commencement and cessation of CRRT for each patient.

Conclusion

In selected patients with acute renal failure, an infusion of enoxaparin at 1.5 mg/kg per 24 hours appears to be an effective mode of circuit anticoagulation. This leads to a significant degree of systemic anticoagulation, the degree of which varies widely. A large controlled study is required to provide better safety data.

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