



## Full Length Article

# Plasma anti-FXa concentration after continuous intravenous infusion and subcutaneous dosing of enoxaparin for thromboprophylaxis in critically ill patients. A randomized clinical trial<sup>☆</sup>



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## ABSTRACT

**Introduction:** In intensive care unit (ICU) patients, subcutaneous low-molecular weight heparin thromboprophylaxis results in lower plasma anti-factor Xa (anti-FXa) levels compared to general ward patients. The aim of this study was to examine whether enoxaparin thromboprophylaxis given as a continuous intravenous infusion (CII) results in more constant and predictable anti-FXa concentration than standard subcutaneous bolus (SCB) administration.

**Materials and methods:** This was a prospective, single-blind, multicenter, randomized controlled trial where ICU patients requiring thromboprophylaxis received enoxaparin either 40 mg as a SCB once daily or 40 mg as a CII over 24 h for three consecutive days.

The primary outcome was maximum serum anti-FXa concentration ( $C_{\max 24\text{ h}}$ ) within the first 24 h; the secondary outcome was anti-FXa area under the curve ( $AUC_{(0-24\text{ h})}$ ). Trough level was measured at 72 h.

**Results:** Thirty-nine patients were included in the intention to treat analysis. The median anti-FXa  $C_{\max 24\text{ h}}$  was 0.05 (interquartile range, IQR, 0.05–0.18) IU/ml in the CII group and 0.18 (IQR, 0.12–0.33) IU/ml in the SCB group ( $p = 0.05$ ). Median anti-FXa  $AUC_{(0-24\text{ h})}$  was 1.20 (IQR, 0.98–2.88) in the CII and 1.54 (IQR, 1.22–4.12) in the SCB group ( $p = 0.095$ ). After 72 h, 66.7% of patients in the CII group had a detectable anti-FXa concentration of  $> 0.1$  IU/ml, compared with 16.7% in the SCB group ( $p = 0.019$ ).

**Conclusions:** Continuous infusion of enoxaparin led to lower anti-FXa  $C_{\max 24\text{ h}}$  than standard SCB administration. No difference in anti-FXa  $AUC_{0-24\text{ h}}$  was detected.

## 1. Introduction

Despite pharmacologic thromboprophylaxis, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are common complications of critical illness, and substantially increase morbidity and mortality [1,2]. Low-molecular-weight heparins (LMWHs) have become the drug of choice for thromboprophylaxis, as they have a more predictable and reproducible dose response than low-dose unfractionated heparin. The monitoring of anticoagulant effect is not generally recommended when using LMWHs [3]. Nonetheless, the measurement of plasma anti-factor Xa (anti-FXa) concentration has been described, although its efficacy as a means of monitoring therapeutic effect and association with clinical

thromboembolic events is thought to be inadequate [4].

There is growing evidence that critically ill patients have lower anti-FXa concentration than general ward patients after the initiation of standard LMWH thromboprophylaxis [5,6]. It has been proposed that the bioavailability of subcutaneous LMWH is impaired in critically ill patients, due to low cardiac output, impaired peripheral blood flow, concomitant use of vasoconstrictors [6] and subcutaneous edema [7]. In support of this hypothesis, subcutaneous LMWH thromboprophylaxis in ICU patients receiving vasopressor therapy has been shown to result in substantially lower anti-FXa activity than in patients not receiving vasoconstrictors [6].

To investigate whether the current practice of subcutaneous bolus (SCB) LMWH thromboprophylaxis is suitable for critically ill patients,

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we compared SCB therapy with a continuous intravenous infusion (CII) in this randomized clinical trial (RCT).

## 2. Materials and methods

### 2.1. Trial design

This prospective, randomized, single-blind clinical trial was conducted in two Finnish university hospital mixed ICUs at Tampere University Hospital and Meilahti University Hospital. The trial was conducted in accordance with the amended Declaration of Helsinki. The study design was approved by the local ethics committee of Pirkanmaa, Finland and the Finnish Medicines Agency, and it was registered in the Clinical Trials database ([ClinicalTrials.gov](http://ClinicalTrials.gov); NCT02095509). Before enrolment, written informed consent was obtained from each patient, or his or her legal representative.

### 2.2. Study population

Adult ICU patients aged between 18 and 80 years with an indication for pharmacologic thromboprophylaxis, a body mass index (BMI) 18–30 kg/m<sup>2</sup> and an expected ICU stay  $\geq$  72 h were eligible. Exclusion criteria were: indications for anticoagulant therapy other than thromboprophylaxis; intracranial hemorrhage or central neurosurgical operation within 3 months of ICU admission; diagnosis of disseminated intravascular coagulation according to International Society on Thrombosis and Haemostasis criteria [8]; known heparin-induced thrombocytopenia (HIT); hypersensitivity to enoxaparin or heparin; blood platelet count  $< 20 \times 10^9/l$ , prothrombin time (PT)  $< 20\%$  or International Normalized Ratio (INR)  $> 1.7$ ; major hemorrhage within the last week unless definitively treated; glomerular filtration rate  $< 50$  ml/min/1.73 m<sup>2</sup> estimated from serum creatinine concentration by applying the Cockcroft-Gault equation [9] or chronic dialysis; known HIV, hepatitis B or hepatitis C infection; pregnancy; and known liver disease. A patient who had received LMWH thromboprophylaxis within 24–72 h of ICU admission could be included if measured anti-FXa concentration was  $< 0.1$  IU/ml at the time of randomization. Basic patient characteristics, comorbidities and Acute Physiology and Chronic Health Evaluation (APACHE II) score were also recorded at baseline.

### 2.3. Study intervention

Patients were randomized to receive 40 mg enoxaparin (Klexane®, Sanofi-Aventis, Helsinki, Finland) either as an SCB every 24 h or as a CII over 24 h for three consecutive days. Block randomization into two groups was performed using sequentially numbered, sealed envelopes that were stratified according to the use of a vasopressor (yes or no). The SCB dose was administered once daily from a prefilled single-dose syringe containing 40 mg enoxaparin. The CII (40 mg enoxaparin diluted in 100 ml 0.9% sodium chloride solution) was prepared by a pharmacist or ICU nurse, divided in two syringes of 50 ml and infused intravenously (via either a central or peripheral venous catheter) over 24 h via an automatic pump. Any discontinuations of the study drug were recorded; if the infusion was stopped for  $> 2$  h, the patient was excluded from the final analysis. Mechanical thromboprophylaxis was undertaken according to normal clinical practice. The study period was 72 h, after which thromboprophylaxis was continued according to routine clinical practice in the ICUs.

Plasma anti-FXa concentration was determined at 0, 3, 6, 9, 12, 15, 18, 24, 27, 48, 51 and 72 h after the beginning of the study, where 24, 48 and 72 h samples represented trough concentrations and 27 and 51 h peak concentrations for SCB dosing. Additional samples were obtained from patients in the CII group at 1.5 and 4.5 h. The total dose of norepinephrine was documented daily. Blood chemistry, serum C-reactive protein concentration, platelet count, INR and PT were checked

daily. All blood samples were drawn from an arterial catheter that did not contain any heparin. Anti-FXa activity was measured in fresh blood samples in the core laboratory of each study hospital using a validated chromogenic assay (STA-Liquid anti-Xa, Diagnostica Stago, Asnières-sur-Seine, France).

### 2.4. Outcome measurements

The primary outcome measure was maximum plasma anti-FXa concentration within 24 h after initiation ( $C_{\max 24 \text{ h}}$ ). The secondary outcomes were maximum anti-FXa  $C_{\max}$  within 72 h ( $C_{\max 72 \text{ h}}$ ), area under the time-concentration curve at 24 and 72 h ( $AUC_{(0-24 \text{ h})}$  and  $AUC_{(0-72 \text{ h})}$ ) determined by standard pharmacokinetic procedures. The trough level was evaluated by anti-FXa concentration after the study period at 72 h. The influence of norepinephrine infusion (yes/no) and total norepinephrine dose on anti-FXa  $C_{\max 24 \text{ h}}$  and  $AUC_{0-24 \text{ h}}$  were also examined.

Clinically relevant complications were defined as follows: major hemorrhage (requiring  $> 2$  units transfusion of red blood cells, intracranial bleeding, or bleeding requiring major therapeutic intervention, causing hemodynamic compromise or resulting in death), minor hemorrhage (any other bleeding), DVT (confirmed by compression ultrasound, if clinically suspected), PE (confirmed by chest computed tomography angiography if clinically suspected) and HIT [10]. During the study period, the duration of mechanical ventilation and daily Sequential Organ Failure Assessment score were recorded, as well as the length of ICU stay and all-cause mortality at day 90 after ICU admission.

### 2.5. Statistical analysis

Standard sample size calculations indicated that at least 20 patients would be needed in each group to detect a clinically meaningful 33% reduction (from 0.30 to 0.20, standard deviation 0.11) in peak anti-FXa concentration, assuming a power of 80% and a significance level of 5%.

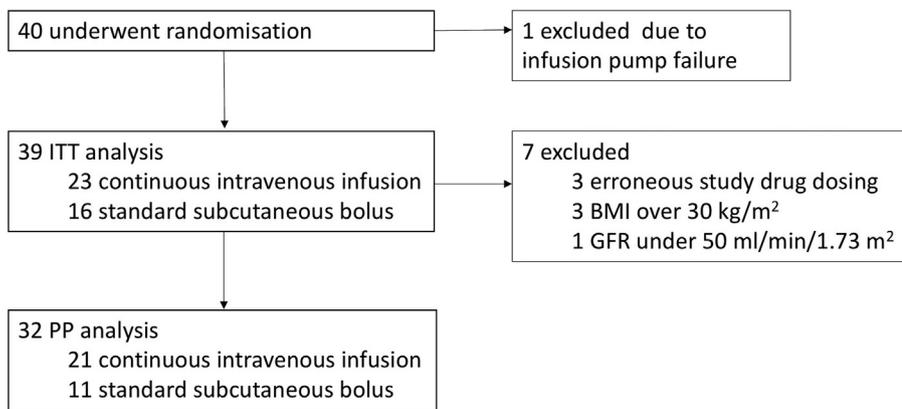
The distribution of data was assessed with the Shapiro-Wilk test. Non-normally distributed data are presented as the median (interquartile range, IQR). All comparisons between the study groups were performed with the Mann-Whitney  $U$  test, the  $\chi^2$  test, Fisher's test and Spearman's correlation coefficient as appropriate. All statistical analyses were performed using the SPSS statistical software program (version 23.0; IBM, Armonk, NY).

## 3. Results

Forty patients were randomized between March 2014 and July 2016. One patient did not receive the study drug because of infusion pump failure, and was excluded from the modified intention to treat (ITT) analysis. There were four randomization errors and three protocol violations, leaving 32 patients in the per protocol (PP) analysis (Fig. 1). Baseline characteristics and laboratory values are shown in Table 1; the study groups were well balanced.

### 3.1. Outcomes

In the ITT analysis, the median  $C_{\max 24 \text{ h}}$  was 0.05 (IQR, 0.05–0.18) IU/ml in the CII group and 0.18 (IQR, 0.12–0.33) IU/ml in the SCB group ( $p = 0.05$ ). The median  $AUC_{(0-24 \text{ h})}$  was 1.20 (IQR, 0.98–2.88) IU/l/h in the CII group and 1.54 (IQR, 1.22–4.12) IU/l/h in the SCB group ( $p = 0.095$ ). Per protocol analysis did not change the results (Table 2). After the study period of 72 h, the trough anti-FXa concentration was 0.12 (IQR, 0.05–0.17) IU/ml in the CII group and 0.05 (IQR, 0.01–0.05) IU/ml in the SCB group ( $p = 0.021$ ), leaving only 16.7% (two out of 10) patients with detectable anti-FXa concentration  $> 0.1$  IU/ml in the SCB group compared with 66.7% (10 out of 15) in the CII group ( $p = 0.019$ ).



**Fig. 1.** Diagram of enrollment. One patient from the CII group was excluded prior the study start due to infusion pump failure leaving 39 patients in the ITT group. From the ITT group 7 patients were excluded (3 erroneous study drug dosing, 3 BMI over 30 kg/m<sup>2</sup> and 1 GFR under 50 ml/min/1.73 m<sup>2</sup>) leaving 32 patients in the PP group. Abbreviations: ITT, intention to treat; CII, continuous intravenous infusion; SCB, standard subcutaneous bolus; BMI, body mass index; GFR, glomerular filtration rate; PP, per protocol analysis.

No correlations between the first ICU day total norepinephrine dose and C<sub>max24 h</sub> or AUC<sub>(0–24 h)</sub> were observed: Spearman's correlation coefficients were  $-0.176$  for C<sub>max24 h</sub> ( $p = 0.291$ ) and  $-0.171$  for AUC<sub>(0–24 h)</sub> ( $p = 0.305$ ). Norepinephrine infusion at randomization did not affect significantly the anti-FXa concentration: C<sub>max24 h</sub> was 0.05 (IQR, 0.05–0.20,  $p = 0.93$ ), mean difference + 0.001 [95% confidence interval, CI,  $-0.08, +0.008$ ] and 0.13 (IQR, 0.05–0.28,  $p = 0.174$ ), mean difference + 0.08 [95% CI  $-0.03, +0.20$ ] in the CII and SCB groups, respectively. And 0.13 (IQR, 0.05–0.28,  $p = 0.174$ ) in the CII and SCB groups, respectively. The effect of the baseline norepinephrine infusion on AUC<sub>(0–24 h)</sub> is shown in Fig. 2.

The follow-up data are provided as Supplementary material (Suppl. 1). Three PEs were diagnosed; two in the CII group and one in the SCB group. Four patients (three in the CII group and one in the SCB group) had minor bleeding. None of the adverse events were assessed to be

associated with the anti-FXa concentration (data not shown). The 90-day mortality was 12.8% ( $n = 5$ ); all deaths were judged to be independent of the study drug.

#### 4. Discussion

We found that continuous intravenous enoxaparin infusion as thromboprophylaxis therapy resulted in lower plasma anti-FXa concentration than standard subcutaneous administration during the first 24 h. No associations between anti-FXa concentration and clinical endpoints (bleeding or thromboembolic complications) were detected. This result supports our previous findings [4].

In medical and surgical patients, the recommended peak anti-FXa concentration for thromboprophylaxis is 0.1–0.3 IU/ml [11], but there are no recommendations on adequate anti-FXa concentration in

**Table 1**  
Baseline characteristics and laboratory values according to route of enoxaparin administration.

Patient characteristics	Continuous intravenous infusion $n = 23$	Standard subcutaneous bolus $n = 16$		$p$ -Value	
Male sex	13	56.5	14	87.5	0.076
Age, years	52	45–59	56	42–64	0.646
BMI, kg/m <sup>2</sup>	26.8	22.9–29.5	26.5	23.9–29.6	0.940
Active cancer	2	8.7	2	12.5	1.000
Diabetes	4	17.4	2	12.5	1.000
Smoking	13	56.5	5	31.3	0.119
Alcohol abuse	11	47.8	8	50.0	0.894
Hypertension	9	39.1	6	37.5	0.918
APACHE II	16.0	14–20	17.5	11.3–25.8	0.536
Creatine clearance, ml/min	121.4	83.5–152.0	121.5	94.3–162.0	0.848
Norepinephrine	8	34.8	7	43.8	0.571
Sepsis/septic shock					
Sepsis	7	30.4	7	43.8	0.692
Septic shock	2	8.7	1	6.3	
Primary admission diagnosis					0.991
Cardiovascular	1	4.3	0	0.0	
Respiratory	10	43.5	6	37.5	
Gastrointestinal	7	30.4	6	37.5	
Neurologic	1	4.3	0	0.0	
Infection	2	8.7	2	12.5	
Trauma	1	4.3	1	6.3	
Metabolic	1	4.3	1	6.3	
LMWH prophylaxis before inclusion	11	47.8	5	31.3	0.301
Length of ICU stay before LMWH, h:mm	18:56	10:18–26:47	17:33	13:55–24:55	0.471
Mechanical ventilation	15	65.2	12	75.0	0.726
Platelet count, 10 <sup>9</sup> /l	195	153–319	142	122–192	0.135
WBC count, 10 <sup>9</sup> /l	13.4	7.6–16.5	11.6	9.9–21.3	0.848
CRP mg/l	236	140–295	262	190–393	0.848
Hct%	0.36	0.30–0.38	0.34	0.29–0.43	0.399
Bilirubin μmol/l	12	7–20	13	9–15	0.646

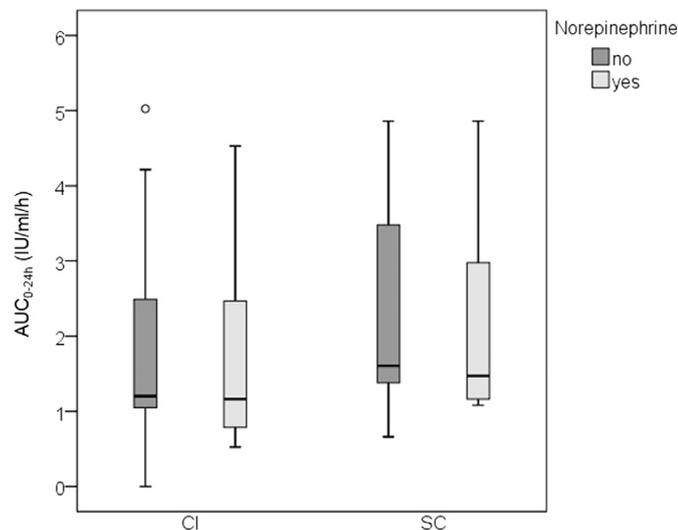
Data are presented as n (%) or median (interquartile range).

Abbreviations: BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; VTE, venous thromboembolism; LMWH, low-molecular weight heparin; WBC, white blood cell; CRP, C-reactive protein.

**Table 2**  
Maximum enoxaparin concentration and area under the curve by route of administration.

	Pharmacological parameters	Continuous intravenous infusion		Standard subcutaneous bolus		p-Value
		Median	Q <sub>1</sub> –Q <sub>3</sub>	Median	Q <sub>1</sub> –Q <sub>3</sub>	
ITT	Anti-FXa C <sub>max</sub> 24 h	0.05	0.05–0.18	0.18	0.12–0.33	0.005
	Anti-FXa C <sub>max</sub> 72 h	0.14	0.05–0.22	0.23	0.20–0.38	0.009
	AUC <sub>(0–24 h)</sub>	1.20	0.98–2.88	1.54	1.22–4.12	0.095
	AUC <sub>(0–72 h)</sub>	5.37	3.60–10.90	7.74	5.89–11.67	0.427
PP	Anti-FXa C <sub>max</sub> 24 h	0.05	0.05–0.16	0.19	0.11–0.34	0.008
	Anti-FXa C <sub>max</sub> 72 h	0.11	0.05–0.19	0.22	0.18–0.34	0.006
	AUC <sub>(0–24 h)</sub>	1.20	0.79–2.67	1.61	1.26–4.77	0.113
	AUC <sub>(0–72 h)</sub>	4.10	1.83–7.91	5.70	3.06–7.98	0.506

Abbreviations: FXa, activated Factor X; C<sub>max</sub>, maximum concentration; AUC, area under the curve; ITT, intention-to-treat; PP, per-protocol.



**Fig. 2.** The effect of the baseline norepinephrine infusion on anti-FXa AUC<sub>(0–24 h)</sub>.  
Abbreviations: AUC, area under the curve; CI, continuous intravenous infusion; SC, subcutaneous bolus.

critically ill patients, nor is it known whether peak or trough concentration should be measured. In previous studies, ICU patients have had lower peak anti-FXa concentration than ward patients [5,6]. However, when administering enoxaparin 40 mg once daily or 30 mg twice daily subcutaneously, peak anti-FXa concentration reportedly reaches the lower target concentration of 0.1 IU/ml [7,12–19], consistent with our findings in the SCB group. In the CII group, C<sub>max24 h</sub> remained < 0.1 IU/ml and the target concentration was not reached until 72 h. This could likely have been avoided by giving a loading dose.

To our knowledge this is the first RCT to have examined continuous dosing of thromboprophylactic LMWH in ICU patients. Previous studies have found that trough anti-FXa concentration tends to be low in these patients [14,17,18,20]. In this trial, anti-FXa concentration remained low in the CII group, but by the end of the study period (at 72 h) most of the patients in the CII group had a measurable anti-FXa concentration, whereas the concentration in the SCB group was comparable with those reported in previous trials. This supports our hypothesis that CII could offer more consistent anticoagulation; however, the clinical relevance of this finding is unclear. Furthermore, there is no consensus whether the laboratory target for LMWH prophylaxis should be a high peak anti-FXa concentration or a constant anti-FXa concentration.

The findings of previous trials suggest that suboptimal anti-FXa concentration in ICU patients could be explained by reduction in the bioavailability of subcutaneous LMWH, due to subcutaneous edema [7] or concomitant vasopressor therapy [6]. Moreover, the procoagulant effect of exogenous epinephrine is well established in historic trials, and

there is some evidence that norepinephrine infusion (0.15–0.75 µg/kg/min) promotes platelet aggregation [21]. Johansson and colleagues have demonstrated that even though higher endogenous norepinephrine concentration was associated with increased endothelial activation and fibrinolysis, exogenous norepinephrine infusion did not further potentiate these changes in patients with septic shock [22]. Our trial did not identify any significant effect of norepinephrine infusion on anti-FXa concentration in either of the study groups. However, it must be remembered that the choice and dose of LMWH used here differed from the study design of Dörffler-Melly and colleagues, who used nadroparin 2850 IU instead of enoxaparin 40 mg [6]. In a more recent trial in which the enoxaparin dose was similar to ours, norepinephrine did not have any effect on peak or trough anti-FXa concentration [23]. Additionally, despite lacking statistical significance our findings cannot refute a clinically meaningful effect size (upper confidence interval for difference in means antiFXa 0.20) of norepinephrine in subcutaneous dosing of enoxaparin.

The clinical relevance of anti-FXa concentration to bleeding or VTE is unclear; however, in one study a low trough anti-FXa concentration increased the risk of DVT [13]. In this trial, three patients were diagnosed with PE irrespective of the anti-FXa concentration; screening ultrasound was not undertaken in these patients in line with current guidelines [24]. The therapeutic benefits of mechanical thromboprophylaxis for these thrombotic events are uncertain. Nearly all our patients had compression stockings and/or pneumatic compression devices.

Our study had some limitations. First, the PP group was smaller than planned. Nevertheless, the results of the ITT and PP groups were broadly comparable. Second, our decision to stratify groups with norepinephrine administration in two different study sites led to different number of patients in each study group. However, differing numbers in the study groups do not compromise statistical testing and we considered it important to stratify according to norepinephrine dosing due to preliminary reports suggesting marked confounding influence of norepinephrine [6]. Third, as the study period was only 72 h, it is possible that we missed the opportunity to observe enoxaparin accumulation and its consequences. Fourth, we excluded patients with acute kidney injury and obesity to avoid bias. Fifth, the sample size was not designed to detect clinically relevant endpoints. Finally, we acknowledge that anti-FXa concentration is only a surrogate marker for thromboprophylaxis, and ignores the anticoagulant effect of enoxaparin on other plasma proteins (such as thrombin and platelet factor 4).

## 5. Conclusions

Continuous intravenous infusion of enoxaparin as thromboprophylaxis led to lower 24 h anti-FXa C<sub>max</sub> compared with standard SCB administration. No difference in anti-FXa AUC<sub>0–24 h</sub> was detected. Our findings could not confirm or refute a clinically relevant effect of norepinephrine infusion on antiFXa levels using subcutaneous dosing of

enoxaparin. Further studies scrutinizing enoxaparin infusion with a loading dose in critically ill patients are warranted.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.thromres.2017.08.014>.

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