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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☆

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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 ($C_{max24\ h}$) within the first 24 h; the secondary outcome was anti-FXa area under the curve $(AUC)_{(0–24\ h)}$. Trough level was measured at 72 h.

Results: Thirty-nine patients were included in the intention to treat analysis. The median anti-FXa $C_{max24\ h}$ 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 $AUC_{(0–24\ h)}$ 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 $C_{max24\ h}$ than standard SCB administration. No difference in anti-FXa $AUC_{0–24\ h}$ 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; 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^2 and an expected ICU stay ≥ 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 × 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^2 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 ($C_{max24\ h}$). The secondary outcomes were maximum anti-FXa C_{max} within 72 h ($C_{max72\ h}$), area under the time-concentration curve at 24 and 72 h ($AUC_{(0–24\ h)}$ and $AUC_{(0–72\ h)}$) 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 $C_{max24\ h}$ and $AUC_{0–24\ h}$ 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 χ^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 $C_{max24\ h}$ 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 $AUC_{(0–24\ h)}$ 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).