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# Pharmacokinetic profiles of intravenous versus subcutaneous administration of low molecular weight heparin for thromboprophylaxis in critically ill patients: A randomized controlled trial

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ABSTRACT

*Background:* Low molecular weight heparins (LMWH) are recommended for thromboprophylaxis in ICU patients but often fail to reach adequate peak anti-Xa activity.
*Objective:* To compare the pharmacokinetic profiles of intravenous (IV) versus subcutaneous (SC) route of administration of LMWH.
*Method:* This was a prospective, monocentric, randomized trial. Patients were randomized to the IV route of administration with a 4-h infusion of nadroparin 3800 IU or to the SC route of administration. Randomization was stratified according to the need for vasopressor or not. Anti-Xa activity was measured at baseline, and at 1, 2, 4, 6, 8, 12 and 24 h after the administration was started.
*Results:* Sixty patients were included, of whom 30 were randomized to the IV group and 30 to the SC route. Pharmacokinetic profiles were significantly different. Mean peak anti-Xa activity was 0.38 IU/ml in the IV group vs 0.20 IU/ml in the SC group ($p < 0.001$). Trough values and AUC (0-24 h) were similar in both groups. Pharmacokinetic profiles were similar whether patients received vasopressors or not.
*Conclusions:* The IV route of administration with a 4-h infusion lead to a significantly higher peak anti-Xa activity without affecting trough value or the AUC (0-24 h). Whether the IV administration of LMWH might improve the efficacy of thromboprophylaxis requires further research.
Registration: ClinicalTrials.gov, NCT04982055, retrospectively registered 08 July 2021, https://clinicaltrials.gov/ct2/show/NCT04982055?cond=NCT04982055&draw=2&rank=1



## 1. Introduction

Critically ill patients carry a high risk of thromboembolic events due to various factors associated with severe illness including sepsis, surgery, bed rest, vasopressor use, venous catheters, respiratory or renal failure [1-3]. The incidence of deep vein thrombosis in intensive care unit (ICU) patients varies widely in the literature, depending on the studied population and the method of screening but have been reported to be as high as 37% [1,4-8].

Thromboembolic events are associated with a higher morbidity including prolonged duration of mechanical ventilation and increased ICU length of stay [1,8,9], and, in some studies, with a higher mortality [2].

Thromboprophylaxis is therefore highly recommended for critically ill patients [10-12] and it has been shown that subcutaneous (SC) administration of low molecular weight heparin (LMWH) is proven to be effective in reducing the rate of both symptomatic and asymptomatic deep vein thrombosis by about one half [7,13,14].

Low molecular weight heparins express their anticoagulant effect by binding to antithrombin and increasing its inhibitory effect on activated factor Xa (FXa) and, to a lesser extent, by direct inhibition of thrombin (FIIa) [15].

Low molecular weight heparins theoretically have a predictable dose response effect and therefore do not require any monitoring of their plasmatic effect. However, in specific populations, such as those where the thrombotic or the hemorrhagic risk might be elevated or in case of renal failure, plasmatic monitoring could be useful. Plasmatic monitoring of SC LMWH is usually evaluated by the measurement of the peak antifactor-Xa (anti-Xa) activity, with a range of 0.2–0.5 IU/ml

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considered to be effective for thromboprophylaxis in medical and surgical patients [16-18].

However, in recent years, it has been highlighted that critically ill patients frequently have low anti-Xa activities when prophylactic doses of LMWH are administered through the subcutaneous route and might therefore not be adequately protected against the thromboembolic risk. In particular, the use of vasopressors has been described to impair LMWH absorption when administered subcutaneously [19-24].

Therefore, we sought to determine whether the IV route of administration of LMWH for thromboprophylaxis would achieve greater peak anti-Xa activity than the SC route.

When LMWHs are administered subcutaneously, plasmatic anti-Xa activity peaks 3 to 4 h after administration, then gradually decreases thereafter. Based on this pharmacokinetic profile, we compared the plasmatic anti-Xa profile of a 4-h intravenous infusion of 3800 anti-Xa IU dose of nadroparin to the subcutaneous administration of the same dose nadroparin.

## 2. Material and method

### 2.1. Trial design

This trial was a prospective, randomized, open-label trial conducted in a single center 15-bed mixed ICU. The trial was performed in accordance with the Declaration of Helsinki. The trial design was approved by the local ethics committee and written informed consent was obtained prior to enrolment from each patient or his/her legal representative. This study was supported partly by an unrestricted grant from ASPEN. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### 2.2. Study population

Adult patients >18 years old admitted to the ICU, and for whom thromboprophylaxis was indicated were eligible to participate in the study. Exclusion criteria included renal failure determined by glomerular filtration rate (GFR) < 30 ml/min or need for renal replacement therapy, liver cirrhosis, disseminated intravascular coagulation, contra-indication to thromboprophylaxis for any reason as decided by the treating physician, or indication for therapeutic dosing anticoagulation (recent thrombo-embolic event, atrial fibrillation, etc). Patients receiving low dose vasopressor (norepinephrine <0.25 μg/kg/min) were also excluded to allow stratification and comparison between patients not on vasopressors and patients with a significant dose of vasopressors (norepinephrine ≥0.25 μg/kg/min).

### 2.3. Study intervention

Eligible patients were randomized to receive a single dose of 3800 IU nadroparin through the subcutaneous route (SC group) or the intravenous route (IV group), by means of sealed envelopes. Randomization was stratified according to the use of vasopressor (norepinephrine ≥0.25 μg/kg/min) or no vasopressor. In the SC group, nadroparin 3800 IU was administered subcutaneously ≥24 h after last dose of LMWH administered. Monitoring of the antifactor Xa activity was performed immediately before (H0) and 1 (H1), 2 (H2), 4 (H4), 6 (H6), 8 (H8), 12 (H12), and 24 (H24) hours after the last dose of LMWH was administered. In the IV group, nadroparin 3800 IU was administered over a 4-h intravenous infusion (nadroparin 0.4 ml added to 39.6 ml of 0.9% saline). Monitoring of the antifactor Xa activity was performed immediately before (H0) and 1 (H1), 2 (H2), 4 (H4), 6 (H6), 8 (H8), 12 (H12), and 24 (H24) hours after the start of infusion. Blood samples were drawn from an arterial catheter which did not contain any heparin. Anti-Xa activities were determined using a validated chromogenic assay (HemosIL, Liquid Anti-Xa, Werfen, Barcelona, Spain), with a detection limit of 0.04 IU/ml. The anti-Xa Liquid kit was used on an ACLTop system. The method is calibrated between 0.0 IU/ml and 2.0 IU/ml using WHO calibrated standards. Results above 2.0 IU/ml were diluted in diluent buffer (Werfen) to fit into the calibration slope. After the last anti-Xa activity (H24) was drawn, each patient returned to standard thromboprophylaxis using the SC route.

### 2.4. Statistical analysis

All statistical analyses were performed using the SPSS 21 software (SPSS software [IBM Corp. 2011. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA]), with graphs drawn using Graphpad Prism 8.4 (GraphPad Software, La Jolla, CA, USA). Values were expressed as mean (± standard deviation) or median (interquartile range) for continuous values and counts (per percent of group) for qualitative variables. The data were subjected to the Kolmogorov-Smirnov normality test and Bartlett's test for homogeneity of variance. We compared clinical and demographic variables between patients with intravenous vs subcutaneous LMWH administration, using the chi-square test (or Fisher's exact test when appropriate) and the unpaired *t*-test (or the Wilcoxon rank-sum test according to statistical distribution) for quantitative (or qualitative) data, respectively. Time trends were compared between groups using generalized linear mixed models with the group (SC vs IV) as a fixed factor and time as a random repeated factor. Area under the curve (AUC) was calculated using the log-trapezoidal rule, applied to arithmetic means at each time point of the elimination phase of the concentration-time profile. In order to find factors influencing the peak anti-Xa activity, a logistic regression model was built as follows: all the variables significant in the univariate analysis ($p < 0.20$) were entered into a multivariate logistic regression with a backward elimination procedure, based on the likelihood ratio. Co-linearity between variables was excluded prior to modelling. The results were expressed as odds ratio (OR) with 95% confidence intervals [95%CI]. All tests were two-sided, with significance set at the 0.05 probability level.

## 3. Results

Sixty patients were included in the study, of whom 30 were randomized to the SC group and 30 to the IV group. Baseline characteristics are shown in Table 1. Both groups had similarly low anti-Xa activity at baseline (0.03 ± 0.03 and 0.02 ± 0.02 IU/ml in the SC and IV group respectively). After LMWH administration, the pharmacokinetic profile of anti-Xa activities differed significantly between the two groups (Fig. 1). Peak anti-Xa activity was reached 4 h after starting administration in both groups. Mean peak anti-Xa activity was 0.38 ± 0.15 IU/ml in the IV group and 0.20 ± 0.09 IU/ml in the SC group ($p < 0.001$). In the SC group, 16 patients (53%) had peak anti-Xa activity at 4 h < 0.2 IU/ml as compared with only 3 patient (10%) in the IV group ($p < 0.001$). Six patient (20%) in the IV group and none in the SC group had an anti-Xa activity >0.5 IU/ml ($p = 0.01$). Trough anti-Xa activity 24 h after nadroparin administration was similar in both groups (0.04 ± 0.04 IU/ml in the SC group and 0.01 ± 0.01 IU/ml in the IV group; $p = 0.83$). The AUC (0-24 h) did not differ between groups (2.30 ± 0.39 IU.h/ml in the IV group vs 2.51 ± 0.53 IU.h/ml in the SC group; $p = 0.74$) (Table 2).

We compared the pharmacokinetic profiles in patients receiving vasopressors to those who did not and observed very similar profiles; neither the peak nor trough anti-Xa activity or the AUC (0-24 h) differed (Table 3).

In multivariate analysis, body mass index (BMI) and route of administration (SC vs IV) were significantly associated with a peak anti-Xa activity <0.2 IU/mL (Table 4). Glomerular filtration rate, norepinephrine use, and fluid balance since ICU admission were not associated with the peak anti-Xa activity.

**Table 1**
Baseline characteristics, ICU admission diagnosis, adjuvant treatment use and relevant clinical parameters in the trial population.

| | | IV (N = 30) | SC (N = 30) | p |
|---|---|---|---|---|
| Age (years), mean ± SD | | 63 ± 14 | 65.4 ± 14 | 0.56 |
| Weight (kg), mean ± SD | | 69.5 ± 13.5 | 70.6 ± 16.7 | 0.79 |
| BMI (kg/m$^2$), mean ± SD | | 24.2 ± 4.6 | 25.3 ± 5.8 | 0.4 |
| Male sex, n (%) | | 21 (70) | 18 (60) | 0.59 |
| Hypertension, n (%) | | 16 (53) | 16 (53) | 1 |
| Ischemic heart disease, n (%) | | 7 (23) | 2 (7) | 0.07 |
| Diabetes, n (%) | | 6 (20) | 6 (20) | 1 |
| Cancer, n (%) | | 1 (3) | 0 (0) | 0.313 |
| COPD, n (%) | | 5 (17) | 12 (40) | 0.045 |
| Cirrhosis, n (%) | | 4 (13) | 0 (0) | 0.112 |
| Days since ICU admission, median (IQR) | | 1 (0.75–2) | 2 (1–7) | 0.037 |
| APACHE II score, mean ± SD | | 22.4 | 21.2 | 0.63 |
| Norepinephrine use, n (%) | | 15 (50) | 15 (50) | 1 |
| Norepinephrine mean dose (μg/kg/min), mean ± SD | | 0.35 ± 0.19 | 0.44 ± 0.37 | 0.35 |
| Creatinine clearance (eGFR; ml/min/1.73m$^2$), mean ± SD | | 81.6 ± 37.6 | 80.6 ± 33.2 | 0.91 |
| Bilirubin (μmol/l); mean ± SD | | 30.8 ± 53 | 13.7 ± 8.5 | 0.09 |
| Fluid balance (ml), mean ± SD | | 3329 ± 4740 | 3771 ± 4424 | 0.72 |
| Mechanical ventilation, n (%) | | 15 (50) | 14 (48) | 0.89 |
| ICU admission diagnosis, n (%) | | | | 0.17 |
| | septic shock | 15 (50) | 14 (47) | |
| | sepsis | 3 (10) | 4 (13) | |
| | pancreatitis | 2 (7) | 2 (7) | |
| | COPD exacerbation | 3 (10) | 5 (17) | |
| | cardiovascular | 4 (13) | 1 (3) | |
| | liver failure | 1 (3) | 0 (0) | |
| | abdominal surgery | 1 (3) | 0 (0) | |
| | metabolic | 0 (0) | 3 (10) | |
| | other | 1 (3) | 1 (3) | |

IV: intravenous; SC: subcutaneous; BMI: body mass index; COPD: chronic pulmonary obstructive disease; eGFR: estimated glomerular filtration rate; ICU: intensive care unit.

Finally, no thromboembolic nor hemorrhagic event was observed during ICU stay after a mean follow-up of 9.5 days (±9.1 days). Mean ICU stay was 12.7 days (±11 days).

## 4. Discussion

In this prospective randomized study comparing two routes of administration of nadroparin 3800 IU for thromboprophylaxis in critically ill patients, we found that the 4-h IV administration resulted in a higher peak anti-Xa activity and in a higher likelihood of obtaining peak anti-Xa activity ≥0.2 than the SC route of administration, while trough anti-Xa activities and AUC (0-24 h) were similar in both groups.

Several studies have previously reported that critically ill patients who were administered LMWH for thromboprophylaxis had lower anti-Xa activities than non-critically ill patients [19-24]. Similarly, in our study, 16 patients (53%) in the SC group failed to have peak anti-Xa activity ≥0.2 IU/ml whereas, in the IV group, only 3 patients (10%) did not reach this target. Whether this observation translates into differences in efficacy of thromboprophylaxis in critically ill patients requires however further clinical investigation.

The choice of anti-Xa activity measurement as a surrogate marker for the efficacy of LMWH may be questionable. If anti-Xa activity correlates with the concentration of LMWH in plasma in in vitro studies [25], it best reflects its pharmacokinetic profile rather than its pharmacodynamic activity. LMWHs exert their anticoagulant effect indirectly by factor Xa inhibition but also through direct inhibition of thrombin. It could be therefore hypothesized that other tests measuring thrombin generation may better quantify the anticoagulant effect of LMWH. However, in vitro studies have shown excellent correlation between thrombin generation and anti-Xa activity measurement [25]. Thus, anti-Xa activity measurement remains the most widely used method for the quantification of LMWH effect in vivo.

The decision to measure anti-Xa activity at the peak of its PK profile may also be debated. Peak anti-Xa activity is generally thought to reflect the efficacy of LMWH while the trough value, its safety regarding the hemorrhagic risk. Other studies have investigated anti-Xa activity 12 h after admission, trough levels or even AUC (0-24 h) [26,27]. To date, it is unclear whether reaching a specific level of peak anti-Xa activity or maintaining anti-Xa activity as long as possible above a specific cutoff is a better approach to achieve efficient thromboprophylaxis. Even if peak anti-Xa activity remains the usual test of choice for assessing the efficacy of LMWH [17], it is therefore possible that trough values or AUC (0–24) could differently assess the efficacy and safety of LMWH. Importantly, in our study, only peak anti-Xa activity significantly differed between the IV and the SC groups, whereas trough values and AUC (0-24 h) were similar.

Additionally, no definite peak anti-Xa target range has been validated for evaluating the efficacy of LMWH thromboprophylaxis. Although a target of 0.2–0.5 IU/ml is commonly used, evidence supporting this range is limited and is largely derived from trials involving general surgical, orthopaedic patients [16-18]. Several of these studies have shown an association between plasmatic anti-Xa activity and the incidence of venous thromboembolism [26-29], while other failed to [16]. Few studies have investigated this relationship in ICU patients and these were performed mostly in trauma patients [4,30], who represent a very specific high risk population known to have lower antithrombin levels [31]. It has also been suggested that high-risk critically ill patients may require higher peak anti-Xa activities than the usually recommended range (0.2–0.5 IU/ml) [32].

To our knowledge, our study is the first to investigate an IV infusion of LMWH over 4 h in a trial of thromboprophylaxis. The duration of 4-h was chosen to best mimic the pharmacokinetic profile of LMWH administered subcutaneously. Few studies have investigated the IV route of administration of LMWH for thromboprophylaxis, and these used a bolus or continuous infusion. One previous study comparing the SC and the continuous IV (over 24 h) administration of enoxaparin 40 mg showed that the IV route was associated with lower peak anti-Xa activity despite similar AUC (0-24 h) [33]. In another study comparing an IV

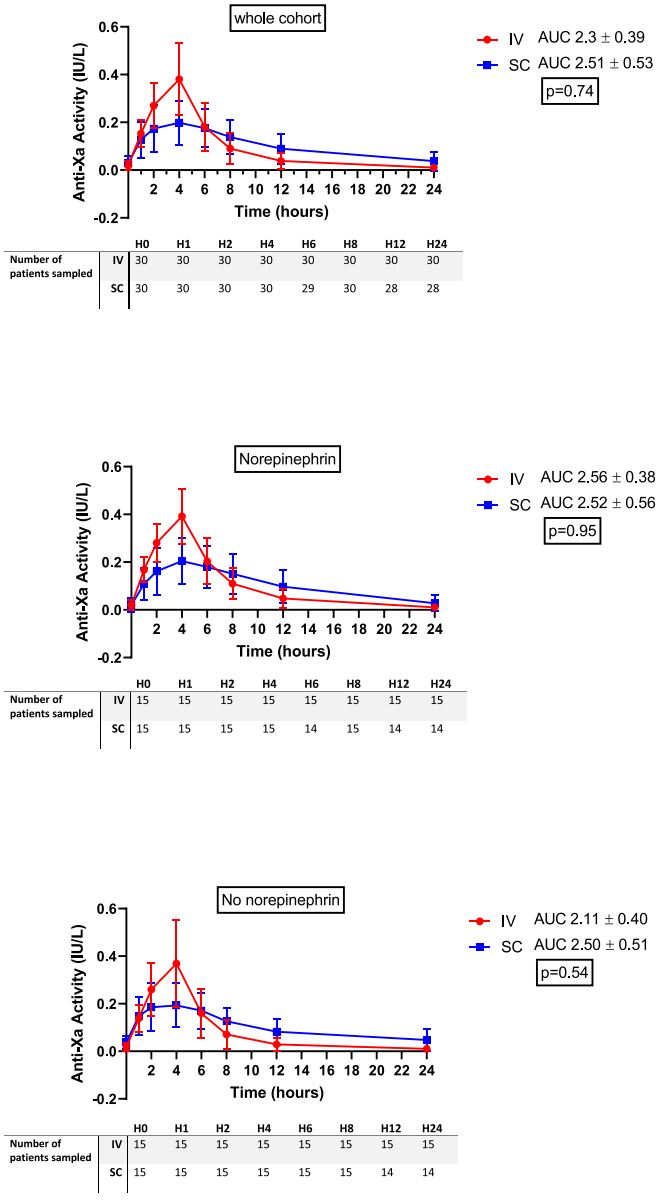


**Fig. 1.** Anti-Xa pharmacokinetic profile in the whole cohort, and in the subgroups with, and without vasopressor.
Pharmacokinetic profiles assessed by measuring the anti-Xa activities at baseline, and 1, 2, 4, 6, 8, 12 and 24 h after starting the LMWH administration, in the whole cohort (n = 60), in the subgroup of patient with vasopressor, and in the subgroup of patient with no vasopressor. IV: intravenous; SC: subcutaneous; AUC: area under the curve (expressed in IU.h/ml).

**Table 2**
Anti-Xa activities (entire cohort).

| | IV (n = 30) | SC (n = 30) | p-value |
|---|---|---|---|
| Peak, mean ± SD | 0.38 ± 0.15 | 0.20 ± 0.09 | < 0.0001 |
| Peak ≥0.2 IU/ml, n (%) | 27 (90%) | 14 (47%) | 0.001 |
| Peak >0.5 IU/ml, n (%) | 6 (20%) | 0 (0%) | 0.01 |
| Peak in the 0.2–0.5 IU/ml range, n (%) | 21 (70%) | 14 (47%) | 0.11 |
| Trough, mean ± SD | 0.01 ± 0.01 | 0.04 ± 0.04 | 0.83 |
| AUC (0-24 h), mean ± SD | 2.3 ± 0.39 | 2.51 ± 0.53 | 0.74 |

AUC (0-24 h): area under the curve; anti-Xa activities are expressed in IU/ml; AUC are expressed in IU.h/ml. Peak and trough anti-Xa activities were measured 4 and 24 h respectively after the LWMH administration was started.

**Table 3**
Anti-Xa activities (subgroup analysis according to the use of vasopressor (norepinephrine ≥0.25 μg/kg/min or not).

| | IV (n = 15) | SC (n = 15) | p-value |
|---|---|---|---|
| Vasopressor use | | | |
| Peak, mean ± SD | 0.39 ± 0.12 | 0.20 ± 0.10 | <0.0001 |
| Peak ≥0.2 IU/ml, n (%) | 14 (93%) | 8 (53%) | 0.01 |
| Peak >0.5 IU/ml, n (%) | 3 (20%) | 0 (0%) | 0.068 |
| Peak in the 0.2–0.5 range, n (%) | 11 (73%) | 8 (53%) | 0.26 |
| Trough, mean ± SD | 0.01 ± 0.01 | 0.03 ± 0.03 | 0.99 |
| AUC (0-24 h), mean ± SD | 2.56 ± 0.38 | 2.52 ± 0.56 | 0.95 |
| No vasopressor use | | | |
| Peak, mean ± SD | 0.37 ± 0.18 | 0.19 ± 0.09 | <0.0001 |
| Peak ≥0.2 IU/ml, n (%) | 13 (87%) | 6 (40%) | 0.008 |
| Peak >0.5 IU/ml, n (%) | 3 (20%) | 0 (%) | 0.068 |
| Peak in the 0.2–0.5 range, n (%) | 10 (67%) | 6 (40%) | 0.14 |
| Trough, mean ± SD | 0.01 ± 0.01 | 0.05 ± 0.05 | 0.86 |
| AUC (0-24 h), mean ± SD | 2.11 ± 0.40 | 2.50 ± 0.51 | 0.54 |

AUC (0-24 h): area under the curve; anti-Xa activities are expressed in IU/ml; AUC are expressed in IU.h/ml. Peak and trough anti-Xa activities were measured 4 and 24 h respectively after the LWMH administration was started.

bolus administration of nadroparin 3800 IU to SC administration of half this dose in ICU patients requiring vasopressors, peak anti-Xa was 0.42 IU/ml in the IV bolus group versus 0.16 IU/ml in the SC group. In this study however, a trend toward a lower AUC (0–24) was observed in the IV bolus group [23]. In our study, by choosing to administer nadroparin over a 4-h intravenous infusion, we could reach a higher peak of anti-Xa activity than in the SC group, without modifying the trough value or the AUC (0-24 h).

### Vasopressor use

Several factors have previously been reported to be associated with lower anti-Xa activities in ICU patients. Vasopressor use, by inducing vasoconstriction of the skin and soft tissue blood vessels and thereby decreasing LMWH absorption when administered through the SC route, has been associated with very lower anti-Xa activities in a study comparing ICU patient with and without vasopressors, and ward patients [19]. In our study, the pharmacokinetic profiles were very similar between patients receiving vasopressors or not. Although the mean doses of vasopressors in our study tended to have been lower, our results are supported by two other studies which did not found a relation between vasopressor doses and peak anti-Xa activities [21,34]. Other factors associated with critical illness, such as modified renal clearance, increased distribution volumes or peripheral edema, may also modify drug absorption and elimination. Peripheral edema has been reported to be associated with lower anti-Xa activities in the ICU, by reducing the bioavailability of LMWH administered subcutaneously [35], although this observation was not confirmed in another subsequent study [36]. In our study, neither renal function nor fluid balance since ICU admission that could reflect peripheral edema, showed any correlation with anti-Xa activity. Finally, our study showed that body mass

**Table 4**
Multivariate regression analysis for variables associated with peak anti-Xa activity ≥0.2 IU/ml.

| Variable | Odds ratio | 95% CI | p-value |
|---|---|---|---|
| Age | 0.99 | 0.93 to 1.04 | 0.63 |
| BMI | 0.85 | 0.72 to 0.99 | 0.04 |
| Male Sex | 0.45 | 0.09 to 2.17 | 0.33 |
| IV/SC | 15.93 | 3.50 to 110.8 | 0.0012 |
| Norepinephrine | 0.54 | 0.052 to 5.31 | 0.59 |
| Creatinine clearance | 1.00 | 0.98 to 1.03 | 0.92 |
| Bilirubin | 0.69 | 0.44 to 1.10 | 0.12 |
| Fluid balance | 0.99 | 0.99 to 1.00 | 0.45 |
| Invasive mechanical ventilation | 1.77 | 0.15 to 19.42 | 0.63 |

index was also associated with lower peak anti-Xa activities. This finding is consistent with many other previous studies [21,34], and confirms that LMWH doses should be modified in obese patients.

We have to acknowledge some limitations to our study. First, as the primary goal of the study was to evaluate the pharmacokinetic profile, the sample size was limited. Second, as the PK profile was performed over a 24-h period, we did not search for thrombo-embolic events and we are not able to analyze any association between anti-Xa activity and a clinical efficacy or safety endpoint. Conversely, achieving higher peak anti-Xa levels by administering LMWH through the IV route might expose the patients to a higher bleeding risk, even if a potential relationship between anti-Xa levels and bleeding events is poorly established [20,28]. Third, we analyzed anti-Xa profiles following a single dose of nadroparin and timing between ICU admission and the inclusion in the study was not standardized. Therefore, the number of doses of LMWH administered before the study varied between patients [0–19]. For these reasons, we could not exclude bioaccumulation after multiple days of treatment. However, this is unlikely as we measured the trough values of anti-Xa activity and observed them return to baseline levels in both groups. Previous studies also suggested that no accumulation occurred after multiple dosing [6,16,22]. Fourth, we used nadroparin at a recommended dose of 3800 IU. Different doses or other LMWHs could present different pharmacokinetic profiles [37] as well as different clinical outcomes. Fifth, patient inclusion was not consecutive and the number of patients excluded from study participation as well as the reasons for exclusion are lacking.

## 5. Conclusions

In conclusion, we compared the pharmacokinetic profiles of a single dose of nadroparin 3800 IU for thromboprophylaxis in critically ill patients administered by the subcutaneous route or through a 4-h IV infusion. The IV administration was associated with a higher peak anti-Xa activity and with a higher probability of a peak anti-Xa activity ≥0.2 IU/l with similar trough values and AUC (0-24 h). Whether the 4-h IV infusion translates into better thromboembolic event prophylaxis without increasing the bleeding risk needs to be further studied.

## Ethics approval and consent to participate

The study was approved by the Comité d'Ethique Hospitalo-facultaire Saint-Luc – UCL. 2015/10FEB/054. Belgian registry number: B403201524065. Written informed consent was obtained prior to study enrolment from each patient or his/her legal representative.

## Consent for publication

Not applicable.

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This study was supported in part by an unrestricted grant from ASPEN. The funders of the study had no role in the study design, data collection, analysis, or interpretation, writing of the manuscript, or decision to submit for publication.

## Availability of data and material

Study data are available from the corresponding author on reasonable request.

## Author's contributions

ND and XW designed the study. ND collected study data. LG performed the statistical analysis. The first draft was written by ND. All authors participated in writing, and revising the manuscript.

## Conflict of interest

None to declare.

## Acknowledgements

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154029.

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