Research letters

Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors

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Venous thromboembolism is a frequent complication in patients admitted to intensive care units (ICU), despite prophylactic treatment with subcutaneous low-molecular-weight (LMW) heparin. We postulated that poor efficacy of subcutaneous heparin might be due to administration of vasopressors, which could cause impaired peripheral circulation and inadequate systemic bioavailability of the anticoagulant. We compared concentrations of factor Xa activity in three groups of 15 patients: individuals in ICU who had and had not received vasopressors, and general surgery patients. Those who received vasopressors had lower plasma concentrations of factor-Xa activity than patients in ICU not on vasopressors and postoperative controls. Patients in ICU who take vasopressors could need higher doses of LMW heparin, or a different mode of administration of the drug, to attain adequate thrombosis prophylaxis.

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Venous thromboembolism is a frequent complication in critically ill patients, with deep vein thrombosis arising in 22–80% of patients admitted to intensive care units (ICU). Thromboprophylaxis with unfractionated heparin lowers this risk by 20%, and low-molecular-weight (LMW) heparins reduce the risk by 50%.[1,2] Nevertheless, the likelihood of venous thromboembolism in critically ill patients who receive LMW heparin prophylaxis remains high. Optimum efficacy and safety of LMW heparin for thromboprophylaxis in orthopaedic and abdominal surgery is achieved with doses of heparin that result in peak plasma factor Xa activity of between 0·25 IU/mL and 0·29 IU/mL during the first 3 postoperative days, and of between 0·33 IU/mL and 0·37 IU/mL from days 4 to 10.[3] Several factors could explain the higher frequency of venous thromboembolism in critically ill patients, such as immobilisation or withholding anticoagulant prophylaxis because of a high bleeding risk. However, we postulate that the high prevalence of venous thromboembolism is, at least in part, caused by limited bioavailability—ie, low concentrations of factor Xa activity in the plasma—of subcutaneously administered heparin in patients with impaired peripheral circulation, due to vasopressor medication given to maintain central blood pressure.

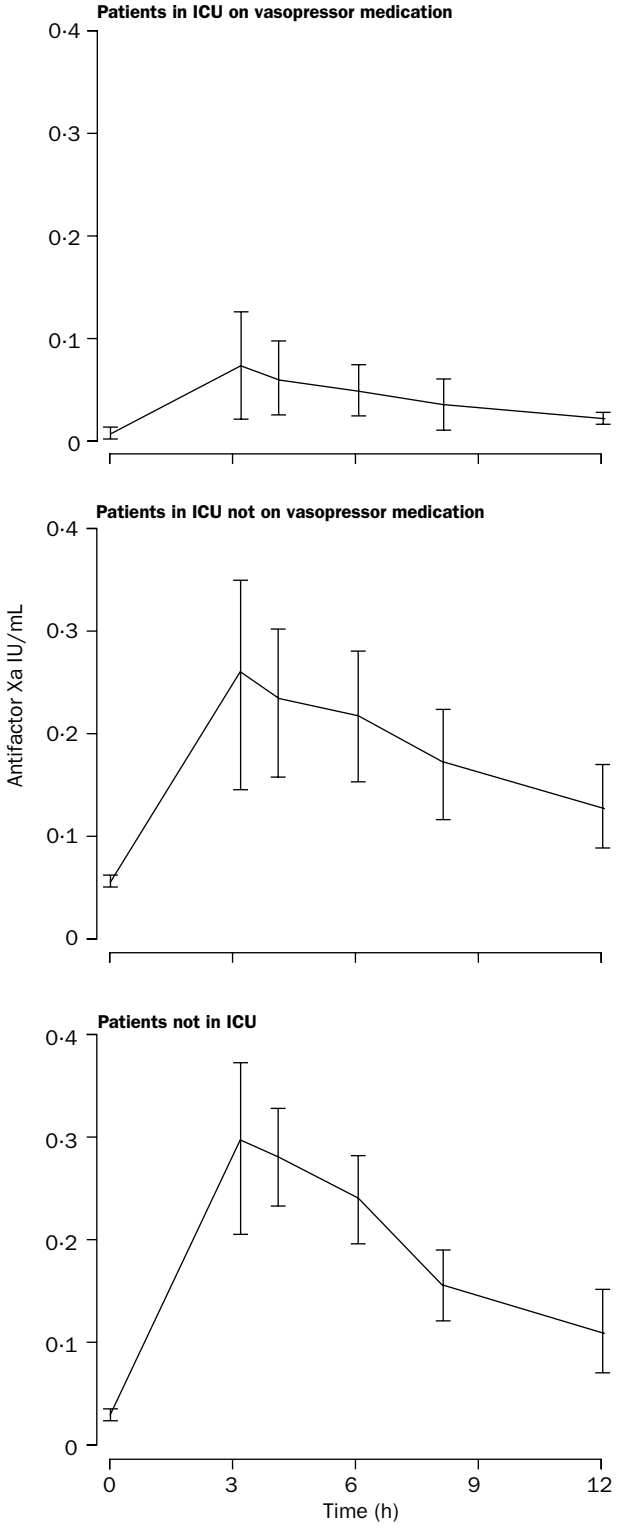
Between December, 2000, and April, 2001, we investigated three consecutive groups of patients at the Academic Medical Centre, Amsterdam: 15 individuals in ICU who received vasopressors consisting of one or more of dopamine (>10 μg/kg per min), norepinephrine (>0·25 μg/kg per min), or phenylephrine (>2 μg/kg per min); 15 patients in ICU who did not receive vasopressor medication; and 15 postoperative patients from a general surgical ward (eight of whom had major orthopaedic surgery and seven of whom had abdominal surgery). Our institutional review board approved the study, and we obtained written informed consent from all patients or their representatives.

The table shows the baseline characteristics of patients. Individuals were treated with prophylactic doses of subcutaneous LMW heparin once daily (nadroparin 2850 IU, Sanofi, Paris, France). We included in analyses only patients who had been given LMW heparin for at least 3 days. All patients who had surgery were included between the third and seventh postoperative day. We excluded patients treated with a vitamin K antagonist or therapeutic doses of unfractionated or LMW heparin, and those with severe liver failure (bilirubin >40 μmol/L), renal insufficiency (creatinine clearance <30 mL per min), or signs of disseminated intravascular coagulation (platelets $<100\times10^9$/L, prolonged prothrombin time, and activated partial thromboplastin time).

	Patients in ICU on vasopressors (n=15)	Patients in ICU not on vasopressors (n=15)	Patients not in ICU (n=15)
Age (mean, 95% CI) (years)	59·2 (54·3–63·5)	48·1 (43·7–54·2)	54·5 (49·2–58·1)
Men	11 (73%)	12 (78%)	11 (72%)
Body-mass index (mean, 95% CI) (kg/m²)	25·3 (23·1–28·0)	24·0 (21·9–26·3)	26·2 (24·4–28·8)
Vasopressor (number, %)*			
Dopamine (mean dose 17 μg/kg per min)	9 (60%)	0	0
Norepinephrine (mean dose 1·2 μg/kg per min)	6 (40%)	0	0
Phenylephrine (mean dose 4·5 μg/kg per min)	2 (13%)	0	0
Arterial pressure (mean, 95% CI) (mm Hg)	64·3 (61·1–67·5)	66·8 (62·2–70·4)	87·3 (82·8–92·5)
Artificially ventilated	15 (100%)	13 (87%)	0
APACHE II score (mean, 95% CI)	15·1 (13·2–16·9)	14·2 (12·5–16·1)	4·4 (3·8–5·2)
Diagnosis (number)			
Medical sepsis	3	2	0
Surgical sepsis	4	6	0
Trauma	4	3	0
Neurosurgery	2	2	0
Cardiac surgery	2	1	0
Orthopaedic surgery	0	0	8
Uncomplicated abdominal surgery	0	1	7

ICU=intensive care unit. *Some patients were on more than one vasopressor.

Baseline characteristics



Concentrations of factor Xa activity after subcutaneous injection of low molecular weight heparin (2850 IU)
ICU=intensive care unit.

We obtained blood samples, drawn in sodium-citrated tubes (final concentration 3·2%) immediately before and 3, 4, 6, 8, and 12 h after administration of LMW heparin. We centrifugated samples for 20 min at 2500 *g* and collected the plasma, in which we measured concentrations of factor Xa activity with a chromogenic test (COAMATIC, Chromogenix, Mölndal, Sweden).

We analysed results with repeated measures ANOVA and posthoc Newman Keuls tests.

Mean plasma concentrations of factor Xa activity in the ICU group on vasopressors were significantly lower at all time points (p=0·0007) after subcutaneous injection of LMW heparin than in the other two groups (figure). In all three groups, peak concentrations of factor Xa activity were seen 3 h after LMW heparin injection, with mean values of 0·23 IU/mL (95% CI 0·18–0·27) and 0·28 IU/mL (0·23–0·31) for ICU patients not on vasopressor medication and non-ICU patients, respectively, and mean values of only 0·09 IU/mL (0·05–0·10) for ICU patients receiving vasopressors. The concentrations of the ICU group not on vasopressor medication and the non-ICU group were consistent with those reported for patients undergoing elective orthopaedic surgery and being treated with prophylactic doses of LMW heparin.[3]

Our results suggest that critically ill patients who receive vasopressor treatment have significantly lower systemic concentrations of factor Xa activity and might, therefore, be insufficiently protected from venous thromboembolism by the administration of the usual prophylactic dose of LMW heparin. Low concentrations of factor Xa activity could be caused by impaired perfusion of subcutaneous tissue due to physiologically or pharmacologically induced adrenergic vasoconstriction of the peripheral blood vessels, thereby impeding adequate absorption of subcutaneously administered LMW heparin. Our findings do not accord with an alternative explanation that enhanced clearance or metabolism of LMW heparin in patients on vasopressor medication occurs (figure). Although plasma concentrations of factor Xa activity do not directly represent lower clinical efficacy of LMW heparin prophylaxis, much lower concentrations seem to result in less effective prevention of venous thromboembolism.[4] Patients in ICU who are taking vasopressor medication could need higher doses of LMW heparin, or a different mode of administration, to attain adequate thrombosis prophylaxis.

Contributors
J Dörffler-Melly, E de Jonge, and A-C de Pont were responsible for patient selection and clinical measurements; J Meijers did the laboratory analyses; M Vroom, H Büller, and M Levi designed the study and analysed the data. All authors wrote the manuscript.

Conflict of interest statement
None declared.

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