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Prophylactic range anti-factor Xa activity 24 hours after subcutaneous injection of 40 mg of enoxaparin in a patient with an epidural catheter in situ

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Dear Editor,

We present a case report of a 37-year-old female patient who was admitted electively to the local intensive care unit (ICU) following extensive ovarian cancer surgery – hysterectomy with bilateral adnexa, omentectomy, removal of neoplastic infiltrations (sigmoid colon, sigmoid mesentery, small intestine), appendectomy, aspiration of free fluid (2000 mL), insertion of a pelvic drain. The patient received general anesthesia with continuous epidural anesthesia. Directly before surgery approximately 4200 mL of fluid was drained from the right pleural cavity. There was no comorbidity other than obesity (BMI 38.3 kg m^{-2}). History revealed past cigarette smoking (no smoking in the last month) and no drug history. At admission to the ICU the patient was hemodynamically unstable, supported with norepinephrine (0.22 µg kg^{-1} min^{-1}), with no signs of peripheral perfusion deficit (capillary refill time < 2 s). On day 2 of the ICU stay (D2) hemoglobin concentration dropped from 85 to 57 g L^{-1} (Table 1); therefore urgent ultrasound examination of the abdominal and pelvic cavity was performed (no abnormalities) and gynecological consultation was requested. The operator allowed for the administration of pharmacological thromboprophylaxis and 40 mg of enoxaparin (Clexane, Sanofi-Aventis, Germany) was administered subcutaneously (approximately 18 hours after conclusion of surgery). One unit of packed red blood cells (PRBC) was transfused according to the local hospital guidelines on PRBC use in non-bleeding hospital patients [1]. Our patient had multiple risk factors for thrombosis, with high risk of venous thromboembolism (VTE) according to the Padua Prediction Score for Risk of VTE (9/11 points) [2] and the Caprini Score for VTE (8 points, 4% risk of VTE) [3]. The extra risk factor for VTE in our patient was PRBC transfusion. On the other hand, our patient had an epidural catheter in situ, with increased risk of an epidural hematoma when administered even with a standard prophylactic dose of enoxaparin. Therefore, to optimize the dose of low-molecular-weight heparin (LMWH), we performed a coagulation screen directly before and 4 hours after administration of enoxaparin (Table 1). To our surprise the anti-factor Xa activity (chromogenic assay; HemosIL, Werfen, Poland) 24 hours after a standard prophylactic dose of enoxaparin was 0.14 and increased to 0.30 IU mL^{-1} 4 hours following subcutaneous injection, both results being within the prophylactic activity reference range. The patient was discharged from the ICU on the same day with a recommendation that an epidural catheter should be removed 36 hours following the last enoxaparin sodium dose. Written informed consent was obtained from the subject.

Low-molecular-weight heparins are produced by depolymerization of unfractionated heparin. Anticoagulant potency of LMWHs depends on their anti-factor Xa and negligible anti-factor IIa activities [4]. The chromogenic assay

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TABLE 1. Selected laboratory parameters during hospitalization

Laboratory parameter	Adm	D1 pm	D2 am	D2 pm	D3 am	D3 pm	Reference range
Creatinine (mg dL^{-1})	0.88	0.92	0.68	–	0.63	–	0.51–0.95
eGFR (mL min^{-1})	> 60	> 60	> 60	–	> 60	–	> 60
CrCl (mL min^{-1})	73	64	86	–	93	–	88–128
Blood urea nitrogen (mg dL^{-1})	–	15.1	15.0	–	20.9	–	7.9–20.0
Urea (mg dL^{-1})	–	32.4	32.1	–	44.8	–	16.6–48.5
Bilirubin (mg dL^{-1})	–	0.39	0.24	–	0.25	–	0.3–1.2
Haemoglobin (g L^{-1})	113	85	57	63	67	–	115–150
Platelets ($\times 10^3$ µL^{-1})	652	745	485	470	528	–	130–400
Fibrinogen (Clauss) (mg dL^{-1})	924	550	430	471	460	430	200–393
Prothrombin time (s)	13.0	16.0	15.3	15.7	13.2	13.3	9.4–12.5
INR2	1.08	1.33	1.27	1.30	1.09	1.10	0.8–1.2
Prothrombin activity (%)	83.0	61.0	65.0	63.0	81.0	80.0	80.0–120.0
Thrombin time (s)	–	15.8	15.5	15.5	15.8	16.3	10.3–16.6
D-dimers (ng mL^{-1})	7604	6673	3599	4184	5456	5272	< 500
aPTT (s)	32.2	32.7	37.4	37.9	32.5	36.6	25.4–36.9
Anti-factor Xa (IU mL^{-1})	–	–	–	–	0.14	0.30	0.1–0.3
Antithrombin (%)	–	–	–	–	73	–	75–120

Adm – admission to hospital, aPTT – activated partial thromboplastin time, CrCl – creatinine clearance according to Cockcroft-Gault, D – day of the intensive care unit stay, eGFR – estimated glomerular filtration rate according to Modification of Diet in Renal Disease, INR – international normalized ratio

for anti-factor Xa constitutes the gold standard for monitoring therapy with both LMWH and fondaparinux [5]. However, it is worth mentioning that anti-factor Xa activity is a pharmacokinetic marker changing with absorption constant, volume of distribution, and clearence. Deterioration of clinical condition may change pharmacokinetic properties of LMWHs [6]. The peak effect of LMWHs is present 3-5 hours after subcutaneous injection; their half-life is on average 4-5 hours [7]. The half-life of enoxaparin is approximately 7 hours [8]. International guidelines on antithrombotic medication and regional anesthesia recommend, to minimize the risk of an epidural hematoma, a 12-hour time interval between the last prophylactic dose of LMWH and epidural catheter removal [9]. In the study by Douketis *et al*., 12 out of 25 patients receiving a higher prophylactic dose of enoxaparin (30 mg s.c. twice daily) had anti-factor Xa activity > 0.1 IU mL^{-1} at the time of epidural catheter removal (on average 10.4 hours after the last dose of LMWH) [10]. In our case the anti-factor Xa activity after a single dose of 40 mg of enoxaparin was still within the prophylactic reference range 24 hours after the injection. This is concerning since the most recent regional anesthesia guidelines suggest measuring anti-factor Xa activity in patients receiving high doses of LMWH and keeping it ≤ 0.1 IU mL^{-1} before high-risk regional anesthesia interventions, such as removal of an epidural catheter [9]. We were not able to explain this fact. Renal failure and advanced age are known factors delaying elimination of LMWH; however, in our patient neither of these was relevant. Anyway, the interpretation of a single anti-Xa activity measurement is challenging and should be cautious [9]. Given that prothrombin activity in our patient was at the lower reference limit (81%; reference range 80–120%), the activity of factor X could be slightly lowered. However, we are not able to resolve this issue as factor X activity was not determined. Nevertheless anti-factor Xa activity should not be affected by coagulation factor concentrations. On the other hand, there were factors that could potentially make the standard prophylactic dose of LMWH insufficient in our patient: excess weight (106 kg) [7], high platelet number (528 $\times 10^3$ µL^{-1}), high fibrinogen concentration (460 mg dL^{-1}), low antithrombin activity (73%). Only because we measured anti-factor Xa activity we have potentially prevented a serious reginal anesthesia complication in the form of an epidural hematoma.

In conclusion, our case report shows that anti-factor Xa activity may be within the prophylactic reference range in a patient with normal renal function receiving a standard prophylactic dose of enoxaparin. Whether removal of an epidural catheter in this situation is safe in the context of epidural hematoma formation remains an unresolved issue. There is urgent need for prospective studies of chemical thromboprophylaxis with LMWHs in patients in whom continuous epidural anesthesia is used to assess the clinical utility of anti-factor Xa activity monitoring and its safe levels before regional anesthesia interventions.

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