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Case Report

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Bleeding After the Use of Enoxaparin in Kidney Patients: Case Reports and Review of the Literature

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ABSTRACT

Low-molecular-weight heparins, particularly enoxaparin, are widely used for pulmonary embolism prophylaxis in hospitalized patients. Although rare, bleeding has been reported due to these drugs. Because of their excretion from the kidney, the risk of bleeding is higher in the kidney patient population, and these patients should be careful, and dose adjustment should be made. This article reports 2 cases of bleeding due to enoxaparin in 2 different kidney patients who then required transfusion, the literature on this topic has been reviewed.

Keywords: Enoxaparin, bleeding, renal patients

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INTRODUCTION

Low-molecular-weight heparins (LMWHs) are used in many indications such as venous thrombosis, pulmonary embolism, myocardial infarction (MI) treatments, and thromboembolism prophylaxis. Since they are seen as superior in terms of bioavailability and anticoagulant efficacy compared to classical heparin, their frequency of preference is increasing day by day. LMWHs also have extra advantages such as less thrombocytopenic side effects, no need for laboratory follow-up, and much less interaction with food and drugs. The fact that they are administered subcutaneously also provides ease of use. Thus, their use is preferred not only in hospitalized patients, but also in patients who need to be followed up at home. LMWHs have found use in clinical practice in many different forms such as enoxaparin, tinzaparin, dalteparin, and bemiparin. Enoxaparin is used more frequently than the others.[1-3]

Due to the renal elimination of LMWHs, their half-life may be prolonged and their elimination may be delayed, and consequently, unexpected bleeding may be observed in patients with renal failure. Therefore, careful use is recommended for this patient group, combined with regular follow-up with anti-factor Xa activity (anti-Xa).[4]

Patients with kidney failure are hospitalized and followed up for many different indications. Because they are immobilized, prophylactic enoxaparin may be required for deep vein thrombosis (DVT), and LMWHs may be required during dialysis sessions, because the procedure is safer when performed in the hospital.

It is important to remember that besides the increasing frequency of the use of LMWHs, they are drugs that should be used carefully in terms of possible life-threatening complications, and we want to discuss the issue in the light of the literature, based on the 2 patients we followed.

CASE-1

A 78-year-old male patient with a known history of diabetes, hypertension, previous coronary by-pass surgery, and chronic obstructive pulmonary disease

(COPD) was referred to us for acute kidney failure requiring hemodialysis. The metformin, acetyl salicylic acid, and valsartan+hydrochlorothiazide treatments that he was using were discontinued, COPD treatment was arranged, and prophylactic enoxaparin treatment was started for the immobile patient. The patient, who had low urine output and developed uremic symptoms, was taken to hemodialysis repeatedly. Enoxaparin was used as an anticoagulant in the dialysis procedures. His blood parameters were as follows: blood urea nitrogen: 86 mg/dL, creatinine: 4.3 mg/dL, white blood cells: 9.600/mm^3, hemoglobin: 7.2 g/dL, platelets: 411 × 10^9/L, PT: 14 seconds, aPTT: 25.2 seconds, and INR: 1.16. The patient, who had a decrease of 3 points of hemoglobin level, was evaluated for gastrointestinal bleeding. No bleeding focus was detected. The patient, whose hemoglobin level was still decreased, experienced pain in the left flank, and physical examination revealed tenderness in the left lateral region and a newly developed ecchymotic area of approximately 20 × 15 cm (Figure 1). On ultrasonography (USG), a 13 × 8 × 5 cm hematoma was observed in the left retroperitoneal area. The presence of hematoma was also confirmed by computed tomography (CT) (Figure 2). The patient had no history of trauma. Enoxaparin treatment was discontinued. Hemoglobin values were increased with the support of erythrocyte suspension. In the follow-ups, the bleeding was brought under control and the hematoma resorbed over time. The bleeding was thought to be related to enoxaparin.

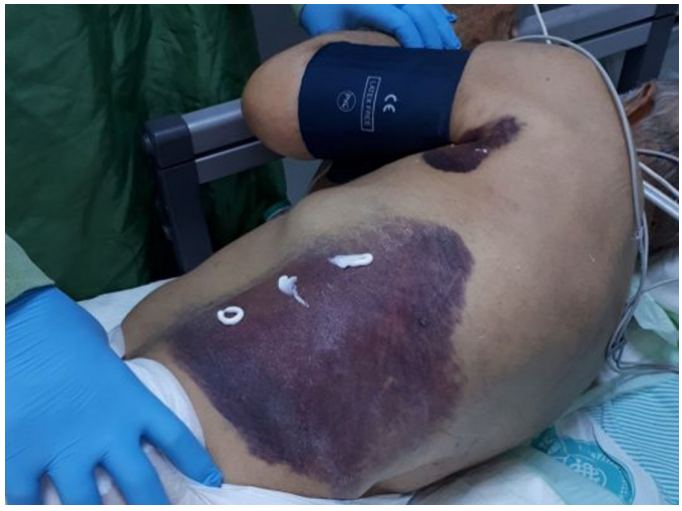

Figure 1. Lumbar ecchymosis of Case 1.

CASE-2

A 51-year-old patient, who had undergone hemodialysis for 11 years due to chronic renal failure secondary to diabetic nephropathy, underwent kidney transplantation from a cadaver. The patient was started on mycophenolate mofetil 2 × 720 mg, tacrolimus 2 × 3 mg, prednisolone 20 mg/day, valganciclovir, trimethoprim-sulfamethoxazole, diltiazem and nystatin treatment. On the 13th day after transplantation, the patient's blood analysis results were as follows: blood urea nitrogen: 41 mg/dL, creatinine: 1.4 mg/dL, white blood cells: 10.100 /mm^3, hemoglobin: 6.7 g/dL, platelet: 231 × 10^9/L, PT: 12 seconds, aPTT: 27.9 seconds, and INR: 1.04. The patient had pain, loss of strength, and coldness in the left leg. Therefore, Doppler USG was performed, and an approximately 5-fold increase in velocity was detected in the left external iliac artery, in the distal part of the renal artery end-to-side anastomosis line. The patient, who was consulted to the cardiovascular surgery clinic, was asked to undergo MR angiography. In MR angiography, more than 70% stenosis was detected in the 12-13 mm segment of the external iliac artery on the left. Angioplasty was performed on the patient and his complaints improved significantly. It was recommended to use 1 × 4000 units of subcutaneous enoxaparin as an anticoagulant during his stay. Two days later, the patient developed a sudden onset of abdominal pain in the right lower quadrant. In the physical examination; blood pressure was 130/80 mmHg and heart rate was 82 beats/min. On abdominal examination, there was defense and a palpable mass in the right lower quadrant. Emergency abdominal USG was performed immediately in the patient with acute abdomen and a rectus sheath hematoma measuring 9.5 × 4 cm was detected on the anterior abdominal wall in the right lower quadrant. The presence of hematoma was also confirmed on CT (Figure 3). Enoxaparin treatment was discontinued. The patient was given 3 units of erythrocyte suspension and 2 units of fresh frozen plasma. In the follow-up, abdominal pain decreased, and the size of the hematoma decreased in the control USG.

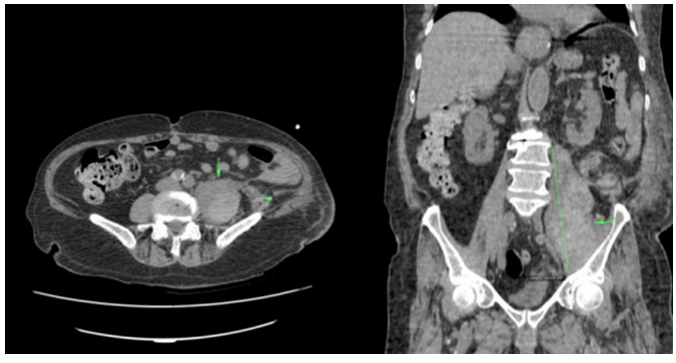

Figure 2. CT image of Case 1.

Main Points

- Enoxaparin is frequently used for prophylaxis of deep vein thrombosis (DVT), especially in hospitalized patients.
- Patients with kidney failure have a tendency for bleeding.
- When there is a decrease in hemoglobin in patients with renal failure, the possibility of spontaneous bleeding should be kept in mind if enoxaparin is being used.
- When the creatinine clearance (CrCl) is <30 mL/min, the dose should be adjusted and the anti-Xa level should be monitored in patients at risk, for optimum efficacy.

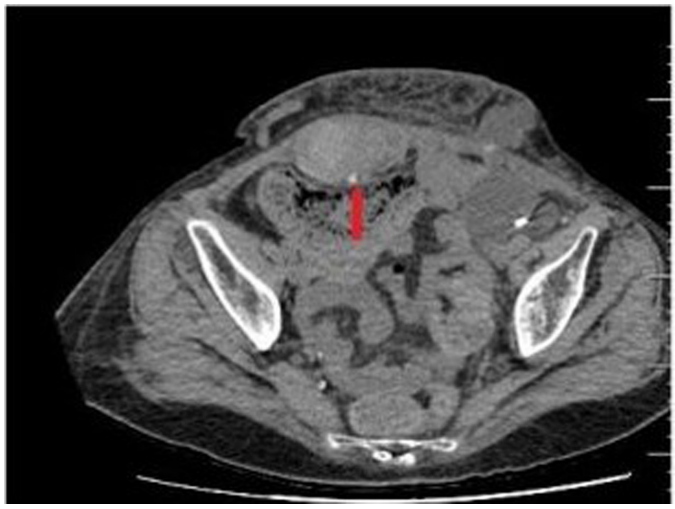

Figure 3. CT image of Case 2.

DISCUSSION

Although anti-Xa monitoring is recommended in the use of LMWH in patients with kidney failure, anti-Xa level cannot be routinely studied in many laboratories, and there are no clear data on its target therapeutic range.[4] In addition, it has been stated in the literature that the risk of bleeding is higher over the steady state of anti-Xa level of 0.8-1.0 IU/mL.[5]

In patients with renal failure, the half-life of LMWHs is prolonged and their excretion decreases. Although some sources have specified creatinine clearance (CrCl) <30 mL/min and some <50 mL/min as the limit for this, the generally accepted view is that double-dose use of LMWHs in a day may increase the risk of bleeding when CrCl is <50 mL/min.[4,6] There is a suggestion that a 50% reduction of the treatment or prophylactic dose would be appropriate when CrCl is <30 mL/min.[7]

Life-threatening spontaneous hemorrhages due to the use of LMWHs have been reported in the literature, outside of the usual body parts (retroperitoneal, rectus muscle, internal oblique muscle, breast, etc.).[8-13] Since enoxaparin is used more frequently than other LMWHs, spontaneous bleeding due to enoxaparin has been reported more frequently in the literature, but there are also reports of spontaneous bleeding due to Dalteparin.[14] Details about the reports and bleeding sites identified in the literature are summarized in Table 1. The fact that the elimination and half-life of LMWHs vary in these patients, and the fact that the need for appropriate dose reduction according to CrCl during use may be overlooked, may be responsible for the higher incidence of spontaneous bleeding outside the usual body parts, especially in patients with renal failure.

Table 1. Case Reports of Spontaneous Bleeding Due to LMWHs and Bleeding Sites

Literature	Bleeding site	LMWH
Melde[8]	Retroperitoneal	Enoxaparin
Karabulut et al.[9]	Retroperitoneal	Enoksaparin
Solak et al.[10]	İnternal oblik muscle	Enoksaparin
Sunar et al.[11]	Rectus sheath	Enoksaparin
Malik et al.[12]	Retroperitoneal	Enoksaparin
Shokri et al.[13]	Breast	Enoksaparin
Egger et al.[14]	Retroperitoneal	Dalteparin

There are case reports on this subject in the literature. The first of the 2 cases reported by Melde reported that the CrCl of a 71-year-old patient, who had a history of coronary artery bypass grafting and who underwent single-kidney nephrectomy for renal mass, was 50 mL/min. The patient, who was hospitalized due to MI, was started on enoxaparin 0.8 mg/kg twice a day. On the eighth day of the treatment, the patient, who developed retroperitoneal bleeding, had to be given 5 units of erythrocyte suspension. The second case was of a 70-year-old patient with a CrCl value of 49 mL/min, who was diagnosed with dementia, hypertension, diabetes, atrial fibrillation and stroke. Enoxaparin 0.9 mg/kg twice a day was administered to the patient, who developed MI during follow-up. The patient developed retroperitoneal bleeding on the fourth day of the treatment, and had to be administered 9 units of erythrocyte suspension.[8]

The case reported by Solak et al. was of a patient whose CrCl was 34 mL/min and who was administered enoxaparin 0.4 mL twice a day due to pulmonary embolism. The patient developed a hematoma in the internal oblique muscle on the 10th day of enoxaparin treatment, and required the administration of an erythrocyte suspension.[10] Again, a case reported by Sunar et al. was of a 70-year-old patient with a history of chronic renal failure (CrCl 14 ml/min), who was using enoxaparin for transient ischemic attack. On the sixth day of the treatment, erythrocyte suspension was transfused due to the development of bleeding in the rectus sheath.[11]

In addition, retroperitoneal bleeding resulting in death due to the use of LMWHs in combination with acetylsalicylic acid (ASA) has been reported in the literature.[15] In our patient in case 1, the use of ASA before LMWH, even if not simultaneously, may have been a factor that facilitated bleeding by causing platelet dysfunction. Again, in patients using LMWH, the use of additional drugs that may facilitate bleeding, or the use of drugs that will increase the effect of LMWHs may not be adequately considered. Both of our cases were of patients with poor renal function, who were using enoxaparin. Retroperitoneal hematoma and rectus sheath hematoma were detected in patients who did not have any other focus that would cause a decrease in hemoglobin. In both cases, there was no use of facilitating agents other than enoxaparin. Although the patients did not require surgical intervention, a large amount of blood transfusion was needed.

When the dose is calculated according to weight, obese patients may experience bleeding due to exposure to high doses of the drug, since LMWHs are not distributed in adipose tissue. Therefore, it should be considered that the dose should be adjusted according to the ideal weight of the patient.[4]

In case of warning signs such as abnormal abdominal pain, palpable swelling, bruising in the body, sudden hypotension and low hemoglobin levels that cannot be explained by any other reason, considering unusual bleeding may limit the hematoma with early intervention.

In such a case, LMWH treatment is immediately discontinued, and protamine sulfate can be administered, although it cannot completely reverse the anticoagulant effect of the LMWH. Bleeding is usually controlled with conservative methods, and surgical intervention is rarely required.[10]

In conclusion, LMWHs should be used more carefully, especially in the elderly patients, those with renal failure, obese patients, and those who are using additional drugs that may facilitate bleeding, and close follow-up should be carried out knowing that the risk of developing life-threatening bleeding is higher in this group.

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