

# Hemorrhage Caused by Invasive Procedures and Trauma in Patients Treated with Low Molecular Weight Heparin

Martin H. Ellis MD<sup>1</sup> and Rivka Zissin MD<sup>2</sup>

<sup>1</sup>Division of Transfusion Medicine and <sup>2</sup>Department of Diagnostic Imaging, Meir Hospital, Kfar Saba, Israel  
Affiliated to Sackler Faculty of Medicine, Ramat Aviv, Israel

**Key words:** enoxaparine, hemorrhage, invasive procedure, trauma

IMAJ 2002;4:1087-1088

Low molecular weight heparins, a new class of anticoagulant, are easily administered by subcutaneous injection and reliably inhibit factor X and thrombin in a dose-dependent manner. LMWH do not require routine monitoring of clotting tests. These features may lead to an underestimation of the degree of anticoagulation that has been attained in patients receiving therapeutic doses of LMWH. Derived from heparin by a process of fractionation, LMWH differ from unfractionated heparin in their mode of administration, namely once or twice daily subcutaneous injection, in their fixed dose-response relationship that obviates the need for laboratory monitoring of coagulation tests, and in their long half-life of approximately 4-6 hours.

These features make LMWHs easy to administer and may lead physicians to overlook the risk of hemorrhagic complications that is associated with their use and indeed, spinal cord and epidural hematomas following the administration of spinal or epidural anesthesia to patients treated with LMWH have been described [1].

We describe the clinical course and diagnostic imaging findings of six patients who either underwent an invasive procedure or sustained blunt trauma during treatment with LMWH, and we emphasize the potential for hemorrhage in such patients.

## Patient Descriptions

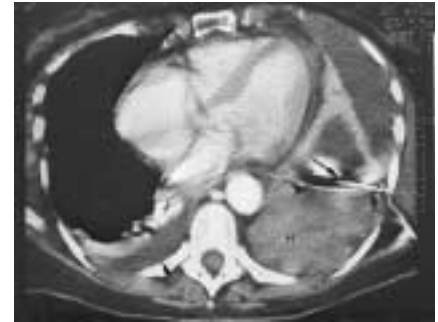
### Patient 1

A 74 year old woman with a history of ischemic heart disease developed complete atrioventricular heart block. A temporary pacemaker was inserted via the right subclavian vein and its placement was confirmed with a chest X-ray. Two days later the patient complained of pain in the right arm and physical examination revealed marked

swelling of the limb. Enoxaparine 60 mg twice daily was instituted for a catheter-associated thrombosis of the subclavian vein. Two days thereafter a permanent pacemaker was installed via the left subclavian vein. Twelve hours after surgery her blood pressure fell and she became dyspneic. A chest X-ray revealed a massive left-sided pleural effusion. The hemoglobin was 8.4 g/dl as compared to 13.8 g/dl 48 hours earlier. Despite vigorous resuscitation that included intubation and the administration of packed red blood cells and plasma, the patient died on the same day.

### Patient 2

A 62 year old woman with a long history of ischemic heart disease and congestive heart failure was admitted because of increasing dyspnea. A moderate-sized left pleural effusion was diagnosed. Because of the possibility that the patient was experiencing acute myocardial ischemia, enoxaparine 80 mg twice daily by subcutaneous injection and aspirin 100 mg daily were administered. Twenty-four hours later a thoracentesis was performed to relieve the patient's dyspnea and 1,200 ml of straw-colored fluid with the characteristics of a transudate were removed. Twelve hours later the patient developed dyspnea and tachycardia. The hemoglobin dropped from 11.4 to 7.1 g/dl and chest X-ray showed reaccumulation of the left pleural effusion. Thoracic computerized tomography demonstrated a large amount of mixed-density pleural fluid with "hematocrit effect" (i.e., separation of the cellular and liquid components of the blood) indicating hemothorax. The patient received 3 units of packed red blood cells and an intercostal drain was inserted through which approximately 1,800 ml of blood was removed. The patient subsequently made a full recovery and was discharged from the hospital.



**Figure 1.** Patient 3: Contrast-enhanced thoracic CT shows a left-sided pleural effusion with dependent hyperdensity in the posterior portion of the hemithorax due to "hematocrit effect." Note a small amount of pleural effusion with water density on the right, and the left-sided thoracic drain.

### Patient 3

A 71 year old woman was admitted because of dyspnea and a cough. Chest X-ray on admission revealed a moderate left pleural effusion. Diagnostic thoracentesis yielded bloody pleural fluid and pulmonary embolism was suspected. Enoxaparine 60 mg twice daily was begun. Two days later another thoracentesis was performed because of worsening dyspnea, and 1 L of serosanguinous fluid was removed. Six hours later, the patient developed tachycardia and her hematocrit was 24%. Repeat chest X-ray showed opacification of the entire left hemithorax with the mediastinum shifted to the right. A CT scan showed a large left-sided hemothorax [Figure 1]. The patient was resuscitated with 6 units of packed red blood cells and 3 units of plasma.

### Patient 4

An 87 year old man was admitted because of macroscopic hematuria. He was receiving warfarin for a pulmonary embolus diagnosed one month earlier, and on admission his INR was 2.1. Warfarin was withheld and enoxaparine was given by subcutaneous

LMWH = low molecular weight heparins

injection at a dose of 60 mg twice daily. Attempts to insert a urinary catheter via the urethra failed, and a suprapubic catheter was inserted on the following day. Four hours later the patient complained of severe abdominal pain and abdominal distension. CT disclosed massive hematomas of both the abdominal and bladder walls. The patient required transfusion with 8 units of packed red blood cells and 6 units of fresh frozen plasma and recovered fully.

#### Patient 5

A 72 year old woman with severe ischemic cardiomyopathy was admitted because of worsening congestive heart failure. A chest radiograph showed cardiomegaly and pulmonary venous congestion. Because of poor contractility of the left ventricle, anticoagulation was begun using enoxaparine 60 mg twice daily. On the third day of admission, the patient fell while walking in the ward and fractured two ribs on the left side. Some hours later she was noted to be pale and sweaty with a non-palpable pulse. Chest X-ray revealed a massive amount of left-sided pleural fluid. The patient underwent a left thoracotomy; 2 L of fresh blood were removed from the pleural cavity and lacerations to the intercostal veins were repaired. She required 8 units of packed red cells and 4 units of plasma. Her hospitalization was further complicated by the development of empyema on the left side, which required prolonged chest-tube drainage and antibiotics.

#### Patient 6

A 50 year old man was admitted after falling 4 meters and sustaining an open-book pelvic fracture. He had a history of myocardial infarction 6 years previously and was a heavy smoker. Two days after admission, while in traction, he complained of retrosternal chest pain. Treatment with subcutaneous enoxaparine 80 mg twice daily and aspirin 75 mg daily was begun. Ten hours later the patient was noted to be pale and sweaty. His hemoglobin was 10 g/dl as compared to 15 g/dl on the previous day. An abdominal CT scan revealed a massive pelvic hematoma. Packed red blood cell units were adminis-

tered but his hemoglobin continued to fall and disseminated intravascular coagulopathy developed. He subsequently developed renal and respiratory failure that required hemodialysis and artificial ventilation respectively. His condition gradually improved and he was discharged to a rehabilitation facility after 22 days in the intensive care unit.

#### Comment

In this paper we have focused on hospitalized patients receiving therapeutic doses (1 mg/kg twice daily) of a LMWH (enoxaparine), who underwent an intercurrent invasive procedure (patients 1–4) or who experienced significant trauma while (patient 5) or before (patient 6) receiving the drug. Radiologic studies played an important role in diagnosing the hemorrhagic complications: CT scanning in the patients with abdominal and pelvic hematomas, and chest X-ray and subsequent CT confirmation (in two cases) in those in whom hemothorax developed.

LMWH are administered by subcutaneous injection. This, together with their fixed dose-response pharmacokinetic profile that makes monitoring by clotting tests unnecessary, simplifies their administration for both nursing and medical staff. However, physicians should be aware that despite the simplicity of LMWH administration, these compounds are associated with hemorrhagic complications in up to 5% of patients, and that some of these bleeds may be fatal [2]. Therefore, knowledge of some of the potential problems associated with the use of LMWH is essential. Firstly, the therapeutic dose of 1 mg/kg (or 100 U/kg) twice daily applies to patients with a body mass of 50–80 kg. Secondly, in patients with impaired renal function, arbitrarily defined as a serum creatinine higher than 1.8 g/dl, monitoring of the anti-factor Xa activity is indicated since LMWH are excreted by the kidneys. Finally, LMWH lack a reliable means of reversal. Protamine has been shown to reverse the anti-IIa effect of LMWH, but not the anti-Xa activity. Also, the appropriate dose of protamine and the timing of its administration for LMWH reversal are not clear [3]. For these reasons, Spandorfer et al [4] have recommended that in patients

receiving enoxaparine in anticoagulant doses (2 mg/kg/day), the last dose of the drug should be administered 24–36 hours prior to the performance of invasive procedures.

Imaging is crucial in the diagnosis of extracranial hemorrhage in patients receiving LMWH [5]. In particular, abdominal CT is a safe technique to rapidly diagnose abdominal and pelvic hematomas and delineate their precise location. Regarding intrathoracic hemorrhage, the appearance of a pleural effusion on chest radiograph, along with a decrease in hematocrit in a patient receiving anticoagulant treatment, most likely indicates a hemothorax. This diagnosis may be confirmed by thoracic CT, thus obviating the necessity for thoracentesis.

In conclusion, we recommend that the indications for the use of LMWH in hospitalized patients be carefully weighed, especially in those with recent severe trauma or those scheduled for invasive procedures. Before performing such procedures, the potential thrombotic risks associated with withdrawal of anticoagulant therapy versus the risk of bleeding if such treatment is continued should be assessed.

#### References

1. Wysowski DK, Talarico L, Bacsanyi J, Botstein P. Spinal and epidural hematoma and low molecular weight heparin. *N Engl J Med* 1998;338:1774.
2. Samama MM, Cohen AT, Darmon J-Y, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999;341:793–800.
3. Makris M, Hough RE, Kitchen S. Poor reversal of low molecular weight heparin by protamine. *Br J Haematol* 2000;108:884–5.
4. Spandorfer JM, Lynch S, Weitz HW, Fertel S, Merli GJ. Use of Enoxaparine for the chronically anticoagulated patient before and after procedures. *Am J Cardiol* 1999;84:478–80.
5. Zissin R, Shapiro-Feinberg M. Computerized tomography findings of extracranial hematomas in patients treated with anticoagulants. *Harefuah* 2000;138:1064–70 (Hebrew).

**Correspondence:** Dr. M.H. Ellis, Blood Bank, Meir Hospital, Kfar Saba 44281, Israel.  
Phone: (972-9) 747-1504  
Fax: (972-9) 747-1295  
email: martinel@clalit.org.il