Intra-Abdominal Hematoma Following Enoxaparin Injection

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ABSTRACT: An elderly patient, who was being treated for therapeutic enoxaparin for a couple of days due to suspected deep vein thrombosis, was admitted to hospital following a collapse and severe abdominal pain. She was in hypovolemic shock and was fluid resuscitated. Ultrasound scan and computed tomography (CT) scan showed a large pelvic hematoma. Radiologists also suspected a possibility of bleeding from inferior epigastric artery following a CT angiogram. The patient was stabilized and transferred to intensive care unit (ICU) for further hemodynamic supports and close monitoring. The patient was then transferred back to the general ward when she was stable. She was managed conservatively as there were no more signs of active bleeding. Unfortunately, she died of recurrent bleeding three days after ICU discharge.

KEYWORDS: intra-abdominal bleeding, enoxaparin, deep vein thrombosis

Background
Low-molecular-weight heparin (LMWH) has been increasingly used by doctors to initiate anticoagulation in many clinical conditions, such as deep vein thrombosis (DVT), atrial fibrillation, and pulmonary embolism. LMWH is usually safe to be used due to its improved bioavailability and pharmacodynamic characteristics. Therefore, the subcutaneous injection of LMWH can be carried out by district nurses, patients, relatives, or even carers with appropriate training. One of the most common side effects of LMWH is bleeding. Although fatal bleeding is uncommon, it is important to note that it could happen.

Case Presentation
The case was an elderly patient, with a medical history of chronic chest pain, diabetes, hypertension, chronic obstructive pulmonary disease, and osteoporosis, who attended her general practitioner (GP) for right calf pain and swelling few days prior to hospital admission. She was prescribed therapeutic enoxaparin 140 mg (1.5 mg/kg) for suspected DVT, and her GP had arranged an outpatient Doppler ultrasound scan for her one week later. She had been receiving therapeutic enoxaparin injection daily in the community while waiting for the Doppler ultrasound scan. Three days after receiving the therapeutic enoxaparin injection, she was admitted to hospital following a collapse and complained of severe abdominal pain radiating to the back for one day. The pain was throughout the abdomen and worse on the lower abdomen and both groins.

She felt cold, drowsy, and tired. She denied nausea, vomiting, bowel problems, urinary symptoms, loss of consciousness, chest pain, or confusion. The collapse was swift without tongue biting, loss of consciousness, and postictal confusion.

On examination, she appeared to be drowsy, anemic, and tired. She was in hypovolemic shock with a blood pressure of 87/39 mmHg, pulse of 96, respiratory rate of 16, oxygen saturation of 100% on air, and temperature of 35.2°C.

The abdomen appeared to be distended. A bruise area was noticed in left iliac fossa where the therapeutic enoxaparin was injected. The patient also had generalized abdominal tenderness and severe lower abdominal tenderness.

The patient developed acute renal failure (urea: 26.1 mmol/L; creatinine: 321 μmol/L) and was transferred to intensive care unit (ICU) seven hours after admission.

Investigations
Blood test was done on admission that showed a sodium level of 133 mmol/L (135–145 mmol/L), potassium of 7 mmol/L (3.5–5.0 mmol/L), urea of 26.1 mmol/L (2.5–6.7 mmol/L), creatinine of 321 μmol/L (70–150 μmol/L), adjusted calcium of 2.38 mmol/L (2.12–2.65 mmol/L), albumin of 32 g/L (35–50 g/L), normal liver function, amylase of 26 U/L (0–180 U/L), C-reactive protein of 100 mg/L (<10 mg/L), glucose of 10.2 mmol/L (3.5–5.0 mmol/L), hemoglobin of 7.6 g/dL (13–18 g/L), white cell count of 21.7 × 10^9/L (4–11 × 10^9/L) and platelets of 385 × 10^9/L (150–400 × 10^9/L),
prothrombin time of 10 seconds (12–14 seconds), and partial prothrombin time of 26.8 seconds (26–33.5 seconds).

The erect chest X-ray and abdominal X-ray were unremarkable. Ultrasound scan of abdomen and pelvis revealed a calcified gallstone and a very large mass within the lower abdomen with patchy hypoechoic characteristic and multiple septae of its part. The appearance was consistent with hematoma, which extended into the pelvis.

A computed tomography (CT) angiogram was carried out. The CT scan showed a huge hematoma (15 × 14 × 13 cm) in anterior lower abdomen/pelvis. No obvious source of bleeding was seen. The CT scan was then discussed with other radiologists from another hospital in which they believed that the left inferior epigastric artery was bleeding into the retroperitoneum. After a long discussion between the radiologists and the surgeon, a decision was made that the patient was not fit for any interventional procedures. It was felt that the bleed would stop with tamponade effect.

**Differential Diagnosis**

On admission, we were suspecting ruptured abdominal aortic aneurysm, leaking abdominal aortic aneurysm, bleeding secondary to therapeutic enoxaparin 1.5 mg/kg, bleeding from injured internal organs, bowel perforation, and bowel ischemia.

**Treatment**

Within 24 hours following admission, the patient was resuscitated with two units of packed red blood cells and 3.5 L of intravenous (IV) fluids. During ICU stay, the patient had received protamine beriplex calcium and tranexamic acid to prevent her from further bleeding. She continued to have fluid resuscitation until she was stable. She then became oliguric and hyperkalemic again. It was believed that the acute renal failure was, as a result of the intra-abdominal bleeding, leading to hypotension and prerenal failure. She was put on continuous venovenous hemodialysis to treat the acute renal failure. Her condition improved after receiving the appropriate treatment in ICU. Following discharge from ICU, the blood test result showed a sodium level of 136 mmol/L, potassium of 4.5 mmol/L, urea of 9.9 mmol/L, creatinine of 169 µmol/L, adjusted calcium of 2.46 mmol/L, normal liver function, white cell count of 15.7 × 10⁹/L and platelets of 180 × 10⁹/L, INR of 1.1, and heparin dosage ratio of 1.2.

**Outcome and Follow-up**

The patient spent three days in ICU. The renal team reviewed her the next day following her discharge from ICU. She appeared to be clinically stable at that time. Two days after her discharge from ICU, she suddenly deteriorated. She was complaining of severe abdominal pain radiating to the back. She became clammy and distressed. She became unresponsive the following day. Decision was made by the clinical team not to perform cardiopulmonary resuscitation if she went into cardiac arrest. Given her comorbidities and clinical condition, it was felt that cardiopulmonary resuscitation would be futile. Unfortunately, she passed away few hours later and a postmortem was carried out. It was believed that recurrent abdominal bleeding contributed to her deterioration and death.

**Postmortem Report**

A bruise was noted from umbilicus downward covering an area of 15 × 8 cm. There was a thrombosis within the left external iliac vein. However, it was not clear whether this was there at the time of treatment with anticoagulant or was a subsequent development. A large hematoma covering an area of 16 × 15 × 10 cm was noted in the anterior abdominal wall.
**Discussion**

DVT is estimated to affect 1 in 1000 people every year. The major risk factors of DVT include age >60 years, surgery, obesity, previous history of DVT, cancer, immobility, and pregnancy. LMWH such as enoxaparin is usually prescribed for suspected DVT while awaiting for urgent duplex ultrasound scan. The side effects of enoxaparin include bruising, nose bleed, hematuria, gastrointestinal bleeding, allergic reaction, itching, urticaria, bleeding from the brain, retroperitoneal bleeding, anaphylactic reactions, and vasculitis. About 1 in 1000 people who has enoxaparin will have bleeding from brain and retroperitoneal bleeding, which could be fatal. Anterior abdominal wall hematoma or retroperitoneal hematoma is an uncommon complication of subcutaneous injection of enoxaparin, although it is a documented complication of IV unfractionated heparin and oral anticoagulants. There have been case reports demonstrating the risk of having life-threatening bleed following the administration of subcutaneous LMWH.

Other reported cases of bleeding secondary to LMWH injection are as follows:

- A 76-year-old woman died of rectus sheath hematoma following the administration of enoxaparin subcutaneously into the abdominal wall in hospital. She had been receiving enoxaparin 6000 IU twice daily and warfarin 5 mg daily for atrial fibrillation.
- Rectus sheath hematoma with severe hemodynamic instability secondary to subcutaneous injection of enoxaparin 150 mg daily in a 60-year-old woman for unstable angina.
- A 75-year-old inpatient woman complained of acute abdominal pain following the one-day administration of subcutaneous enoxaparin 70 mg/12 hours. A CT scan of the abdomen was carried out three hours later, which demonstrated a 21 × 14 × 8 cm hematoma in the right rectus shear. An aortollic and pelvic arteriography with superselective catheterization revealed bleeding from two small collaterals of right inferior epigastric artery.
- A 86-year-old woman had intrahepatic hemorrhage following the administration of LMWH as a prophylactic treatment for total hip arthroplasty.

It is important to understand that the death of the patient in this case might have been avoided if the appropriate management was carried out. According to National Institute for Health and Clinical Excellence, Wells’ diagnostic algorithm should be used to assess the pretest probability.

**Wells’ Diagnostic Algorithm**

Because of the unreliability of clinical features, several diagnostic scoring systems have been validated whereby patients are classified as having a high, intermediate, or low probability of developing DVT, based on history and clinical examination.

- Score one point for each of the following:
  - Active cancer (treatment ongoing or within the previous six months, or palliative).
  - Paralysis, paresis, or recent plaster immobilization of the legs.
  - Recently bedridden for three days or more, or major surgery within the previous 12 weeks, requiring general or regional anesthesia.
  - Localized tenderness along with the distribution of the deep venous system (such as the back of the calf).
  - Entire leg is swollen.
  - Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity).
  - Pitting edema confined to the symptomatic leg.
  - Collateral superficial veins (nonvaricose).
  - Previously documented DVT.

Subtract two points if an alternative cause is considered at least as likely as DVT.

The risk of DVT is likely if the score is two or more and unlikely if the score is one or less. This patient had scored two due to the swelling of leg and tenderness in her leg. She should have been referred urgently to have Doppler ultrasound scan on the same day or within 24 hours of the suspected DVT. However, the GP had arranged a Doppler ultrasound scan for this lady one week after the suspected diagnosis of DVT and prescribed daily therapeutic enoxaparin injection for the DVT. The Doppler ultrasound scan on admission was normal after she had taken three doses of therapeutic enoxaparin. This could mean that the DVT had resolved or the patient was misdiagnosed with DVT. As suggested by previous case reports and studies, rectus sheath hematoma, retroperitoneal hemorrhage, and intrahepatic hemorrhage are severe complications of LMWH treatment. In this particular case, the patient had suffered from anterior abdominal hemorrhage following the treatment of enoxaparin. Subsequent abdominal ultrasound scan and CT angiogram revealed a bleeding in anterior abdominal wall. She became clinically stable before she was discharged from the ICU. No interventional radiology procedure was considered appropriate at that time as it was believed that the bleeding had stopped. A decision was made not to carry out cardiopulmonary resuscitation on her should her heart stop as it was unlikely that she would survive the resuscitation. Postmortem report also confirmed the diagnosis. It was believed that the bleeding was either due to enoxaparin treatment itself or injury to the collaterals of inferior epigastric artery by the needles. This case report is important to raise the awareness of health-care professionals about the importance of following protocols and understanding the potential harms of enoxaparin treatment.
Management of Intra-Abdominal Bleeding Secondary to LMWH Injection

There is little evidence to guide the management of the anticoagulated patient with intra-abdominal bleeding. As these cases are rare, it is unlikely that randomized controlled trials or even large cohort studies will be carried out to establish an algorithm to manage this condition. The management will include cessation of the anticoagulation therapy, early resuscitation, reversal of anticoagulation effects, and identification of the bleeding point.

Patients who have intra-abdominal bleeding secondary to the administration of LMWH require resuscitation similar to other causes of intra-abdominal bleeding. They should be fluid resuscitated with crystalloids/colloids and packed red blood cells. Platelets may be given if the patient has thrombocytopenia.

As LMWH does not have a specific antidote, protamine can be used to reverse about 60% of the anticoagulant effect of LMWH. It is important to note that the slow administration of protamine is advised to reduce the risk of protamine-induced hypotension and bradycardia. CT angiogram can be done to identify the bleeding point. Angioembolization can be carried out to cease the bleeding if active extravasation can be identified.

Learning Points

- Understand the importance of following protocol.
- LMWH is usually safe. However, it could also cause a rare and life-threatening bleed.
- Medical or nursing staff should be well trained for giving subcutaneous enoxaparin injection. They should at least understand the basic anatomy to avoid accidental intramuscular injection that can potentially injure the inferior epigastric artery.

Author Contributions

Conceived and designed the experiments: KTC. Analyzed the data: KTC. Wrote the first draft of the manuscript: KTC. Contributed to the writing of the manuscript: KTC. Agree with manuscript results and conclusions: KTC. Jointly developed the structure and arguments for the paper: KTC. Made critical revisions and approved final version: KTC. The author reviewed and approved of the final manuscript.

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