Bilateral spontaneous, simultaneous lower extremity hematomas in a patient on dalteparin

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ABSTRACT

INTRODUCTION: Bleeding related to low-molecular-weight heparins (LMWHs) is typically described as an excess of minor bleeding; however, several reports of spontaneous major bleeding have been noted. PRESENTATION OF CASE: A 58-year-old female presented to the hospital with bilateral spontaneous lower extremity hematomas which rapidly enlarged. CT studies demonstrated active arterial extravasation from small vessels at multiple sites within each leg with no dominant feeding artery identified on either side. She required multiple transfusions, administration of protamine, fresh frozen plasma (FFP), recombinant activated Factor VII and eventual surgery.

DISCUSSION: Dalteparin provides an effective and economical method of anticoagulation, however there is a risk of significant, spontaneous arterial hemorrhage even in the absence of risk factors.

CONCLUSION: Dalteparin can cause major spontaneous bleeding from multiple arterial sources.

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1. Introduction

Low-molecular-weight heparins (LMWHs) have become the predominant choice as first line agents for both the prophylaxis of and treatment for deep venous thrombosis (DVT). These agents are popular for inpatient and home administration because of the decreased need for laboratory monitoring, resulting in lower costs, and their limited interactions with other medications or foods.1 Other advantages of Dalteparin (Fragmin®; Pfizer inc., New York, NY) are the simplified fixed dosing and the improved safety in patients with severe renal insufficiency, though it is not recommended for those with severe liver or kidney disease.2 Dalteparin is comparable in safety and efficacy to unfractionated heparins and has a lower risk of heparin induced thrombocytopenia. However, LMWHs have been shown to increase bleeding complications. In a study of 1873 patients given Dalteparin, 5.5% of the patients experienced major bleeding and 0.7% had serious adverse events.2 The occurrence of a bilateral spontaneous bleed represents a rare and serious complication of dalteparin.

2. Discussion of case

A 58-year-old female with a remote history of a laryngeal squamous cell carcinoma treated with a laryngopharyngectomy reported to the rapid care unit with a complaint of bilateral lower extremity swelling, blister formation and severe pain. The patient reported that her symptoms began earlier in the morning after having a bowel movement (BM). The patient stated that after standing up, she immediately noticed bruising on the medial aspect of her right leg and the anterolateral aspect of her left leg. She denied any significant straining with her BM or preceding trauma. Her vital signs were unremarkable: temperature of 37 °C, pulse of 75 beats/min, blood pressure of 118 mmHg/67 mmHg, and a respiratory rate of 18 breaths/min.

The patient had recently been discharged from the hospital after treatment for a polymicrobial bacteremia, during which she developed a three vessel upper extremity deep venous thrombosis (DVT) at the site of her PICC line. At the time she was also noted to have idiopathic transaminitis. Her discharge medications included furosemide, piperacillin-tazobactam, micafungin, ranitidine, oxybutynin, levethoxyroine, risperidone, oxcodone and dalteparin. This was her first time receiving dalteparin injections. There was no history of diabetes, cardiac, liver or kidney disease.

Initial examination revealed two large bullous lesions measuring 14 cm × 8 cm on the right and 7 cm × 5 cm on the left. The lesions and the distal extremities were very painful to palpation, however, sensation was intact and 2+ palpable dorsalis pedis and posterior tibial pulses were noted. The patient was admitted to intensive care for hourly neurovascular checks, and the surgery team was involved for possible compartment syndrome. On further examination,
compartment syndrome was excluded, and the masses were felt to likely be hematomas. Admission laboratory tests revealed anemia with a hemoglobin (Hgb) of 8.3 g/dL, a white blood cell count of 10.45 × 10^3/mcL and a platelet count of 418,000/mcL. Coagulation studies showed a PT of 12.6 s and a PTT of 43.5 s. Transaminases were mildly elevated with an AST of 73 U/L and ALT of 140 U/L. Fibrinogen was measured to be 343 mg/dL and the d-dimer was less than 0.5 mcg/L.

The patient was initially managed conservatively with compressive dressings and elevation. However, within 3 h, the masses had expanded rapidly to 22 cm × 8.5 cm on the right and 12 cm × 8 cm on the left. The overlying skin had become taut and the masses very firm, though ballotable. Concern that this could represent arterial bleeding prompted a consult request to interventional radiology, and angiography and coiling were anticipated. However, a pre-procedural CT demonstrated an essentially unremarkable abdomen and pelvis with large fluid collections affecting bilateral lower extremities consistent with hematomas. Active arterial extravasation from small vessels was noted at multiple sites within each leg, although no dominant feeding artery was identified on either side (Fig. 1A and B). Given these findings, conservative management was continued with one dose of protamine (150 mg) given to potentially counteract dalteparin toxicity.

Throughout this time, the hematomas continued to increase in size (Fig. 2) with stable vital signs and serial neurovascular examination. However, 5 h after presentation, a repeat complete blood count (CBC) returned with a hemoglobin of 5.2 g/dL and platelets of 405,000/mcL. Three units of packed red blood cells (pRBC) and 2 units of FFP were transfused immediately. A post-transfusion CBC showed an appropriate hemoglobin response to 7.9 g/dL, platelets of 256,000/mcL, a PT of 12.2 s and a PTT of 35.3 s. The hematomas continued to enlarge and the following morning, 11 h after presentation, the patient became tachycardic and hypotensive. Her hemoglobin had dropped again, to 5.7 g/dL. She was given more IV fluids, an additional 2 units of pRBC and 2 units of FFP, but remained hypotensive until she was started on a neosynephrine drip. She was given a 90 mcg/kg dose of recombinant activated Factor VII. Her hemoglobin rose to 7.2 g/dL and her PT was 9.6 s and PTT 25.3 s. She received an additional 2 units of pRBC and 2 units of FFP, resulting in a final hemoglobin of 9.6 g/dL. Given the patient’s instability and failure to respond to medical management, the decision was made to take the patient to the operating room (OR) for incision and drainage of bilateral lower extremities.

The patient did stabilize in the late morning prior to the procedure roughly 14 h after presentation and 25 h after the bruising was first noted. In the OR, exploration revealed massive hematomas (Fig. 3) apparently arising from diffuse bleeding from the underlying wound bed; no specific points of major bleeding were found. Of note, the area where the patient’s hematoma initially began appeared to be intradermal, as though within a bulla, however, as it expanded, the hematoma had extended into the superficial subcutaneous space. Hemostasis was achieved using a combination of electrocautery, the Aquamantys system (Medtronic, Portsmouth, NH) and topical thrombin. The skin flaps were loosely closed over drains and dressed with gauze bandage rolls and compressive elastic bandage wraps. The patient was returned to the ICU where she received an additional 3 units of pRBC, bringing the haemoglobin to 6.3 g/dL. An additional CBC that evening yielded a hemoglobin of 12.7 g/dL and platelets of 144,000/mcL (Fig. 4).

The patient remained stable and bleeding gradually resolved over the following day. Of note, the drop in her platelets, from 500,000/mcL to 256,000/mcL to 144,000/mcL, was transient, rebounding to 203,000/mcL on hospital day 4. On hospital day 4, the results of the factor X activity returned with 57% activity. The
transaminits resolved as well. The affected skin underwent necrosis. On hospital day 9, the patient underwent split-thickness skin grafting to her bilateral lower extremity wounds. She recovered well from this operation and was eventually discharged on hospital day 22.

3. Discussion

Documented risk factors for LMWH-induced bleeding include: advanced age, concurrent medications such as aspirin, use of high doses, concomitant thrombocytopenia and impaired renal function. There have been several reported incidences of patients developing spontaneous hematomas related to the use of LMWH in the absence of any trauma. These have ranged from retroperitoneal hematomas to spontaneous splenic rupture. Several reports of spontaneous unilateral lower extremity hematomas involved significantly older patients with one or more risk factors such as diabetes or kidney disease. One of these studies noted multiple sites of arterial extravasation. However, this patient developed bilateral, simultaneous arterial hemorrhage from multiple small vessels without any history of trauma. Additionally, this occurred in a 58 year-old female on a fixed dosing regimen without any known underlying diabetes or kidney disease or thrombocytopenia. While the patient did have a brief transaminits prior to the event, this resolved and she carries no diagnosis of liver disease.

Dalteparin is convenient in not requiring monitoring of laboratory values. However, the lack of an ability to effectively monitor can prove to be a significant detriment. Current management of LMWH-induced hematoma formation includes administration of protamine sulfate and FFP. However, as demonstrated here, this does not always ensure a timely reversal and cessation of bleeding. Resolution of this patient’s coagulopathy required Factor VII, a very costly therapy. Additionally, the significance of the patient’s progressive, though transient, thrombocytopenia is difficult to determine in the setting of multiple transfusions and aggressive volume resuscitation, but a delayed HIT response cannot be excluded. Given the increasing number of reports of LMWH-induced arterial bleeding from multiple small vessels, the difficulty in effectively treating this situation, and the expanding use of LMWHs on the perioperative setting, the relative safety of LMWHs compared to other therapies remains an area for future research.

4. Conclusion

This case demonstrates a unique and very serious bleeding complication of dalteparin use. It demonstrates that significant uncontrolled bleeding from multiple separate sites can occur spontaneously despite a lack of trauma or significant risk factors.

Conflict of interest statement
None.

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Ethical approval
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions
Justin Daggett – Writing, photo collection, literature review.
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Paul Smith – Writing.

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