

## Case report

## Enoxaparin-induced skin necrosis at injection site after total knee arthroplasty

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## ABSTRACT

Enoxaparin is a widely used low-molecular-weight heparin for perioperative thromboembolic prophylaxis. Enoxaparin-induced skin necrosis in the setting of arthroplasty has been rarely reported in the literature with varying outcomes and management decisions. Our patient developed skin necrosis at his injection site and thrombocytopenia 10 days following left total knee arthroplasty surgery and after receiving subcutaneous Lovenox injections postoperatively. The patient was started on an alternative anticoagulation based on a high suspicion for heparin-induced thrombocytopenia and the wound was monitored without surgical debridement. Our case highlights the key clinical management decisions when facing this potentially life-threatening adverse reaction.

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## Introduction

Lovenox (generic name: enoxaparin) is a low-molecular-weight heparin (LMWH) that prevents coagulation by primarily inhibiting factor Xa [1]. It is frequently given in the setting of knee and hip arthroplasty in preventing perioperative deep vein thrombosis (DVT) and venous thromboembolism. Along with bleeding risk, rare cutaneous side effects have been reported in the literature [2,3]. Enoxaparin-induced skin necrosis, as seen in our case, has been associated with grave consequences, including death [4,5].

The precise mechanism for this notable side effect is unknown but frequently occurs along with heparin-induced thrombocytopenia. Given the potential for severe morbidity, it is important for physicians using LMWH for DVT prophylaxis to recognize and appropriately manage this side effect. To our knowledge, 3 cases of Lovenox-induced skin necrosis following TKA have been reported with differing management and outcomes [4,6,7]. We hope our

case highlights a successful management option when facing this rare and potentially life-threatening clinical problem.

## Case history

The patient is a 60-year-old man with a history of a previous right total knee arthroplasty (TKA) who presented with left knee degenerative joint disease that led him to undergo a left TKA. He was discharged without complications on postoperative day (POD) 4 with 2 weeks of Lovenox 30 mg subcutaneous injections given twice per day. The patient had received the same dosing regimen during his first 3 days postoperatively prior to discharge with his first injection having been given preoperatively and then again 12 hours later.

On POD 10 the patient presented in clinic with a necrotic skin reaction over the abdominal Lovenox injection site measuring 5 cm × 3 cm × 1 cm. His Lovenox injections were discontinued and he was sent to the emergency department for concern about possible Lovenox-induced skin necrosis and heparin-induced thrombocytopenia.

On presentation to the emergency department, his complete blood count and basic metabolic panel were within normal limits except for a platelet count of 81. He was afebrile with an otherwise normal physical examination and without signs of systemic illness. A 4T score was calculated to be >6, indicating a high risk for heparin-induced thrombocytopenia (HIT) (Fig. 1). He was then started

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4Ts HIT Probability Testing (Pretest)	Score
<b>Thrombocytopenia</b>	
- 50% decrease in platelets AND nadir $\geq$ 20,000 AND no surgery within preceding 3 days	2
- > 50% decrease BUT surgery within preceding 3 days OR any combination of platelet decrease and nadir that does not fit the criteria for Score 2 or Score 0	1
- < 30% decrease OR platelet nadir < 10,000	0
<b>Timing (from first day of most recent heparin/LMWH exposure)</b>	
- Platelet drop day 5-10 after start of heparin OR within 1 day if previous exposure within the last 5-30 days	2
- Consistent with fall between days 5-10 but not clear OR within 1 day of start with exposure in past 31-100 days OR onset of thrombocytopenia after day 10	1
- Platelet fall is within 4 days of start without recent heparin exposure in the last 100 days	0
<b>Thrombosis</b>	
- New thrombosis, skin necrosis at injection sites, post-heparin acute systemic reaction, adrenal hemorrhage	2
- Progressive or recurrent thrombosis on therapeutic anticoagulant, suspected thrombosis not yet proven, OR erythematous skin lesions at heparin injection sites	1
- Thrombosis not suspected	0
<b>Other Causes for Thrombocytopenia</b>	
- No other cause for platelet count fall is evident	2
- Possible other cause is evident (e.g. sepsis without proven source, thrombocytopenia associated with initiation of ventilator, other)	1
- Probable other cause is present (e.g. within 72 hours of surgery, confirmed bacteremia/fungemia, chemotherapy/radiation within 20 days, DIC, post-transfusion purpura, nadir < 20 AND with other potential drug cause, non-necrotizing skin lesions at injection sites, other)	0
<b>Pretest Probability Score:</b> 6-8 = high 4-5 = intermediate 0-3 = low	<b>Total = ____</b>
<b>Assessment and Action:</b> Score $\leq$ 2 – no presence of HIT or need to test for antibody Score of 3-4 – warrants additional consideration and potential need to request an antibody assay Score $\geq$ 5 – request antibody assay and consider initiating a alternative anticoagulant	<b>(8 maximum)</b>
References: Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e495S-530S. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. <i>British Journal of Haematology</i> 2003; 121:535-55.	

Figure 1. Outline for calculating 4T scores.

on an intravenous bivalirudin (direct thrombin inhibitor) drip. On day 2 after admission his HIT assay returned back positive. His wound was monitored by a multidisciplinary team and felt not to require surgical debridement or biopsy. The patient had a lower extremity venous duplex that was negative for DVT bilaterally. On POD 14 the patient was discharged from the hospital on an oral anticoagulation schedule of dabigatran 150 mg given twice per day for 4 weeks with follow-up scheduled in 1 week at clinic.

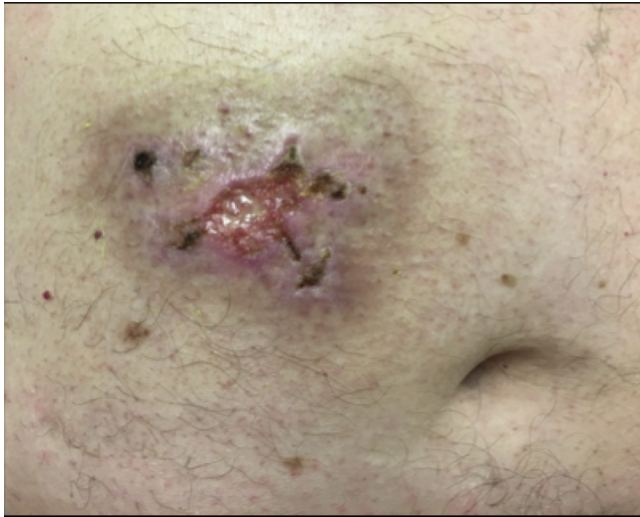
The patient was followed at scheduled intervals for the coming months after discharge without complications as his abdominal wound healed. A picture of his abdominal wound at 2 weeks (Fig. 2) and 2 months (Fig. 3) postop is shown. By 4 months postop the patient had only minor scabbing and by 5 months the wound had completely healed. A picture of his wound at his 7-month follow-up is shown in Figure 4.

## Discussion

According to practice guidelines updated in 2011, the American Academy of Orthopedic Surgeons recommends the use of LMWH for venous thromboembolism prophylaxis in patients undergoing



Figure 2. Injection site wound at 2 weeks postop.



**Figure 3.** Injection site wound at 2 months postop.

TKA and total hip arthroplasty [8]. This recommendation was also agreed upon by the American College of Chest Physician practice guidelines published in 2012 [9]. When compared to unfractionated heparin, LMWH is easier to monitor pharmacokinetics, lower incidence of HIT, reduced risk of bleeding, and thromboembolic complications [10]. Given these attributes, its use is widespread, but not without complications. Our case report features the rare but potentially life-threatening skin necrosis that may occur with the use of LMWH.

We are aware of 3 prior case reports in the literature documenting Lovenox-induced skin necrosis in the setting of TKA. In the case by Maruan et al [5], thrombocytopenia was found on POD 4, followed by skin necrosis developing on POD 5. The LMWH was discontinued but there was no mention of starting aspirin or a direct thrombin inhibitor. They elected to not debride the wound due to the extent of skin necrosis. Necrosis found outside of the site of injection was not seen in our case but was seen in Maruan's case as well as others [11]. Unfortunately, the patient described in the Maruan case report did not survive, likely due to overwhelming sepsis originating from the necrotic wound. In the second case by

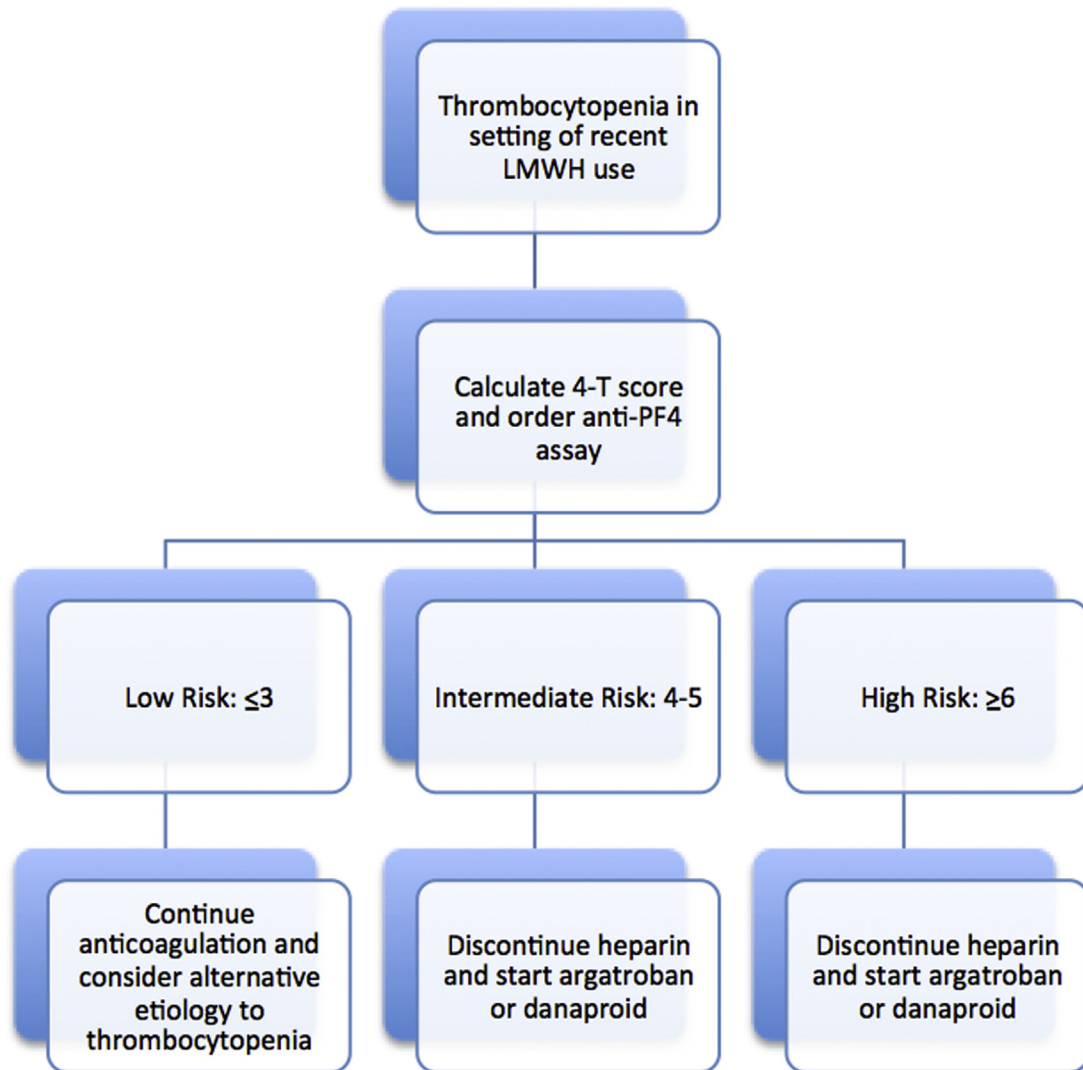


**Figure 4.** Healed wound at 7 months postop.

Karuppiah and Johnstone [6], the patient undergoing TKA developed injection site necrosis on POD 14 without thrombocytopenia present. LMWH was discontinued and she was started on aspirin 150 mg administered orally once a day without surgical debridement. The wound was healed without complication by follow-up at 3 months. Finally, in a case report by Karmegam et al [7], the patient was noted to have injection site irritation that started on POD 1 and eventually progressed to skin necrosis. He did not have thrombocytopenia on hematologic evaluation. The wound was surgically debrided and ultimately required a split-thickness graft by a plastic surgeon, which healed without complication.

Based on the 3 previous case reports mentioned and our own, heparin-induced thrombocytopenia may or may not be present during incidences of LMWH-induced skin necrosis. However, the presence or absence of thrombocytopenia is of critical importance for management. According to the current American College of Chest Physician practice guidelines from 2012, patients strongly suspected or confirmed to have HIT should be treated with a non-heparin anticoagulant over unfractionated or an alternative LMWH [9]. Currently, the alternative anticoagulant recommended by the American College of Chest Physician is argatroban or danaproid as first line over other nonheparin anticoagulants [9]. Furthermore, they recommend using argatroban in patients with renal insufficiency [9]. As used in our patient, the "4T" test can be used to help appraise the likelihood of HIT being present and the need for starting a nonheparin anticoagulant before the HIT assay result is available. Figure 1 outlines the clinical components used in calculating this score. This test has been shown to have a high-negative predictive value and predominately should be applied as a rule-out test [12]. A meta-analysis by Cuker et al [12] that involved 13 studies and 3068 patients suspected of having HIT found the negative predictive value of low ( $\leq 3$ ) 4T scores to be 0.998 (95% confidence interval [CI] 0.970-1.000) after confirming HIT with follow-up immunoassays. Additionally, they found that the positive predictive value of an intermediate and high probability 4T score was 0.14 (95% 0.09-0.22) and 0.64 (95% 0.40-0.82), respectively [12]. Furthermore, a study done by Vatanparast et al demonstrated the importance in a 4T test in ruling out HIT and the potential harm that can occur from treating with an alternative anticoagulant empirically. In their retrospective review, 14 of the 72 patients with a low ( $\leq 3$ ) 4T score received alternative anticoagulation for suspected HIT, 10 of which developed bleeding complications required blood transfusion and all 14 patients were later found to be negative for HIT based on immunoassay [13]. For our patient we felt it was appropriate to start alternative anticoagulation given that he had a 4T score of  $>6$  in the setting of recent Lovenox use. Based on the aforementioned data, we have suggested a treatment algorithm centered on the patient's 4T score (Fig. 5). For cases of skin necrosis in which HIT is absent, there are not published guidelines for us to make appropriate clinical recommendations. However, as in any adverse drug reaction, it is critical to remove the offending agent. As soon as skin necrosis is suspected, in the presence of HIT or not, the clinician should promptly discontinue the anticoagulant.

Another important consideration for management of this side effect is the decision whether or not to surgically debride the wound. In our case, the patient had no systemic signs of infection with a limited area of necrosis that did not extend beyond the subcutaneous fat. After dermatology and general surgery were consulted we decided to pursue nonoperative care. In the Maruan case, the area of skin necrosis was felt to be too widespread to surgically debride, while the Karmegam patient had his wound surgically debrided. In the latter case, the patient was on long-term corticosteroids for treatment of rheumatoid arthritis, which placed him at increased risk for wound infection. The patient



**Figure 5.** Treatment algorithm for HIT using 4T score. HIT, heparin-induced thrombocytopenia.

additionally was noted to have local pruritus and erythema without overt systemic signs of infection. The decision to debride is not as algorithmic as the treatment for HIT. Instead, we recommend consultation with our general surgery and dermatology colleagues who have more soft tissue infection expertise in order to determine the need for debridement. In addition, further imaging with magnetic resonance imaging or computed tomography to determine the depth of invasion can be helpful in making this decision.

Finally, it is worth noting that our patient had a previous uncomplicated right TKA with the use of postoperative Lovenox subcutaneous injections in the same dosing regimen. Clinicians should be aware that skin necrosis may occur in both naïve and patients previously exposed to Lovenox. Other risk factors have been correlated with heparin-induced skin necrosis, including diabetes, obesity, and recent antibiotic use [11,14].

### Summary

Although we currently do not have interventions to prevent this dangerous cutaneous effect, early recognition and proper

management can improve patient outcomes. Our case highlights the important management considerations that a clinician faces with enoxaparin-induced skin necrosis. We hope this case helps guide clinicians on the use of 4T scores, anticoagulation choices, and deciding on wound debridement when a patient develops skin necrosis with or without HIT.

### References

- [1] Martinez C, Savadogo A, Agut C, Anger P. Reproducibility of the anti-Factor Xa and anti-Factor IIa assays applied to enoxaparin solution. *J Pharm Biomed Anal* 2013;81-82:138.
- [2] Schliep S, Kiesewetter F, Simon M, Grupp C, Heinzerling L. Drug-induced dilemma: angiokeratomas and decreased renal function. *Am J Med* 2014;127(7):598.
- [3] Issa AA, Simman R. Lovenox induced tissue necrosis, a case report and literature review. *J Am Coll Clin Wound Spec* 2013;5(3):66.
- [4] Singh S, Verma M, Bahekar A, et al. Enoxaparin-induced skin necrosis: a fatal outcome. *Am J Ther* 2007;14(4):408.
- [5] Maruan H, Gabriel N, Mazen F, Nahum R. Abdominal skin necrosis after enoxaparin treatment. *Open J Clin Diagn* 2014;4:53.
- [6] Karupiah SV, Johnstone AJ. Skin necrosis associated with thromboprophylaxis after total knee replacement. *Case Rep Orthop* 2014;2014:139218.
- [7] Karmegam A, Desai A, Peter V, Raut V. Tissue necrosis after use of enoxaparin in total knee arthroplasty: a case report. *Am J Orthop* 2011;40(8):E152.

- [8] Jacobs JJ, Mont MA, Bozic KJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Bone Joint Surg Am* 2012;94(8):746.
- [9] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):7S.
- [10] Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330.
- [11] Levine LE, Bernstein JE, Soltani K. Heparin-induced cutaneous necrosis unrelated to injection sites. A sign of potentially lethal complications. *Arch Dermatol* 1983;119(5):400.
- [12] Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood* 2012;120(20):4160.
- [13] Vatanparast R, Lantz S, Ward K, Crilley PA, Styler M. Evaluation of a pretest scoring system (4Ts) for the diagnosis of heparin-induced thrombocytopenia in a university hospital setting. *Postgrad Med* 2012;124(6):36.
- [14] White PW, Sadd JR, Nensel RE. Thrombotic complications of heparin therapy. *Ann Surg* 1979;190:595.