

Necrotizing skin lesions induced by enoxaparin after knee arthroplasty

Pablo Priego, José M^a Daroca, Carmen Villegas, Vicente Ángel, Javier Escrig, José Luis Salvador.

Department of General Surgery. Hospital General de Castellón, Spain.

Abstract

Skin necrosis caused by heparins is a rare complication. We report a case of a 71-year-old woman who developed the unusual complication of focal necrotizing skin lesions in the injection site after undergoing thromboprophylaxis with enoxaparin after right knee arthroplasty. Laboratory investigations for heparine-induced thrombocytopenia (HIT), disseminated intravascular coagulation, protein C, protein S, factor V, factor VIII, antithrombin III, and homocysteine deficiency were negative. Fortunately, despite aggressive management, the postoperative evolution was uneventfully.

Key words: Skin necrosis, enoxaparin, low molecular weight heparin, thrombosis, heparin.

Introduction

Enoxaparin is a low-molecular-weight heparin (LMWH) currently used not only in the prophylaxis but also in the treatment of deep venous thrombosis (DVT) and pulmonary thromboembolism. Compared with standard unfractionated heparin (UFH), adverse effects appear to be less with LMWH^{1,2}.

Skin necrosis caused by LMWH is a rare and probably under-reported complication.

The first symptoms were usually described as erythematous, subcutaneous lesions with edema and pain at the injection sites. Subsequently, full skin necrosis occurred. The average time between first administration of LMWH and onset of skin necrosis was 2-5 days³.

Most part of patients develop an established heparin-induced thrombocytopenia (HIT) syndrome, where an antibody-platelet-heparin complex leads to an activation of the coagulation cascade that results in microthrombosis of dermal vessels and skin necrosis³.

However, thrombosis induced by heparin with no evidence of HIT is seldom described⁴.

Case report

A 71-year-old obese woman was admitted to our hospital with advanced bilateral gonarthrosis requiring operative intervention. Her past medical history revealed arterial hypertension, dyslipemia, ischemic cardiopathy. Perioperatively, thromboprophylaxis was achieved by subcutaneous injection of enoxaparin 40 mg/24 hours. After a successfully performed right knee arthroplasty, mechanical and medical approaches were instituted for the prevention of postoperative venous thromboembolism. From the first postoperative day, 40 mg of enoxaparin were daily used. After 8 days of LMWH administration, it was observed a progressive, painful erythematous lesion at the injection sites (abdo-

men) with black centers appeared. Coagulation tests and platelet count were normal (211000 cells/ml). The patient was evaluated by dermatologists and a local hematoma was suspected, leading to the selection of an alternative puncture site, so was discharged two weeks after the intervention with postoperative anticoagulant (Sintrom[®]) and antiagregant (Disgren[®]) treatment.

Four days later, the General practitioner (GP) sent the patient to our department because of the progression of the size and necrosis of the lesions in spite of local cures.

At that point, physical examination revealed three necrotic lesions of 11, 7 and 5 cm respectively located in abdomen (Fig 1) related to site injection of enoxaparin.



Figure 1. Peri-umbilical skin necrosis at the site of LMWH administration.

Skin necrotic lesions were surgically removed and antibiotic treatment was prescribed.

The biopsy showed extended hemorrhagic hypodermal and skin necrosis with an inflammatory reaction in dermal vessels with vasculitis.

Considering that an adverse effect of LMWH might be involved, the subcutaneous enoxaparin was immediately discontinued and the hematologists prescribed treatment with salicylic acid 100 mg intravenous daily.

Heparin-induced thrombocytopenia (HIT) test results were found to be negative.

Others parameters of coagulation (anti-thrombin III, protein s, protein c, prothrombin time, activated partial thromboplastin time) were normal.

Laboratory investigations for factor V of Leyden, factor VIII, anti IgG cardiolipin, homocysteine deficiency and mutation of prothrombin 20210A gen were negative.

Postoperative evolution was uneventfully. First of all we used Hypergel® (made of a 20 % sodium chloride solution in gel form) during 3 days until removal of dry necrosis. After that we used Normlgel® (a gel with 0.9% sodium chloride) that helped create an optimal moist wound healing environment and dissolved the fibrin. Finally we used Mepilex® Ag (Antimicrobial dressing with Ag, coal and technology Safetac) that inactivates wound pathogens within 30 minutes and for up to 7 days (Figure 2).



Figure 2. Wound healing.

Twenty days later a reconstructive surgery was performed, and the patient was discharged hospital (Figure 3).



Figure 3. Aspect of wound after reconstructive surgery.

Discussion

The incidence of skin necrosis caused by LMWH is an exceptionally rare event. The outcome of LMWH-induced skin necrosis is usually uneventful in the majority of the cases when LMWH is stopped and changed to alternative anticoagulatory drugs. Unfortunately, there have been described some cases in which the patient has developed a severe sepsis and has died⁵.

In this case, in spite of a conservative management with stopping the LMWH and local cures, the large size of the skin necrosis (>11 cm one of them) and the progression of the disease, led us to perform the surgical resection of the necrosis and to prescribe antibiotics. There are not many cases of surgical treatment of this rare event described in the literature^{6,7}.

Several pathophysiological mechanisms have been proposed: The most frequent is the association with an HIT syndrome. In these cases, an antibody-platelet-heparin complex leads to an activation of the coagulation cascade result in microthrombosis of dermal vessels and skin necrosis. A second way is the development of a vasculitis of dermal vessels induced by a type III hypersensitivity reaction to the LMWH. This could be the pathogenesis of our case, supported by the identification of vasculitis signs in the skin biopsy. The last and not immunological path is due the result of repeated local trauma at the injection site, resulting in skin necrosis³.

In conclusion, it is mandatory to follow up the platelet count to detect thrombocytopenia and irrespective of the grade of thrombocytopenia; it is recommend testing for HIT using the heparin-induced platelet activation assay, and furthermore it is advice to realize some coagulation and laboratory tests to rule out the diagnosis of disseminated intravascular coagulation, protein C and S, Factor V, Factor VIII, antithrombin III and homocysteine deficiency, antiphospholipid syndrome⁸⁻¹¹.

Acknowledgments The authors thank all the equipment of nurses of our department (5 B) for their great management in surgical postoperative cares.

References

1. Plath J, Schulze R, Barz D, Krammer B, Steiner M, Anders O, Mach J. Necrotizing skin lesions induced by low-molecular-weight heparin after total knee arthroplasty. *Arch Orthop Trauma Surg* 1997; 116:443-445.
2. Sanchez-Politta S, Angelillo-Scherrer A, Masouyé I Borradori L. Wide-spread skin necrosis associated with unfractionated heparin therapy in a patient under chronic coumarin anticoagulation. *J Eur Acad Dermatol Venereol* 2006; 20(3): 327-30.
3. Handschin AE, Trentz O, Kock HJ, Wanner GA. Low molecular weight heparin-induced skin necrosis- a systematic review. *Langenbecks Arch Surg* 2005; 390:249-254.
4. Nadir Y, Mazor Y, Reuven B, Sarig G, Brenner B, Krivoy N. A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; 77:166-168.
5. Singh S, Verma M, Bahekar A, Agrawal P, Duggal J, Ilescu M, Kholsla P, Muzaffar S. Enoxaparin-induced skin necrosis: a fatal outcome. *Am J Ther* 2007; 14(4): 408-10.
6. Cordoliani F, Saiag P, Guillaume JC, Roujeau JC, Wechsler J, Clerici T, Touraine R. Necroses cutanees etendues induites par la fraxiparine. *Ann Dermatol Venereol* 1987; 114:1366-1368.

7. Drew PJ, Smith MJ, Milling MA. Heparin-induced skin necrosis and low molecular weight heparins. *Ann R Coll Surg Engl* 1999; 81:266-269.
 8. Ng T, Tillyer ML. Warfarin-induced skin necrosis associated with Factor V Leiden and protein S deficiency. *Clin Lab Haematol* 2001; 23(4): 261-4.
 9. Prasad HK, Govindarajan R. Heparin-induced skin necrosis associated with thrombocytopenia and acquired protein C and protein S deficiency. *Am J Hematol* 2007; 82(12): 1116-7.
 10. Tai CY, Ierardi R, Alexander JB. A case of warfarin skin necrosis despite enoxaparin anticoagulation in a patient with protein S deficiency. *Ann Vasc Surg* 2004; 18(2):237-42.
 11. Warkentin TE, Roberts RS, Hirsch J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome. A nested cohort study. *Chest* 2005; 127:1857-1861.
-

Author for correspondence:

Pablo Priego Jiménez
C/Fermín Caballero 26 1ºA, 16004. Cuenca
Teléfono: 667858557.
papriego@hotmail.com