

# The Challenge of Hemorrhagic Shock Management During Low-Molecular-Weight Heparin Treatment

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**Abstract:** The reversal of low-molecular-weight heparin (LMWH) and the management of bleeding patients on LMWH remain highly challenging. Even if LMWH is very extensively administered in the prophylaxis and treatment of venous thrombosis, specific antidotes are lacking, and reversal strategies have very weak grade of evidences on clinical effectiveness. We here describe a reversal strategy with protamine and FVIIa in a patient presenting with hemorrhagic shock and cardiocirculatory arrest.

**Keywords:** LMWH bleeding, LMWH reversal, FVIIa, protamine, mantle lymphoma

## Introduction

The reversal of low-molecular-weight heparin (LMWH) and the management of bleeding patients on LMWH remain highly challenging.<sup>1</sup> Even if LMWHs are very extensively administered in the prophylaxis and treatment of venous thrombosis, specific antidotes are lacking, and reversal strategies have very weak grade of evidences on clinical effectiveness. Protamine is recommended for the reversal of LMWH but it is able to partially revert the LMWH anti-Xa activity.<sup>2-4</sup> Furthermore, protamine efficacy appears to be time-dependent, rendering it highly challenging when treating bleeding patients on LMWH. Protamine-alone strategies to neutralize LMWH are indeed unreliable, especially in life-threatening bleeding.

Guidelines did not include or suggest other antidotes or procoagulants able to cooperate with protamine in such scenario. Few reports have been published describing the administration of FVIIa, which is not indicated for this clinical condition.<sup>5</sup>

The management of life-threatening bleeding upon/or during LMWH remains challenging and without precise indication from the guidelines. In the following case report, we will discuss LMWH reversal for severe bleeding in a lymphoma patient.

## Case Report

An 86-year-old patient was admitted to our Division of Internal Medicine – Hematology – due to the diagnosis of Non-Hodgkin Lymphoma, mantle cell type. Presentation included stage IV disease with lung involvement, splenomegaly, lymphadenomegaly and clonal lymphocytosis at the peripheral blood. The patient was suffering from chronic atrial fibrillation and was under chronic anticoagulation with vitamin K antagonists. During hospitalization, VKA was substituted with LMWH therapy to easily perform diagnostic biopsies (bone marrow) and invasive procedures upon transitorily interruption of the LMWH anticoagulation. Due to the need for

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adequate venous access, we disposed for the placement of a central venous catheter, with ultrasound guidance at the subclavian vein. This procedure was complicated by the development of a pneumothorax which required drainage. The day after drainage removal, LMWH (enoxaparin) was administered at a dose of 100 U/Kg twice daily. Forty-eight hours later the patient presented with severe hypotension and signs of peripheral hypoperfusion. Lactic acid was elevated (11 mMol/L). A thorax Computer Tomography (CT) scan with contrast was performed revealing the occurrence of severe bleeding on the previous site of pneumothorax. No variation in the clotting times was observed and no significant changes in kidney and liver function were documented before this acute event. While attempting to dispose for a novel thoracic drainage, the patient's clinical conditions were dramatically worsening with the development of cardiocirculatory arrest, due to pulseless electrical activity (PEA). Resuscitation was started accordingly following the guidelines for PEA.

It became clear that the only way to save the patient's life would be to reverse the bleeding, the drainage and the blood transfusion to achieve an adequate perfusion. During cardiopulmonary resuscitation (CPR) – although LMWH was administered around 8 hrs earlier – we decided to administer 1 mg protamine followed by 90 µg/kg of Factor VIIa. Simultaneously, a blood transfusion was started. In the absence of clear guidelines, we used protamine sulfate to potentially reverse those LMWH molecules which were still circulating and complexed with anti-thrombin. Due to the partial reversal potential of protamine and the presence of cardiac arrest, we realized that this strategy would not have been sufficient for a rapid and strong reversal. Thus, we decided to rapidly administer Factor VIIa hoping to trigger coagulation, maximizing the activation of residual factor-X. At the end of this combinatorial therapy, and still during CPR, the thoracic drainage was positioned. Progressively, signs of perfusions were observed and CPR was stopped. The patient was subsequently transferred to the Intensive Unit Care where he also received a plasma transfusion (15 mg/kg). Two hours later, the patient was transferred to the operating room and a thoracoscopy was performed. A clear bleeding site was observed close to the previous drainage site and was treated accordingly. Recovery was complete and in two days the patient was transferred back to our Division. No neurological defects were observed, and no sign of deep vein thrombosis and/or pulmonary embolism were detected. However, transient kidney failure was observed, but without the need for renal dialysis kidney

function subsequently recovered. Subsequently, mantle cell lymphoma was treated with a rituximab-chlorambucil-prednisone regimen. Three months later the patient was well and continued a monthly chemotherapy regimen as an outpatient.

## Conclusions

This case report describes a hemorrhagic shock evolving into cardiac arrest in a patient receiving LMWH. In such a dramatic clinical scenario, our bleeding reversal strategy included the administration of protamine and FVIIa, allowing us to achieve a complete hemostasis without side effects. It is worth noting that the dosage of protamine was very low, considering the time of LMWH administration, and that plasma was infused when the patient was already stable. Therefore, FVIIa appeared the most effective strategy to promote LMWH reversal. This case report may lead to the following comments:

- (i) In older patients with comorbidities, such as lymphomas, the indication of every invasive procedures should be carefully reviewed. The dramatic story described above may be prevented with the use of a peripherally inserted central catheter (PICC) despite the placement of a central vein catheter.
- (ii) The management of major bleeding in patients on LMWH remains challenging. This case report questions whether protamine alone is effective enough to attempt LMWH reversal.
- (iii) Lastly, we may provide some insight on the safety of the combinatorial therapy, protamine and FVIIa. In this life-threatening situation, FVIIa should activate FX, allowing us to bypass the residual inhibition by LMWH. Interestingly, the association protamine and FVIIa did not promote any thrombotic complications in our patient, even when protamine was used at low dose.

## Ethical Disclosure

The case report was described upon written informed consent of the patient's son and daughter to have the case details published. The patient passed away before publication for causes independent of the case report. Institutional approval was not required for publication.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Dhakal P, Rayamajhi S, Verma V, et al. Reversal of anticoagulation and management of bleeding in patients on anticoagulants. *Clin Appl Thromb Hemost.* 2017;23(5):410–415. doi:10.1177/1076029616675970
2. van Veen JJ, Maclean RM, Hampton KK, et al. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis.* 2011;22(7):565–570. doi:10.1097/MBC.0b013e3283494b3c
3. Wakefield TW, Andrews PC, Wroblewski SK, et al. Reversal of low-molecular-weight heparin anticoagulation by synthetic protamine analogues. *J Surg Res.* 1994;56(6):586–593. doi:10.1006/jsre.1994.1093
4. Sokolowska E, Kalaska B, Miklosz J, Mogielnicki A. The toxicology of heparin reversal with protamine: past, present and future. *Expert Opin Drug Metab Toxicol.* 2016;12(8):897–909. doi:10.1080/17425255.2016.1194395
5. Goodnough LT, Levy JH. The judicious use of recombinant factor VIIa. *Semin Thromb Hemost.* 2016;42(02):125–132. doi:10.1055/s-0035-1569068

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