

Life-threatening hemorrhage following subcutaneous heparin therapy

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Abstract: Prophylactic administration of unfractionated heparin is a common practice in a perioperative period. Heparin monitoring with subcutaneous dosing is not recommended; however it becomes important in selected patients. We report a case of massive hemorrhage with subcutaneous heparin administration in an HIV-positive male patient with cachexia and mild liver dysfunction. Prolonged activated plasma thromboplastin time and thrombin time, but normal reptilase time well as response to protamine sulfate point towards the heparin effect. Inhibitor screen was negative and factor VIII activity was normal. All these rule out the possibility of acquired factor VIII inhibitor or any other inhibitor and confirm that this bleeding was due to heparin overdose. We believe that delayed clearance of UH secondary to possible involvement of reticuloendothelial system might have been responsible for heparin overdose even though inadvertent administration of large dose of heparin intravenously can not be completely ruled out. Administration of unfractionated heparin to a patient with cachexia and abnormal liver function warrants close attention to heparin monitoring or switch to low molecular weight heparin since its mechanism of elimination differs.

Keywords: unfractionated heparin, bleeding, prophylaxis, liver dysfunction, cachexia, HIV

Introduction

In critically ill patients, venous thromboembolism (VTE) prophylaxis has been included in the bundle of measures designed to prevent the development of complications in ventilated patients and became a core indicator of the quality of intensive care.¹ Either low-dose unfractionated heparin (UH) or low molecular weight heparin (LMWH) is regularly used for prophylaxis. We report a life-threatening hemorrhage with UH in an human immunodeficiency virus (HIV)-positive patient with mild liver impairment.

Case report

A 48-year-old male patient (body mass index [BMI] 21.5 kg/m²) with a history of HIV infection, bipolar disorder, metastatic bladder cancer, and persistent pleural effusion with left lower lobe collapse was admitted to the surgical intensive care unit (SICU) after a left video assisted thoracoscopy and pleurodesis. Surgery was smooth and bleeding was minimal. Preoperative medication consisted of abacavir, tenofovir, lopinavir-ritonavir, bupropion, divalproex, olanzapin, citalopram and pantoprazole. Prior to surgery the patient had elevated serum transaminases (ALT 49 IU/L, AST 169 IU/L), and bilirubins (total bilirubin 2.2 mg/dL and direct bilirubin 1.8 mg/dL), serum albumin was 1.5 g/dL, creatinine was 0.7 mg/dL and serum electrolytes were normal. Coagulation tests were elevated, activated partial thromboplastin time (PTT) more than prothrombin time (PT) (Table 1). On admission to the SICU patient was intubated and mechanically ventilated, two chest tubes were on suction. VTE prophylaxis was initiated with the UH at a regimen of 5,000 units twice a day subcutaneously. Postoperative course was complicated by rapid atrial fibrillation which responded to cardioversion. Patient was weaned off the ventilator and extubated

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Table 1 Perioperative values of relevant blood tests

| | Htk (%) | PTT (22–35s) | PT (10.4–13.1s) | TT (16–20s) | Plat (150–440 K/uL) | Fibr (150–400 mg/dL) | FDP (0–10 ug/mL) | Hapt (50–220 mg/dL) | LDH (94–250 IU/L) |
|---------------------------|---------|--------------|-----------------|-------------|---------------------|----------------------|------------------|---------------------|-------------------|
| Preoperative values | 23 | 47.4 | 13.2 | NA | 230 | NA | NA | NA | 693 |
| Postoperative values | 27 | 44.7 | 14.5 | NA | 227 | NA | NA | NA | 672 |
| Event of hemorrhage | 18.3 | 150 | 13.8 | 124 | 104 | 217 | 10–40 | 299 | 379 |
| After protamine treatment | 27 | 43 | 10.1 | 17.6 | 107 | 277 | NA | NA | NA |
| Discharge from the SICU | 29.9 | 42.5 | 12 | NA | 110 | 248 | NA | NA | 282 |

Abbreviations: Htk, hematocrit; PTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; Plat, platelets; Fibr, fibrinogen; FDP, fibrin degradation products; Hapt, haptoglobin; LDH, lactate dehydrogenase; SICU, surgical intensive care unit.

within 24 hours. The next day chest tubes were disconnected from an active suction and placed to the underwater seal. PTT, hematocrit and platelet count were checked on a daily basis. PTT climbed slightly during his SICU stay with the value of 52.6 s shortly prior to discharge. Patient remained hemodynamically stable, there was no output from the chest tubes and chest X-ray did not show any significant fluid accumulation. He was transferred from the SICU to the regular floor on the postoperative day (POD) 3. On the POD 5 patient was readmitted to the SICU because of massive hemorrhage from the left hemithorax, up to 900 mL/hour. Prior to immediate resuscitation with blood products, blood sample was sent for coagulation evaluation, cell blood count, blood smear, lactate dehydrogenase and haptoglobin (Table 1) and heparin was discontinued. Patient was given a recombinant activated factor VII (rFVIIa) at a dose of 40 µg/kg as a rescue therapy for massive hemorrhage. Prolonged PTT of 150 s as well as thrombin time (TT) of 124 s raised suspicion of heparin effect. Protamine sulfate was given intravenously at a dose of 100 mg and resulted in normalization of TT and shortening of PTT to a patient's baseline value (Table 1). Bleeding decreased significantly; however did not stop at the time of initial intervention and required continued resuscitation with blood products. Within 12 hours hemorrhage subsided. The total chest tubes output reached 4360 mL of blood. Patient received 10 units of packed red blood cells (PRBC), 6 units of fresh frozen plasma (FFP), 15 units of cryoprecipitate. Results of additional coagulation tests (reptilase time [RT], circulating inhibitors, and levels of factors VIII, IX, XI, and XII) became gradually available and are shown in Table 2.

The rest of the ICU stay was uneventful. One of the chest tubes could be removed on the POD 8, the other one was clamped and patient was transferred to the standard floor in a good condition.

Discussion

All patients admitted to the SICU are at risk of developing VTE. The risk varies with the type of surgery; however other factors like age, coexistent malignancy, infection, mechanical ventilation, and paralysis play an important role in the thrombus formation. Deep venous thrombosis prophylaxis is necessary in all seriously ill and especially in those with HIV infection. The literature suggests that hematological abnormalities are common in HIV-positive patients.^{2,3} Many of them develop a hypercoagulable state secondary to production of antiphospholipid antibodies, lupus anticoagulant antibodies, and increased levels of von Willebrand factor. Others might acquire deficiencies of protein C, protein S, antithrombin, and heparin

Table 2 Complementary coagulation tests

| Reptilase time (13.5–19.5 sec) | Inhibitors screen | Factor VIII (50%–150%) | Factor IX (50%–150%) | Factor XI (50%–150%) | Factor XII (40%–150%) |
|-----------------------------------|-------------------|---------------------------|-------------------------|-------------------------|--------------------------|
| 17.7 | NEG | 62 | 89 | 60 | 57 |

cofactor II (HC) during the course of their disease.^{2,4} Treatment with protease inhibitors like ritonavir has been reported as a cause of thrombosis in this group of patients as well.²

Our patient presented to the SICU with several risk factors of VTE: surgery, mechanical ventilation, history of malignancy and HIV status. He was started on UH at a dose of 5,000 units twice a day. On POD 5 he developed massive hemorrhage from the operated hemithorax. The most noticeable from coagulation tests was significantly prolonged PTT. This test is used to assess intrinsic and common pathway of clot formation. PTT evaluates following factors: fibrinogen, prothrombin, V, VIII, IX, X, XI, and XII. Inadequate quantity of any of these factors results in prolongation of PTT. Factors deficiency can arise from insufficient synthesis as in liver disease, consumption as in consumptive coagulopathy, or inactivation either by circulating inhibitors or through an action of heparins. Based on those facts, our differential diagnosis included heparin overdose, acquired factors deficiencies, presence of circulating inhibitors, and disseminated intravascular coagulopathy (DIC).

A battery of laboratory tests was done at time of the event but only some were readily available. Heparin overdose was suspected from prolonged PTT and TT. Protamine sulfate was given intravenously and resulted in normalization of TT and return of PTT to the baseline. RT and TT measure fibrinogen conversion to fibrin and are prolonged with low levels of fibrinogen, qualitatively abnormal fibrinogens, or in presence of fibrin/fibrinogen degradation products. The thrombin time, but not the reptilase time, is prolonged in the presence of heparin. RT was normal and reinforced our suspicion of heparin effect. Heparin levels were checked more than twelve hours after the onset of hemorrhage, discontinuation of UH, and after protamine sulfate administration. A level of less than 0.5 U/mL was detected (therapeutic goal 0.3–0.5 U/mL) and indicated the presence of heparin.

It is not uncommon that patients with a history of HIV (especially those with hemophilia A or B) develop inhibitors to factors VIII or IX during the course of their disease.^{5,6} Mixing studies were performed to rule out circulating inhibitors. Inhibitors were not detected. Assays for factors VIII, IX, XI, and XII were also done and found normal levels of measured factors (Table 2).

DIC, a process known to complicate certain pathologies including underlying malignancy and liver dysfunction, might manifest as a life-threatening hemorrhage and was considered in this patient as well. Laboratory tests such as low platelets, low fibrinogen, presence of fibrin degradation products (FDP) or D-dimer and occurrence of schistocytes in peripheral blood smear are used to confirm this predominantly clinical diagnosis.⁷ Laboratory results were inconclusive with mild drop in platelet count (nadir of 104 K/uL), normal fibrinogen (not a sensitive indicator since it is an acute phase protein), moderately elevated FDP and occasional schistocytes in peripheral blood smear (Table 1). Bleeding did not resemble oozing from puncture sites as frequently seen with DIC even though its clinical presentation frequently varies. Most importantly, we did not interfere with the underlying pathology as recommended in DIC to correct coagulopathy.

A drop in platelet count made us to consider bleeding secondary to heparin-induced thrombocytopenia. Blood was examined for heparin-induced antibodies and the test was negative.

The heparin overdose remained the most likely explanation for bleeding in our patient. We carefully analyzed possible triggering events. There was a certain chance of inadvertent administration of large dose of UH intravenously. We excluded extensive heparin flush as a cause of UH overdose since plain saline flush is used for central venous catheters and arterial lines in all our patients. Patient received nine doses of UFH prior to readmission to the SICU. Probability that one of the doses was given accidentally intravenously instead of subcutaneously is not negligible even though only subcutaneous administration was documented. Administration of UH from a vial with different concentration than 5,000 units/cc is certainly a possibility to consider especially after the patient was transferred to a regular surgical ward.

We explored other potential causes of heparin effect in this patient and concluded that the most probable explanation for bleeding would be delayed elimination of UH. After parenteral injection UH is removed via two mechanisms, saturable and non-saturable which operate in conjunction with each other.⁸ Reticuloendothelial system (RES) and endothelial cells represent the saturable mechanism while

renal elimination stands for nonsaturable or linear removal mechanism.⁸ Lower doses of UH are cleared by RES whereas kidneys are responsible for clearance of LMWH and higher doses of UH.⁸ The blockage of the phagocytic capacity of RES may prolong the half-life of UH significantly.⁸ Multiple conditions may cause RES compromise in HIV-infected individual, such as viral infection of monocytes or macrophages, effect of antiretroviral therapy with subsequent lipodystrophy or simply liver steatosis from malnutrition. We believe that it was the delayed clearance of heparin which contributed significantly to bleeding in our patient. Fragility of vessel walls in this profoundly malnourished cachectic patient might have played a role as well.

The purpose of our report is to caution about the possibility of major hemorrhage with low dose of UH and not to discourage VTE prophylaxis. There are multiple studies evaluating and comparing safety of UH and LMWH and only two are being mentioned here. Freedman et al performed a meta-analysis of thromboembolic prophylaxis after total hip arthroplasty. Fifty-two studies with total 10,929 patients were included in the analysis. The authors compared the incidence of major wound bleeding and nonmajor wound bleeding (gastrointestinal, retroperitoneal, intracerebral, and epidural hematoma) with the use of various anticoagulants and placebo. The risk of total major bleeding was 3.46% with UH 2.2% with LMWH, and 0.56% with placebo and the difference was statistically significant ($p < 0.0001$).⁹ A recent review by Crowther and Warkentin quotes several meta-analyses and pooled analyses and concludes that major bleeding is uncommon with LMWH and UH, bleeding is less common when agents are given in prophylactic rather than therapeutic doses, and bleeding risk may vary with clinical circumstances.¹⁰ We believe that both agents have a good safety profile if appropriately used, pharmacokinetics of agents is considered, and the effect is monitored.

Conclusion

Prophylactic subcutaneous administration of UH might be complicated by a massive hemorrhage in a patient with multiple comorbidities, especially in an HIV-infected individual with preoperatively compromised liver function and cachexia. DVT prophylaxis with LMWH would be preferable since clearance of LMWH by saturable mechanism is negligible.⁸

Disclosure

The authors report no conflicts of interest in this work.

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