Life-threatening hemorrhage following subcutaneous heparin therapy

Jana Hudcova
Daniel Talmor
Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

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 as 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. 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.
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.²³ 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 1: Perioperative values of relevant blood tests |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Prooperative values             | Postoperative values | Event of hemorrhage | After protamine treatment | Discharge from the ICU |
| Htk (%)                        | PTT (22-35s)     | PT (10.4-13.1)   | PTT (23-35s)     | Htk (%)         |
| Preoperative values             | NA              | NA              | 12.5            | 13.2            |
| Postoperative values            | 47.4            | 14.5            | 14.7            | 15.0            |
| Event of hemorrhage             | 13.8            | 12.4            | 13.8            | 12.5            |
| After protamine treatment       | 10.1            | 27.7            | 10.1            | 27.7            |
| Discharge from the ICU          | 29.9            | 28.7            | 29.9            | 28.7            |

**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.
Subcutaneous heparin and life-threatening hemorrhage
cofactor II (HC) during the course of their disease. Treatment
with protease inhibitors like ritonavir has been reported as a
cause of thrombosis in this group of patients as well.

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 notice-
able 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 defi-
ciencies, 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 fibrino-
gen conversion to fibrin and are prolonged with low levels
of fibrinogen, qualitatively abnormal fibrinogens, or in pres-
ence 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
(epecially those with hemophilia A or B) develop inhibitors
to factors VIII or IX during the course of their disease.
Mixing studies were performed to rule our 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. 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 expla-
nation for bleeding in our patient. We carefully analyzed
possible triggering events. There was a certain chance of inad-
vertent 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 subcutane-
ous 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. Reticuloendothelial system (RES) and
endothelial cells represent the saturable mechanism while

| 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 |
renal elimination stands for nonsaturable or linear removal mechanism. Lower doses of UH are cleared by RES whereas kidneys are responsible for clearance of LMWH and higher doses of UH. The blockage of the phagocytic capacity of RES may prolong the half-life of UH significantly. 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). 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. 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.

**Disclosure**

The authors report no conflicts of interest in this work.

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