Staged Management of Heparin-Induced Thrombocytopenia for Renal Cavo-Atrial Cancer Removal on Cardiopulmonary Bypass

Salim Aziz[1], Shailendra Sharma[1], Jenna Aziz[2], James Gould[1], and Xiomara Fernandez[1]

[1]The George Washington University Hospital
[2]Howard University College of Medicine

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Abstract

Management of patients with acute heparin-induced thrombocytopenia (HIT) with cavo-atrial renal cancer requiring surgery on cardiopulmonary bypass (CPB) and possible deep hypothermia circulatory arrest is a challenge. A staged approach using Bivalirudin, plasmapheresis, and intravenous immunoglobulin (IVIG) was used to preoperatively de-escalate HIT guided by enzyme-linked immunosorbent assay (ELISA) and serotonin release assay (SRA). Intraoperatively heparin was used as the anticoagulant for CPB as DHCA was likely to be used to remove the atrio-caval tumor. Heparin is effective in preventing clots in the circuit during DHCA. To prevent HIT upon re-exposure to heparin during CPB, a bolus of a Cangrelor (reversible P2Y12 platelet receptor inhibitor) was given before heparin and during CPB whilst platelet activity was monitored using platelet reactivity units (PRU). Postoperatively, to prevent recurrence of HIT, plasmapheresis was used until SRA and optical density (OD) resulted. The patient had a successful outcome.

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Salim Aziz MD[1], Shailender Sharma MD[2], Jenna E Aziz MS[3], James Gould MD[4], Xiomara Fernandez MD[5]

1. Division of Cardiac Surgery, George Washington University Hospital, Washington DC, USA
2. Division of Nephrology, George Washington University Hospital, Washington DC, USA
3. Howard University College of Medicine, Washington DC, USA
4. Department of Anesthesia, George Washington University Hospital, Washington DC, USA
5. Department of Pathology, George Washington University Hospital, Washington DC, USA

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Corresponding Author:

Salim Aziz MD, FACS

Professor, Division of Cardiovascular & Thoracic Surgery

George Washington University

2175 K. St. NW. Suite C-100

Washington DC 20037

Phone: 202-775-5111

Fax: 202-775-5112

salimazizmd@gwu.com

INTRODUCTION:

Surgical management of cavo-atrial renal cancer using cardiopulmonary bypass (CPB) and deep hypothermia circulatory arrest (DHCA) can improve survival.[1] We present a patient with Stage IV renal carcinoma that invaded the inferior vena cava (IVC) with extension into the right atrium who developed acute heparin-induced thrombocytopenia (HIT). We "prepared" the patient preoperatively using a staged approach with Bivalirudin, plasmapheresis, and intravenous immunoglobulin (IVIG). The therapy was guided by results from both enzyme-linked immunosorbent assay (ELISA) and serotonin release assay (SRA) to de-escalate HIT. As intraoperative DHCA was planned, we used heparin for CPB. A bolus of Cangrelor was given before heparin and during CPB, using platelet reactivity units (PRU) to monitor platelet activity. Postoperatively, plasmapheresis was used until SRA and optical density (OD) resulted. The patient tolerated the procedure well and had an uneventful recovery.

Case Report:

A 71-year-old female with history of uterine carcinoma-sarcoma was found to have pulmonary embolism (PE) and a left renal mass invading her IVC with extension into the right atrium. (Figure 1) Biopsy of the renal mass showed clear cell carcinoma. Echocardiography showed moderate aortic stenosis and a bicuspid aortic valve. Coronary angiography showed no significant stenotic disease. After multidisciplinary discussion, we elected to proceed with surgical resection using CPB and possible DHCA.

IV heparin was initiated for PE; on day 8 of therapy, the patient's platelet count dropped to 120,000/uL from 306,000/uL. The HIT panel was positive by ELISA and SRA. Heparin was discontinued and Bivalirudin was started; by day 6, her platelet count returned to normal. (Figure 2) However, because the ELISA and SRA tests remained positive, surgery was delayed. In an effort to de-escalate HIT, plasmapheresis was started with trending of the HIT panel. Three sessions of plasmapheresis failed to convert the SRA, while EIA-IgG remained highly positive (2.43 to 1.33 OD units). (Figure 2) Two doses of IVIG (1g/kg) were administered. This dual approach resulted in normal platelet function (negative SRA) and lowering of OD measurements. (Figure 2) Therefore, the patient could now proceed with surgery.

Prior to surgery, Bivalirudin was discontinued. To protect against HIT upon re-exposure to heparin for CPB/DHCA, a combination of Cangrelor (bolus followed by infusion) with heparin was used following completion of abdominal and chest dissection. Cannulation sites for CPB included the ascending aorta, superior vena cava, and femoral vein.

Baseline and repeat measurements of PRU were done using the VerifyNow test. (Figure 3) A bolus of Cangrelor was given (30mcg/kg) followed by an infusion (4mcg/kg/min) for the duration of CPB. Ten minutes after Cangrelor administration, an IV bolus of heparin (300 units/kg) was administered to maintain an activated clotting time (ACT) $>$ 450 seconds. While on CPB, the tumor was extracted from the right atrium and IVC, and the left kidney was removed. The patient was then weaned off CPB without use of DHCA. Lastly, hysterectomy and bilateral salpingo-oophorectomy (BSO) were performed. A splenectomy was also performed after intraoperative splenic injury.

Postoperatively, two additional sessions of plasmapheresis were used (postoperative (POD) days 1 and 3) whilst waiting for results of a repeat HIT panel. Bivalirudin was restarted on POD 2, and the patient was transitioned to and discharged on Fondaparinux.

DISCUSSION

Type 2 HIT is an immune-mediated, prothrombotic, adverse reaction that occurs 4 to 10 days after exposure to heparin.[2] It is due to formation of IgG auto-antibodies against platelet factor (PF) 4 and heparin complexes that cause platelet aggregation and thrombocytopenia. The diagnosis is made using a combination of clinical assessment and laboratory tests, such as ELISA to detect IgG-specific PF4 antibodies and SRA.[3]There are no universally agreed "cutoffs" for defining antibody titers in HIT that confer a heightened risk of thrombosis. Some studies suggest an OD >1.0 leads to a higher risk for thrombosis, whereas others highlight the importance of antibody-mediated platelet activation, which may occur at values of OD >1.4.[4]

Direct thrombin inhibitors (DTI) such as Bivalirudin are used to treat HIT and as an alternative anticoagulation in patients with history of HIT who require cardiac surgery.[5] However, DTIs may be contraindicated in DHCA due to stasis, thrombotic risk, and unpredictable pharmacokinetics during the periods of circulatory arrest.

The effect of DTIs on PF4/heparin antibody titers and platelet function is not well established. In our case it took six days for the platelet count to normalize on Bivalirudin. However, both the ELISA (OD 1.366) and SRA remained positive. (Figure 2) Therefore, we initiated additional measures to de-escalate HIT by reducing anti-heparin antibody titers and improving platelet functional activity as there was a high likelihood of using a heparin-based regimen for DHCA during this complex surgery.

As depicted in Figure 2, despite three sessions of plasmapheresis, the OD remained elevated and the SRA stayed positive. Two sessions of IVIG resulted in a negative SRA and a further reduction in OD. These findings suggest the importance of performing platelet activation assays and EIA, when testing patient samples following interventions to de-escalate HIT and evaluate patient suitability for heparin re-exposure.

Therapeutic plasmapheresis (TPE) has been used to reduce heparin antibody titers quickly to allow use of heparin in patients with HIT.[3] However, plasmapheresis does not remove all anti-heparin HIT antibodies. Owing to a much larger volume of distribution, IgG is not removed as well as IgM.[6] In our case, after three sessions of TPE, the SRA still remained positive.

IVIG has also been used to treat HIT.[3] Intact IgG Fc fragments inhibit FcγRIIa-mediated platelet activation through competition by higher levels of plasma IgG. In our case, after IVIG treatments, repeat testing for platelet activation of SRA was in the normal range despite presence of EIA. This suggests that both platelet activation and EIA should be performed before proceeding with surgery requiring heparin re-exposure. (Figure 2)

Various agents have been used prior to re-exposure to heparin in HIT-positive patients requiring DHCA. These agents affect platelet activity and include iloprost, Abciximab, a glycoprotein IIb/IIIa inhibitor, and Cangrelor, a potent reversible P2Y12 platelet receptor inhibitor.[7-9] Cangrelor has rapid distribution, inhibits platelet aggregation in approximately two minutes and has a half-life of 3 to 6 minutes. It is not affected by blood stasis during DHCA, and its effects can be measured using VerifyNow.[10]

Intra-operatively, we used the combination of heparin and Cangrelor. Post-operatively, immediate HIPA and SRA levels were drawn. (Figure 2) Plasmapheresis was started on POD 1 since HIT panel levels would not be resulted until POD 3. The patient was extubated on POD 2 and recovered well thereafter. Bivalirudin was restarted on POD 2 and transitioned to Fondaparinux for long-term anticoagulation. There was no evidence of peri- or postoperative thrombosis. The cannulation and surgical approach we used permitted avoidance of DHCA.

CONCLUSION:

A staged approach was used to de-escalate acute HIT preoperatively in a patient with renal carcinoma requiring CPB. This was guided by monitoring of anti-heparin-PF4 antibody titers and platelet function. Prior to intraoperative heparin re-exposure, Cangrelor was used with PRU monitoring. Postoperatively, plasmapheresis and Bivalirudin were used and then transitioned to Fondaparinux for long-term anti-coagulation.

Figure Legends

Figure 1. Coronal MRI abdomen/pelvis

Figure 2. Platelet count, heparin-induced platelet antibody (HIPA), and serotonin release assay (SRA) are displayed from admission to 36 days. Red bold arrows: days plasmapheresis (TPE) given; red bold arrows. Black arrows: days IVIG given.

Figure3. Graph of P2Y12 platelet reactivity units (PRU) throughout the operation. PRU value < 180 indicates adequate platelet effect.

Author Contributions

Salim Aziz, MD - Lead surgeon, Operative strategy, concept, drafting article, revisions

Shailendra Sharma, MD - Critical revision, patient care viz plasmapheresis

Jenna Aziz, MS - Data collection, editing, revisions

James Gould, MD - assisted with patient management in OR, handled anticoagulation on bypass, data collection

Xiomara Fernandez, MD - Protocols to de-escalate HIT pre-operatively, revisions, data collection

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