CASE REPORT

Successful anticoagulation with fresh frozen plasma for cardiopulmonary bypass in a patient with heparin resistance: a cautionary tale

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SUMMARY

Heparin resistance (HR) is an increasingly common occurrence due to a greater awareness of the benefits of antithrombosis prophylaxis in hospitalised patients with low molecular weight and unfractionated heparin. Furthermore as more high-risk patients with prior heparin exposure undergo cardiac surgery we can expect to encounter more such cases. Adequate anticoagulation is essential for the safe conduct of any operation requiring cardiopulmonary bypass and is usually achieved with systemic heparinisation. We report a case of successful anticoagulation with the intraoperative administration of fresh frozen plasma in a high-risk coronary patient with HR and highlight the perils of unwitting overheparinisation in such cases. This case highlights the importance of clinical awareness of this phenomenon and the available alternative anticoagulants.

BACKGROUND

Adequate systemic anticoagulation is essential for any operation requiring cardiopulmonary bypass (CPB) to ensure no in vivo or extracorporeal circuit thrombosis. Anticoagulation is usually achieved with parenteral heparin. The standard heparin dose required is variable but typically 3–4 mg/kg (1 mg=100 IU heparin) and monitored with the activated clotting time (ACT). Heparin resistance (HR) is defined as the failure to achieve an ACT of at least 450–480 s after the standard dose administration.¹ HR is an increasingly observed phenomenon due to more high-risk patients with prior heparin exposure. We report a case of successful anticoagulation with fresh frozen plasma (FFP) in a high-risk coronary patient with HR and highlight the perils of unwitting overheparinisation.

CASE PRESENTATION

A 58-year-old man with dialysis-dependent end-stage renal failure was scheduled for coronary artery bypass graft (CABG) surgery for unstable (Canadian Cardiovascular Society—classes 3 and 4) angina. Preoperative echocardiography demonstrated a dilated impaired left ventricle (EF 30%) with mild-moderate functional mitral and tricuspid regurgitation. Coronary angiography revealed severe triple vessel disease; 80% ostial stenosis of the left main stem and chronic total occlusions of the circumflex and right coronary arteries. The patient had insulin-dependent diabetes mellitus, a previous inferior myocardial infarction and a

stroke. He underwent a triple CABG with autologous saphenous vein utilising CPB and a prophylactic preinduction intra-aortic balloon pump. Following sternotomy and harvest of vein conduit, heparin was routinely administered to facilitate anticoagulation for CPB. The patient's baseline ACT was 122 s and the standard heparin dose was administered but failed to achieve the target ACT. The ACT (initially 332 s, then 328 s, then 369 s and then 351 s, respectively) was refractory to three additional boluses of heparin. In total 60 000 IU (8.5 mg/kg) of heparin was administered; almost three times the weight-adjusted standard dose. A therapeutic ACT of 470 s was finally achieved and CPB instituted and maintained following the intraoperative administration of 4 units of FFP. The operative procedure conducted with moderate systemic hypothermia (32°C), was technically demanding due to a calcified aorta, but overall uneventful. Following weaning from CPB, systemic heparinisation was reversed with protamine. The corrected ACT was 130 s, not dissimilar to the preoperative baseline. The immediate postoperative haematocrit (27%) did not suggest excessive haemodilution.

The patient's chest was re-explored twice in the first 24 h following a surgery for excessive mediastinal haemorrhage despite prophylactic administration of a continuous tranexamic infusion postoperatively. His initial coagulation screen was normal (prothrombin time (PT) 18.9 s, international normalised ratio (INR) 1.26, activated partial thromboplastin time (APTT) 54 s and APTT ratio 1.8), however a subsequent screen was abnormal (PT 2.49, INR 1.89, APTT > 120 s and APTT ratio 3.8). On both occasions no surgical bleeding site was identified. In total the patient received three cycles of our local disseminated intravascular coagulopathy) regime (each cycle comprises 6 units of cryoprecipitate, 4 units FFP and 4 units platelets) over the ensuing first 36 h for persistent bleeding. The chest was 'packed' after the second re-exploration and the sternum formally closed 48 h later. The patient's recovery was initially good but he developed pulmonary sepsis due to a multi-resistant *Klebsiella* infection and died 10 days later.

DISCUSSION

Heparin is an intravenously administered anticoagulant with a dual mechanism of action; antithrombin III (AT-III) dependent and AT-III-independent. Preoperative exposure to heparin causes depletion

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of AT-III levels, which is thought to be the basis for HR.^{2,3} The precise mechanism remains unclear although successful anticoagulation with concomitant administration of AT-III or FFP lends credence to this theory. HR is generally termed as the failure to achieve an ACT of 450–480 s or greater, after administration of a standard heparin dose of 3–4 mg/kg (1 mg=100 IU heparin). The reported incidence is variable but as high as 22% in some cardiac patients.³ This phenomenon is becoming more frequent as more patients with unstable angina requiring urgent revascularisation within the same admission and more renal dialysis patients are offered surgery.

The principle action of heparin is to potentiate a thousand-fold, the anticoagulant effect of AT-III, an endogenous serine protease inhibitor which irreversibly binds to several coagulant enzymes; thrombin and factor Xa. Several retrospective studies and case reports have demonstrated the efficacy of FFP in prolonging the ACT and reducing the cumulative heparin dose required in patients with HR.^{4–6}

Alternative anticoagulants to heparin include danaproid, the leech-derived direct thrombin inhibitors such as lepirudin and bivalirudin, and the platelet glycoprotein IIb/IIIa receptor antagonist tirofiban. Danaproid is a factor Xa inhibitor used in cases of heparin-induced thrombocytopenia (HIT) or HR. However there is a higher risk of excessive bleeding due to its long half-life and resistance to protamine reversal. Danaproid should be considered in patients with associated multisystem disease and sepsis with an increased risk of HIT or HR. Bivalirudin is more effective and associated with less bleeding than heparin in patients who require percutaneous coronary revascularisation.⁷ Although its short half-life and a largely non-organ-specific independent elimination mechanism makes it an attractive alternative, the lack of a reversal agent and its cost precludes more widespread use.

The patient had a clear and definite history of prior heparin exposure. He received regular heparin boluses preoperatively for his renal dialysis. His dual antiplatelet therapy was stopped a fortnight earlier and he was started on daily prophylactic low-molecular-weight subcutaneous heparin (enoxaparin) 40 mg. Preoperative therapy with enoxaparin has been found to manifest with intraoperative HR in CABG patients.⁸ In retrospect, we should have anticipated earlier possible HR with this patient. Repeated boluses of heparin to achieve the target ACT as illustrated here may be unsuccessful and can result in inadvertent systemic over heparinisation. We believe this, coupled with suspected low endogenous AT-III levels, was a major contributory factor to the non-surgical coagulopathic bleeding encountered on both occasions the chest was re-explored. The two re-explorations and the 'open' chest invariably contributed towards the fatal pulmonary sepsis 10 days later, possibly exacerbated by a transfusion-related acute lung injury.

Limitations of FFP include its relative scarcity, the small risk of viral transmission, the large volume transfusion required and the fact it has to be thawed and hence is not immediately available intraoperatively. FFP may also be only effective in 50% of suspected HR cases hence an awareness and availability of alternative anticoagulants is vital.² Recombinant AT is a good ready-to-use alternative that can be reconstituted in minutes but is expensive. Our institution does not have synthetic AT.

Learning points

- ▶ Heparin resistance is an increasingly observed phenomenon hence an increased awareness by cardiothoracic clinicians is essential to ensure alternative anticoagulant strategies are rapidly considered and instituted early in such patients.
- ▶ Merely administering additional boluses of heparin may be ineffective and detrimental.
- ▶ Despite the eventual adverse outcome, this case demonstrates the efficacy of fresh frozen plasma, an established and inexpensive therapy when synthetic alternatives are unavailable.

Competing interests None.

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