Anticoagulation Management

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Case Vignette

A 75-year-old man who requires coronary artery bypass graft surgery with cardiopulmonary bypass is fully anticoagulated with heparin with a target activated clotting time (ACT) of 480 s using celite-mediated activation of the coagulation pathway. The anesthesiologist started with a regular bolus of heparin of 300 IU/kg, which resulted in an ACT of 300 s. More heparin was administered, and after two additional boluses an ACT of 450 s was achieved. The patient is diagnosed with heparin insensitivity. The surgical team decided to start surgery, and heparin was added to the priming solution (5000 IU). During the procedure, several doses of heparin needed to be administered in order to maintain the target ACT. At the end of the procedure, heparin is neutralized by a dose of protamine calculated from the total dose of heparin that is administered during surgery. After protamine administration, the patient shows microvascular bleeding. The anesthesiologist is not in favor of an additional bolus of protamine, since protamine has anticoagulation properties by itself. Rotational thromboelastometry shows a reduced clot firmness in the fibrinogen assay, and after a bolus of fibrinogen concentrate the oozing is stopped.

Why Is It Important?

In order to prevent intraoperative hemostatic activation, patients receive unfractionated heparin (UFH) for full anticoagulation during cardiopulmonary bypass (CBP) or partial anticoagulation during off-pump coronary artery bypass graft surgery. The

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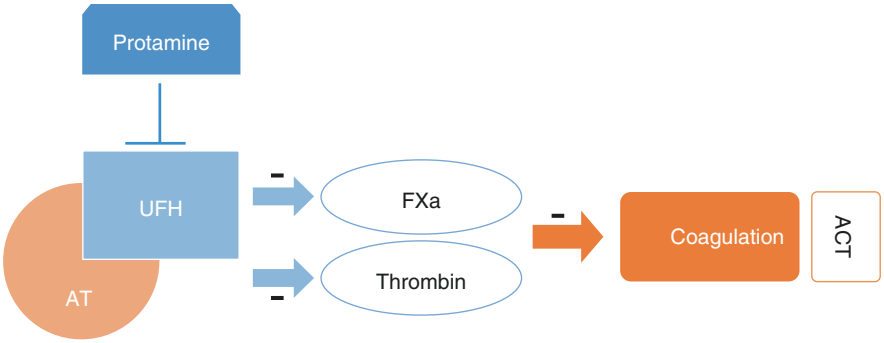

Fig. 11.1 The binding of heparin and antithrombin results in an inhibition of factor Xa and thrombin, leading to a reduction of the coagulation capacity. The effects of heparin on the coagulation are monitored by the activated clotting time. *UFH* unfractionated heparin, *AT* antithrombin, *ACT* activated clotting time

body itself also produces heparinoids to prevent thrombin formation, but these concentrations are insufficient to compensate for intraoperative massive hemostatic activation. Heparin consists of a mix of long and short chained molecules, with a high affinity for thrombin (long chain) or factor X (short chain). It binds to antithrombin, thereby inhibiting the activated clotting factors II, VII, IX, X, and XI. Heparin further binds to the endothelial glycocalyx and plasma proteins affecting its biological availability and half-life. Heparin is neutralized by protamine, which is administered at the end of CPB (Fig. 11.1).

Heparin and protamine are routinely used during cardiac surgery with CPB. Heparin dosing is usually based on the whole-blood activated clotting time (ACT), but some patients have difficulties to achieve a sufficient ACT due to heparin insensitivity. Moreover, the ACT is not sensitive enough to titrate protamine, while excessive protamine itself may exert anticoagulant effects. Correct heparin and protamine dosing therefore requires insight in the characteristics of both drugs and the limitations of available measurement methods. The purpose of this chapter is to discuss anticoagulation strategies during cardiopulmonary bypass, including heparin and protamine management, monitoring tools, and alternatives for heparin.

Heparin Anticoagulation and Monitoring

The ACT is based on activation of the intrinsic coagulation pathway by celite or kaolin, which both exert different test reference values. The dosing of heparin is commonly based on body weight (300–600 IU/kg), followed by additional doses when the ACT drops below target clotting times. Target clotting times may vary between 300 and 600 s, depending on the type of surgery, the use of a closed or open circuit, biocompatible coating of the circuit, and local protocols. The ACT is relatively inaccurate, as its results are influenced by hemodilution, temperature, and

platelet count. There is no correlation between the plasma heparin concentration and ACT [1].

Alternatively, a heparin dose–response test may be used to determine the sensitivity of a patient for heparin, which may differ due to previously used medication, a variation in antithrombin levels, or the potency of heparin. In particular, lower levels of antithrombin reduce the effect of heparin on thrombin, leading to a relative resistance to heparin. In some patients this might be solved by the administration of additional heparin or fresh frozen plasma. Alternatively, antithrombin is administered to increase heparin sensitivity which is indicated in patients with antithrombin deficiency, aiming for plasmatic levels of antithrombin of 80%. Administration of 50 IU/kg of antithrombin increases the plasmatic concentration to approximately 120% in a heterozygous, antithrombin deficient patient with an initial plasmatic concentration of 50% [2]. It is however not recommended to prophylactically administer antithrombin to reduce bleeding following CPB [3].

There are several publications that aimed to find a reduction in postoperative bleeding and transfusion requirements by individual heparin titration using monitoring devices like the HMS/HepCon™ (Medtronic, Minneapolis, MN, USA), Hemochron RxDx™ (Accriva Diagnostics, San Diego, CA, USA), or anti-Xa measurements in addition to the ACT. When a HepCon™-based heparin and protamine management was compared to a conservative anticoagulation strategy in CABG patients there was no difference in total heparin use between groups, while protamine requirements decreased in the HepCon™ group [4]. There were however no clinically relevant differences in 12-h blood loss and transfusion requirements between groups [4]. Others showed that the use of a HepCon™-based strategy increased heparin dosing and reduced protamine requirements in valve surgery when compared to an ACT-based strategy, with more 24-h blood loss in the control group [5]. A third study showed that heparin and protamine dosing and bleeding rates did not differ between a HepCon™ and ACT-based anticoagulation strategy [6]. All studies were relatively small and lacked clinically relevant primary endpoints, and larger multicenter studies are warranted to determine the added value of individual heparin and protamine titration.

In addition to the ACT and individual heparin dosing, statistical models have been developed to calculate heparin and protamine requirements during surgery. Studies evaluating the effectiveness of these models on clinically relevant endpoints are however lacking [7].

Heparin Rebound

Heparin rebound is re-heparinization after adequate heparin reversal following cardiopulmonary bypass. This re-heparinization is caused by the release of heparin from the endothelium and plasma proteins, and takes place when the patient is admitted to the postsurgical or intensive care ward. Unfortunately, most studies on this topic are relatively old, and focus on residual plasma heparin following cardiac surgery or the occurrence of postoperative bleeding in case of residual plasma

heparin. Only one study showed that continuous postoperative protamine infusion (25 mg/h for 6 h) to neutralize residual heparin resulted in reduced mediastinal blood loss when compared to control subjects who did not receive extended protamine infusion [8]. While protamine infusion resulted in a reduction in 24-h blood loss of approximately 100 mL, this was however not associated with a reduced transfusion rate. Blood heparin levels in the control group were the highest at 3 h following surgery, and normalized within 9 h postoperatively. The study was however limited by the possibility to administer additional protamine to normalize ACT values to pre-heparin values, which occurred more frequently in the control group and might have enhanced postoperative bleeding [8]. The administration of protamine to neutralize heparin may however lead to a contrary effect, since protamine exerts anticoagulation properties by itself. Other studies suggested that the clinical relevance of heparin rebound is limited, showing that heparin levels after surgery are insufficiently low to induce anticoagulation and bleeding [9, 10]. When heparin rebound is suspected, it is important to first measure heparin plasma concentrations rather than the blind administration of protamine.

Protamine

At the end of CPB, protamine is administered to neutralize heparin. Protamines are small basic, arginine-rich, positive charged proteins, and were formerly isolated from salmon sperm. Nowadays, protamine is increasingly produced through recombinant biotechnology. It binds to the anionic heparin in a 1:1 ratio, and has a rapid onset of action. Within seconds, a neutral protamine–heparin salt is formed. The protamine–heparin complex that is formed leads to dissociation of heparin from antithrombin, thereby restoring the procoagulant properties of blood. In parallel, the platelets produce platelet factor 4 (PF4), which also binds to heparin and contributes to the stability of the protamine–heparin complex. It is unclear how the neutral protamine–heparin complex is metabolized, and animal studies suggest a dual route through liver and kidneys.

Protamine has immunological and inflammatory properties, and may induce a response with allergy, hypotension, bradycardia, and pulmonary vasoconstriction as most frequently reported side effects. Patient risk factors for an anaphylactic response include treatment of diabetes mellitus with protamine-containing insulin and allergies for fish proteins [7].

Protamine is regularly dosed based on the initial or total administered dose of heparin throughout the procedure. However, protamine itself exerts anticoagulant effects through interference with pro-hemostatic pathways when excessively dosed [7, 11]. In particular, protamine interacts with platelet function, interferes with coagulation factors, and stimulates clot breakdown [7]. Interventions that may contribute to tailored protamine dosing include the use of heparin measurements, anti-Xa measurements, or computer-based dosing models. Inadequate protamine dosing may influence patient hemostasis and the risk for postoperative bleeding.

Several studies show that individual titration of heparin and protamine results in more heparin and less protamine administration compared to ACT-based strategies.

Protamine dosing based on the initial heparin dose results in a longer clotting time and microvascular bleeding when compared to protamine dosing based on the measured heparin concentration [12]. Others showed that a higher protamine-to-heparin (1.3) dosing ratio is associated with coagulation abnormalities, decreased restoration of post-protamine thrombin levels, and more postoperative blood loss when compared to a lower protamine-to-heparin dosing ratio (0.8) [13]. In contrast, a recent trial in CABG patients showed that a protamine-to-heparin ratio below 0.6 was associated with enhanced blood loss and transfusion requirements compared to patients subjected to a ratio exceeding 0.8, which is suggestive for residual heparin following surgery [6]. In many institutions, the initial ACT is compared to the post-weaning ACT to assess the heparin-neutralizing effect of protamine. Due to the inaccuracy of the ACT, this comparison should be valued with caution. Overall, it can be concluded that liberal protamine administration is unfavorable for the restoration of coagulation, and heparin measurements or calculations might prevent this.

Alternatives for Heparin

Alternatives for heparin or patients with a severe protamine allergy include direct thrombin inhibitors, such as bivalirudin. The only available method to reliably measure therapeutic levels of bivalirudin is the ecarin clotting time, although the ACT can also be used. A baseline ACT value is measured before bivalirudin administration, aiming for a target of an ACT that is 2.5 times the baseline during CPB. Bivalirudin is usually administered in patients with known heparin-induced thrombocytopenia. Bivalirudin has a short elimination half-life (25 min) and its elimination is mainly achieved by proteolytic cleavage and not influenced by impaired hepatic or kidney function [14]. Bivalirudin and heparin are equally safe and effective for systemic anticoagulation during cardiac surgery, without differences in blood loss [15]. However, as stasis should be avoided during bivalirudin, this anticoagulation therapy requires adjustments of perfusion approaches. Its use is, therefore, mainly restricted to patients with heparin-induced thrombocytopenia.

Implications for Daily Practice

Heparin and protamine are among the most frequently used drugs during cardiac surgery, but monitoring of the anticoagulation effect is still limited due to the gross results of the ACT and the influence of exogenous factors on the ACT. Patients with heparin resistance who require subsequent doses of heparin during extracorporeal circulation may therefore benefit from individual heparin titration, for instance, by using a heparin dose–response curve.

While heparin administration may be complicated by the sensitivity of the patient and the quality of heparin, one should also take the side effects of protamine into account. Protamine exerts anticoagulant properties that are mainly present when there is insufficient heparin available to bind. Overdosing of protamine may

therefore lead to disturbed coagulation and prolonged bleeding. In this case, a protamine titration curve might be helpful in determining the adequate protamine dose that will neutralize heparin.

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