Management of prekallikrein deficiency during cardiac surgery

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Dear Sirs,

The contact factor system includes factor XII (FXII), high-molecular-weight kininogen (HMWK), and prekallikrein (PK). Even in the absence of one of these factors, no bleeding tendency during surgery has been reported (1). This physiological system is rather thought to exert anticoagulant, profibrinolytic, pro-inflammatory, and anti-adhesive activities (2).

In vitro coagulation tests for heparin monitoring, such as the activated partial thromboplastin time (aPTT) and the activated clotting time (ACT), rely on the presence of contact activation factors to the extent that a deficiency in one of the contact factors renders heparin monitoring with these assays unreliable.

Cardiac surgical procedures requiring systemic anticoagulation have been successfully performed for decades using heparin. Heparin shares features of an ideal anticoagulant in that the onset of its activity is rapid, its anticoagulant action is readily reversed using protamine sulfate, and its activity can be conveniently measured using the activated coagulation time (ACT, normal value: 100–140 seconds [sec]) (3). Protamine administration has been associated with a spectrum of adverse effects: histamine-related hypotension, mild to severe anaphylactoid reactions, marked hypersensitivity, etc. Moreover, protamine has anticoagulant effects when given alone or in excess of heparin. The dose of protamine should therefore be carefully controlled based on the ACT (4).

It is current practice in many institutions, including ours, to administer a single bolus of heparin (300 UI/kg) in order to achieve the therapeutic ACT target (more than 300 sec for off-pump procedures and more than 400 sec for on-pump procedures) (5–7). ACT is then monitored during the surgical procedure, and additional doses of heparin are administered if needed. At the end of the procedure, the dose of protamine is adjusted in order to achieve an ACT value that approximates the pre-heparin level.

While little is known about the sensitivity of ACT to individual coagulation factor deficiencies, ACT prolongation due to contact factor pathway deficiencies has been reported (8–10), making it unsuitable for heparin monitoring during cardiac surgery.

A 50-year-old man, admitted to our institution for off-pump coronary bypass, was found to have a prolonged aPTT (140 sec, normal values: 23–33 sec) during preoperative screening. Correction of aPTT was obtained by mixing the patient plasma with normal plasma (50/50), suggesting a factor deficiency in the intrinsic pathway (normal plasma alone: 27.9 sec, mixed plasma: 28.4 sec). Surprisingly, FVIII, FIX, FX, and FXII levels were normal (78, 94, 113, and 94%, respectively) as were the von Willebrand factor levels (94%), and no inhibitors were found. The patient had no personal or family history of bleeding or thrombosis. Finally, correction of the aPTT was obtained by prolonged incubation (15 minutes [min] instead of 120 sec) of his plasma with cephalin, strongly suggesting prekallikrein deficiency (11). This deficiency was later confirmed by clotting assay as a severe deficiency in prekallikrein (<1%) whereas high-molecular-weight kininogen level was found to be normal (68%).

As a result of these findings, an ACT measurement was performed the day be-
fore surgery and showed a value greater than 300 sec, which prevented ACT being used for anticoagulation monitoring during surgery. In order to counter this, we transfused two units of compatible fresh frozen plasma (FFP) prior to surgery. ACT before FFP perfusion was 316 sec (Fig. 1). Four min after the end of the transfusion, ACT normalised, dropping to 140 sec. ACT measurements after each heparin administration (81, 90, and 101 min) were 204, 238, and 249 sec, respectively. At the end of the coronary bypass surgery, and immediately prior to protamine administration, the ACT measurement was 227 sec. After administering 40 mg of protamine, reversal of ACT was obtained (154 sec, Fig. 1). The patient did not experience any excess bleeding or thrombotic complications following surgery.

The aPTT remained normal during the four days following surgery, which may be accounted for by prekallikrein’s 35-hour half-life.

As an alternative to ACT, other authors (9, 12) have suggested monitoring heparin activity/concentration during cardiac surgery using an anti-Xa assay in patients with contact factor deficiencies. These assays are not available as point-of-care testing and must be performed in a haemostasis laboratory, postponing heparin dose adjustment. The sensitivity of aPTT and ACT methods to contact factor pathway deficiencies is known to vary widely, and although insensitivity is not clinically relevant in terms of bleeding, it can lead to confusion about a possible bleeding tendency and delays in surgery (11).

In conclusion, transfusion of FPP just prior to surgery is an original, simple, and secure method for correcting prekallikrein deficiency, which allows for heparin monitoring using ACT and without the need for anti-Xa measurements.

References