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Editorial

Antifibrinolytics

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Antifibrinolytics have been increasingly used during operations associated with high risk of bleeding. New research and understanding of coagulation and access to point of care coagulation monitors allow a goal-directed perioperative coagulation management strategy. Certain drugs, such as aprotinin (1) and hydroxyethyl starch solutions, have been temporarily suspended from the market (2, 3) because of safety concerns.

Recent transfusion guidelines recommend (Class 1A) antifibrinolytics for routine administration in cardiac procedures if there are no contraindications (4).

Fibrinolysis is a physiological process where the activated plasminogen removes excess fibrin and promotes better fibrin clot formation and wound healing. Tissue plasminogen activator (t-PA) and other activators of plasminogen are first line agents in lysis therapy. Inhibitors of this process act at the step where plasminogen is converted to plasmin, by reversely blocking the lysine binding sites of plasmin or by active inhibition of plasmin via serine protease inhibition. The drugs used for inhibition of fibrinolysis are the lysine analogues, tranexamic acid and ε-aminocaproic acid, and the serine protease inhibitor, aprotinin. Aprotinin also inhibits kallikrein and trypsin, and decreases the activation of neutrophils and platelets (5).

Inhibition of fibrinolysis reduces bleeding and blood transfusions in many types of surgery. Cardiopulmonary bypass (CPB) and cardiovascular surgery activate inflammatory pathways, coagulation cascades, and fibrinolysis. Additionally, hemodilution and hypothermia during CPB also have detrimental effects on coagulation. However, one-third of off-pump coronary bypass patients receive blood products and this percentage might be reduced by the usage of antifi-

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brinolytics (6). The recently-described regional hypercoagulable state which leads to thromboembolic events might also be prevented by the usage of antifibrinolytics (7). While antifibrinolytics are useful drugs in the management of optimal coagulation, it is not a drug for all purposes. In elective surgery, the first outpatient evaluation should ask about the type and combination of antithrombotic agents, the presence of drug eluting stents, inherited or acquired coagulation disorders or organ dysfunction, presence of anemia, and even religious considerations. The interruption of long half-life anticoagulant and antiplatelet drugs and the bridging with short term agents for the perioperative period should be discussed. The surgeons should ensure meticulous haemostasis and apply blood-sparing surgical techniques. Topical administration of antifibrinolytics is becoming common, but according to the consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) 2011 it is not recommended (8). Anesthesiologists should optimize blood conservation and cell-salvage strategies, and proper administration and titration of pharmacological agents to avoid coagulopathy. Intraoperative fluid management optimization to avoid hemodilution is also an important. Point-of-care instruments provide additional information about the coagulation state (activated clotting time, thromboelastography). These provide more detailed information about the hemostatic system, supporting patient safety (9, 10).

Aprotinin was considered the best pharmacological approach to blood conservation in cardiac surgery. As a result, the vast majority of studies on this subject used aprotinin and only few reports were available for the lysine analogues. In 2008, aprotinin was withdrawn from the market following the early release of the results of the Blood Conservation using Antifibrinolytics in a Randomized Trial (BART) study which found increased mortality associated with its use (11). An international consensus conference subsequently identified aprotinin as one of the few drugs that increases 30-day mortality after cardiac surgery (12). More recently, the BART study data have been independently re-analyzed by the European Medicines Agency and Health Canada, with both agencies recommending a lifting of the suspension of aprotinin (13, 14) suggesting that it can be used in non-complex cardiac surgery. While the benefits of aprotinin would seem to be greater in more complex cardiac surgical procedures, the effect on mortality and morbidity in this high-risk patient group has not been defined by randomized controlled trials with sufficient statistical power.

An updated re-analysis of the Cochrane Database has found no difference in mortality when aprotinin was compared with placebo control (6). Similarly, there was no difference in mortality if aprotinin is compared either to tranexamic acid or to epsilon aminocaproic acid. However, the risk of death was higher in aprotinin-treated patients when compared with both lysine analogues, if the BART study data were included, (relative risk 1,22; 95 % confidence interval: 1.08-1.39) (6).

Tranexamic acid and ε-aminocaproic acid seem not to increase the occurrence of thromboembolic events, but few studies have included relevant endpoints in their design and so the evidence base is incomplete (15). The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial is enrolling 4,600 cardiac surgical patients to definitively evaluate the risk of thrombotic complications in this setting (16). A retrospective study showed a two-fold increase of convulsive seizures in patients undergoing open-heart surgery even after propensity score adjustment. Administration of tranexamic acid is not recom-

mended in neonates and infants below 12 months of age (17).

Recent guidelines state that ε-aminocaproic acid and tranexamic acid reduce exposure to allogenic blood transfusions in patients undergoing on-pump cardiac surgery. These agents are recommended to be used routinely as part of the blood conservation strategy, especially in patients undergoing on-pump cardiac surgery (Class I, Level A) and also in high-risk patients undergoing off-pump coronary artery bypass (OPCAB) surgery (Class I, Level A). It is important not to exceed maximum tranexamic acid total dosages (50-100 mg/kg) because of potential neurotoxicity in the elderly and open-heart procedures (Class IIb, Level C) (8).

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