Editorial

Updates on Coagulation Management in Cardiac Surgery

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Perioperative coagulopathy is regularly observed in patients undergoing cardiovascular surgery and is associated with massive bleeding, increased need for blood products transfusion, and re-exploration for surgical hemostasis. All these factors will exert a negative impact on postoperative morbidity, mortality, and costs.1 Coagulopathy is related either to preoperative etiologies (e.g. anticoagulants, antiplatelet agents, and hereditary bleeding disorders) or to intraoperative factors (e.g. hemodilution, activation and consumption of coagulation factors and platelets, heparin administration, hypothermia, hypocalcaemia, metabolic acidosis, and excessive fibrinolysis).2 Both preventive and therapeutic measures are recommended for the perioperative management of coagulopathy. A cornerstone of bleeding reduction and blood product administration is the prophylactic administration of antifibrinolytic agents. On the other hand, the increased availability of point-of-care (POC) devices for use in the perioperative setting has allowed rapid bedside assessment of coagulopathy. This new approach enables physicians to adopt a goal-directed approach in which therapy specifically targets the underlying hemostatic pathology.3

Preventive measures

The first step of this preventive approach is the preoperative assessment of coagulation status, treatments that interact with coagulation, and identification of the risk factors that could lead to intraoperative coagulopathy. Platelet dysfunction is a major source of bleeding during cardiovascular surgery, especially in patients treated with antiplatelet agents. Although platelet function assays are available, their role in evaluating actively bleeding patients has not yet been established. The 2011 Update of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists’ Blood Conservation Clinical Practice Guidelines recommended preoperative platelet function testing to determine the best timing of surgery in patients treated with Clopidogrel (ClassIIb recommendation, level of evidence C).4 In a recent study, Mahla et al.5 evaluated a strategy based on preoperative platelet function testing to determine the ‘optimal’ timing for coronary artery bypass graft surgery (CABG) in patients treated with Clopidogrel.5 They observed that preoperative platelet function testing could be used to assess platelet function in Clopidogrel-treated patients and lead to a 50% shortened waiting period.

In the adult cardiac population, Karkouti et al.6 reported that 22% to 30% of patients scheduled for a cardiac surgery with cardiopulmonary bypass (CPB) were anemic. Anemia in this population was associated with an increased risk of acute kidney injury and increased incidence of early and late mortality.7 As a consequence, preoperative identification of anemia is now integrated into different multidisciplinary ‘patient blood management’ approaches.8 Although there is growing evidence that preoperative hemoglobin optimization is feasible using iron supplementation, with or without the administration of recombinant human erythropoietin (rhEPO), further studies are needed to better define the efficacy and the safety of this approach.9

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The other measure is the employment of autologous blood-saving methods. There are several methods for perioperative blood saving, including preoperative autologous blood donation, cell salvage, and retrograde autologous priming (RAP). Whereas preoperative autologous blood donation is no longer recommended, RAP is deemed vitally important. Indeed, RAP is readily possible to perform in most patients, while there are more limitations in the application of the other methods.

**Point of care**

POC is the milestone of coagulopathy management in cardiac surgery. Standard laboratory tests for coagulation are performed using plasma and usually take 30-60 minutes to be reported. In addition, standard laboratory tests only assess the initiation phase of clot formation and give no information on the amount of thrombin generated, the quality of the clot formed (amplitude), and the stability of the clot (fibrinolysis) (Figure 1). Conventional laboratory analyses in cardiac surgery include activated partial thromboplastin time (aPTT), International Normalization Ratio (INR), platelet count, and fibrinogen concentration. POC tests improve the quality of coagulopathy management, decrease costs, and reduce time to around 10 to 15 minutes.

The activated clotting time (ACT) test is a standard coagulation assessment in cardiac surgery with CPB. This test has a high sensitivity but a very poor specificity. Indeed, most anticoagulants (e.g. Aspirin, Clopidogrel) and factors such as low platelet count and dysfunction, and clotting factors deficiency didn’t uniformly altered ACT. This leads to a high risk of inadequate management.

Thromboelastography is a dynamic qualitative and quantitative evaluation of clot formation that consists of three stages: clot initiation, clot firmness, and clot stability (fibrinolysis). Performing thromboelastography via the viscoelastic POC technique is feasible using two very similar devices, namely TEG® (Haemoscope Corporation, Niles, IL) and ROTEM® (TEMs International GmbH, Munich, Germany), both of which are increasingly employed in clinical practice. Although viscoelastic methods are very helpful, they do not obviate the need for other POC techniques that allow platelet function assessment (e.g. aggregometry). Platelet function monitoring has been integrated into some algorithms. However, there is a paucity of evidence to support the routine use of these devices. As much as POC techniques are potentially helpful in the diagnosis of coagulopathies, their role as predictors of coagulation disorders is more than controversial.

Figure 1. Schematic representation of aPTT/PT on normal and abnormal thrombin generation curves and on rotational thromboelastometry (ROTEM®)
Therapeutic measures: the stepwise algorithm-based approach

The first step is to maintain or restore optimal physiologic conditions for hemostasis: body core temperature (> 36°C), blood pH (> 7.3), ionized serum calcium (> 4 mg/dL), and hematocrit concentration (> 25%). Beside POC, the algorithm-based approach plays a pivotal role in the management of coagulopathy and hemostatic therapy. Confronting postoperative (post CPB) coagulopathy, we consider adequate Heparin antagonism, consistent clot stability/firmness by antifibrinolytics and blood products, and finally platelet dysfunction in a stepwise approach.

The plasmatic level of Heparin rather than the administered dose is appropriate for the determination of the ‘optimal’ protamine dosage. Studies show that usually excessive doses of protamine are administered in the clinical setting, which potentially increases coagulopathy and bleeding tendency.

Hyperfibrinolysis plays an important role in perioperative bleeding by causing clot instability and lysis. Antifibrinolytic agents are routinely administered to prevent excessive clot lysis by inhibiting the conversion of plasminogen to plasmin. Following the publication of the “Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population (BART) study”, Aprotinin was removed from the market, although it is still available for compassionate use. However, Karkouti et al. reported a retrospective single-center cohort study of 15365 cardiac surgical patients, 1017 of whom received Aprotinin and 14358 received Tranexamic acid (TXA). They noted that Aprotinin had a better risk-benefit profile than did TXA in high-risk, but not low- to moderate-risk, patients and suggested that its use in high-risk cases might therefore be warranted. In 2011, Health Canada concluded that the benefits of Aprotinin outweigh the risks when Aprotinin is used as authorized by Health Canada, followed by the European Medicine’s Agency in 2012. The complete story has important lessons about clinical trials’ designing and execution.

TXA and Epsilon-aminocaproic acid (EACA) are the most routinely used antifibrinolytic agents in cardiac surgery. Recent meta-analyses have reported that the prophylactic administration of antifibrinolytic agents is associated with a decrease in perioperative bleeding and the need for blood transfusion. Although TXA is routinely used, the ‘optimal’ dosage is not yet known. As the administration of TXA could be associated with a dose-dependent increased incidence of seizures in patients undergoing open-heart surgery, further studies are needed to assess the relationship between lower dosages based on pharmacokinetics, blood loss, and the incidence of side effects.

POC coagulation management with ROTEM® and impedance aggregometry is now frequently used to determine first-line therapy with specific coagulation factor concentrates such as fibrinogen concentrates and prothrombin complex concentrates (PCCs). In 2011, Gorlinger et al. retrospectively reviewed more than 3000 patients managed before and after the implementation of an algorithm-based approach. The authors observed that the implementation of a coagulation management algorithm using POC devices significantly decreased blood product requirements as well as the incidence of thromboembolic complications. In 2012, Weber et al. published the results of a prospective randomized trial in which they aimed to study the efficacy of hemostatic therapy guided either by conventional coagulation analyses or POC testing in coagulopathic cardiac surgery patients. Those patients in whom diffuse bleeding was diagnosed after Heparin reversal or increased blood loss during the first 24 postoperative hours were enrolled and randomized to the conventional group or the POC group. Hemostatic therapy algorithms in conjunction with POC testing reduced the number of transfused units of packed erythrocytes when compared with conventional laboratory coagulation testing. Moreover, POC-guided therapy was associated with decreased fresh frozen plasma (FFP) and platelet concentrates usage and costs as well as an improved clinical outcome.

In comparison with FFP, synthetic products are advantageous inasmuch as not only do they have lower volumes, possibility of rapid infusion, and risk of infection but also they obviate the need for cross-matching. Nevertheless, physicians should keep in mind that the amount of FFP needed to obtain a significant increase in coagulation factors has been reported to be up to 30 ml/kg, which could be associated with a high risk of transfusion-associated circulatory overload (TACO), acute respiratory distress syndrome (ARDS), and multiple organ dysfunctions (MODS).

Fibrinogen plays a central role in the prevention and treatment of acquired bleeding in cardiac surgery. Fibrinogen is the first coagulation factor reaching critically low levels during major bleeding. Cryoprecipitate is the main source of supplemental fibrinogen in North America. In Europe and Asia, fibrinogen concentrate has been approved for clinical usage. Fibrinogen concentrate is a human product which is commercially available as a lyophilized powder. The dosage of fibrinogen in each 50 ml vial of concentrate is constantly around one gram (900-1300 mg) or 20 g/L; accordingly, it is very different from the amount of fibrinogen in each unit of FFP, which ranges from 1 to 3 g/L.

On the one hand, it has been shown that low preoperative plasma levels of fibrinogen are associated with excessive bleeding after cardiac surgery. On the other hand, the critical level of plasma fibrinogen that could trigger supplementation in bleeding patients has been challenging in recent years. First, the recommended threshold by the American Society of Anesthesiologists was 80 to 100 mg/dL while it was recently changed to 150-200 mg/dL by the European Society...
of Anaesthesiology31 and expert opinions.37

It is possible to individualize the dosage of fibrinogen concentrate to be administered based on the initial plasmatic fibrinogen level and the extent of bleeding. It is, however, important to know that the total required dose is usually much higher than 1-2 g, recommended as the initial dose.37 Each vial of 1g fibrinogen concentrate increases the plasma fibrinogen level by 30 mg/dL.32,42 Thus, as it can be expected, the median dose of supplementary fibrinogen concentrate in bleeding cardiac patients ranges between 6 and 8 g.37 This huge dose was recently used by Rahe-Meyer et al.,44 who reported in a prospective trial that hemostatic therapy with fibrinogen concentrate in patients who underwent aortic surgery significantly reduced the transfusion of allogeneic blood products.

However, the use of factor concentrates as first-line therapies is still a matter of intense debate and further studies are urgently needed to define the behavior of fibrinogen levels during and after cardiac surgery, relationship between low fibrinogen levels and postoperative bleeding, adequate dose for fibrinogen supplementation, and efficacy and safety of fibrinogen concentrate supplementation.45 A recent pilot study showed that giving fibrinogen in the initial stages of bleeding provided better coagulation state compared to supplemental platelet.46 This study reconfirms the important role of fibrinogen in platelet aggregation.37

Prothrombin complex concentrate (PCC), which has been used principally to reverse Warfarin, depending on the product, contains factors II, VII, IX, and X as well as proteins C and S and Antithrombin and Heparin in various commercial brands.13 PCC is probably an appropriate substitute for FFP after adequate supplementation of fibrinogen. Currently, there is no consensus on the dosage and timing for the administration of PCC, and the increased risk of thromboembolic complication should always be balanced for the administration of PCC.37 With regard to single factors such as recombinant factor VIIa (rFVIIa) and factor XIII, studies have shown that these factors have low efficacy in coagulation management.47, 48 Since a recent meta-analysis reported that rFVIIa increases the risk of thromboembolic events,49 rFVIIa should only be considered in cases of massive uncontrolled bleeding after the administration of routine hemostatic therapies.50

Considering developments in equipment, medications, and diagnosis such as POC techniques, algorithms will undergo constant changes and guidelines will be revised extensively. Further investigations are still required to know about the optimum usage of POC devices, best algorithms for coagulation management, and best approach for the administration of coagulation factors.

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