Blood is thicker than water: coagulation challenges in the perioperative period

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Abstract

This manuscript serves to highlight some novel approaches to perioperative coagulation abnormalities and to address unanswered questions.

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Does a low haematocrit increase bleeding?

There has been a suggestion that a low haematocrit contributes towards coagulopathy. Iselin et al examined in vitro isolated low haematocrit and bleeding tendency.[1] Using a normal platelet count, clotting factors, and a low haematocrit, they tested the viscoelastic properties with a thromboelastogram (TEG®). Their results reflected an increase in coagulability in keeping with the properties of a crystalloid solution which they used in the reconstitution of a lower hematocrit. Darlington et al found a strong correlation between a low haemoglobin, platelet count and fibrinogen level with bleeding.[2]

Point-of-care devices

It takes at least 30 minutes for results to be obtained with laboratory coagulation assessment tests. Plasma is used to evaluate whole blood and endothelial processes. The newer point-of-care devices, ROTEM® and TEG®, assess the viscoelastic processes of coagulation by thromboelastometry and thromboelastography.[3-6]

The ROTEM®, by using different types of new reagents, can be used to evaluate the intrinsic pathway (INTEM®), the extrinsic pathway (EXTEM®), fibrinogen activity (FIBTEM®), heparin activity (HEPTEM®) and aprotinin effect (APTEM®). Thrombocytopenia can be diagnosed with the EXTEM®-A.

The TEG®, with an interpretation of the maximum amplitude, reation time, coagulation time and clot strength, can be used to evaluate platelet function, factor activity and clot lysis.[3-5] The Multiplate®, a TEG® modification, can be used for platelet mapping to measure platelet aggregation in antiplatelet therapy. The VerifyNow® measures the platelet reactivity degree in patients undergoing treatment.[4,5] These tests cannot be used to predict postoperative bleeding, but can be used to diagnose and guide treatment of the underlying cause of coagulopathy.

Fibrinogen concentrate, prothrombin complex concentrates and recombinant factor VII

Fresh frozen plasma (FFP) contains ± 250 mg in 100 ml of fibrinogen, while cryoprecipitate contains ± 225 mg in 15 ml (1 g of fibrinogen in five units of cryoprecipitate). Fibrinogen concentrate has a predictable dose per vial with a long shelf life (900-1 300 mg/vial), less side-effects and is not blood group-specific.[5-9] A dose of 7.6-mg/kg fibrinogen is needed to increase the FIBTEM® by 1 mm.[3,4]

Prothrombin complex concentrates (PCCs) are produced in 3-factor and 4-factor formulations. The 4-factor PCC contains factor VII additionally to factor II, IX and X. Recombinant factor VIIa was licensed to treat haemophilia patients with antibodies. It is widely used off label for massive haemorrhage from surgery and anticoagulants. It can be used in combination with 3-factor PCC.[5-9] Thromboembolic phenomena and thrombosis are common side-effects.

Pharmacological procoagulation therapy

The protamine prescription for the reversal of heparin often overlooks the elimination and metabolism factor.[10-11] More than adequate amounts of protamine lead to increased bleeding. Although protamine has been postulated to activate platelets, affect clot initiation time and clot kinetics, the real mechanism is not fully known. Ainle et al have suggested that it downregulates thrombin generation by inhibition of factor V activation.[11]

Tranexamic Acid Epsilon Aminocaproic Acid (EACA) are used to treat hyperfibrinolysis by competitively inhibiting the conversion of plasminogen into plasmin. Tranexamic acid is available orally, as a mouthwash and in intravenous preparations.[12] The oral dose is 15-30 µg/kg given two hours preoperatively, and every 6-8 hours over 7-10 days.

Desmopressin Acetate (DDAVP®) stimulate the endogenous release of von Willebrand factor and factor VIII in patients with haemophilia A and von Willebrand disease. It has no effect on patients with haemophilia B.[12,13] It can be used subcutaneously or intravenously in doses of 3 µg/kg one hour pre-procedure intranasally in a dose of 150 µg in a 50-kg patient, and 150 µg in each nostril in a ≥ 50-kg patient. Fluid restriction in 24-hour post-administration assists with a reduction in the risk of hyponatremia. DDAVP® may cause tachycardia, headaches, abdominal cramps and hypotension.

Premarin® increases levels of fibrinogen and fibrinogen activity and increases plasminogen antigen and activity. It was shown to reduce the volume of postoperative bleeding by 37% (ml/kg), when compared to the control group, without any complications in paediatric patients undergoing scoliosis surgery.[14] Premarin® was shown to reduce bleeding to 50% below pretreatment values over a few days in patients with renal failure, platelet dysfunction and clinical bleeding.

Aprotinin is now only used in patients at very high risk of bleeding owing to the risk of cardiovascular events observed during the Blood Conservation Using Antifibrinolytics in a Randomised Controlled Trial.[12] More research is underway to examine these facts closely.

Local haemostatic mechanisms in the form of tissue glues, include Surgicel®, Gelfoam®, Lyostpt® and Ankaferd Blood Stopper®.[15] Newer bioagents are entering the market.[16]

Anticoagulants in the perioperative period

Warfarin should be stopped seven days preoperatively and recommenced soon postoperatively if there is no risk of bleeding.[5-9,17] FFP (10-30 ml/kg) is used to reverse the effects of warfarin. With the use of point-of-care devices, PCC dosages can be used more predictably. Four-factor PCC (25 IU/kg) can be used if EXTEM®-CT is > 80 seconds or TEG® R-time is > 10 seconds.

Unfractionated heparin has a half life of 40 minutes. It is traditionally monitored using activated thromboplastin time (APTT) or activated clotting time.[18] Low-molecular-weight heparin (LMWH) has an anti-factor Xa to anti-factor IIa ratio of up to 4:1 in commercial preparations. It cannot be monitored with the use of APTT.[18] The HEPTEM®-directed protamine administration is an option.

Antiplatelet drugs

Clopidogrel has a half-life of four hours, but has to be stopped 5-7 days preoperatively because of irreversible platelet inhibition.[18,19] The glycoprotein IIb/IIIa agents have short half-lives, with a return to > 50% of platelet activity ranging from 4-48 hours, allowing bridging therapy after the cessation of clopidogrel. EXTEM®-A-measured thrombocytopenia (< 40-mm) and TEG-Max® (< 50-mm) guided platelet transfusion can be used as guided antidote therapy.[18,19]

Thrombin inhibitors

Rivaroxaban has a renal clearance of 80% and a half-life of 14-17 hours. Thrombin time is a sensitive monitor of antithrombin activity, although it is not accurate with extreme dosages.[18,20] There is a curvilinear relationship between dabigatran and APTT. International normalised ratio (INR) is also not useful. The Hemoclot® direct thrombin inhibitor assay has been used for the quantitative measurement of dabigatran. Ecarin clotting time, although it has limitations, can also be used to measure the activity of direct thrombin inhibitors.[20] Gastric lavage, activated charcoal and dialysis can be utilised in emergency situations. Recombinant factor VIIa (1 mg/kg) or activated PCC (40-80 U/kg) might have antidote activity.

Factor Xa inhibitors, rivaroxaban and apixaban, have half-lives ranging from 7-14 hours, and APTT cannot be used to monitor them. Prothrombin time correlates with the plasma concentrations of rivaroxaban, while INR relates in a dose-dependent manner with apixaban.[21] The plasma concentration of factor Xa inhibitors can be measured by assays of factor Xa activity. Four-factor PCC at a dosage of 50 IU/kg can be used to reverse effects.[21]

Bleeding in the trauma patient

The use of a "coagulation box" by Hilbert et al resulted in massive amounts of blood products needing to be used in a haemoglobin-driven algorithm, with a high mortality outcome.[22] This study is in clear contrast with the blood conservation principles advocated by both the Society of Thoracic Surgeons/Society of Cardiovascular

Anesthesiologists and European guidelines.[18,23] The APTEM® can be used to measure hyperfibrinolysis associated with massive bleeding, whereas the EXTEM®-A measures thrombocytopenia.[3-6] The hypofibrinogenemia, which follows massive bleeding, can be shown on the FIBTEM® or with kaolin-TEG® α angle < 52 degrees. The Multiplate® showed that platelet aggregation induced by collagen was lower in high bleeding patients.[3-6] The debate continues as to whether or not a higher FFP to packed red blood cell ratio should be used. The military results of early plasma and platelet transfusion are promising.[24-26]

Bleeding in cardiovascular patients

There are multifactorial causes of coagulation problems in cardiovascular patients. Fibrinogen is the first to reach critically low levels in the perioperative period, with a decrease of up to 40%. FFP, cryoprecipitate or fibrinogen concentrate, up to doses of 6-7 g, guided by FIBTEM®-CF, increases of 1 mm per 7.6-mg/kg fibrinogen dose, is used. Four-factor PCC (25 IU/kg) can be used if EXTEM®-CT is > 80 seconds or TEG® R-time is > 10 seconds.[5,6,9,12,18-21,27] The FIBTEM®, as guidance towards transfusion in one study, reduced the number of units used, sevenfold (2.5 vs. 16.4 units).[5,6,9,12,18-21,27]

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