

Perioperative Coagulopathy and the Clinical Implications.

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ABSTRACT

Perioperative bleeding as conceived in this review refers to the clinical scenario whereby there is impairment of blood coagulation leading to prolonged or excessive bleeding, accompanying trauma or surgical exposure. Aetiology of bleeding disorders could be classified under the following subheadings: vascular disorders, Thrombocytopenia, Platelet function defects, Coagulation factors disorder(s). Primary haemostasis is initiated or triggered by the release of tissue factor at the site of injury leading to generation of small quantity thrombin, sufficient to activate platelets leading to the formation of prothrombin complex. The ability of FXa to activate FVII creates a link between the extrinsic and intrinsic coagulation pathways; leading to the generation of sufficient thrombin to convert fibrinogen to fibrin which organizes platelet plug to indissoluble clots (Secondary haemostasis) or thrombus formation. A balance is required between haemostasis, thrombosis and fibrinolysis to prevent perioperative coagulopathy. Whenever positive findings in the history and physical examination suggests an increased risk of significant bleeding, then it is more cost effective to carry out routine screening tests of coagulation. Specific coagulation tests used routinely has longer turnaround times and is not appropriate in the perioperative setting. Current recommendations for the prevention of massive bleeding in the perioperative setting; requires communication of appropriate treatment plans in a multidisciplinary setting, intraoperative monitoring, the treatment of underlying disorder, and replacement therapy with blood products. As point-of-care diagnostics becomes available in emergency areas, timely targeted intervention for haemorrhage control will result in better patient outcomes and reduced demand for blood products.

Keywords: coagulopathy, Perioperative, Clinical implications.

INTRODUCTION

Perioperative bleeding as conceived in this review refers to the clinical scenario whereby there is impairment or derangement of blood coagulation leading or resulting in prolonged / excessive bleeding, accompanying trauma or surgical exposure.

Haemostasis is traced from the primitive man's realisation that unchecked bleeding would lead to death.^[1] The prevention of Blood loss from damaged blood vessels and maintenance of blood flow in the circulatory system is an essential feature of life and homeostasis.^[2]

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History of coagulation started around 400BC with Hippocrates when he noticed that blood of wounded soldier congealed as it cooled and also bleeding from small wound stop as skin covered

the wound. Aristotle noted that blood cooled when removed from the body and also initiates decay.^[3] Mercurialis in 1627 believe that blood clot in vein at body temperature.

William Hewson in 1770 challenge the cooling theory and believe that air and lack of motion was responsible for clotting. He named plasma coagulable lymph and perform the first clotting time.^[3]

Paul owren 1944 identified factor IV and Loeliger in 1952 identified factor VII.

In 1955 Ratnoff and Colopy identify a patient John Hageman (XII) that died of a thrombotic event in 1957, factor X was discovered by Prower (a woman) and Stuart (a man).

Bizzozero in 1882 discovered platelet. Haemophilia was known as early as 200AD, but was identified in contemporary times at the beginning of the 19th century. The discovery of the anti-haemophilic globulin (AHG) in the middle of the 20th century led to the production of cryoprecipitate and FVII and FIX concentrates.^[4]

Eric Adolf von Willebrand in 1924 investigated a family suffering from a bleeding disorder named (VWD) which was apparently different from haemophilia. By the end of 1960 vWD was accepted as a combined deficiency of FVIII and

platelet adhesion factor, Jerry Koultz provided evidence that both are linked but separate molecules. VWF is responsible for collagen binding, platelet glycoprotein 1b binding, and FVIII binding.^[4]

Patient's with Glanzmann thrombasthenia were found by Alan Nurden in the 1960's to lack two major platelet surface glycoprotein's (GP's) which mediates platelet adhesion and aggregation. Subsequent studies by Alan defined the function of the GpIIb – IIIa complex, known as integrin alphaIIb beta3, in binding fibrinogen and other adhesive proteins on activated platelets and formation of the protein bridges that joins platelets together in the platelet aggregate.^[4]

Also patients with Bernard- Soulier Syndrome has macro thrombocytopenia and absence of Gp1b; which interacts with VWF and mediates platelet attachment to injured sites in the vessel wall.^[4]

The plasminogen-plasmin (fibrinolytic) system consists of several serine proteases and their inhibitors involved in fibrinolysis, embryogenesis, cell migration, wound healing and pathogenesis of many diseases including atherosclerosis, obesity, cancer, autoimmune disorders and neuronal degeneration.^[2,4]

PATHOPHYSIOLOGY

The haemostatic response to injury and surgery requires interactions of the damaged vessel wall, platelets and the plasma coagulation proteins (Factors-F).^[2,5]

Fibrin clot formation by the activation of the tissue factor pathway (TFP) in response to tissue injury or surgery is the dominant haemostatic mechanism under normal physiological conditions. In order for haemostasis to occur von Willebrand factor (from platelet alpha granules, sub endothelial connective tissue, and megakaryocytes) must act as a bridge between platelets surface glycoprotein (GPIb-IX-V) and exposed collagen fibrils from injured vessels leading to platelets de-granulation and release of Ca^{2+} , ADP, serotonin, lipoproteins, phospholipids, arachidonic acid and thromboxane A (TXA₂), which causes vasoconstriction and platelet aggregation, adhesion, and formation of primary haemostatic or platelet plug.^[6]

Primary haemostasis is initiated or triggered by the release of tissue factor at the site of injury leading to generation of small quantity thrombin (limited by TF pathway inhibitor), sufficient to activate platelets leading to the formation of prothrombin complex (which consists of TF-FIII, FVII, Ca^{2+} , FVa, Xa, FII). The ability of FXa to activate FVII creates a link between the extrinsic (TFP) and intrinsic or the contact system coagulation pathways (consisting of prekallikrein, HMWK, bradykinin, VLDL's, oxidized LDL's and clotting

factors XII, XI, X, VIII, IX); also TFIII and FVIIa can activate FIX- leading to the generation of sufficient thrombin to convert fibrinogen to fibrin which organises platelet plug to indissoluble clots (Secondary haemostasis).^[2,6,7]

Plasmin (formed from plasminogen by the action of thrombin, 'tissue-type Plasminogen activator's t-PA and "urokinase-type Plasminogen activator" u-PA) lyses fibrin and fibrinogen; producing fibrin degradation products (FDP), which inhibits thrombin- discouraging clot formation. Deficiency of any of t-PA and u-PA or both promotes fibrin/thrombus formation, which might lead to thrombosis in the surgical patient. Disseminated intravascular coagulation (DIC) may result from increased generation of thrombin due to increased thromboplastin (TPL) activity without adequate tissue factor inhibitory (TFI) pathway activity- leading to uncontrollable fibrin generation and lysis; resulting in consumption of coagulation factors including fibrinogen with resultant coagulation failure.

Fibrin stabilization is catalysed by thrombin, XIIIa, and calcium, to produce the definitive clot to achieve haemostasis.^[2,6,7]

Platelets localise coagulation to the haemostatic thrombus and protect coagulation enzymes from inhibition by both plasma and platelet thrombin inhibitors thereby preventing disseminated intravascular coagulopathy DIC.^[7,8]

The tendency of blood to clot is balanced in vivo by reactions that prevent clotting inside the vessels and or breakdown any clots that do form. These reactions include the balance between the aggregating effect of the platelet thromboxane A₂ and the anti-aggregating effect of platelet prostacyclin. In addition, circulating protease inhibitors e.g. Anti-thrombin III, facilitated by heparin binds to serine proteases (e.g. thrombin, thereby inhibiting factors IX, X, XI, and XII) in the coagulation system, blocking their activity as clotting factors. In addition, thrombomodulin (a thrombin- binding protein, produced by endothelial cells) complexes thrombin (thrombomodulin-thrombin complex) activates protein C (APC), coupled with the co-factor protein S, inactivates factors FVa, FVIIIa, discouraging clot formation.^[2,6]

Deficiencies of thrombin inhibitors can lead to thrombosis, DVT and PE. Other pathological states as in hyperlipidaemia and bacteria invasion can lead to thrombosis, by the activation of the intrinsic coagulation cascade. A balance is required between haemostasis, thrombosis and fibrinolysis.^[2,6]

Aetiology of bleeding disorders could be classified under the following subheadings:

Vascular disorders- Hereditary haemorrhagic telangiectasia is an inherited vascular disease while

acquired causes are simple easy bruising, senile purpura, purpura associated with infections, hench-schonlein syndrome, Scurvy, and CT disorders.^[6]

Thrombocytopenia (low platelet count)- causes are enormous and includes failure of platelet production e.g. selective megakaryocytes depression from drugs, chemicals and viral, bone marrow failure, cytotoxic drugs, radiotherapy, aplastic anaemia, leukaemia, myelodysplastic syndrome, myelosclerosis, marrow infiltration with CA or Lymphoma, multiple myeloma, anemia and HIV infection. Increased consumption could arise from immune diseases like autoimmune (idiopathic), drug induced, SLE, infections e.g. HIV and viral, heparin, post transfusion purpura, and DIC. Abnormal distribution from splenomegaly and dilutional loss from massive blood transfusion.^[6]

Platelet function defects (thrombocytopathia) - could be hereditary as seen in thrombasthenia (Glanzmann's disease), bernard-soulier syndrome, and storage pool dx or acquired as seen in aspirin therapy, hyperglobulinemia, myeloproliferative disease, uraemia, and heparin therapy.^[6]

Coagulation factors disorder(s): could be hereditary- as seen in haemophilia A, haemophilia B, and Von-Willibrand's disease, acquired Vitamin K deficiency, haemorrhagic disease of the newborn, Liver disease, DIC, auto antibodies, over dosage of anticoagulant, and massive transfusion syndrome. Congenital deficiencies of coagulation factors (V-parahemophilia, VII-hypoproconvertinaemia, VIII haemophilia A, IX-haemophilia B, X, XI-PTA, XII-Hageman trait and I-afibrinogenemia "pregnancy states"),⁹ Acquired deficiencies of coagulation factors may result from vitamin K and other fat soluble vitamin deficiencies, massive transfusion of blood containing citrates or oxalates produces low levels of calcium, and inhibitors like heparins interfering with clotting factors. Drugs, interfering with clotting factors, e.g. oral anti-coagulants (dicumarol and warfarin) inhibit the action of vitamin K, non-vitamin k antagonists' oral anti-coagulants (NOAC's). e.g. Dabigatran, Rivaroxaban. Also antiplatelet drugs like aspirin and clopidogrel, fibrinolytic drugs (human t-PA, rt-PA and Streptokinase) used in the treatment of ACS \ early myocardial infarction.

The usual clinical presentation includes- history of bleeding from surfaces as seen in epistaxis (esp. bilateral), Hematemesis, Hematochezia, Melena, HypHEMA, Heamaturia, and Menorrhagia. Significant or prolonged bleeding after injury or surgery with or without exsanguinations requiring blood product therapy, others includes obstetric haemorrhage, bleeding from dental procedures,

bleeding from circumcision., bleeding during tumor surgery, other massive surgical haemorrhage, neurosurgical bleeding in the cranium, bleeding into cavities like joints, pleural space, abdomen, and muscular hematomas.^[10-12]

There is a battery of coagulation screening / tests to guide patient management in the Perioperative period. Whenever findings in the history, such as comorbidities, previous abnormal bleeding, a detailed family history, current medications (antiplatelet, oral anticoagulants, fibrinolytic), and physical examination suggests an increase risk of significant bleeding, then it is more cost effective to carry out routine screening tests of coagulation (especially before invasive procedures), such as Full blood count, platelet count, prothrombin time (PT) / activated partial thromboplastin time (aPTT). Additional specific tests of coagulation factor deficiency identification should be carried out, to identify and quantify the factor activity levels.^[13,14]

Individuals with mild impairment may not present with significant bleeding. PT and aPTT may identify significant coagulation impairment, but they assess limited part of the coagulation and do not diagnose the underlying defect.^[13,14]

Prolonged aPTT may suggests conditions such as factor deficiencies except FVII, inhibitors like heparin, lupus anticoagulant, specific factor inhibitors and FDP's. It is a screening tool for haemophilia A, haemophilia B, coagulation inhibitors, and to monitor un-fractionated heparin.^{[13,14].}

Specific laboratory tests of coagulation used routinely has longer turnaround times and is not appropriate in the intraoperative settings. The following represents trigger points/minimum threshold values beyond which intervention is required by using appropriate replacement products; platelet count $<50 \times 10^9 \text{ litre}^{-1}$, PT or aPTT at >1.5 times normal values. Satisfactory platelet plug will not be formed if platelet count is too low or functionally impaired, stored blood for more than 3 days, concurrent aspirin therapy, uraemia, congenital impairment. Platelet count is crucial in assessing heparin-induced thrombocytopenia in patients on heparin. Fibrinogen consumption without DIC is an important cause of severe surgical bleeding, levels less than 100mg/dl is inadequate for haemostasis. FDP's and D-dimers assesses fibrinolysis. D-dimer reflects widespread lysis of an established thrombus in DIC, DVT, PE. Anti-Xa assay is used in monitoring LMWH and indirect FXa inhibitors^{[13,14].}

TREATMENT OPTIONS

Current recommendations for intraoperative monitoring, treatment and prevention of massive

bleeding in surgical, trauma, and obstetric setting; requires general measures, such as avoiding high risk bleeding cases. Selecting invasive procedures with the minimum bleeding risk, ensuring communication of appropriate treatment plans in a multidisciplinary setting including hematologists. Treatment of the underlying disorder is very essential and clotting factors deficiencies should be replaced with clotting factors concentrates, cryoprecipitate, recombinant factors concentrate, prothrombin complex concentrate (PCC), fresh frozen plasma, purified blood product, Plasma infusion, or whole blood. Platelet transfusion may be necessary in some circumstances. Adjuncts such as topical prohemostatic agents, endocrine therapy for menstrual bleeding, Tranexamic acid, Aprotinin or other fibrinolytics. Tranexamic acid is given not later than 2 hours pre-procedure to ensure peak plasma levels at the time of haemostatic challenge (it is contraindicated in renal bleeding and any thrombotic risk). Selection of therapeutic products- In cases of mild bleeding or minor surgery in FID, FIID, FXD, or vitamin k dependent coagulation factors deficiency; Antifibrinolytics agents has been used e.g. Tranexamic acid 15-20 mg/kg or 1gm four times daily; in severe bleeding or major surgery, PCC 20-40 i.u/kg to maintain FII activity >0.2 i.u/ml, FFP is a suitable alternative. Also, non-blood derived alternative like DDAVP (1-deamino-8-D-arginine vasopressin). Vitamin k in doses of 0.1-0.5mg/kg has been used to treat hemorrhagic disease of newborn.^[13-15]

Treatment of identified specific factor deficiency with specific recombinant factors concentrate, such as FXII A-subunit and FVIIa, or virally inactivated plasma derived factor concentrates such as Fibrinogen, FVII(novo-seven), FX, FXI, and FXIII(novo-thirteen).

PCC is a four factor, plasma derived concentrate (FII, FVII, FIX & FX), for the treatment of prothrombin deficiency, vitamin k dependent factor deficiency, and for FX, FVII.

FFP is the only currently available replacement therapy available for isolated or combined FV & FVIII deficiencies or in emergencies where diagnosis of factor deficiency is uncertain or specific factor replacement is unavailable.

Most surgeons have adopted damage control surgery for severely injured patients, in which the initial operation is abbreviated after control of bleeding and contamination to allow on-going resuscitation in the intensive-care unit. Developments in early resuscitation that emphasized rapid control of bleeding, restrictive volume replacement, prevention or early management of coagulopathy and improved topical haemostatic agents and interventional radiology, are making definitive surgery during the first operation possible for many patients.^[16]

CONCLUSION

As point-of-care diagnostics becomes available in emergency areas, timely targeted intervention for haemorrhage control will result in better patient outcomes and reduced demand for blood products.

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