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Review Article

Perioperative management of the bleeding patient

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Abstract

Perioperative bleeding remains a major complication during and after surgery, resulting in increased morbidity and mortality. The principal causes of non-vascular sources of haemostatic perioperative bleeding are a preexisting undetected bleeding disorder, the nature of the operation itself, or acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption. In the bleeding patient, standard therapeutic approaches include allogeneic blood product administration, concomitant pharmacologic agents, and increasing application of purified and recombinant haemostatic factors. Multiple haemostatic changes occur perioperatively after trauma and complex surgical procedures including cardiac surgery and liver transplantation. Novel strategies for both prophylaxis and therapy of perioperative bleeding include tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrates. Point-of-care patient testing using thromboelastography, rotational thromboelastometry, and platelet function assays has allowed for more detailed assessment of specific targeted therapy for haemostasis. Strategic multimodal management is needed to improve management, reduce allogeneic blood product administration, and minimize associated risks related to transfusion.

Key words: coagulopathy; direct oral anticoagulants (DOACs); hemostasis & thrombosis; point-of-care testing; thromboembolism; transfusion algorithm

Multiple factors contribute to the complex causes of bleeding in surgical patients that include blood loss, haemodilution, acquired platelet dysfunction, coagulation factor consumption in extracorporeal circuits, activation of fibrinolytic, fibrinogenolytic and inflammatory pathways, and hypothermia.[1,2] Acquired haemostatic defects often present in surgical patients as a result of prescribed oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) and platelet inhibitors (P_2Y_{12} receptor inhibitors-clopidogrel, prasugrel, or ticagrelor). Thus, bleeding after surgery includes both preexisting and/or acquired defects in haemostasis. Congenital bleeding disorders are less common and, hopefully already addressed if a patient presents for surgery. From a preoperative evaluation standpoint, the ISTH bleeding questionnaire is as effective as multiple, laboratory tests for identifying perioperative bleeding risk.[3]

Surgical bleeding is usually characterized by a site of bleeding and confined exclusively to the operative site. Meticulous surgical technique, patience, and good patient selection all contribute significantly to minimizing surgical bleeding in the high-risk patient. The spectrum of available topical haemostatic agents and devices are beyond the scope of this review.[4] **The focus of this review is** microvascular or coagulopathic bleeding as a consequence of abnormal haemostatic mechanisms. While typically manifested as generalizing bleeding within the operative site, this can extend to percutaneous cannulation sites, nasogastric tubes, and urinary catheters.

Management of perioperative bleeding consists of identifying patients at risk, understanding the impact of the operation on haemostasis, institution of allogeneic blood and factor concentrate based therapies, utilizing point-of-care laboratory

Editor's key points

- Perioperative bleeding can involve acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption.
- Novel approaches for prophylaxis and therapy of perioperative bleeding include use of tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrate.
- Point-of-care testing of haemostatic function using thromboelastography, thromboelastometry, and platelet function assays allows specific targeted therapy of coagulopathy.

testing, and understanding the limitations of monitoring techniques.[5] Clinically important bleeding can paradoxically evolve into pathologic thrombosis, with the transition of perioperative coagulopathy to hypercoagulability related to the acute phase response. This can be exacerbated by overzealous replacement of deficient procoagulant factors, inattention to deficient anticoagulant factors, and reluctance to initiate needed anticoagulant agents for venous thromboembolic prophylaxis after a recent bleed. Navigating this complex, rapidly changing haemostatic balance exemplifies the value of the perioperative physician with detailed knowledge of haemostasis, anticoagulation, and transfusion medicine. In this review, we address specific and general considerations for various pathophysiological states or circumstances and haemostatic agents and provide algorithmic approaches to bleeding management, in order to place the administration of agents in clinical context.

The following section represents general considerations of haemostasis related to hypothermia and fibrinolysis, which can occur in all patient populations undergoing invasive procedures and require review before approaching the coagulation defects particular to specific patient populations.

General considerations: hypothermia and fibrinolysis

Temperature regulation and the coagulopathy of hypothermia

In controlled circumstances, such as during cardiopulmonary bypass or hypothermic circulatory arrest, hypothermia is used as a neuroprotective mechanism.[6] Inadvertent hypothermia seen with severe trauma, or poorly maintained intraoperative temperature regulation can be associated with worse outcomes. For example, isolated hypothermia of 32.2 °C is associated with a 23% mortality rate, while trauma-induced hypothermia below 32 °C is associated with 100% mortality.[7–8,9] The coagulopathy of hypothermic patients includes dysregulation of coagulation enzyme processes, platelet function, activation of fibrinolysis, and endothelial injury.[10] Bleeding observed at reduced temperatures (33 – 37 °C) often occurs because of defects in platelet adhesion, while at temperatures below 33 °C, both reduced platelet function and coagulation enzyme activity contribute.[11] Active warming should be applied perioperatively if exposed surface area allows. Additionally, hypothermia and acidosis frequently occur together requiring correction of metabolic abnormalities.[11–14]

Fibrinolysis

Activation of the fibrinolytic system is an important mechanism of vascular homeostasis (Figure 1). Mechanistically, plasmin generation is the enzymatic serine protease responsible for fibrinolysis and is formed after the action of t-PA on plasminogen. Plasmin cleaves key coagulation proteins such as fibrin and fibrinogen, but also causes proteolysis of other critical proteins, including fibronectin and von Willebrand factor.[15] In the urogenital tract, hyperfibrinolysis occurs as a result of liberation of the urokinase plasminogen activator system.[16] After cardiopulmonary bypass and/or tissue injury that occurs with surgery or trauma, fibrinolysis is activated and represents an important cause of coagulopathy.[17] In trauma, orthopaedic surgery, and cardiac surgery, multiple studies support the role of antifibrinolytic agent administration in order to decrease bleeding and the need for allogeneic transfusions.[17] These agents can also be used as an adjunct to treating congenital bleeding disorders.[18]

Since CRASH-2 was published in 2010,[19] meta-analyses recommend antifibrinolytic use (mostly tranexamic acid) in abdominal bleeding[20] and trauma, while on-going major studies are being conducted for gastrointestinal bleeding (HALT-IT trial)[21] and postpartum haemorrhage (WOMAN trial).[22] The use of tranexamic acid (TXA) is increasing and additional data are forthcoming. Despite initial concerns about aprotinin, this agent is now being reintroduced in many European markets.[23]

While we will not discuss postpartum haemorrhage in detail, three major considerations are emerging for managing bleeding parturients: routine use uterotonics, aggressive fibrinogen replacement, and prevention of excessive fibrinolysis, as recently reviewed.[24,25]

Antifibrinolytic agents: lysine analogues

The two antifibrinolytic agents administered clinically include epsilon aminocaproic acid (EACA) and TXA.[26] While both medications competitively inhibit plasminogen conversion to the active protease plasmin,[27] only TXA has been shown to inhibit higher plasma concentrations of plasmin.[28,29] Although most of the data for the antifibrinolytic lysine analogues are with TXA, EACA continues to be extensively utilized in the USA.[30] Although multiple studies (primarily meta-analyses of randomized-controlled trials) have shown that lysine analogues decrease bleeding in cardiac surgical patients, there are limited prospective safety data regarding the use of antifibrinolytic agents. Most dosing studies include total EACA doses of 20 to 30 g per patient, or total TXA doses from 2 to 25 g, mainly from 2 to 8 g.[26]

An increase in the incidence of seizures after cardiac surgery from 1.3% to 3.8% has been temporally associated with higher-dose TXA use.[31] The mean age of patients in this report was ~70 yr, and open chamber surgery, with possible air entrainment, was a risk factor.[31] Mechanistically, TXA enhances neuronal excitation by antagonizing inhibitory gamma-aminobutyric acid (GABA)[32] and glycine[33] neurotransmission at the receptor level, an established cause of seizures. This side-effect was not noted in prospective trials, which were notably underpowered for this outcome. Seizure activity has not been described in patients receiving EACA. For other indications such as orthopaedic, trauma and obstetric indications, the data are mostly for patients receiving a total of 2 g of TXA, where seizures have rarely been reported.