A Brief Review of 50 Years of Perioperative Thrombosis and Hemostasis Management

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Perioperative thrombosis and hemostasis management has changed dramatically over the past 50 years. From two anticoagulants and one anti-aggregant, the number of currently available drugs has recently increased several-fold, leaving clinicians with the problem of choosing the optimal agent. Individualized preoperative assessment of bleeding risk based on bleeding history and testing limited to high-risk patients is an emerging concept. Based on the identification of risk factors for venous thromboembolism (VTE), pharmacologic and non-pharmacologic strategies for perioperative VTE prophylaxis have had a major impact on patient outcome. For patients undergoing surgery who are treated with anticoagulants and anti-aggregants, "bridging" strategies have been proposed. Bleeding management strategies have shifted focus from replacing lost blood volume to new approaches aimed at preventing blood loss, reducing the potential complications of blood loss, and preventing the transfusion of blood products. For some areas of perioperative thrombosis and hemostasis management, randomized controlled trial (RCT) data are emerging, but the database remains insufficient to date. Clearly, more RCTs need to be published for perioperative thrombosis and hemostasis management to become an evidence-based approach.
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EDITOR'S NOTE

This is a "special" article celebrating the 50th anniversary of *Seminars in Hematology*. Dr Serena Valsami from the University of Athens, Greece and Dr Lars Asmis from the University of Zurich, Switzerland, in a comprehensive review, discuss management of perioperative thrombosis and hemostasis. Identification of risk factors and development of new drugs greatly changed the incidence and evolution of thrombotic and hemorrhagic complications, which was the "nightmare" of patients and surgeons. The value of prospective randomized clinical trials in the elaboration of guidelines in this matter is clearly seen in this well-written review.

INTRODUCTION

The management of patients undergoing a surgical procedure has changed considerably over the past 50 years. This brief review will focus on some of the key changes in the field of perioperative thrombosis and hemostasis management, discussing where the field set out 50 years ago, what changed since then, and where it is today.

DEVELOPMENTS IN ANTICOAGULANTS

In the 1960s when *Seminars in Hematology* was founded, the mainstay of anticoagulant therapy was unfractionated heparin and vitamin K antagonists (VKAs). In the first half of the past 50 years much was learned about the mechanism of action of these drugs, while in the second half new molecules were added to the palette of available anticoagulants.

Heparin was discovered by McLean in 1916 and was isolated from dog livers (Greek for liver: *hepar*), which gave the anticoagulant its name.[1] VKAs were determined to be a cause of a hemorrhagic disease in cows by Charles Link. They were first used as a potent poison for rodents. It was not until the 1950s that the drug found its way into clinical medicine.

In 1968, Abildgaard showed that the protein antithrombin was necessary for heparin's anticoagulant action, illustrating that the heparins were indirect anticoagulants.[2] Warfarin inhibits coagulation by disturbing hepatic post-translational modification of coagulation factors (FII, FVII, FIX, and FX) and inhibitors (proteins C and S). Without the postranslationally added carboxyl groups,

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these factors cannot bind to the surface of activated platelets and thus are dysfunctional. Because neither anticoagulant family, the heparins and the vitamin K antagonists (VKAs), binds directly to the active center of coagulation factors, they are called indirect anticoagulants. One of the problems with unfractionated heparins (5–30 kd; mean molecular weight [MW], 15 kd) was that they did not have a fixed dose-response relationship. This was in part due to unspecific binding of these long, negatively charged molecules to many other targets, including acute-phase reactants, platelets, and endothelial cells. Monitoring was necessary to titrate the correct dose in each patient.

Fractionation or isolation of smaller heparin fragments provided a solution to the dose-response problem. By generating mixtures of small fragments of heparin (2–9 kd; mean MW, 4–6 kd) the product obtained a fixed dose-response relationship and weight-based dosing was possible. Monitoring was no longer obligatory. The exact mechanism of heparin action was elucidated in the late 1970s by the finding that heparins bind to antithrombin through a unique pentasaccharide motif. Only molecules that harbor this pentasaccharide sequence are biologically active in coagulation inhibition. The exact sequence was identified by Choay in 1985.[3] This paved the way to the generation of a synthetic pentasaccharide, fondaparinux.

Even though hirudin, derived from the medicinal leach (*hirudo medicinalis*), was one of the first anticoagulants to be described in the late 19th centrury, it could not be used for clinical anticoagulation in view of the narrow therapeutic window and lack of adequate monitoring tests.[4] Hirudin found an application as an alternative anticoagulant in case of heparin-induced thrombocytopenia (HIT).[5] HIT is an antibody-mediated adverse drug effect with antibodies directed against complexes of heparin and platelet factor 4 that was described in 1958 by Weismann and Tobin.[6] Hirudin derivatives, such as lepirudin and bivalirudin, still are used for this indication. These anticoagulants are characterized by directly attacking the active sites of thrombin or FIIa. The molecule binds directly to the so-called serine protease domain, thereby inhibiting the activated coagulation factor. All of these direct anticoagulants had the problem that they could only be used parenterally. The search for new oral agents began.

The first new oral direct anticoagulant that made it into clinical practice was ximelagatran, a direct thrombin inhibitor. In view of its hepatotoxicity, the drug was withdrawn again from the market in 2006. The next direct thrombin inhibitor to be approved by a large national health agency was dabigatran, with initial indication for the prevention of venous thromboembolism (VTE) in hip or knee replacement surgery in 2008 in Canada and Europe and later for prevention of stroke in atrial fibrillation by the US Food and Drug Administration (FDA) in 2010. Argatroban is another direct thrombin inhibitor that has gained market approval.

Another class of direct oral anticoagulants, the direct inhibitors of FXa, soon followed. Rivaroxaban gained approval by Canadian and European health authorities for VTE prevention in hip and knee replacement in 2008. In 2011 it became FDA-approved for the treatment of deep vein thrombosis (DVT) and stroke prevention in atrial fibrillation. The FDA approved the treatment of DVT and pulmonary embolism in 2012. Apixaban, edoxaban, and other related compounds have or are in the process of obtaining health agency approval for various indications.

DEVELOPMENTS IN ANTIPLATELET AGENTS

In the 1960s aspirin was the main antiplatelet agent in clinical use. Aspirin (acetylsalicylic acid) was first produced by Felix Bayer in 1897 and almost immediately found wide application as an anti-inflammatory and antipyretic drug.[7] Almost 50 years later, in 1938, its impact on impairing hemostasis was noted in patients treated with aspirin who experienced prolonged bleeding after tonsillectomy. In the 1950s, aspirin was then prescribed to prevent coronary and cerebral thrombosis in high-risk patients, with remarkable results.[8] The effect of aspirin on the hemostatic properties of human platelets, by inhibition of adenosine diphosphate (ADP)-induced secondary platelet aggregation, was shown by different groups during the 1960s.[9,10] Shortly after that, aspirin's full mechanism of action through cyclooxygenase inhibition was elucidated.[11,12] In the 1980s, aspirin received approval by the FDA for the secondary prevention of arterial vascular disease and in the same time period, the ISIS-2 trial proved its efficacy in treating myocardial infraction. Currently, aspirin remains an established part of the treatment and secondary prevention of arterial thromboembolism.[13] However, there are issues regarding aspirin that remain unresolved, including the use of aspirin for primary prevention of atherovascular disease and the clinical relevance of suboptimal platelet response to aspirin or aspirin resistance.[14,15]

In 1974 a $P2Y_{12}$ antagonist, a thienopyridine derivate later named ticlopidine, was first discovered. Ticlopidine gained FDA approval in 1991. Its antithrombotic action was found to be equally effective to that of aspirin for the treatment of patients with atherovascular disease. Unfortunately, ticlopidine was associated with serious side effects, including bone marrow toxicity and thrombotic thrombocytopenic purpura. This drug was soon replaced by a second thienopyridine, clopidogrel.[16,17] In 1996, clopidogrel proved its clinical efficacy versus aspirin in patients at risk for ischemic events and was approved for clinical use 2 years later. Clopidogrel is a prodrug that requires oxidation by two-stage hepatic cytochrome (CY) P450 to generate its active metabolites, which inhibit platelets for the lifespan. This explains the delayed onset of platelet inhibition (4–8 hours) by clopidogrel. The variability of the antiplatelet drug effect and the clinical efficacy of clopidogrel therapy were associated with the cytochrome P450 2C19 (CYP2C19) genotype.[18,19] The third thienopyridine approved in 2011 was prasugrel, which requires