

Platelets, Perioperative Hemostasis, and Anesthesia

PATHOLOGIC bleeding or thrombosis can commonly complicate surgical procedures. Although many of these complications are directly related to the anatomic disturbances of the operative procedure, hemostatic abnormalities may also contribute. Perioperative alterations in hemostasis may arise from physiologic or pharmacologic events that are intrinsic to the perioperative experience. The administration of anesthetic agents is one such event that has the potential to influence hemostasis. In this issue of ANESTHESIOLOGY, Nakagawa *et al.*[1] describe the effects of ketamine on platelet function using an *in vitro* model. They report that the addition of ketamine to platelets inhibits agonist-induced aggregation, and that the mechanism of inhibition involves suppression of platelet inositol 1,4,5-triphosphate formation, guanosine 5-triphosphosphatase activity, and calcium currents. Inhibition in response to ketamine occurred in a dose-dependent manner. However, substantial inhibition of function only occurred at *in vitro* concentrations of ketamine that exceed clinical concentrations *in vivo*.

During the past 25 yr, hundreds of articles have been published that describe the impact of various anesthetic agents and techniques on a variety of measures of hemostasis. Many of these studies have focused on the influence of anesthesia on platelets. Because platelets have the preeminent role in primary hemostasis, this focus is appropriate. The adhesion of platelets to subendothelial collagen and von Willebrand factor, and the subsequent aggregation of platelets *via* fibrinogen cross-bridging, is the basis for initial hemostatic plug formation after vascular disruption. In addition, platelets markedly accelerate fibrin clot formation by providing coagulation protein binding sites and phospholipids that improve the enzymatic efficiency of the coagulation cascade. Furthermore, platelets are known to be the hemostatic element primarily involved in arterial thrombotic diseases, and they participate to a lesser degree in the development of venous thrombosis as well. Therefore, studies that examine the effect of anesthetics agents and techniques on platelet function can provide insight into hemostatic processes that may have clinical importance in the perioperative period.

A variety of tests can be used to assess platelet function. The most commonly used clinical test, bleeding time, is not a true test of platelet function. Rather, it is a test of primary hemostasis because it measures the function of endothelial cells and critical adhesive ligands (*e.g.*, fibrinogen, von Willebrand factor, and collagen) in addition to measuring platelet function. Furthermore, bleeding time is known to be a poor test for predicting surgical bleeding complications. The most widely used laboratory test to assess platelet function is platelet aggregometry. This assay can be performed in whole blood or isolated platelet preparations and has excellent sensitivity and specificity for platelet abnormalities. However, because these tests require specialized equipment and expertise to perform, they are not used for routine hemostatic screening, and the relation between these tests and perioperative bleeding and thrombotic disorders is largely unknown. A number of tests have been advocated for bedside assessment of platelet function, including thromboelastography, platelet-activated clotting time, and automated platelet function analysis. Although these tests are easy to perform, the thromboelastogram and platelet-activated clotting time are not specific for platelet function, and the correlation between these three tests and perioperative bleeding has been modest. In addition to the aforementioned tests, a variety of tests can be used to assess the function of specific platelet receptors, proteins, and intracellular signaling molecules. These tests include flow cytometry and quantitative biochemical techniques, such as those used in the article by Nakagawa *et al.*[1] These techniques are powerful because they provide the ability to evaluate specific mechanisms of platelet function; however, they require substantial technical expertise, and the relation between these types of assays and perioperative morbidity is unknown.

The majority of anesthetic agents, including intravenous induction agents, volatile anesthetics, and local anesthetics, have been reported to inhibit platelet function as measured by platelet aggregometry. The magnitude of this inhibitory effect seems to vary among the different agents. For example, the inhibitory effects of halothane and sevoflurane are reported to exceed that of isoflurane,[2–4] and among intravenous induction agents, propofol has been most consistently associated with platelet inhibition.[4–6] The mechanism through which anesthetics inhibit platelet function is largely unknown and probably varies among the different agents. The major contribution of Nakagawa *et al.*[1] is to identify some of the mechanisms that may be involved in mediating the inhibitory effect of ketamine. Unfortunately, stud-

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ies that define the *in vivo* consequences of anesthetic-related platelet inhibition are lacking. There are virtually no data that indicate that any general anesthetic regimen is better than any other for reducing perioperative bleeding or thrombotic complications. Among studies that investigated the impact of regional *versus* general anesthesia, results have been mixed.[7–9]

Does the lack of evidence that anesthetics affect *in vivo* hemostatic outcome mean that all anesthetics are equivalent with respect to these outcomes? Not necessarily. It remains possible that an anesthetic regimen with potent antiplatelet actions could lead to bleeding complications in a patient who is genetically predisposed, whose environment contains additional hemorrhagic risk factors (*e.g.*, hemodilution, anticoagulants), or who is undergoing a procedure that involves a high risk for bleeding complications (*e.g.*, neurosurgery). However, an important lesson can be gleaned from studies that have examined the effect of aspirin on perioperative hemostasis. Although the antiplatelet action of aspirin is indisputable, many studies have shown that aspirin has minimal impact on perioperative blood loss and transfusion.[10–12] Therefore, even if an anesthetic inhibits platelet function, its use will not necessarily lead to clinically relevant bleeding complications.

Basic science reports, such as that of Nakagawa *et al.*,[1] are important because they alert clinicians to the *potential* for hemostatic complications associated with different anesthetics. The clinical implication of these reports is enhanced when (1) platelet inhibition *in vitro* occurs at anesthetic concentrations that are routinely achieved and sustained *in vivo*; (2) the magnitude of platelet inhibition is large; (3) inhibition can be demonstrated using a variety of platelet agonists, tests of platelet function, or both; and (4) *in vivo* administration of anesthetic agents or regimens produces hemostatic alterations consistent with those observed *in vitro*. Ultimately, however, the clinical impact of different anesthetics on hemostasis can only be determined through clinical trials that evaluate well-defined bleeding, thrombotic outcomes, or both. Regrettably, such trials are lacking.

Anesthesiologists have vast experience with surgical bleeding complications. We prescribe and administer more blood products than any other group of physicians. As perioperative and intensive care specialists, we diagnose a variety of thrombotic disorders and administer therapies to prevent and treat these diseases on a daily basis. Indeed, the scope of practice and experience of anesthesiologists has made us leaders in the field of perioperative hemostasis. To retain this leadership, we need to increase our understanding of the pathophysiologic processes that lead to perioperative hemorrhagic and thrombotic disorders. In particular, we need to understand how genetic factors interact with anesthetics and other perioperative influences to alter outcome. In addition, we need to place greater emphasis on the conduct of clinical trials to determine whether specific therapies can reduce morbid outcome.

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