Thoracic and Cardiovascular Surgery

Cardiac Surgery in Patients on Antiplatelet and Antithrombotic Agents

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The widespread application of antithrombotic agents carries significant potential for inducing excessive peri-operative hemorrhage during cardiac surgery. Specific surgical and medical strategies can be employed to attenuate this bleeding. These antithrombotic agents and anti-hemorrhagic measures will be reviewed in depth.
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Antithrombotic, particularly antiplatelet agent utilization has become nearly ubiquitous among patients being referred for cardiac surgery. This widespread application of antithrombotic agents can markedly increase the risk of significant peri-operative hemorrhage during cardiac surgery. Multiple strategies have been developed to mitigate the adverse bleeding effect of such agents. This article will (1) review the clinical aspects of significant mediastinal hemorrhage, (2) survey the most commonly used antithrombotic agents and describe typical clinical scenarios encountered by cardiac surgeons, and then (3) review specific anesthetic, perfusion, surgical, and pharmacologic management strategies to decrease peri-operative hemorrhage.

Impact of Antithrombotic Exposure and Excessive Hemorrhage

Patients who have received antithrombotic agents preoperatively present a modest degree of technical challenge before the administration of heparin for the planned cardiac procedure. For example, harvest of the left internal thoracic artery can be somewhat more challenging in the face of significant anticoagulation, and dissection of mediastinal adhesions during re-operative cardiac surgery can also be more challenging in the face of significant anticoagulation. Clearly, during the fully anticoagulated portion of the cardiac procedure, the presence of preoperative exposure to antithrombotic agents does not present a major issue. On completion of the procedure and initiation of the reversal of the fully anticoagulated state, preoperative exposure to antithrombotic agents can pose major challenges. The capability of reversing the anticoagulation state may require several adjunctive measures ranging from those as simple as administering additional protamine to extensive blood product administration.

Extensive intra- and postoperative hemorrhage markedly increases the risk of peri-operative morbidity and mortality. The hemodynamic status can be compromised from excessive hemorrhage with or without associated cardiac tamponade. The need for re-exploration is increased as is the subsequent risk of sternal wound infection. Blood product transfusion carries a risk of transmission of infectious agents. There is also a risk of pulmonary dysfunction. There can be disruption of the hematologic profile with the creation of either a fibrinolytic state or a pro-thrombotic state with over-administration of clotting factors. There can be sensitization of the immune system, which can become particularly relevant in patients requiring subsequent transplantation. Excessive postoperative hemorrhage extends mechanical ventilation, duration of intensive care unit stay, hospitalization, and recovery periods and costs are also increased. In an interesting analysis of several thousand cardiac surgical patients operated on at a single institution over a several year period, breakdown of patients based on whether or not they underwent re-exploration and also by quantity of immediate postoperative blood loss yielded very interesting findings (Fig. 1).[1] Mortality was particularly high in patients who had less than 1000 mL of blood loss, but did require re-exploration. Presumably, these were patients with unstable hemodynamics.

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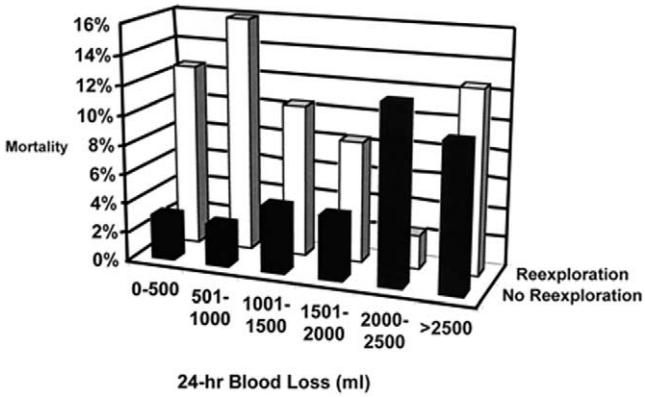

Figure 1 Peri-operative mortality among 6015 cardiac surgical patients stratified by quantity of 24 hour blood loss and by need for mediastinal reexploration (Reprinted from Journal of Thoracic and Cardiovascular Surgery with permission from *American Association for Thoracic Surgery*. Moulton MJ. J Thorac Cardiovasc Surg 111: 1037-1046, 1996).

Interestingly, patients who were not re-explored but had over 2000 mL of blood loss, also had extremely high mortality. These patients likely received significant blood product transfusion. Clearly, patients who experienced significant mediastinal hemorrhage or required re-exploration fared very poorly.

Patients with preoperative administration of antiplatelet and antithrombotic agents are at even greater risk of experiencing significant peri-operative hemorrhage. An example of an extreme scenario with potential for massive peri-operative hemorrhage which recently presented to our hospital is that of a 75-year-old female who arrived at a local hospital with complaints of chest discomfort. Her electrocardiogram demonstrated nonspecific ST- and T-wave changes. She was given a presumptive diagnosis of an acute coronary syndrome. She received aspirin 325 mg, clopidogrel 300 mg, heparin 5000 units IV, and an eptifibatide infusion 2 μg/kg/min in preparation for coronary angiography and planned potential percutaneous coronary intervention (PCI). The patient was found to have normal coronary arteries and an acute type A aortic dissection, which was confirmed with immediate transesophageal echocardiography. The patient was emergently transported by helicopter to the author's hospital, directly to the operating room. The patient underwent repair of her type A aortic dissection consisting of an aortic valve resuspension, ascending aortic replacement, and an aortic arch reconstruction under deep hypothermic circulatory arrest with retrograde cerebral perfusion. The patient also underwent a variety of the measures to be described in this manuscript to counteract the antiplatelet and antithrombotic agents. She did not experience significant postoperative mediastinal hemorrhage, recovered rapidly, and was discharged to home on postoperative day 5.

The next section will review specific antiplatelet and antithrombotic agents, describe the mechanism of action, cite common clinical scenarios in which the cardiac surgeon would encounter patients receiving these agents, describe the impact on peri-operative bleeding (mild, moderate, severe), and provide a recommendation on an appropriate course of action to mitigate a significant hemorrhagic effect.

Aspirin

The mechanism of action is the irreversible inhibition of platelet cyclo-oxygenase resulting in primarily the reduction of thromboxane A_2, and thereby inhibiting platelet aggregation. Aspirin is utilized almost ubiquitously and thus, there is no particular scenario in which cardiac surgical patients are significantly much more likely to be on aspirin. The bleeding effect is mild. There is essentially no need to discontinue aspirin preoperatively.[2,3]

Clopidogrel

Clopidogrel is a platelet adenosine diphosphate receptor antagonist which yields decreased platelet activation.[4] It has essentially supplanted ticlodipine, the other agent in the thienopyridine class. Clopidogrel is rapidly becoming much more widely utilized in several groups of cardiovascular patients:

A. Primary therapy in coronary artery disease: Patients presenting with non-ST-elevation acute coronary syndromes who receive clopidogrel experience lower rates of cardiovascular death, myocardial infarction, stroke, and refractory ischemia.[5,6]

B. Peri-procedural PCI: In the randomized study of pre-PCI clopidogrel and aspirin (CREDO), patients receiving clopidogrel 6 or more hours before PCI experienced a 35% reduction in the combined events of death, myocardial infarction or urgent target vessel revascularization.[7,8]

C. Peripheral vascular disease: Patients with peripheral vascular disease are being managed more frequently with chronic clopidogrel therapy.[9] Also, such patients undergoing peripheral percutaneous or surgical revascularization are often placed on clopidogrel therapy.[10]

Together, these comprise a large population of patients on clopidogrel who may present for cardiac surgery.

The bleeding effect of preoperative clopidogrel exposure is moderate. Exposure to clopidogrel within 5 days of cardiac surgery resulted in significantly higher chest tube output, transfu-

	Clopidogrel (n = 59)	No Clopidogrel (n = 165)	p Value
Chest tube output (ml)			
8-h	775 ± 727	516 ± 533	0.005
24-h	1224 ± 1119	840 ± 621	0.001
Transfusions (U)			
Red blood cells	2,51 ± 2,41	1,74 ± 2,16	0.036
Platelets	0,86 ± 1,20	0,24 ± 0,60	0.001
Fresh frozen plasma	0,68 ± 1,69	0,24 ± 0,85	0.015
Cryoprecipitate	0,19 ± 1,31	0,17 ± 1,20	0.774
Blood product exposure	79,7%	58,2%	0.004
Red blood cells	50,8%	18,2%	< 0.001
Platelets	84,7%	61,3%	0.001
Any blood product			

Figure 2 Impact of precoronary artery bypass grafting clopidogrel exposure on peri-operative hemorrhage and blood transfusion requirements (Reprinted from the Journal of American College of Cardiology with permission from *American College of Cardiology Foundation*. Hongo H, J Am Coll Cardiol 40:231-237, 2002).[3]