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Hybrid Coronary Revascularization: An Overview of Options for Anticoagulation and Platelet Inhibition

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ABSTRACT

Background: Hybrid coronary revascularization, in which coronary bypass grafting is combined with percutaneous coronary intervention, is a promising strategy for optimizing outcomes in the treatment of coronary artery disease. Balancing the risk of surgical bleeding with the risk of percutaneous coronary intervention–related thrombosis is a major challenge inherent in carrying out a successful procedure and requires careful selection of antiplatelet and anticoagulant agents.

Methods: Advantages and disadvantages of antiplatelet and anticoagulant agents in use today for hybrid coronary revascularization are reviewed.

Results: Currently available anticoagulants and platelet inhibitors have been used to provide safe and effective protection from thrombosis while limiting surgical bleeding in hybrid coronary revascularization, but there is no agreement on an optimal strategy, and each patient presents a unique pharmacologic and logistic puzzle.

Conclusion: Knowledge of the salient features of the available medications will allow the cardiologist and surgeon to design the optimal strategy for each patient.

INTRODUCTION

Hybrid coronary revascularization (HCR) is a promising strategy for optimizing outcomes in the treatment of coronary artery disease that combines the most effective revascularization options from surgery and interventional cardiology. The underlying principle behind HCR is that the left internal mammary artery (LIMA) bypass graft to the left anterior descending artery (LAD) provides the most effective and most durable method of revascularization to the anterior wall of the heart. Studies have demonstrated that the LIMA graft to the LAD confers improved survival, whereas such proof is lacking for percutaneous coronary intervention (PCI) of the LAD. Other revascularization targets are treated with stents to eliminate the use of less durable saphenous vein grafts. Combining HCR with minimally invasive surgical approaches reduces morbidity by avoiding a median sternotomy [Byrne 2008; Bonatti 2010] and can enhance postoperative quality of life [Bonaros 2009].

With the hybrid approach, concerns regarding the risk of surgical bleeding must be balanced with the risk of thrombosis related to the PCI, complicating the logistics related to intra- and periprocedure platelet and thrombin inhibition. In addition, a decision must be made regarding which of the procedures is to be performed first. A staged approach involving coronary artery bypass surgery (CABG) first followed by PCI later allows both the surgeon and cardiologist to follow their usual protocols regarding platelet inhibition and anticoagulation; however, this strategy is not always feasible due to complex coronary lesions that may jeopardize nonrevascularized at-risk myocardium during the surgical procedure. Staged procedures with PCI first allow surgical revascularization if PCI fails and are more straightforward for the interventional cardiologist, but present a challenge for managing bleeding risk during subsequent CABG because of the need for uninterrupted dual antiplatelet therapy. The simultaneous approach carried out in a hybrid operating room, though appealing as a "one-stop shop" option, presents unique challenges for designing an optimum strategy for utilization of antiplatelet and antithrombin medications.

Understanding of the salient properties of the available agents is critical for making optimal decisions. This paper provides an overview of the properties of the currently used medications and how they have been utilized in simultaneous HCR. We will also briefly examine drugs currently under development that may simplify the hybrid approach in the future.

THROMBIN INHIBITORS

Unfractionated Heparin

Unfractionated heparin has been the cornerstone of anticoagulation for both PCI and CABG for decades and is the most common thrombin inhibitor in hybrid coronary intervention. For inhibition of thrombin, heparin must bind to both thrombin and antithrombin. The anticoagulant effect of unfractionated heparin is unpredictable, and therefore its effect during surgery and PCI is monitored using the activated clotting time (ACT) [Hirsh 2001]. Although low molecular weight heparin provides more predictable

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anticoagulant effect and has been validated as a safe and effective agent for PCI, it is not used for CABG because of its long half-life and the inability to reverse its effect. Low molecular weight heparin has therefore not been used in simultaneous HCR.

To limit bleeding, heparin's effect is generally neutralized using intravenous protamine after routine CABG, but protamine is generally avoided after PCI because of concerns regarding the potential for precipitating thrombosis in a newly placed stent. This dichotomy presents the first obvious difficulty with anticoagulation strategies for simultaneous HCR. Kon et al have published a series comparing simultaneous HCR with standard off-pump CABG [Kon 2008]. Although protamine reversal was not used in simultaneous HCR, there was less bleeding in that cohort than in the off-pump coronary artery bypass group in which protamine was used. The decreased bleeding was attributed to the minimally invasive surgical approach employed in the simultaneous HCR group [Kon 2008]. In a series by Zhao and colleagues, heparin effect was reversed with protamine after simultaneous HCR with good results, but it was not clear whether rare stent thromboses were related to protamine use [Zhao 2009]. The optimum strategy for heparin use and reversal in simultaneous HCR has not been identified.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor. Its use in PCI is well established and it is sporadically used in CABG for patients with heparin-induced thrombocytopenia. Although not commonly used, prospective multicenter studies have shown bivalirudin to be safe and effective for use in both on-pump and off-pump CABG [Dyke 2006; Smedira 2006]. Its reliable anticoagulant effect and short half-life leading to negligible residual inhibition 2 hours after discontinuation suggests that it might be beneficial in simultaneous HCR. Early promising results by Kiaii and colleagues suggest that this may be an excellent approach, but it requires confirmation by additional studies [Kiaii 2008].

PLATELET INHIBITORS

Aspirin

Aspirin exerts its antiplatelet effect via inhibition of the cyclooxygenase-1 (COX-1) pathway, thereby decreasing production of thromboxane A_2. The effect on platelets is irreversible and continues for the life of the platelet. Inhibited platelet reactivity gradually corrects following drug discontinuation as new platelets are produced. Aspirin has been used empirically for PCI since the introduction of the technique in the 1970s. The efficacy and safety of preoperative aspirin for CABG remains controversial, but current guidelines support its use in appropriate patients [Ferraris 2005]. Aspirin has been used in all published series of simultaneous HCR and is generally started in advance of the procedure.

Ticlopidine

Ticlopidine is an oral thienopyridine, which irreversibly inhibits the platelet adenosine 5′-dipohosphate (ADP) receptor $P2Y_{12}$. It replaced Coumadin for stent procedures after publication of the STARS trial in 1998 [Leon 1998]. Its use both improved and simplified the pharmacology related to PCI and was a major contributor to the wide acceptance of the procedure. However, the occasional occurrence of life-threatening neutropenia, which can occur within weeks of starting the drug, was a major concern and resulted in rapid acceptance of a subsequently developed alternative, clopidogrel.

Clopidogrel

Clopidogrel is an oral thienopyridine, which, like ticlopidine, irreversibly inhibits the platelet ADP receptor $P2Y_{12}$. It is a "pro-drug" and requires conversion to its active metabolite via the hepatic cytochrome P-450 system. Because of this requirement and variability in intestinal absorption, the onset of action is relatively slow and unpredictable, generally requiring at least 6 hours and 2 hours after 300 mg and 600 mg loading doses, respectively. In addition, there is a great deal of inter-individual variation in the cytochrome P-450 metabolic activity, and this pathway produces potential for multiple drug interactions. These metabolic variations result in an unpredictable effect and the possibility of "clopidogrel resistance" that is associated with increased risk of stent thrombosis. When considering HCR, it is important to consider that clopidogrel-mediated ADP receptor blockade is "irreversible," like aspirin, and thus requires days before its effect is overcome by newly manufactured, unaffected platelets after the drug is discontinued [Vivas 2010]. This property has resulted in recommendations to delay CABG for 5 to 7 days after discontinuing the drug in order to minimize bleeding, an obvious issue that must be addressed in simultaneous HCR.

Although there is no consensus regarding the ideal timing of clopidogrel administration in simultaneous HCR, there is published experience documenting the safe use of several strategies. For example, Zhao and colleagues have successfully used a 300 mg clopidogrel load just prior to PCI, which is immediately followed by CABG with sternotomy. Heparin is reversed with protamine after the surgical procedure, by which time it is assumed that P2Y12 inhibition is adequate. An alternate strategy reported by our group involves reversing the procedure order, with CABG (minimally invasive direct coronary artery bypass) prior to PCI. Heparin effect was not reversed with protamine, and a 300 mg clopidogrel loading dose was administered immediately after the hybrid procedure. With this strategy, bleeding was limited and adequate platelet inhibition was documented at 24 hours, as assessed by ADP-induced aggregation [Reicher 2008]. Similarly, Kiaii and colleagues have reported excellent results substituting bivalirudin for heparin during minimally invasive direct coronary artery bypass, continued through the PCI. Clopidogrel loading followed immediately after the sequential procedures. Multiple other combinations of CABG techniques (eg, robotically assisted totally endoscopic coronary artery bypass [TECAB], minimally invasive direct coronary artery bypass, and off-pump coronary artery bypass), procedure order, and timing of clopidogrel loading have been successfully utilized in individual patients. In simultaneous HCR, oral platelet inhibitors can be administered via a nasogastric tube during

the procedure. Correct nasogastric tube placement can be confirmed by the c-arm to ensure that the medication is delivered appropriately.

Prasugrel

Prasugrel, like clopidogrel, is an oral thienopyridine that acts via irreversible blockade of the $P2Y_{12}$ receptor. Although it is a pro-drug, absorption and conversion to its active metabolite is more rapid and reliable than clopidogrel, leading to more uniform and effective platelet inhibition [Wiviott 2010]. With less than 1 year of open-market utilization and concerns regarding surgical bleeding, experience with this drug in simultaneous HCR remains limited.

Ticagrelor

Ticagrelor represents a new direction in oral platelet inhibition. Its mechanism of action involves the $P2Y_{12}$ receptor, but it is not a thienopyridine and is direct-acting without need for conversion to an active metabolite. The effect is reversible with a plasma half-life of 12 hours. Although the relatively rapid onset of action, uniform platelet inhibition, and more rapid reversibility are appealing for simultaneous HCR, there are as yet no published data to guide its use in this setting.

UNDER DEVELOPMENT

Cangrelor

Cangrelor, like ticagrelor, is a non-thienopyridine, direct acting, reversible $P2Y_{12}$ receptor blocker, but it is administered intravenously, requiring only approximately 15 minutes for onset of action and subsequent resolution of effect when discontinued. Although initial clinical trials of this drug using it as an "add on" in PCI have been disappointing, its potential as a "bridging agent" to provide rapid and reversible platelet inhibition for simultaneous HCR is obvious [Harrington 2009].

Elinogrel

Ellinogrel is another direct acting $P2Y_{12}$ receptor blocker, but unlike all previously available agents, it can be administered both intravenously and orally. It could provide rapid and reversible platelet inhibition for simultaneous HCR using the intravenous formulation with a smooth transition to oral therapy after the patient stabilizes. Initial phase 2 trials have been encouraging, and a phase 3 trial is currently planned [Leonardi 2010].

Pegnivacogin/Anivamersen

Although heparin and bivalirudin have been used safely in simultaneous HCR, a rapidly and accurately titratable alternative would be a welcome addition to our pharmacologic armamentarium. Pegnivacogin and anivamersen are 2 nuclease-stabilized RNA aptamers. Pegnivacogin inhibits coagulation factor IXa, and its matched active control agent anivamersen is used to provide titratable reversal of the anticoagulant effect. A phase 2a trial comparing this agent to unfractionated heparin for anticoagulation in PCI has been successfully completed [Cohen 2010].

SUMMARY AND CONCLUSIONS

Balancing the risk of surgical bleeding with the risk of PCI-related thrombosis is a major challenge inherent in carrying out HCR. Currently available anticoagulants and platelet inhibitors have been used to provide safe and effective protection from thrombosis while limiting surgical bleeding, but there is no agreement on an optimal strategy, and each patient presents a unique pharmacologic and logistic puzzle. Inhibition of platelet aggregation has been demonstrated even during off-pump CABG [Poston 2005]. New anticoagulants and intravenous platelet inhibitors are in development, which will simplify and improve the hybrid procedure. As point of care assays to quantify platelet inhibition become more widely available, an individualized management may be important in considering dosing and timing of platelet inhibitors. Knowledge of the salient features of the available medications will allow the cardiologist and surgeon to design the optimal strategy for each patient.

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