Perioperative management of patients with intracoronary drug-eluting stents undergoing noncardiac surgery

Dr. Emilio B. Lobato, MD*

* Professor of Anesthesiology. University of Florida College of Medicine.

INTRODUCTION

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) by Gruntzig in 1977, major advancements have been made in the clinical practice of percutaneous coronary intervention (PCI).

Despite the widespread use of these devices, bare metal stents (BMS) have been associated with a 20-30% restenosis rate requiring reintervention. Restenosis occurs as a result of neointimal hyperplasia—growth of scar tissue within the stent—due to the proliferation and migration of vascular smooth muscle cells. This phenomenon is clinically evident within the first 6-9 months after stent placement, and occurs in response to strut-associated injury and inflammation.(2)

In addition to restenosis, PTCA and BMS implantation cause exaggerated endothelial injury and inflammation, rendering both the stent and vessel highly thrombogenic. A fibrinogen layer covers the stent surface, further inducing platelet activation and thrombosis. Adjunctive anti-platelet medication is crucial in preventing local coronary thrombosis, myocardial infarction (MI), and death. Current recommendations for patients with BMS include dual anti-platelet therapy with aspirin and clopidogrel, which are continued for 6 weeks to allow complete endothelialization of BMS. In a series of vascular surgery patients Wilson et al. reported similar findings. The incidence of MI and death were significantly lower among patients who underwent surgery after their 6-week course of aspirin and clopidogrel were completed.

In 2001, drug-eluting stents (DES) were introduced as a strategy to minimize restenosis and requirement for reintervention. The currently available polymer-coated stents contain antiproliferative agents which elute locally in the implanted coronary artery to prevent neointimal hyperplasia.

Initial animal studies demonstrated a clear benefit over BMS (4-6% restenosis versus 20-30%), and early clinical trials further supported this. A recent pooled analysis demonstrated a 74% reduction in the risk of target lesion revascularization for both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) compared to BMS. At present, 90% of all stents placed in the United States and Europe are DES.

Despite the enthusiasm that resulted with the advent of DES, incomplete endothelialization and stent thrombosis continue to plague these devices. Initial animal studies demonstrated complete endothelialization with BMS at 28 days, whereas DES uniformly showed incomplete healing at 180 days. Based on early observations in both animal and human studies, it was recommended that patients with DES receive dual anti-platelet therapy with aspirin and clopidogrel for at least 3-12 months, followed by lifelong aspirin therapy, depending on the stent placed and the pre-existing comorbidities which further increase the risk of stent thrombosis. Despite this regimen, late stent thrombosis (LST)—defined as occurring > 30 days post-stent insertion—remains a significant complication in patients with DES. Late stent thrombosis carries a 45% mortality rate. It presents as an ST-segment elevation myocardial infarction (STEMI) or sudden death. Late stent thrombosis has been documented in both clinical and autopsy studies in patients as far as 4 years after stent insertion. Further, LST is associated with the 1) discontinuation of clopidogrel + aspirin, 2) stable aspirin monotherapy, or 3) a hypersensitivity reaction to the stent polymer, or to the antiproliferative agent (sirolimus vs. paclitaxel). A recently published study reported that patients with DES implanted had significantly increased rates of death when clopidogrel was discontinued at 6-, 12-, and 24-months when compared to patients who remained on this therapy at the same time intervals(16).
CORONARY STENTS AND SURGERY

Several case reports have been published describing acute perioperative stent thrombosis associated with DES. Of significant concern is the unpredictability of the events, and lack of association with surgical risk. The common denominator appears to be the abrupt discontinuation of the thienopyridine. Thus, it is increasingly recognized that patients with DES pose a particular dilemma in the perioperative period. Current recommendations include delaying noncardiac surgery until the course of dual anti-platelet therapy must continue to prevent LST. It is clear, though, that patients must remain on aspirin forever. This scenario is particularly challenging to anesthesia providers, as there are no guidelines currently to manage these patients perioperatively.

The perioperative period is especially problematic because 1) surgery induces a hypercoagulable state; 2) surgeons often stop aspirin + clopidogrel preoperatively to minimize the risk of surgical bleeding, but without consulting their patients’ cardiologists; and 3) there is a high likelihood that the DES are not yet endothelialized. Thus, each DES patients, if stent thrombosis occurs, has a 45% chance of dying perioperatively.

There are two main issues to consider:

a) Timing of surgery. Recently, the main emphasis to minimize perioperative risk has been the interval between DES placement and the surgical procedure. A recent position paper now recommends that no elective surgery must take place within 12 months of DES placement, which coincides with the advocated length of dual antiplatelet therapy. While this may sound like a reasonable proposition, it is important to stress that it places the responsibility unto the interventional cardiologist. Moreover, this does not address issues such as unplanned urgent and emergent surgery. It is imperative that anesthesiologist acquire some basic understanding on the substrate that places patients at risk. The main determinant factor is delayed DES healing which translates into incomplete endothelial stent coverage. While it is virtually impossible to know the status of each individual patient, two recent retrospective reports have shed a light of optimism. No cases of perioperative DES thrombosis were identified in patients that underwent surgery more than 6 months after stent placement. Thus, it appears that some patients will be able to withstand perioperative stress better than others.

b) Continuation of perioperative antiplatelet therapy. This can be accomplished with one of three approaches. 1) transition of dual anti-platelet therapy in the perioperative period; 2) returning patients to their regimen as soon as possible postoperatively; 3) maintaining these patients on aspirin throughout the entire perioperative period, since perioperative STEMI and death have been associated with the discontinuation of aspirin in these patients(10).

It is important to mention that there is very little published evidence that any of these are effective, and that no prospective studies have been performed. The first approach is the least favored by surgeons, since perioperative dual antiplatelet therapy is associated with increased incidence of major bleeding. The second approach has many limitations since it places patients at risk for pre and intraoperative DES thrombosis, and there is no consensus on the optimal timing for reintroduction of dual antiplatelet therapy. The last approach is maintenance of ASA therapy with the hope to achieve a reasonable balance between the risk of DES thrombosis and perioperative bleeding. While there is substantial evidence on the safety of perioperative ASA in many surgical procedures (except perhaps TURP and craniotomies) there is no data pertaining patients with DES. Thus this approach like the others remains speculative.

Recently, a new proposal has been suggested, utilizing a preoperative infusion of GIIbIIIa inhibitors following discontinuation of chronic dual antiplatelet therapy. At present, this remains as a theoretical consideration, awaiting clinical confirmation.

CONCLUSION

Care for patient with a DES undergoing noncardiac surgery is a tremendous challenge for perioperative physicians. The determinant factor for DES thrombosis is incomplete endothelialization. This is caused not only by the rate of drug elution from the stent, but also by local factors (e.g. stent location, diameter of the vessel affected, hypersensitivity reactions), and systemic conditions (severe Diabetes, renal failure and persistent hypercholesterolemia). Clinically, abrupt cessation of clopidogrel therapy in the presence of delayed stent healing places patients at a very high risk for thrombosis and death. While several strategies have been proposed for noncardiac surgery patients, none of them has been proven superior; thus, each case should be considered individually. Intimate communication between cardiologists, anesthesiologist and surgeon must take place regarding timing of surgery, use of antiplatelet agents, perioperative surveillance, availability of coronary reperfusion strategies and patient’s understanding of potential risks.
REFERENCES