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Coronary artery stents and surgery; the basis of sound perioperative management

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ABSTRACT

The introduction of drug-eluting stents (DES) to interventional cardiology heralded a limited time of increased anaesthetic and surgical complications in patients implanted with these devices. The horns of the dilemma, in the anaesthetic and surgical management of patients in the first 3 - 6 months after the 1st generation DES insertion, were between the risk of bleeding from continued clopidogrel treatment and the risk of in-stent thrombosis and myocardial infarction following discontinuation of dual antiplatelet therapy, clopidogrel and aspirin. Initial accounts of early catastrophic cardiac and haemorrhagic complications, at the time of elective or emergency surgery, following DES insertion, were followed by equally worrying reports of in-stent thrombosis many months after DES insertion. Initial recommendations for the conduct of safe operations were propagated in the literature before formal guidelines were produced. This article summarises the issues identified in the development of interventional cardiology particularly DES and the requirement for ongoing antiplatelet therapy. The article reviews the treatment protocols that are still applicable for the different devices that have been deployed in clinical practice.

Keywords: Coronary Artery Stent; Thrombosis; Haemorrhage; Surgery Complication

1. INTRODUCTION

The development of balloon angioplasty by cardiologists was followed by the introduction of bare metal stents (BMS) to relieve obstructions in the coronary arteries. After the identification of endothelial proliferation, and endothelial hyperplasia, as a cause of late in-stent thrombosis, drug-eluting stents (DES) provided interventional cardiologists with a potentially safe solution to the problem. However, the DES themselves, along with the dual antiplatelet therapy contributed to a time of increased anaesthetic and surgical complications in patients with these devices implanted [1,2]. For patients requiring surgery in the first 3 - 6 months following implantation of a 1st generation DES, the horns of the dilemma were between the risk of bleeding from, continued clopidogrel and aspirin treatment and the risk of in-stent thrombosis and myocardial infarction following discontinuation of dual antiplatelet therapy, clopidogrel and aspirin [3,4].

After accounts of early catastrophic complications from both bleeding and stent thrombosis, at the time of elective or emergency surgery, following DES insertion, there were then also worrying reports of in-stent thrombosis many months after DES insertion [5-12]. Initial recommendations for anaesthetists, perioperative physicians and surgeons relating to the safe conduct of major operations were propagated in the literature and followed by formal guidelines [13-16].

In this article we summarise the issues relevant to the developments in interventional cardiology particularly DES and the requirement for ongoing antiplatelet therapy [17]. We review the treatment protocols that are still applicable to the different devices currently in use in clinical practice and identify safe and appropriate plans for dealing with emergency and elective surgery for these patients [16,18-21].

2. BALLOON ANGIOPLASTY, BARE-METAL AND DRUG-ELUTING STENT INSERTION

Following the demonstration of improved outcomes from coronary artery stenting at the time of balloon angioplasty intimal hyperplasia contributed to a measureable incidence of re-stenosis [22]. It was postulated that inhibiting the division of endothelial cells that might attempt to colonise the new intima in the bare-metal stent could reduce restenosis rates after angioplasty and stenting. The early trials documented further improvements in reducing re-stenosis rates with the use of antimitotic drugs included in the stent covering [23,24]. The drugs used were sirolimus and paclitaxel, which were incorporated into the covering of the metal in the stent and designed to be slowly washed out or eluted from the covering layer [25,26]. These were the drug-eluting stents (DES), which rapidly became very popular with interventional cardiologists [24,27].

The DES had reduced the incidence of intimal hyperplasia and restenosis so for cardiologists all problems seemed to be solved [24,28,29].

3. ANTIPLATELET THERAPY FOR BARE-METAL STENTS AND DRUG-ELUTING STENTS

A metal stent in the coronary circulation is at high risk of causing platelet activation and stimulating platelet thrombus formation [24,27]. Consequently anticoagulant precautions must be employed to prevent thrombus forming in the coronary circulation and precipitating the problem the stent is deployed to prevent, which is myocardial infarction [22,28,30]. The management of periprocedural anticoagulation has evolved along with the technology of the stents. Early bare-metal stents (BMS) were protected with heparin, but the success of the PRISM study confirmed the use of glycoprotein IIb/IIIa inhibitors with heparin as potent prophylaxis against thrombus formation in the presence of high-risk lesions in the coronary circulation [31-34]. With the introduction of long-acting oral P2Y12 receptor blockers the problem of preventing in-stent thrombosis appeared to be solved [8,35,36]. However the question that remained unanswered was "How long do patients need to remain on antiplatelet therapy following DES deployment". The answer was partly provided by the January 4th update from the US Food and Drug Administration, which recommended a longer duration of antiplatelet therapy for both paclitaxel and sirolimus (CYPHER and TAXUS respectively) stents than was then currently included in the product labelling (US Food & Drug Administration update available at http://www.fda.gov/cdrh/news/010407.html last accessed July 2013). The same update admitted that the optimal duration of antiplatelet therapy, specifically clopidogrel, was unknown. The update quoted the then current ACC/AHA/SCAI PCI Practice guidelines, which recommended that patients receive aspirin indefinitely plus a minimum of 3 months clopidogrel for sirolimus (CYPHER) DES patients and 6 months clopidogrel for paclitaxel (TAXUS) DES patients [37]. Meanwhile, further advances with second generation DES such as everolimus-eluting stents (EES) or zotarolimus-eluting stents (ZES) and third generation DES with biodegradable polymers and abluminal coating such as biolimus-eluting stent (BES) have largely replaced first generation DES. These new stents offer improved stent deliverability with equal or superior anti-proliferative efficacy and a consistently lower rate of late or very late stent thrombosis [38,39].

4. EMERGING PERIOPERATIVE RISK

Unfortunately the population that required angioplasty and stent insertion was middle-aged males and elderly males and females [40]. This was exactly the population of patients that often required surgery for other urgent and elective conditions and the treatment of these patients with clopidogrel at the time of surgery caused considerable perioperative bleeding complications [1,3,8,41, 42]. However the cessation of clopidogrel at the time of operation also increased the risk of in-stent thrombosis with a significant risk of acute myocardial infarction and death [1,3,6,42]. The reported high mortality rates from in-stent thrombosis were not experienced by the Geelong group who reported no mortalities in their three patients with in-stent thrombosis [6,8,9,42-47].

Some authors have reported a difference in the residual effect of the "first generation" Paclitaxel and Sirolimus DES [24,25,44]. The advice to surgeons and perioperative physicians can therefore be modified to reduce the time when clopidogrel is required following Sirolimus DES insertion [48-50]. However the requirement for clopidogrel or bridging treatment at the time of surgery may still need to be considered following first generation DES insertion [51]. In-stent thrombosis has been reported up to 7 years following first generation DES insertion [52].

5. THE "BRIDGING" SOLUTION

The solution was developed by interventional cardiologists, perioperative physicians and pharmacists together. This was a bridging therapy that recognised the findings of the PRISM study and the pharmacokinetics of the oral P2Y12 inhibitor clopidogrel and the intravenous glycoprotein IIb/IIIa inhibitor tirofiban [46,47,53, 54]. In Geelong we pioneered the introduction of this

novel "bridging therapy", which appeared to avoid the dual risks of major haemorrhage and in-stent thrombosis [46,47]. The risk of major haemorrhage was avoided by replacing the long acting P2Y12 inhibitor, clopidogrel with a shorter acting intravenous glycoprotein IIb/IIIa inhibitor tirofiban and the anticoagulant heparin in line with the PRISM study [33,55]. The risk of in-stent thrombosis was avoided by strict timing of the drug regime to minimise the time the patient was at risk of thrombosis [46,47]. Using this bridging therapy the Geelong group was able to demonstrate prevention of thrombotic and bleeding complications in about 20 patients [46]. Subsequent authors have endorsed the same principle and achieved similar results without the addition of heparin but the principle of "bridging therapy" for these patients remains sound [53,54]. In Milan Savonnito's group had collected data on an alternative bridging therapy using tirofiban alone with no in-stent thrombosis, although bleeding problems were reported in this group of patients [53]. We have calculated that with the 71 patients reported in the literature and our own unreported experience there have now been >100 patients treated with tirofiban "bridging therapy" with no in-stent thrombosis and minor bleeding complications [47,53,54]. Compared to the earlier "disastrous" data reported for urgent or emergency surgery on patients with DES receiving clopidogrel the bridging therapy showed considerable benefit.

6. THE "BIOCOMPATIBLE" STENT

The interventional cardiology device industry was also evolving with new ideas and a new device trialled that could replace the old antimitotic DES [56]. This was a bare-metal coronary stent that contained a monoclonal antibody that actually attracted endothelial cells to colonise the device and therefore significantly reduced the time that the thrombus generating bare metal was exposed to the platelets and blood clotting factors [57,58]. The newer monoclonal antibody containing BMS have the same intent as the earlier stents. These BMS, unlike their precursors, need a much shorter time of treatment with the potent long acting P2Y12 inhibitor clopidogrel with only 10 days of treatment required [59]. These "biocompatible" stents have further improved the safety envelope, and again modified the guidelines for aspirin, antiplatelet drugs and anticoagulation in the perioperative period.

The upshot of the evolution in the practice of interventional cardiologists and the interventional device manufacturers is that there are now several devices in use with different recommendations for their peri-procedural and subsequent perioperative management [15] (See **Table 1**).

Table 1. Summary of guidelines for perioperative management after stent insertion.

Stent Type	Clopidogrel Treatment	Perioperative management
Bare-metal stent BM	4 - 6 weeks	Tirofiban/Heparin "bridging" if on clopidogrel
CYPHER sirolimus DES TAXUS paclitaxel DES	12 months 12 months	Tirofiban/Heparin "bridging" if on clopidogrel
GENOUS™ R Stent	10 days clopidogrel	No bridging required
Second generation DES	12 months (if implanted for ACS) otherwise 6 months	Tirofiban/Heparin "bridging" if on clopidogrel

In summary the following guidelines are now current for stents deployed in the coronary circulation.

1) Bare metal stents

These devices will require 4 - 6 weeks of dual antiplatelet therapy after insertion followed by aspirin alone. If surgery is required in the first 4 weeks after insertion bridging therapy with tirofiban should be considered if aspirin cannot be maintained. Heparin is optional but the safety profile for bridging with tirofiban is good [47,53, 54]. If surgery is required more than 4 weeks after insertion of a BMS clopidogrel can be ceased and aspirin should be continued at the time of surgery [60].

2) First generation DES: Sirolimus or Paclitaxel DES

The current data and available reports suggest an increased risk of perioperative in-stent thrombosis associated with DES in patients undergoing surgery within 12 months after a percutaneous coronary intervention (PCI) [60]. Furthermore, sudden withdrawal of antiplatelet therapy may trigger a rebound effect and temporarily increase the risk of in-stent thrombosis [61,62]. Therefore, prevention of such potentially high risk coronary events is crucial. Previously reported data have suggested that the rate of major adverse cardiovascular events with DES were higher in early surgery compared with late surgery (>12 months) with no significant difference between either sirolimus eluting stents or paclitaxel eluting stents. Clopidogrel and aspirin should be continued for 12 months after insertion [63]. If surgery is required during this interval bridging therapy with tirofiban and optional heparin should be used to prevent in-stent thrombosis and reduce the risk of catastrophic haemorrhage [47,53,54]. Aspirin should be continued for life as discontinuation, even more than 1 year after insertion, may lead to stent thrombosis [60].

3) Biocompatible stent (Genous™ bio-engineered R-stent™)

The Genous™ bio-engineered R-stent™ would appear to be the safest stents of all with respect to surgical and anaesthetic interventions, with such a short duration of

clopidogrel treatment that the likelihood of complications at the time of surgery is minimal [59]. After stenting patients receive clopidogrel for 10 days and then lifelong aspirin treatment.

4) Second generation DES (EES & ZES)

These second generation stents are the Everolimus eluting stent (EES) and the Zotarolimus eluting stent (ZES). The reports from several recently published studies have shown newer generation DES have beneficial efficacy and safety despite a relatively short duration of dual antiplatelet therapy of 3 to 6 months. However some patient-related factors and device-related criteria that determine safety and allow early dual antiplatelet therapy withdrawal, or interruption e.g. for urgent surgery, still have to be determined [64,65]. It remains unclear whether there is a "safe" time threshold with the 2nd generation DES, for clopidogrel discontinuation, after which event rates are negligible.

7. CONCLUSIONS

The evolution of stent insertion following coronary angioplasty has been complex with four different types of stent deployed in the coronary circulation after the procedure. We have described the recommended use of antiplatelet agents and management of patients who have had coronary stents inserted in the setting of elective or emergency surgery.

Information about the properties of each stent and the details of the antiplatelet therapy inform the process of management for perioperative physicians and anaesthetists at the time of urgent or elective surgery in these patients. Different devices require different management plans at different times after insertion. By summarising this information, we hope to facilitate the optimal management of these patients.

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