"My patient has a coronary stent": concerns for the anaesthetist

Lines D, Chris Hani Baragwanath Academic Hospital
Correspondence to: Des Lines, e-mail: lines@pixie.co.za

Ⓟ **Peer reviewed © Medpharm** **S Afr Fam Pract 2013;55(3)(Suppl 1):S13-S17**

Introduction

Percutaneous coronary intervention (PCI) is a relatively new mode of therapy for the management of patients with coronary artery disease (CAD). Balloon angioplasty, a type of PCI, was first performed in the late 1970s, but suffered the main complications of early restenosis because of an inflammatory reaction in the media, causing neointimal proliferation that required further intervention. In 1986, the French cardiologist, Puel, implanted the first coronary stent in a human in France. However, it was only in 1994 that the US Food and Drug Administration approved the use of coronary stents in human subjects. It has been shown that PCI is no more effective in preventing a major cardiac event or death, than optimal medical therapy, in patients with stable CAD. However, PCI has shown benefits over medical therapy in patients with unstable coronary disease.

As an anaesthetist, it is becoming increasingly common to be confronted, either at the time of surgery, or as part of a multidisciplinary team, with a patient who has a stent. This necessitates the anaesthetist having to decide the best way in which to handle the patient who presents for elective surgery. This lecture will only deal with the patient who presents for noncardiac surgery, either as an elective procedure, or for noncardiac surgery of an emergent nature.

To illustrate the difficulty in managing stents for noncardiac surgery, and also to illustrate the confusion and lack of definitive studies to guide the management thereof, an actual case will be presented.

Case study

A 56-year-old man presented for a face lift using a routine cosmetic plastic surgery slate. The patient had had an uneventful face lift eight years before. Six months after the first face lift, and seven-and-a-half years prior to the present surgery, the patient had a stent inserted by a cardiologist for what was believed to be stable coronary artery disease (CAD).

The patient had been referred back to his cardiologist by the plastic surgeon on discovering that he had a stent in place, prior to proceeding with the surgery. He was on aspirin and the surgeon was unwilling to operate because of the risk of haematoma postoperatively. The patient consulted his cardiologist, who advised that it would be safe to stop the aspirin a week before his surgery. After taking a history and conducting an examination, he was considered to be well. Nothing suggested that he had active CAD. He was a regular gym attendee, with excellent effort tolerance. His only medication was atenolol 50 mg daily for hypertension, which was well controlled. The patient had no knowledge of the type of stent that had been implanted previously. He could only say that he had been on Plavix® for approximately six months. The surgery was uneventful and the patient was sent back to the ward postoperatively. He planned on restarting his aspirin a few days after the surgery.

Two hours postoperatively, the patient developed acute chest pain and an ST-segment elevation anteroseptal infarction was diagnosed on electrocardiogram. The patient was immediately seen by a cardiologist who took him for an angiogram and local clot lysis. It was confirmed on angiogram that he had an in-stent thrombosis. The clot was effectively lysed and the patient transferred to the critical care unit (CCU) for observation.

Unfortunately, he continued to infarct and the cardiologist had no choice but to repeat the angiogram and re-stent the vessel. He was placed on aspirin and clopidegrel as part of his dual anti-platelet therapy. The following day, the patient had bled into the face and the haematoma was so large that it had tracked into his airway. The patient was taken to theatre for clot evacuation. On induction, the airway collapsed and the attendant anaesthetist was unable to visualise any structures at intubation. The patient suffered a cardiorespiratory arrest and was severely hypoxic for a number of minutes while an airway was secured with an endotracheal tube. He remained in CCU on inotropes for a few days. Fortunately, he survived the episode and discharged himself five days later.

A basic understanding of stents, the therapy that patients are on, and the risks associated with percutaneous coronary intervention (PCI), is needed in order to manage these patients safely in the perioperative

period. It is not uncommon for some surgeons and dental practitioners to be poorly informed about stents and the need for appropriate therapy in order to minimise the complications of stents in the perioperative period. A Canadian survey of anaesthetists in 2007 revealed that 63% of respondents were unaware of recommendations about the appropriate duration between stent placement and subsequent surgical procedures.

The following questions need to be answered regarding patients with coronary stents who present for noncardiac surgery:

- What was the indication for the stent (stable CAD, failed medical therapy, or an acute coronary syndrome)?
- How long ago was the stent placed?
- What type of stent was placed and where, and was it an on-off label placement? A stent placed in a left main or proximal left anterior descending artery would carry a much higher mortality were it to thrombose, compared to a stent thrombosis in a more distal vessel.
- What antiplatelet therapy was, or is the patient on, and for what period has he or she been on it?
- Has the patient interrupted his antiplatelet therapy perioperatively, and on whose instruction?
- In the first year after stent placement, is the surgery of a purely elective nature, or is it noncardiac surgery of an emergent nature?
- Is the noncardiac surgery contraindicated in the presence of antiplatelet agents?
- Has the patient developed any new symptoms after stent placement that suggest restenosis or in-stent thrombosis with impending acute coronary syndrome (ACS)?
- Has the patient consulted his or her cardiologist prior to having noncardiac surgery?
- Has the patient been adequately informed of the risks that are associated with stents and noncardiac surgery?

Types of stents

Less than 5% of PCIs that are performed nowadays involve balloon angioplasty only. Balloon angioplasty has a 30-60% rate of restenosis in the first 6-12 months, necessitating further intervention. Placement of a stent to provide a scaffold for the vessel is now the most common PCI that is performed. A stent is made from a metal lattice (metallic alloy) which expands once placed in the diseased coronary. It provides a scaffold with which to keep the vessel open. If this metal lattice is uncovered, it is known as a bare-metal stent (BMS). If the lattice is covered with a polymer and an antiproliferative drug embedded in it to allow the drug to be released slowly over time, it is known as a drug-eluting stent (DES).

A BMS allows a fairly rapid re-endothelialisation over the metal struts, and theoretically, once this is complete, the risk of in-stent thrombosis is less. This process is more or less complete in six weeks. The key biological event associated with restenosis is the proliferation of smooth muscle cells in response to the expansion of a foreign body against the vessel wall, and the trauma that it inflicts. Repeat revascularisation at one year remains relatively high at 10-20%. The advantage of the BMS is that antiplatelet medication can theoretically be given for a short time until the metal struts are covered with endothelium, and then tailored.

On the other hand, the DES prevents aggressive smooth muscle proliferation when the antiproliferative agent is released slowly over a few weeks into the vessel wall. The overall rate of restenosis is less than two per cent. The downside is that the metal struts are exposed for a longer period of time. This increases the chances of in-stent thrombosis. Therefore, theoretically, a DES has a higher rate of late in-stent thrombosis, but a reduced rate of restenosis (reduction of 50-70% in target lesion revascularisation by a DES, compared to a BMS).

The currently approved DESs all have a durable polymer, which remains permanently on the stent after the drug is eluted. This polymer may result in vascular inflammation or delayed endothelialisation (persistent endothelial dysfunction) and healing, therefore contributing to the risk of in-stent thrombosis. More recently, some DESs are coated with a thromboresistant polymer which may further reduce the risk of in-stent thrombosis. Studies seem to indicate that there is no difference in stent thrombosis in patients on appropriate antiplatelet therapy, when comparing a BMS and a DES placed in simple coronary lesions. Because of the fear of late stent thrombosis with the DES, their use declined in 2006. In December 2006, the US Food and Drug Administration announced that the use of a DES "on label" was not associated with an increased risk of MI and death. However, DESs are increasingly being placed in "off label" indications in patients with complex CAD, where the rate of in-stent thrombosis is higher (overlapping, multiple stents and bifurcating lesions).

The first-generation DES used sirolimus (rapamycin) an immunosuppressant agent (rapamycin), or paclitaxel a natural product with anti-tumour properties. Subsequent-generation DESs have used everolimus, a kinase inhibitor, and zotarolimus, a semi-synthetic derivative of rapamycin. Ongoing trials are examining the advantages of the second-generation stents over the first-generation ones, looking particularly at late in-stent thrombosis, with the consequences of myocardial infarction (MI) and death. The search for a safer stent has stimulated active research in this area. Newer stents being assessed include stents where the eluting drug is delivered for a shorter period of time and then stops, a polymer-free stent with less associated chronic inflammation, stents that are absorbed, stents with a bioengineered coating to quickly create a thin all-natural layer in the artery, and stents with a variety of coatings on various platforms, such as

platinum, chromium cobalt and diamond carbon. These newer-generation stents will cost a lot more than stents in use today. A DES costs as much as four times the price of a BMS, and the total cost of placing a DES in South Africa, including hospitalisation and consulting fees, is approximately R70 000 for a single DES.

Assuming a patent stent at the time of noncardiac surgery, the major concern for the anaesthetist relates to the side-effects of the anti-platelet agents, i.e. serious bleeding, and the risk of developing a stent thrombosis in the prothrombotic perioperative period.

Post-percutaneous coronary intervention selection of antithrombotic therapy

Stent thrombosis

Stent thrombosis is an uncommon, but serious complication that almost always presents as death or a large nonfatal MI, usually with ST-segment elevation. The most important risk factors for stent thrombosis are suboptimal flow on coronary angiography, and premature cessation of antiplatelet therapy. Less than 10% of cardiac deaths after stent placement are due to stent thrombosis. The cumulative frequency of stent thrombosis occurs with similar regularity in patients with a BMS or a DES, as long as patients are treated with dual antiplatelet therapy for the recommended duration of the particular stent. BMS thrombosis usually occurs within the first 24-48 hours, or much less within the first month after stent placement. Thrombotic events with a BMS are uncommon after 30 days of treatment with dual antiplatelet therapy. Similar to a BMS, most episodes of DES thrombosis occur in the first years, and many of these within the first 30 days.

Since the introduction of PCI more than three decades ago, the rates of procedural success and associated ischaemic complications have improved substantially. This improvement is mainly because of the improved design of the stents and advancements in antithrombotic pharmacotherapy, targeted at inhibiting platelet activation and aggregation, and thrombin generation or activity that occurs at the site of vessel injury after plaque disruption.

Early studies with a BMS employed a potent antithrombotic regimen of aspirin and warfarin, a vitamin K antagonist. This regimen resulted in a significant bleeding risk after the procedure and an in-hospital stent thrombosis of 3-4%. With the introduction of the combination of thienopyridine antiplatelet agents with aspirin, the risk of bleeding, stent thrombosis and MI decreased substantially. Dual antiplatelet therapy has now become the standard of care, after PCI. Newer antiplatelet agents are being trialled to further reduce the risk of bleeding and improve the rate of stent thrombosis.

The usual antiplatelet therapy for patients is either aspirin alone, or together with clopidogrel.

Aspirin

Aspirin irreversibly blocks cyclo-oxygenase, blocking the production of thromboxane A2, thereby inhibiting platelet aggregation. Aspirin represents the cornerstone of antiplatelet therapy, before and after PCI. The recommended dose of aspirin by most medical societies, after PCI, is between 75 and 100 mg a day. No further benefit in decreasing ischaemic events is obtained with higher doses. There is an increase in bleeding risk with the higher doses.

The $P2Y_{12}$ inhibitors

Inhibition of the $P2Y_{12}$ subtype of the adenosine diphosphate (ADP) receptor attenuates the aggregation of platelets through inhibiting ADP-mediated platelet activation. The oral $P2Y_{12}$ inhibitors include the thienopyridine derivatives, ticlopidine, clopidogrel and prasugrel, as well as the non-thienopyridine agent, ticagrelor.

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor has resulted in a reduced incidence of stent thrombosis of less than one per cent.

The optimal duration of $P2Y_{12}$ therapy is still undefined, and will depend largely on the type of stent inserted. The placement of a DES, as opposed to a BMS, appears to increase the risk of late stent thrombosis because of impaired endothelialisation and inflammation at the site of deployment. In this setting, and prior to endothelialisation in the first six weeks or so after a BMS placement, the premature discontinuation of dual antiplatelet therapy appears to be the most significant risk factor for stent thrombosis, and in particular, late stent thrombosis after DES placement.

In 2007, the American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines recommended at least 12 months of dual antiplatelet therapy with a DES. Studies are ongoing with regard to evaluating the role of dual antiplatelet therapy beyond 12 months. The Dual Antiplatelet Therapy (DAPT) study will compare 12 and 30 months of dual antiplatelet therapy with aspirin, plus either clopidogrel or prasugrel, in stented patients. It is recommended that it is reasonable to continue dual antiplatelet therapy beyond 12 months in patients who are at high risk of stent thrombosis (bifurcation lesions, diabetics and multiple overlapping stents), as long as the risk to benefit ratio of prolonged dual antiplatelet therapy is carefully considered.

Recommendations for the prevention of stent thrombosis after coronary artery stenting in stable patients were also made in 2011 guidelines from the American College of Cardiology Foundation (ACCF), the AHA, the Society for Cardiovascular Angiography and Intervention (SCAI), and in 2012 guidelines from the American College of Chest Physicians (ACCP).

The 2011 ACCF/AHA/SCAI guideline makes strong recommendations for the use of clopidogrel 75 mg daily

in addition to aspirin:

- Clopidogrel should be given for a minimum of one month, and ideally for up to 12 months, to patients receiving a BMS for a non-ACS indication, if the patient is not at increased risk of bleeding.
- Clopidogrel should be given for at least 12 months to patients receiving a DES for a non-ACS indication, unless the patient is at increased risk of bleeding, in which case it should be given for a minimum of two weeks.

The 2012 ACCP guideline makes the following recommendations for the use of clopidogrel, in addition to aspirin:

- A strong recommendation is made to give clopidogrel for one month to patients who have undergone an elective PCI with a BMS. A weak recommendation is made to provide clopidogrel for the subsequent 11 months. A strong recommendation is made to give single antiplatelet therapy after 12 months.
- A strong recommendation is made for clopidogrel to be taken for 3-6 months, with the shorter duration for the sirolimus-eluting stents and the longer duration for paclitaxel-eluting stents, to patients who have undergone elective PCI with a DES. A weak recommendation is made to give clopidogrel for 12 months after the initial 3-6 months. A strong recommendation is made for single antiplatelet therapy to be given after 12 months.

The estimated incidence of very late stent thrombosis varies between 0.2% and 0.6% per year after the first year. The data that support these observations are derived from studies of mostly first-generation DES. Lower yearly rates may exist for newer-generation DES.

Stenting in the face of unstable patients (those with ACS) carries a greater risk of stent thrombosis and the general recommendation is dual antiplatelet therapy is used for at least one year for a BMS, and possibly longer for a DES. As always, the benefit needs to be weighed against the risk of bleeding in these patients.

Ticlopidine

Ticlopidine was the first available thienopyridine. Aspirin with ticlopidine reduced the incidence of death, target lesion revascularisation, vessel thrombosis or MI at 30 days to 0.5%, compared to 3.6% with aspirin as monotherapy, and 2.7% with aspirin plus warfarin, in the STent Antithrombotic Regimen Study (STARS) study. However, ticlopidine has largely been replaced because of the high incidence of associated adverse effects (thrombotic thrombocytopenic purpura and agranulocytosis).

Clopidogrel

Randomised trials have shown that ticlopidine and clopidogrel have similar efficacy in terms of major adverse cardiac events, but clopidogrel was associated with significantly fewer side-effects than ticlopidine.

The efficacy of clopidogrel may be reduced when used in combination with a proton-pump inhibitor. Clopidogrel is a prodrug and needs to be converted into an active drug by oxidation mediated mainly by the liver enzyme cytochrome (CYP)2C19, the same enzyme that metabolises the proton-pump inhibitors. Loss of function mutations in the CYP2C19 allele (2-14% of the USA population) has also been associated with a worse clinical outcome for patients taking clopidogrel after an ACS event. The ACC, AHA and the American College of Gastroenterology recommend the use of a proton-pump inhibitor with a thienopyridine antiplatelet agent in those at high risk of gastrointestinal bleeding. Further studies are ongoing as to whether genetic testing or platelet function testing should play a role in the selection of the dose of clopidogrel, or that of an alternative. However, in a consensus document, the ACC and AHA have stated that an alternative agent should be used in patients at high risk of an adverse event who are identified as poor metabolisers of clopidogrel.

Prasugrel

Prasugrel is a possible alternative to clopidogrel. Prasugrel is a newer, thienopyridine antiplatelet agent, which has a faster onset of action and is a more potent inhibitor of platelet activity than clopidogrel. Unlike clopidogrel, prasugrel is effective in most patients. However, it is contraindicated in patients with a history of transient ischaemic attacks or strokes, and should be avoided in people over the age of 75.

Cangrelor

A new, rapidly acting, reversible ADP-receptor blocker is undergoing phase 111 trials. It binds selectively and specifically to the $P2Y_{12}$ receptor subtype on the surface of the platelet. Unlike the thienopyridine drugs, it offers reversible antiplatelet inhibition with a rapid onset and offset of action, and does not need activation or conversion by the liver to an active metabolite. It is given by intravenous infusion, with a half-life of 3-5 minutes. Platelet function returned to normal within 60 minutes of discontinuing the infusion. This drug may offer a more suitable alternative to the drugs that are presently being used for bridging therapy in the future.

Ticagrelor

Ticagrelor is a reversible, direct-acting, non-thienopyridine inhibitor of the $P2Y_{12}$ ADP receptor. It too has a faster onset and is a more potent inhibitor of platelets than clopidogrel. The PLATelet inhibition and patient Outcomes (PLATO) Invasive analysis examined 13 408 patients, and suggested that ticagrelor may be an attractive option for ACS patients who are being managed for planned, early invasive strategy.

Recommendations

Noncardiac surgery may be required in patients on dual antiplatelet therapy after a PCI with stenting. Cessation of dual antiplatelet therapy, together with the prothrombotic and proinflammatory state of surgery, may contribute to an increased risk of adverse cardiovascular events, such as stent thrombosis, MI and death. On the other hand, for some patients, such as those requiring intracranial surgery or transurethral resection of the prostate (TURP) surgery, the increased risk of bleeding on dual antiplatelet therapy may be greater than that of an adverse cardiovascular event off such therapy.

Patients presenting for urgent life-threatening surgery, who are on dual antiplatelet therapy, need to be assessed for whether or not a platelet transfusion is needed versus the risk of life-threatening bleeds.

It is recommended that elective surgery is delayed for at least one year, irrespective of stent type, and thereafter that it should be performed on aspirin, if at all possible.

It is suggested that an attempt is made to delay surgery of a semi-urgent nature for at least six weeks after the placement of a BMS, and at least six months after a DES. Ideally, the antiplatelet agents should not be stopped, even after this period, but if deemed necessary, the clopidogrel should be stopped for five days prior to the surgery, and ideally the surgery should be performed under the cover of aspirin. The idea of "bridging therapy" will be discussed.

Bridging therapy

Bridging therapy may be considered in situations where clopidogrel must be stopped, and the patient is at high risk of developing stent thrombosis. Many bridging regimens have been suggested, with little definitive evidence for one over another. Suggested regimens have included unfractionated heparin, subcutaneous injection of low-molecular-weight heparin, nonsteriodal anti-inflammatory drugs and glycoprotein 11b/111a inhibitors.

The concept of bridging a gap in platelet $P2Y_{12}$ receptor-blocker therapy, using a glycoprotein 11b/111a inhibitor, such as tirofiban or eptifibatide, is under investigation. These agents have an even greater antiplatelet activity as the glycoproteins on the platelet surface represent the final common pathway in platelet aggregation. They offer reversible platelet inhibition, and normal platelet function returns within 6-8 hours after stopping the infusion. Some centres have been using bridging therapy in patients at high risk of stent thrombosis.

Some investigators (Bolsin et al) have used unfractionated heparin together with tirofiban in high-risk patients, and claim that none of their patients, in an admittedly small population, suffered any adverse cardiac event or excessive bleeding. The use of concomitant anticoagulant therapy, with its additional risk of bleeding, and without any clear rationale for the prevention of stent thrombosis, cannot be recommended at this point in time.

Based on increasing experience in treating these patients, there seems to be some justification in using the G11b/111a inhibitors as bridging therapy as these are effective.

Ticagrelor, the reversible, direct-acting non-thienopyridine inhibitor of the $P2Y_{12}$ ADP receptor may also have a role to play in bridging therapy. It has a shorter clinical half-life than clopidogrel and prasugrel, and can be stopped 48-72 hours before surgery. Its role in this setting has not yet been fully evaluated.

Conclusion

Patients with coronary stents, who are on dual antiplatelet therapy and undergoing noncardiac surgery, are exposed to a high risk of cardiovascular and haemorrhagic complications. These complications are associated with a high risk of death. In this lecture, we have explored several specific and common preoperative predictors of these complications. Maintaining oral antiplatelet therapy throughout surgical and invasive procedures is key to avoiding cardiovascular complications, without increasing haemorrhagic risk. If it is absolutely necessary to interrupt antiplatelet therapy, which is rare, a delay between the interruption and surgery of less than five days is strongly advised for patients being treated with aspirin, clopidogrel or both.

Bibliography

1. Cutlip D, Windecker S. Elective non-cardiac surgery after percutaneous coronary intervention. UpToDate [homepage on the Internet]. 2012. Available from: http://www.uptodate.com/contents/elective-noncardiac-surgery-after-percutaneous-coronary-intervention
2. Cutlip D, Abbott JD. Drug eluting compared to bare metal intracoronary stents. UpToDate [homepage on the Internet]. 2012. c2013. Available from: http://www.uptodate.com/contents/drug-eluting-compared-to-bare-metal-intracoronary-stents?
3. Cutlip D, Abbott JD. Coronary artery stent thrombosis: incidence and risk factors. UpToDate [homepage on the Internet]. 2012. c2013. Available from: http://www.uptodate.com/contents/coronary-artery-stent-thrombosis-incidence-and-risk-factors
4. Cutlip D. Anti-platelet therapy after coronary artery stenting. UpToDate [homepage on the Internet]. 2013. c2013. Available from: http://www.uptodate.com/contents/antiplatelet-therapy-after-coronary-artery-stenting?
5. Vavalle JP, Harrington RA. Post-PCI selection of anti-thrombotic therapy. NBScience Ltd[homepage on the Internet]. c2013. Available from: http:www.nbscience.com/antithrombotic-therapy
6. De Vile MPJ, Foex P. Anti-platelet drugs, coronary stents, and non-cardiac surgery. Continuing Education in Anaesthesia, Critical Care and Pain. 2010;6(10):44.
7. Albaladejo P, Marret E, Samama CM, et al. Non-cardiac surgery in patients with coronary stents. Heart. 2011;97(19):1566-1572.
8. Brancati MF, Giammarinaro M, Burzotta F, et al Outcome of non-cardiac surgery after stent implantation in the DES era. J Invasive Cardiol. 2011;23(2):44-49.
9. Seiler C. Peri-operative management after coronary stenting. Interv Cardiol. 2012;4(2):245-252.
10. Bolsin S, Conroy M, Osborne C. Tirofiban "bridging" therapy for patients with drug eluting stents undergoing non-cardiac surgery. Br J Anaesth. 2010;104(6):779-188.