

Case Report

Successful management of patients with a drug-eluting coronary stent presenting for elective, non-cardiac surgery

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This paper describes the management of three patients for elective surgery with drug-eluting stents in the coronary circulation. The risks posed at the time of surgery by such patients include acute coronary syndromes, as a result of stent thrombosis, after cessation of anti-platelet therapy and excessive bleeding from continued anti-platelet therapy. We describe a regime for the management of such patients that successfully avoided these risks in three patients with paclitaxel drug-eluting stents requiring elective non-cardiac surgery.

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A recent change in the management of patients requiring coronary artery stents has been the introduction of a polymer-based, coronary artery stent eluting sirolimus or paclitaxel. Drug-eluting stents are rapidly replacing bare metal stents in interventional cardiology.^{1,2} A drug-eluting stent releases a compound that prevents endothelial cells coating the bare metal of the stent. A bare metal stent in the coronary circulation is a high-risk lesion for platelet occlusion. The most effective treatment to prevent thrombosis in such a high-risk lesion in the coronary circulation is a combination of tirofiban and heparin.

Both clopidogrel and tirofiban are anti-platelet agents accepted as desirable in the treatment of acute coronary artery lesions.^{3,4} Tirofiban is a direct inhibitor of the platelet surface glycoprotein IIb/IIIa. This glycoprotein is the final linkage of platelet aggregation. The kidneys clear tirofiban, with full coagulation restored 8 h after cessation of an infusion. Clopidogrel is a thienopyridine that selectively binds to the adenylate cyclase-coupled ADP receptor on the surface of the platelet, thus reducing the binding of pro-aggregating substances to the platelet surface. Clopidogrel is a pro-drug that requires metabolism to the active agent.⁵

Drug-eluting stents and dual anti-platelet therapy with aspirin, and a thienopyridine reduce stent rethrombosis rates to <2%.¹ However, the consequences for patients undergoing surgery, or patients with potential bleeding conditions, in whom a drug-eluting stent has been inserted, with

dual anti-platelet therapy are serious and potentially life threatening.^{1,2} We report three cases of patients undergoing elective surgery from 49 days to more than 1 yr after insertion of drug-eluting stents in the coronary circulation.

Case report 1

A 76-yr-old man suffering a 'Non S-T Elevation Myocardial Infarction' (NSTEMI) was transferred from a regional hospital to a tertiary centre for further management. Coronary angiography performed during his admission resulted in the placement of two intracoronary stents; a bare metal stent to his left anterior descending (LAD) coronary artery, and a paclitaxel-eluting stent in the first diagonal branch of the LAD coronary artery.

After this procedure he was commenced on clopidogrel, aspirin and atenolol.

His admission was complicated by confusion, which was attributed to hypercalcaemia. The endocrinology unit and a general surgical team decided that the patient should undergo elective parathyroidectomy. A booking was made for parathyroidectomy 49 days after coronary stenting resulting in an anaesthetic consultation. The anaesthetist (SB) liaised with a cardiologist (AB), intensive care specialist (NO) and senior pharmacist (GB) about how to best manage the patient's anti-platelet therapy in the perioperative period. A plan was carefully documented and forwarded to all parties involved in the patient's management. The patient

remained a general medical inpatient throughout this period as a result of his ongoing confusion.

Five days before surgery the patient's clopidogrel was ceased. Three days before surgery he was transferred to the cardiology unit and commenced on tirofiban and unfractionated heparin infusions. These were maintained until midnight on the night before surgery. Aspirin therapy was continued throughout.

Surgery was performed on a morning list with a high dependency bed available for postoperative care. The anaesthetic technique involved large bore i.v. access, intra-arterial blood pressure monitoring and Bispectral Index analysis (BIS Aspect Medical systems International BV, De Meern, The Netherlands). A 5-lead ECG with S-T segment analysis was also used.

Anaesthesia was induced with fentanyl (100 mcg) and propofol (110 mg). Muscle relaxation was achieved with cisatracurium (10 mg). An oxygen/air/desflurane mixture was used for maintenance with morphine (7.0 mg) and bupivacaine 0.5%+adrenaline infiltration (10 ml of 0.5%) was utilized for analgesia. Metaraminol 4 mg and metoprolol 1 mg were used during the case to maintain haemodynamic stability within 10% of baseline values. The parathyroidectomy proceeded uneventfully, with minimal blood loss and no evidence of myocardial ischaemia. The patient did not require reversal of neuromuscular block before extubation. Duration of anaesthesia was 110 min.

After operation the patient was managed in a high dependency unit for 24 h, with overnight invasive blood pressure and respiratory monitoring before returning to a general surgical ward. Clopidogrel was recommenced on the first postoperative day with a loading dose of 300 mg. The patient also received subcutaneous unfractionated heparin thromboprophylaxis (5000 units b.d.) from the first postoperative day. Serum troponin levels were assayed and 12 lead ECGs were taken on days 1, 2 and 5.

The patient had some mild oozing of blood from the neck wound edges on days 2 and 3 which required redressing. His haemoglobin decreased to 88 g dl⁻¹ on day 3 from 98 g dl⁻¹ in the preoperative period. He was not transfused. He was discharged to rehabilitation care on the ninth postoperative day.

Case report 2

A 67-yr-old lady was booked for elective microlaryngoscopy and vocal cord biopsy for investigation of a hoarse voice. She had suffered a NSTEMI in the preceding 12 months and a paclitaxel drug-eluting coronary stent had been inserted into the mid LAD coronary artery at that time. One year later a follow-up angiogram had shown an in-stent restenosis in the mid LAD region. The stent was unblocked and the patient continued on long-term clopidogrel.

The patient also had a long history of severe chronic obstructive pulmonary disease (COPD) that had required admission to ICU for management of exacerbations of the COPD. She had a chronic productive cough, was still smoking and received home oxygen therapy. Medications included clopidogrel, verapamil, candersartan, salmeterol, fluticasone, theophylline, ipratropium bromide, salbutamol, nystatin and doxycycline.

Examination revealed that she was dyspnoeic at rest and spoke in short 4–5 word sentences. There were coarse wheezes and crackles in both lung fields. Lung function tests demonstrated an FEV₁ of 700 ml (30% of predicted) and an FVC 1.59 litre (53% of predicted).

We decided to follow the same guideline for the management of the drug-eluting stents and clopidogrel as in the previous case. The patient discontinued clopidogrel treatment 5 days before surgery and was admitted to hospital 3 days before operation. She was commenced on intravenous infusions of heparin and tirofiban, which were continued until midnight on the day before surgery.

For surgery and anaesthesia an 18G cannula was placed in the right cephalic vein and a 20G cannula in the right radial artery to monitor blood pressure. A 5-lead ECG, BIS monitor and pulse oximeter were also used. Her arterial oxygen saturation breathing air, before induction of anaesthesia was 88%. Anaesthesia was provided with midazolam 1.5 mg, fentanyl 75 mcg, propofol 100 mg and rocuronium 30 mg. The patient was intubated with a size 5-microlaryngoscopy tube (Portex, Margate, UK). She was ventilated using a Draeger Julian anaesthetic machine with a tidal volume of 550 ml. She remained haemodynamically stable during the procedure requiring three boluses of metaraminol 0.5 mg to maintain blood pressure within 10% of baseline values during the procedure. Neuromuscular block was antagonized with neostigmine and glycopyrrolate. Mild hypotension in the recovery area was treated with 500 ml normal saline and she was discharged to the ward after 45 min.

Clopidogrel was restarted the following day with no bleeding complications. Serum troponin levels were assayed and ECGs taken after operation and on days 2 and 4 after surgery. These investigations were normal. At postoperative review on day 4 the patient reported 1 episode of chest pain the previous day that had lasted 15 min but had been promptly relieved by sublingual GTN. There was no troponin increase associated with this episode of angina.

Case report 3

A 57-yr old man was booked for elective subacromial decompression, turbinectomy for obstructive sleep apnoea, and caudal epidural steroid injection to treat back and radicular pain. His past medical history included insertion of a paclitaxel-eluting stent into his right coronary artery to treat angina refractory to medical therapy 33 months previously. He had suffered a preoperative acute stent

thrombosis, leading to myocardial infarction in the territory of the stent, after withdrawal of clopidogrel therapy for 1 week. The myocardial infarct occurred on day 7 after ceasing the clopidogrel. This was in preparation for subacromial decompression 18 months after DES insertion. His aspirin therapy had not been interrupted. He required emergency angiography and intracoronary abciximab along with aspiration of thrombus from the stent. This episode resulted in multiple episodes of ventricular fibrillation treated with cardioversion and amiodarone and required the use of an intra-aortic balloon pump. His surgery was cancelled.

At this time he was also on the hospital waiting list to have a transurethral prostatectomy, removal of epididymal cyst, haemorrhoidectomy, and a turbinectomy to treat his obstructive sleep apnoea. He also suffered transient ischaemic attacks, asthma, gout, depression, and chronic back and radicular pain resulting from a fall several years previously.

Medications included atorvastatin, esomeprazole, finasteride, meloxicam (ceased 3 days before operation), ramipril, clopidogrel and aspirin. He required large doses (80 mg day⁻¹) of oral hydromorphone for his disabling shoulder and back pain and he was intolerant of nasal CPAP to treat his sleep apnoea. He requested surgical treatment for these conditions.

After consultation with his cardiologist (AB), surgeons, pain physician and anaesthetist (MC) we decided to offer him multiple procedures on one day after withdrawal of clopidogrel. This would be combined with preoperative thrombosis prophylaxis with tirofiban and heparin to minimize the risk of further stent thrombosis. He was offered a laser prostatectomy, which did not require clopidogrel withdrawal, at another institution.

Clopidogrel therapy was ceased 5 days before his surgery and he was admitted to hospital 3 days before operation to commence tirofiban and heparin infusions, which continued until 8 h before operation. Aspirin therapy was continued throughout the perioperative period. He was given a caudal injection of 8 ml 0.125% bupivacaine and 11.4 mg celestone before his general anaesthesia, which lasted 180 min. Monitoring was commenced with pulse oximetry, five lead ECG, intra-arterial blood pressure, via a radial artery catheter, BIS monitoring and a urinary catheter. Anaesthesia and analgesia were provided with midazolam 3.5 mg, propofol 180 mg, rocuronium 60 mg, fentanyl 800 mcg, ketorolac 30 mg, ketamine 60 mg and bolus doses of 0.5 mg metaraminol to maintain a mean arterial pressure >80 mm Hg. Additionally a subacromial local anaesthetic infusion of 1% ropivacaine at 2 ml h⁻¹ was used for postoperative analgesia,⁶ with a ketamine infusion⁷ at 10 mg h⁻¹ and hydromorphone infusion of 1 mg h⁻¹ plus patient-controlled analgesia bolus dose of hydromorphone 0.5 mg. Oral methadone 40 mg day⁻¹ was substituted for the hydromorphone when oral intake was resumed. Pain was well controlled throughout the perioperative course.

Table 1 Perioperative drug guideline for patients undergoing non-cardiac surgery

5 days before surgery	Cease clopidogrel
3 days before surgery	Admit to hospital
	Commence tirofiban infusion
	Commence unfractionated heparin infusion
6 h before surgery	Cease tirofiban infusion
	Cease heparin infusion
First postoperative day	Start loading dose of clopidogrel
Second postoperative day	Commence maintenance dose of clopidogrel
Aspirin continued throughout	

The otolaryngologist was concerned about postoperative bleeding as a result of clopidogrel treatment in the early postoperative period, so the tirofiban infusion was recommenced when no bleeding had occurred 4 h after operation in the high dependency unit. No bleeding problems were encountered overnight, and the tirofiban infusion was ceased at the time of clopidogrel loading dose (300 mg) the next morning. There were no symptoms or perioperative ECG changes to suggest myocardial ischaemia. There were no intraoperative S-T segment changes and a 12-lead ECG on postoperative day 1 was unchanged. Serum troponin I levels were <0.1 µg litre⁻¹ on postoperative days 1 and 2. The perioperative drug guideline for patients undergoing non-cardiac surgery can be found in Table 1.

The guideline calls for clopidogrel to be stopped 5 days before surgery, which is in line with current guidelines.⁸ The time it then takes for adequate platelet function to return is on average 5 days in normal patients.^{8,9} However there is a return of platelet function from day 3 after cessation of the drug.⁹ Patients with a drug-eluting stent are in a real sense not 'normal' in that they have a high reactivity of their clotting cascade as a result of the presence of the metal stent, hence a return to some activity at 3 days puts them at a perceived increased risk of stent thrombosis. It is for this reason that we decided to start tirofiban from day 3. The current data for the use of tirofiban in NSTEMI suggests 3 days therapy is required although in these studies the length of treatment ranged for 1–3 days. In addition, all current trials of tirofiban have used anti-thrombin agents in conjunction with the tirofiban.³ The agents used are either unfractionated heparin or a low molecular weight heparin.³ Currently our laboratory is unable to provide factor Xa assays to assist with monitoring low molecular weight heparin therapy, so it made sense to use unfractionated heparin, with this ceasing 6 h before the procedure.

Discussion

There are few reported cases of patients undergoing non-cardiac surgery with drug-eluting stents and full anti-platelet therapy <2 yr after stent insertion.^{10–13} The risks in

these patients are related to excessive bleeding, as a result of continued, combined anti-platelet therapy on the one hand, and stent thrombosis as a result of withdrawal of combined anti-platelet therapy on the other.^{10 11 13 14} Withdrawal of all combined anti-platelet therapy creates an unstable coronary syndrome as a result of the high-risk lesion (the bare metal stent) in the coronary arteries.¹⁰ Cessation of the anti-platelet therapy increases the relative risk of coronary thrombosis by 90:1.¹⁵ Consequently these patients must be maintained on anti-platelet therapy for as long as possible up to the time of surgery. However continued use of dual anti-platelet therapy confers an excessive risk of bleeding complications. Consequently, the middle course involves the use of short-acting anti-platelet agents (in this case tirofiban and heparin), which are ceased 6 h before surgery in order to minimize their clinical effect during surgery. Recommencement of oral, dual anti-platelet therapy can then occur on the first postoperative day, with minimal impact on either the risk of stent thrombosis or bleeding in the surgical wound.^{13 14}

In the cases described the goal of achieving minimal surgical bleeding and no stent thrombosis appears to have been achieved with the regimen followed. The only bleeding problems that occurred during the surgical course were post-operative bruising and oozing from the skin edges. No deep surgical bleeding was observed as has been described in other cases where clopidogrel treatment was continued throughout surgery.¹³ The site of the parathyroid operation in the neck and adjacent to the trachea made the risk of surgical haemorrhage a particularly important consideration. Furthermore, the serial troponin results indicate that there was no coronary artery thrombosis especially in the territory of the drug-eluting stent.

We propose that a perioperative regimen for non-cardiac surgery should treat a drug-eluting stent in the coronary arteries that is unprotected by dual anti-platelet therapy as a potential high-risk coronary artery lesion. The use of a short-acting anti-platelet agent, tirofiban, substituting for clopidogrel at the time of surgery, should protect the coronary artery lesion and prevent excessive bleeding at the time of surgery.

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