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Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel

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Background. Patients with a recently implanted coronary drug-eluting stent (DES) who need urgent surgery are at increased risk of surgical bleeding unless clopidogrel is discontinued beforehand, but clopidogrel discontinuation has been associated with a high rate of adverse events due to stent thrombosis. This pilot study tested the hypothesis that the i.v. perioperative administration of the short-acting antiplatelet agent tirofiban allows the safe withdrawal of clopidogrel without increasing the rate of surgical bleeding.

Methods. Phase II study with a Simon two-stage design.

Results. Thirty patients with a recently implanted DES [median (range) 4 (1–12) months] and high-risk characteristics for stent thrombosis underwent urgent major surgery or eye surgery. Clopidogrel was to be withdrawn 5 days before surgery, and tirofiban started 24 h later, continued until 4 h before surgery, and resumed 2 h after surgery until oral clopidogrel was resumed. The use of aspirin was decided by the surgeon. There were no cases of death, myocardial infarction, stent thrombosis, or surgical re-exploration due to bleeding during the index admission, with a risk estimate of 0–11.6% (one-tail 97.5% CI). There was one case of thrombolysis in myocardial infarction (TIMI) major and one of TIMI minor bleeding in the postoperative phase; another four patients were transfused without meeting the TIMI criteria for major or minor bleeding.

Conclusions. In patients with a recently implanted DES and high-risk characteristics for stent thrombosis needing urgent surgery, a 'bridging strategy' using i.v. tirofiban may allow temporary withdrawal of oral clopidogrel without increasing the risk of bleeding.

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After the positioning of a coronary drug-eluting stent (DES), patients should receive antiplatelet therapy with aspirin and clopidogrel for at least 1 yr according to the current guidelines,[1] and it has been shown that the premature withdrawal of this therapy for any reason is associated with a high risk of stent thrombosis that often leads to myocardial infarction (MI) or death.[2–4] The discontinuation of clopidogrel because of the need for urgent surgery is becoming an increasingly frequent challenge for surgeons, anaesthetists, and cardiologists because more patients are now receiving drug-eluting coronary stents, the period of mandatory dual antiplatelet therapy is becoming longer,[1 5] and the age of the peak incidence of coronary artery diseases and various forms of cancer coincides.

The clinical dilemma is to balance the risk of cardiac events when dual antiplatelet therapy is withdrawn in order to prevent surgical bleeding[6–11] against the high incidence of bleeding when it is continued.[12 13] The irreversible effect of clopidogrel on platelets requires its

withdrawal at least 5 days before surgery to minimize the bleeding risk,[11] and its oral administration cannot be resumed after surgery until the patient can eat, which may be several days after laparotomy. Finally, surgery has a prothrombotic effect[14] that may increase the risk of stent thrombosis.

In an attempt to overcome these problems, we have developed a clinical and pharmacological strategy aimed at avoiding stent thrombosis and its dramatic outcomes without increasing surgical bleeding in patients with a recently implanted DES who need to undergo urgent major surgery.

Methods

The aim of this study was to evaluate the efficacy and safety of a strategy of: (i) strict cardiological monitoring; (ii) the discontinuation of clopidogrel 5 days before surgery and its replacement by an i.v. short-acting glycoprotein (GP) IIb/IIIa receptor blocker in the perioperative period; and (iii) the resumption of dual oral antiplatelet therapy as soon as possible after surgery.

Patients

The study involved consecutive candidates for urgent major surgery or eye surgery in whom dual antiplatelet therapy could not be withdrawn because they had received a DES within the previous 6 months, or within the previous year if they were considered to be at higher risk of developing stent thrombosis[1–4 10] because of stent implantation due to an acute coronary syndrome (ACS), diabetes, renal insufficiency, severe left ventricular dysfunction, malignancy, or stent placement in the left main coronary artery, the proximal segment of the left anterior descending artery (or equivalent in the case of a stent in an aorto-coronary graft), or on a coronary bifurcation. The patients also had to be at such a risk of surgical bleeding that the surgeon would not operate while the patient was receiving clopidogrel. We excluded patients with ongoing severe bleeding requiring emergency surgery (within 24 h of hospital admission), those with thrombocytopenia $<100\,000\times10^{-9}$ litre^{-1}, a stroke within the previous 30 days or a history of haemorrhagic stroke, intracranial disease or bleeding diathesis, severe hypertension, and those unwilling or unable to sign the informed consent form. The study was approved by the Ethics Committee of Niguarda Hospital, Milan, and the protocol was registered at the Italian Drug Agency (EudraCT No. 2008-000561-28).

Procedures

The timing of surgery was planned in order to minimize the pre-surgical hospital stay. Given the reported high risk of stent thrombosis and need for emergency percutaneous coronary intervention (PCI), the participating hospitals were capable of providing such interventions immediately at any time. The patients were admitted to the coronary care unit (or cardiac–thoracic intensive care unit in the case of cardiac surgery) during the post-surgical phase until the resumption of clopidogrel. In addition to the need for rapid diagnosis and intervention in the event of acute myocardial ischaemia, admission to a cardiological unit was considered ideal because of the staff's accumulated experience in monitoring myocardial ischaemia and handling antithrombotic agents.

Clopidogrel was discontinued 5 days before surgery, and hospital admission was planned for the day after the last clopidogrel intake (4 days before surgery), when i.v. tirofiban infusion was started according to the schedule approved for patients with ACS: that is, 0.4 μg kg^{-1} min^{-1} over 30 min, followed by 0.1 μg kg^{-1} min^{-1}.[15] The tirofiban dose was reduced by 50% if creatinine clearance was <30 ml min^{-1}. The infusion was stopped 4 h before surgery (8 h in the case of creatinine clearance <30 ml min^{-1}), resumed at the same schedule (including the 30 min bolus) 2 h after the end of surgery, and continued for up to 6 h after the resumption of clopidogrel, unless oral administration could be resumed on the same day as surgery. After surgery, clopidogrel was reintroduced using a loading dose of 300 mg (four tablets) as soon as the patient could resume oral administration, and then continued at a once daily dose of 75 mg. Aspirin (75–100 mg once a day) was ideally to be continued throughout the perioperative period: in the case of laparotomy, its administration was resumed 12 h after the intervention as an i.v. injection of 250 mg of lysine acetyl salicylate once a day until the patient could resume oral administration, and then 75–100 mg once a day orally. Although tirofiban has been approved for use in combination with unfractionated heparin in ACS patients, we considered anticoagulation not useful (and possibly dangerous) for this protocol because of the increased risk of bleeding and thrombocytopenia. When indicated, low-molecular-weight heparin could be administered s.c. for the prevention of venous thromboembolism.

A 12-lead ECG was recorded every morning and in the case of ischaemic symptoms, and patients underwent continuous 12-lead monitoring during the CCU/ICU stay. Blood samples for CK-MB determinations were collected every morning before and after surgery throughout the hospital stay, and 6 h or more after any suspicious symptoms or ECG signs of ischaemia. In the case of an increase in CK-MB levels, further samples were collected at 6 h intervals until the values had normalized.

The primary endpoint of the study was the composite of cardiovascular death, MI, the angiographic demonstration of an acute occlusion of the target lesion during index hospitalization, and the need for surgical re-exploration because of bleeding. MI was defined as clinical signs or symptoms of myocardial ischaemia together with an

increase in CK-MB levels to >3 times above the normal limit. In the case of coronary bypass surgery, both enzyme and electrocardiographic criteria were required in the case of CK-MB levels >5 but <10 times above normal; in the case of CK-MB levels >10 times above normal, ECG criteria were not required. The safety of the proposed strategy was also evaluated in terms of the number of transfused units of blood constituents and non-operative bleeding, which was defined according to the thrombolysis in myocardial infarction (TIMI) criteria[16] as major (intracranial, overt bleeding with a decrease in haemoglobin of $\geq$5 g dl^{-1} or haematocrit of $\geq$15%) or minor (spontaneous gross haematuria or haematemesis with a decrease in Hb of $\geq$3 g dl^{-1} but a <15% decrease in Ht). Blood loss was recorded during surgery and for the following 24 h. Transfusion decision-making was left to the discretion of the individual surgeon, anaesthetist, or cardiologist. Blood haemoglobin, haematocrit, and platelet counts were checked once daily or more frequently depending on the patient's clinical condition.

Statistical design and analysis

As the safety of a perioperative tirofiban infusion was unknown, patient risk was minimized by using a Simon two-stage design for phase II clinical trials[17] in which the planned study size is reached only after a preliminary verification of safety in a first series of patients. Although the study was exploratory, we based our sample size calculation on the largest series of consecutive patients undergoing surgery after stent implantation published at the time:[9] that paper described a 30% rate of cardiovascular death, MI, and stent thrombosis during index hospitalization in patients withdrawn from antiplatelet therapy during the period recommended for such treatment. We aimed at reducing that incidence to <5%, which required a total of 21 patients undergoing the experimental strategy: four in the first (safety) stage and, provided that none of them experienced the primary endpoint, 17 in the second stage. The experimental strategy would be considered superior to the standard approach only if >18 of the 21 had not experienced the primary endpoint at the end of the study. On the basis of these figures, the two-sided α-level was calculated as 0.048 with an expected power of $1-\beta_{eff}=0.807$. Owing to the satisfactory results after the completion of the prospective number of patients, the study was continued beyond the planned sample size of 21 patients in order to get a more robust estimate of the risk.

Results

None of the first four patients died or experienced MI, stent thrombosis, or surgical re-exploration because of bleeding. The Ethics Committee therefore approved continuation of the study and, at the time of writing, 30 patients with a mean age (range) of 65 (25–80) yr had been treated: 14 hypertensives, five diabetics, three with chronic kidney dysfunction, and four with overt peripheral vascular disease. Their median ejection fraction (range) was 55% (35–68%), 21 (70%) were taking a beta-blocker and 23 (77%) a statin before operation.

Table 1 shows the individual patient data reported in chronological order: nine underwent cardiovascular surgery, 10 gastrointestinal surgery, six urinary tract surgery, and five mixed surgery. These patients were at high risk for stent thrombosis or catastrophic outcomes as 16 had cancer, three chronic kidney dysfunction, five a DES positioned in the left main coronary artery, and 17 in the left anterior descending artery; 14 had received multiple stents; 20 had been stented during an ACS; and the median time (range) between stenting and surgery was 4 (1–12) months. The patients were considered to be at high risk of surgical bleed due to the types of surgery performed. Six patients had been transfused previously due to pre-existing anaemia.

Clopidogrel was discontinued a median (range) of 5 (3–15) days before surgery: two patients discontinued more than 6 days before surgery as they came from referring hospitals where clopidogrel had been withdrawn 3 and 8 days previously because of renal cancer or gastric cancer with severe bleeding. The median (range) preoperative duration of tirofiban infusion was 4 (3–5) days, and the drug was stopped a median (range) of 5 (1–8) h before surgery. Fifteen patients resumed clopidogrel a median (range) of 8 (2–24) h after the end of the operation, and therefore did not resume tirofiban. Two patients did not resume clopidogrel because of the concomitant administration of anticoagulant therapy (no. 2) or as the stented artery had been bypassed (no. 23). The remaining 13 patients (all of whom had undergone major abdominal surgery) resumed tirofiban a median (range) of 4 (2–20) h after surgery and continued receiving it for a median (range) of 2 (1–16) days until the resumption of clopidogrel. Aspirin was discontinued in 16 patients a median (range) of 5 (2–7) days before surgery. Enoxaparin was administered before operation to four patients, and after operation to 13.

There were no adverse cardiac events during the index hospitalization, and no patient required surgical re-exploration because of bleeding: the point estimate of the primary endpoint rate was 0% (one-tailed 97.5% CI 0–11.6%). No patient experienced any major or minor TIMI bleeding during the preoperative phase, although one (no. 1) received 2 U of RBCs due to pre-existing anaemia.

Twenty-eight patients showed no major or minor TIMI bleeding during the postoperative phase. One patient (no. 29) undergoing hemicolotomy for cancer experienced TIMI major bleeding due to proctorrhagia on the seventh postoperative day, 4 days after resuming clopidogrel; he was transfused 4 U of red blood cells (RBCs), and bleeding from the enterocolic anastomosis was stopped by placing

Table 1 List of the individual patients, procedures, and bleeding events: patients are listed in order of enrolment. PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; ACS, acute coronary syndrome; DES, drug-eluting stent; LMCA, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; SVG, saphenous vein graft; CABG, coronary artery bypass grafting. *See Methods for definitions of bleeding

Patient no.	Gender	Age	Stented artery	Months after DES, type of DES	Reason for PCI	Type of surgery; diagnosis	Tirofiban pre-surgery (h)	Tirofiban post-surgery (h)	Aspirin discontinued before surgery	Enoxaparin pre-/ post-surgery	Bleeding events*
1	Male	68	LMCA, LAD	1, paclitaxel	STEMI	Hemicolotomy; cancer	62	120	Yes	No/no	No bleeding, 2 U RBC before operation
2	Male	50	RCA, LCx	7, sirolimus	STEMI	Mitral valvuloplasty	72	0	Yes	No/no	No bleeding, no transfusion
3	Male	48	RCA, LCx	4, paclitaxel	Stable angina	Vitrectomy and macular pucker peeling	120	0	Yes	No/no	No bleeding, no transfusion
4	Male	46	LCx	4, paclitaxel	STEMI	CABG; 3-vessel disease	120	0	Yes	No/no	No bleeding, no transfusion
5	Male	79	RCA	2, sirolimus	Stable angina	Femoral fracture	112	0	Yes	Yes/yes	No bleeding, 1 U of GRC post-surgically
6	Male	56	LMCA, RCA	6, sirolimus	Stable angina	Bladder surgery; cancer	100	0	Yes	No/no	No bleeding, no transfusion
7	Male	79	LAD	12, sirolimus	STEMI	Bladder surgery; cancer	120	0	Yes	No/no	No bleeding, no transfusion
8	Male	48	LMCA, LCx	10, sirolimus	NSTEACS	CABG; 3-vessel disease	72	0	Yes	No/yes	No bleeding, no transfusion
9	Male	60	LCx, RCA	3, sirolimus	Stable angina	Conservative nephrotomy; cancer	96	48	Yes	No/no	No bleeding, no transfusion
10	Female	74	LCx, RCA	7, sirolimus	NSTEACS	Hysterotomy, cancer	120	24	No	Yes/yes	No bleeding, no transfusion
11	Male	76	LAD	2, everolimus	NSTEACS	Conservative nephrotomy; cancer	120	48	No	Yes/no	No bleeding, transfusion of 3 U RBC due to proctorrhagia on sixth postoperative day; angiodysplasia
12	Male	54	RCA	2, sirolimus	STEMI	CABG; 3-vessel disease	72	0	No	No/yes	No bleeding, no transfusion
13	Female	78	LAD	12 days everolimus	Stable angina	Hemicolotomy; cancer	72	120	Yes	No/no	No bleeding, no transfusion
14	Male	78	RCA	2, everolimus	Stable angina	Bladder surgery; cancer	120	0	No	No/no	No bleeding, no transfusion
15	Female	72	LAD	8, paclitaxel	NSTEACS	Off-pump CABG; 3-vessel disease	120	0	Yes	Yes/yes	No bleeding, no transfusion
16	Male	59	LAD	4, paclitaxel	STEMI	Endoscopic bladder surgery; cancer	114	288	No	No/no	Minor bleeding, transfusion of 4 U RBC
17	Male	60	LCx	11, sirolimus	Stable angina	Vitrectomy	120	0	No	No/no	No bleeding, no transfusion
18	Male	71	LMCA, LCx, RCA	4, paclitaxel, everolimus	NSTEACS	Cholecystectomy, recurrent cholecystitis	114	48	No	No/no	No bleeding, no transfusion
19	Male	69	LAD, Lcx	8, paclitaxel	Stable angina	Pharyngotomy, cancer	111	0	No	No/no	No bleeding, no transfusion
20	Female	25	LAD	4, everolimus	NSTEACS	CABG; 3-vessel disease	72	0	Yes	No/yes	No bleeding, no transfusion
21	Female	72	LAD	1, paclitaxel	NTEACS	Hemicolotomy; cancer	113	312	No	No/yes	No bleeding, no transfusion. Re-operation due to intestinal obstruction

22	Male	80	LAD	9, everolimus	Stable angina	Endoscopic polypectomy, cancer	72	0	No	No/no	No bleeding, no transfusion
23	Male	65	LAD	7, everolimus	NSTEACS	CABG; 3-vessel disease	120	0	No	No/yes	No bleeding, no transfusion
24	Female	76	LAD	5, everolimus	NSTEACS	Femoral fracture	112	0	Yes	No/yes	No bleeding, no transfusion
25	Male	60	LAD	7, everolimus	STEMI	Resection of the rectum, cancer	112	384	Yes	No/yes	No bleeding, no transfusion. Re-operation due to intestinal obstruction
26	Male	65	RCA	2, sirolimus	NSTEACS	Gastrectomy, hemicolotomy, cancer	120	120	No	No/no	No bleeding, no transfusion
27	Male	72	LAD	4, everolimus	NSTEACS	CABG; 3-vessel disease	72	0	No	No/no	No bleeding, no transfusion
28	Female	77	LAD	4, sirolimus	NSTEACS	Sigmoid resection, cancer	113	98	Yes	No/yes	No bleeding, no transfusion
29	Male	73	LAD	3, everolimus	STEMI	Hemicolotomy, cancer	105	94	Yes	No/yes	Major bleeding from enterocolic anastomosis on 7th postop. day resolved by operative coloscopy (2 clips). Transfusion of 4 U RBC
30	Male	71	LMCA, LAD, LCx	3, everolimus	Stable angina	Abdominal aortic aneurysm	91	35	No	No/yes	No bleeding, transfused 2 U of RBC on 1st postop. day

two clips via colonoscopy while clopidogrel and aspirin were stopped for 1 day. One patient (no. 16) experienced TIMI minor bleeding and required a transfusion (also because of pre-existing anaemia). One patient (no. 11) with severe renal insufficiency and renal cancer experienced rectal bleeding on the sixth postoperative day, 4 days after resuming clopidogrel. His haemoglobin levels decreased from 11.9 to 9.2 g dl^{-1}, associated with dyspnoea and ST segment depression, and he received 3 U of PRBCs: the ECG returned to normal after transfusion and there was no increase in markers of cardiac damage; colonoscopy revealed intestinal angiodysplasia with no obvious source of bleeding. Two other patients (nos 30 and 5), respectively, received 2 and 1 U of GRCs: they had mild anaemia at baseline and did not meet the TIMI criteria for minor bleeding. One patient experienced mild thrombocytopenia with a nadir platelet count of 71 000 μl^{-1} on the second postoperative day (baseline 161 000 μl^{-1}).

Discussion

This is the first prospective study of bridging therapy with a short-acting i.v. antiplatelet agent during clopidogrel withdrawal because of urgent major surgery in patients with a recently implanted DES. The median of 4 months from placement of a DES to surgery is less than other series of patients with high-risk coronary and surgical characteristics.

The risk of urgent surgery after recent stent implantation

Current recommendations concerning the perioperative management of patients with coronary stents[10 11 18–23] indicate that non-urgent surgery should be postponed until the end of the period of susceptibility to stent thrombosis: that is, the time needed for the stent endothelialization or at least 6 weeks for uncoated stents, 6 months for DESs, and 1 yr or longer in the case of complex coronary lesions or other high-risk coronary conditions.[1 10] However, when surgery cannot be delayed because it is needed to treat a life-threatening condition, all that can be done is to minimize the risks of ischaemia and bleeding by closely monitoring the patient, ensuring the availability of immediate PCI in the case of acute ischaemia, and pharmacologically preventing thrombosis. The first two factors are of utmost importance: an awareness of the risk and admission to an appropriate facility are essential because coronary stent thrombosis usually presents with acute MI, cardiogenic shock, and sudden death,[24] and the only suitable therapeutic option is immediate PCI with thrombus aspiration.

Prevention of stent thrombosis and surgical bleeding

As clopidogrel reduces platelet aggregation by inducing an irreversible conformational change in the $P2Y_{12}$ receptor

for ADP, it takes at least 5 days before haemostatic competence is restored by new circulating platelets after its discontinuation.[25] Since the CURE study[12] revealed an increased bleeding risk in patients undergoing cardiac surgery within 5 days of clopidogrel discontinuation, Kapetanakis and colleagues[13] have confirmed that patients receiving clopidogrel in the 7 days before off-pump coronary artery bypass surgery have a five-fold risk of requiring a second haemostatic operation and a significantly increased need for packed RBC and platelet transfusions, albeit with no difference in mortality. In addition to the intrinsic risk of stent thrombosis associated with clopidogrel discontinuation, the risk is further increased by the hypercoagulable state caused by the stress response to major surgery.[14] Early attempts to replace antiplatelet therapy with low-molecular-weight heparin proved to be ineffective because heparin does not mimic the effect of antiplatelet agents such as clopidogrel or aspirin.[26]

We took advantage of the reported experience of the use of the i.v. GPIIb/IIIa receptor blocker tirofiban to treat ACS patients.[15 27] The dosing schedule used in ACS (and by us in the present study) ensures an almost complete platelet blockade within 2–4 h; furthermore, the short half-life and rapid clearance of tirofiban means that haemostatic competence returns to normal within ~2 h of stopping the i.v. infusion.[28] We had to prolong tirofiban administration beyond the 48–72 h approved for use in ACS: to up to 120 h before surgery and until the patients were able to resume oral clopidogrel (up to 384 h in one case). The safety figures coming from the randomized controlled trials of tirofiban in ACS,[15 27] always given in combination with heparin, indicate that major bleeding is mainly limited to the arterial access sites, with no increased incidence of intracranial haemorrhage or thrombocytopenia. Both the efficacy and safety of our strategy were completely positive: none of the patients experienced a cardiac ischaemic event during the perioperative period, and bleeding did not exceed that commonly accepted for the type of operation. It is also worth bearing in mind that, in addition to the risk of stent thrombosis, most of our patients were at risk of perioperative cardiac ischaemic events due to a recent ACS or multivessel disease.

The zero rate of cardiac ischaemic events should be interpreted cautiously because of the limited number of patients treated. The favourable outcomes may have been due to the close cardiac surveillance, the extensive use of beta-blockers in the perioperative period, and the possible protective effect of GPIIb/IIIa blockade (described as platelet anaesthesia in a previous study).[29]

Study limitations

The lack of a control group and the small sample size may be considered the major limitations of this study. The study was designed in the absence of a standard alternative regimen and after careful analysis of the evidence available at the time of its inception. With 30 successful cases and no failures, the upper 97.5% confidence limit of the primary endpoint rate estimate is 11.6% which may still be considered too large to allow firm recommendations. Postoperative cell necrosis is better recognized by measuring cardiac troponin levels rather than our use of CK-MB, and so it is likely that we missed some cases of minor myocardial damage which may well have occurred in our patients as they all had severe coronary disease. However, these cases are unlikely to be due to stent thrombosis which generally manifests as acute cardiogenic shock, a large MI, or ventricular fibrillation.

Conclusion

The risk of major cardiac events in patients operated during the recommended period of double antiplatelet therapy after DES implantation is still poorly defined. There is a general consensus that patients operated early after stent implantation are at higher risk, and that withdrawal of clopidogrel before surgery further increases this risk. A recent retrospective analysis of consecutive patients undergoing any kind of non-cardiac surgery after DES implantation has reported a 6% rate of major cardiac events among those operated within 1 yr of DES implantation,[30] but no multivariate analysis could be performed in order to identify patient subsets for which this risk might be higher. Careful risk stratification with regard to both ischaemic events and bleeding requires strict collaboration among surgeons, cardiologists, and anaesthetists. Our study offers the first evidence supporting the need for larger scale clinical testing of a pharmacological strategy in patients who are considered to be at high risk for both stent thrombosis and surgical bleeding.

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