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ORIGINAL ARTICLE

Bridging therapy for early surgery in patients on dual antiplatelet therapy after drug-eluting stent implantation

E. G. Marcos · A. C. Da Fonseca · S. H. Hofma

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Abstract
Objectives To evaluate stent-related adverse cardiac events and bleeding complications within 30 days after surgical procedures in patients with recent drug-eluting stent (DES) implantation, in whom a bridging protocol was used.
Methods In our centre a bridging protocol is used in patients scheduled for cardiac or non-cardiac surgery within 6 months after PCI with DES implantation. Clopidogrel and in some cases also acetylsalicylic acid is discontinued 5 days prior to the planned intervention and patients are admitted 2 to 3 days before the intervention for tirofiban infusion. This is discontinued 4 h before intervention. Close postoperative monitoring is performed and double anti-platelet therapy is restarted as soon as possible. Thirty-six consecutive patients were included in the protocol, 15 receiving coronary artery bypass graft and 21 non-cardiac interventions. Thrombotic and bleeding complications were studied for up to 30 days after the bridged procedure.
Results No incidences of stent thrombosis or other adverse cardiac events (mortality, myocardial infarction) were seen in up to 30 days of follow-up. However, 6 bleeding events were reported of which 5 required a blood transfusion.
Conclusion Our bridging protocol in patients requiring surgery after recent PCI with DES seems adequate to prevent stent thrombosis in this high-risk group. The bleeding risk is not insignificant but in our patient group controllable without major late sequelae. Larger studies should be performed to establish safety and efficacy in order to develop guidelines for these patients.

Keywords Drug eluting stents · Anti-platelet therapy · Stent thrombosis · Bridging therapy

E. G. Marcos (✉) · S. H. Hofma
Department of Cardiology, Medical Center Leeuwarden,
Henri Dunantweg 3,
8932 BA Leeuwarden, the Netherlands
e-mail: er-naldo@hotmail.com

A. C. Da Fonseca
Department of Cardiology, Isala Hospital,
Zwolle, the Netherlands

Introduction

Drug-eluting stent

Drug-eluting stents (DES) have revolutionised interventional cardiology over the last 7 years. Compared with the bare-metal stent (BMS), DES significantly reduce coronary restenosis and the subsequent need for repeat coronary intervention [1–5]. DES reduce restenosis by preventing neointimal proliferation after PCI [2]. In contrast to BMS, the endothelialisation process of DES is delayed which leaves the device vulnerable to acute thrombosis for an extended period [6–10].

Because of the increased risk for stent thrombosis, the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend a dual antiplatelet therapy with clopidogrel and aspirin for up to 12 months or longer after DES implantation or during the first 4 weeks after BMS implantation [11–13].

Intervention

Previous study shows that approximately 5% of all patients will have to undergo surgery within the first year after a stent implantation [14]. Continuing dual antiplatelet therapy may increase perioperative haemorrhage and withdrawing or cessation of therapy is a risk factor for stent thrombosis

[15–20]. It takes approximately 5 days for platelets to return to an adequate function after stopping clopidogrel [21, 22]. To prevent bleeding complications the guidelines recommend discontinuation of clopidogrel 5 days prior to surgical procedures [11, 13, 23].

Bridging therapy

Some clinicians recommend the use of tirofiban as bridging therapy during the perioperative period [24]. There is a case report showing good results with this therapy [25].

Tirofiban is a nonpeptide tyrosine derivate that binds selectively to the glycoprotein IIb/IIIa receptor which causes inhibition of platelet aggregation. It has a half-life time of approximately 2 h, with platelet function returning to over 50% of normal within 4 h after discontinuing the infusion [26]. Some studies show no increased risk of postoperative bleeding in patients who ceased tirofiban 4 h before cardiac surgery [27].

Purpose

There are no current studies published about the effectiveness and safety of tirofiban as bridging therapy for preventing perioperative stent thrombosis in a larger study group. It is also difficult and potentially harmful to perform a randomised clinical trial comparing tirofiban with placebo. Moreover, are no data published about postoperative bleeding in patients receiving tirofiban as bridging therapy who underwent a non-cardiac surgery procedure.

In this study we evaluate the occurrence of major adverse cardiac events (MACE) and bleeding events within 30 days postintervention when tirofiban is used as bridging therapy. MACE was defined as any death, repeat myocardial infarction, target vessel revascularisation (TVR), target lesion revascularisation (TLR) or stent thrombosis.

Bleeding events were defined as haematuria, gastrointestinal bleeding, blood transfusion without bleeding, decrease in haemoglobin concentration or postoperative bleeding that required re-intervention.

The hypothesis of this study is that the use of tirofiban as bridging therapy before intervention is safe and effective to prevent stent thrombosis.

Methods

Patients

All patients included in this study were treated with DES in the Medical Centre Leeuwarden (MCL) during the last three and a half years (October 2006–March 2010). Patients with DES were prescribed lifelong aspirin as well as clopidogrel for at least 12 months as recommended by the AHA and ACC. All consecutive patients who needed an unplanned cardiac procedure or a non-cardiac procedure (minor or major surgery procedure) within 6 months after DES implantation were included. All included patients were bridged with tirofiban. The exclusion criteria for this bridging therapy were thrombocytopenia, anaemia, decreased kidney function, serious liver disease and recent cerebral vascular accident or any operation <6 weeks.

The Medical Ethics Committee gave permission for performing this study.

Study design

This study is a retrospective observational study. Thirty-six consecutive patients were included in this study and data were collected from the clinical files. Data from one week before the procedures until 30 days after the procedure were used.

Data analysis

The Microsoft Excel program was used to make a database with different variables. With this database variables were analysed. Variables are presented as mean value ± SD.

Bridging protocol

In MCL, a bridging protocol was used in patients scheduled for cardiac or non-cardiac intervention. Clopidogrel was discontinued 5 days before the intervention and patients were admitted to the coronary care unit two days before the procedure. Patients who discontinued clopidogrel and aspirin were admitted 3 days beforehand. The haemoglobin, haematocrit and thrombocytes were assayed 2 h before starting and 6 h after starting intravenous tirofiban therapy. Lab controls were continued once a day in combination with a 12-lead ECG control twice a day. Tirofiban therapy was interrupted exactly 4 h before planned intervention. If there was no postoperative risk of bleeding complications, clopidogrel was resumed within 12–24 h postintervention. In case of a high risk for a bleeding complication, the patient was treated with heparin intravenously until the risk decreased. Postintervention the patient was monitored and an ECG was taken every 2 h during recovery and in case of complaints of chest pain after recovery.

Results

Tables 1 and 2 show the baseline characteristics of patients involved in this study. Most of the patients were men and the mean age was 66 years. Most stented coronary arteries

Table 1 Baseline characteristics of study population

Variable	Patients
Patients included (n)	36
Men (n)	25
Women (n)	11
Age, years ± SD	66±11
Smoking	2
Diabetes	4
Hypertension	8
Hypercholesterolaemia (n)	6
Previous MI	3

MI myocardial infarction

were the left anterior descending (LAD) and right coronary artery (RCA). The mean stented length was 28 mm with a mean diameter of 3.2 mm. The mean time from DES implantation to intervention was 80 days. The Cypher and the Xience V stents were most used in this study population. In 78% of the cases acute coronary syndrome (ACS) was the indication for DES implantation.

Table 2 Baseline angiographic characteristics

Variable	Patients
Previous CABG (n)	2
Previous PCI (n)	8
Time from last stent implantation to procedure, days ± SD	80±66
Indication of stent implantation	
Main stent stenosis	1 (2.7%)
Elective PCI	3 (8.3%)
ACS	28 (77.7%)
Prior stent stenosis	1 (2.7%)
Prior stent thrombosis	3 (8.3%)
Type of last DES before intervention	
Xience V	14 (37.8%)
Cypher	19 (51.4%)
Taxus	2 (5.4%)
Endeavor	2 (5.4%)
Related vessel lesion	
RCA	13 (35.1%)
Left main stem	2 (5.4%)
LAD	17 (45.9%)
Rcx	5 (13.5%)
Stented length, mm ± SD	27.7±15.8
Stented diameter, mm ± SD	3.2±0.6

CABG coronary artery bypass graft, *PCI* percutanous coronary intervention, *ACS* acute coronary syndrome, *DES* drug eluting stent, *RCA* right coronary artery, *LAD* left anterior descending artery, *Rcx* ramus circumflexus

Table 3 Type of intervention

Intervention	Patients
CABG	15 (41.7%)
Minor non-cardiac procedure	
PEG	1 (2.7%)
TU biopsy of prostate	1 (2.7%)
TU biopsy of bladder	1 (2.7%)
TU bladder polypectomy	1 (2.7%)
Gall bladder drainage	1 (2.7%)
Lung biopsy	1 (2.7%)
Colon polypectomy	1 (2.7%)
Ureterescopy	1 (2.7%)
Bronchoscopy	1 (2.7%)
Major non-cardiac procedure	
TUR of bladder tumour	2 (5.5%)
TUR of prostate	1 (2.7%)
Lobectomy	1 (2.7%)
Uterus extirpation	2 (5.5%)
Laparoscopic hemicolectomy	3 (8.3%)
Cholecystectomy	1 (2.7%)
Reposition of hip prosthesis	1 (2.7%)
Hernia operation	1 (2.7%)

CABG coronary artery bypass graft, *PEG* percutaneous endoscopic gastrostomy, *TU* transurethral, *TUR* transurethral resection

Table 3 shows the type of intervention that was done in the patient group. There were 15 cases of cardiac intervention, all coronary artery bypass grafting (CABG). The rest of the patients underwent a variety of major or minor non-cardiac procedures as shown in Table 3. It is not shown in the table, but patients for CABG in this study underwent procedures a mean time of 2 months after DES implantation, patients for minor intervention 3 months and patients for major intervention 6 months after DES implantation.

Table 4 Bridging therapy information

Variable	Total
Stopped clopidogrel before intervention, day ± SD	5.2±1.0
Stopped ASA before intervention, (n)	
Yes	7
No	29
Length of tirofiban use before intervention, day ± SD	4.0±1.5
ST-segment change during tirofiban (n)	0 (0%)
Anaemia during tirofiban therapy (n)	0 (0%)
Thrombocytopenia during tirofiban (n)	0 (0%)
Start of clopidogrel after intervention, day ± SD	1.7±1.1
ASA after intervention, day ± SD	1.6±1.2

ASA acetylsalicylic acid

Table 5 Major adverse cardiac events 30 days after intervention

MACE	Total, n (%)
Death	0 (0%)
Repeat MI	0 (0%)
Stent thrombosis	0 (0%)
TLR	0 (0%)
TVR	0 (0%)

MACE major adverse cardiac events, *MI* myocardial infarction, *TLR* target lesion revascularisation, *TVR* target vessel revascularisation

As shown in Table 4, the mean discontinued time of clopidogrel before interventions was between 5 and 6 days. The mean time for bridging with tirofiban was approximately 4 days. Most patients did not stop aspirin before the procedure. There were no incidences of ST-segment changes on ECG, anaemia or thrombocytopenia during tirofiban therapy. The mean initiation of clopidogrel and aspirin after the procedure was approximately 2 days. In the CABG group 3 patients restarted clopidogrel 2 days after procedure. In the group of minor and major procedures, all patients restarted clopidogrel 1 or 2 days after the procedure.

As shown in Table 5, there were no incidences of death, repeat myocardial infarction, TLR, TVR or in-stent thrombosis within 30 days after cardiac or non-cardiac procedure.

There were 6 bleeding events within 30 days after intervention, as shown in Table 6. Two bleeding events occurred after CABG: bleeding from the left internal mammary artery (LIMA) a few hours after surgery, and in the second patient the haemoglobin dropped without any bleeding focus. Re-surgery was required for the LIMA bleeding. Only one patient was taking aspirin during these bleeding events.

One gastrointestinal bleeding event occurred after colon polipectomy. This event occurred after restarting clopidogrel in combination with aspirin. Blood transfusion was required.

One urinary tract bleeding event occurred on the same day after transurethral resection of a bladder tumour. Clopidogrel was not restarted and aspirin was discontinued before intervention. There were 6 units of blood transfusion required for this patient. The bleeding site was immediately coagulated. In the other urinary tract bleeding, aspirin was not discontinued before the intervention. No blood transfusion was required because the haemoglobin was stable. The last bleeding case occurred in a patient who underwent hip prosthesis repositioning. The wound bleeding was a week after procedure. The patient was taking clopidogrel in combination with aspirin. Blood transfusion was also needed.

Discussion

Dual antiplatelet therapy with aspirin and clopidogrel after DES implantation is strongly advised within 12 months after implantation [11–13]. Interruption of this therapy before intervention can lead to death or repeat myocardial infarction due to in-stent thrombosis [6–9]. In a study with 192 patients, Schouten et al. showed a MACE rate of 13.3% in the early surgery group, which were all fatal in this group. Both antiplatelet agents were discontinued without a bridging therapy before intervention. The duration of the interrupted therapy before intervention was not mentioned in this study [28]. In a study of 103 patients who underwent non-cardiac surgery within 12 months of coronary stenting, Vicenzi et al. showed a total of 5 deaths, 12 myocardial infarctions, 8 re-PCIs and 5 cases of unstable angina pectoris. The risk of an event was 2.11-fold higher in patients with stenting less than 35 days before surgery compared with patients with an intervention more than 90 days before. This high complication rate occurred despite the continuation of aspirin in over 80% of patients and clopidogrel in over 40% in combination with the universal use of heparin before the intervention [14]. In a report by Compton et al. 38 patients underwent an intervention 260 days after DES implantation; there were no cardiac events. Aspirin was continued in 94% and clopidogrel was continued in 39% of the patients during the perioperative period [29].

In our study patients underwent a surgical or non-surgical procedure within 2 to 6 months after DES implantation. Despite the relatively short period between

Table 6 Bleeding events within 30 days after intervention

Bleeding	Intervention	Restart clopidogrel	Withheld ASA	Blood transfusion
GI	Colon polypectomy	Yes	No	2 units
Urinary	TUR of bladder tumour	No	Yes	6 units
Urinary	TUR of bladder tumour	No	No	0 units
Wound	Repositioning of hip prosthesis	Yes	No	4 units
LIMA	CABG	No	Yes	Cell saver
Hb↓, no focus	CABG	No	No	2 units

ASA aspirin, *GI* gastrointestinal, *TUR* transurethral resection, *LIMA*, left internal mammary artery, *CABG* coronary artery bypass graft, *Hb* haemoglobin

stenting and surgical procedure no major adverse cardiac events occurred.

The increased chance of stent thrombosis is not the only perioperative problem, there is also a risk of perioperative haemorrhage from using dual antiplatelet therapy.

Tirofiban is a nonpeptide tyrosine derivate that binds selectively to the GP 2b/3a receptor which causes inhibiting of platelet aggregation. In a case report, three patients received tirofiban plus heparin prior to a non-cardiac procedure without postoperative bleeding complications [30]. Bizzari et al. evaluated the bleeding complications in patients undergoing urgent bypass grafting after treatment with tirofiban plus aspirin and in patients after treatment with heparin plus aspirin. There was a significant difference in the heparin group, in haemoglobin level and platelet count, at postoperative time and before hospital discharge. More blood transfusions were used in the heparin group (28%) than in the tirofiban group (10%) [31]. In our study 5 patients (14%) (2 cardiac and 3 non-cardiac) required blood transfusion post-intervention. There are no data published about the risk of postoperative bleeding by using tirofiban plus aspirin in patients undergoing non-cardiac surgery.

In this study there were no bleeding events during tirofiban infusion and thrombocyte counts were stable. Despite discontinuation of clopidogrel prior to intervention, there were 6 bleeding events. Two of the bleeding events occurred after restarting clopidogrel in combination with aspirin, which may be the cause of bleeding. Two of the bleeding events occurred despite ceasing aspirin and clopidogrel prior to intervention. Four bleeding events required blood transfusion and one required immediate re-operation. It is not clear whether there is a greater chance of bleeding after the procedure by using tirofiban as bridging therapy because we did not have a control group.

Despite the bleeding complications there was no mortality and bleeding severity was not high in most of the patients.

Conclusion

The use of tirofiban as bridging therapy prior to a cardiac or non-cardiac procedure within 6 months after DES implantation seems safe in our small study population. There was no incidence of stent thrombosis within 30 days after procedure. Discontinuation of clopidogrel prior to a surgical or non-surgical procedure in combination with a short bridging therapy period with tirofiban may be a factor in reducing the chance of stent thrombosis. However, 6 bleeding events occurred, most of them needing blood transfusion. Larger studies are necessary to confirm safety and efficacy of tirofiban as bridging therapy.

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