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Major Noncardiac Surgery Following Coronary Stenting: When Is It Safe to Operate?

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The optimal timing for elective noncardiac surgery (NCS) after coronary stenting is uncertain. We identified 47 patients who underwent elective NCS within 90 days of coronary stent placement between January 1995 and December 2000. Twenty-seven patients had NCS within 3 weeks of coronary stenting. Six of the seven in whom thienopyridine antiplatelet therapy was discontinued died postoperatively in a manner suggestive of stent thrombosis. In contrast, only 1 of the 20 patients in whom the thienopyridine was continued through the NCS died. The frequency of perioperative hemorrhage was similar whether or not the antiplatelet agent was continued. Only 1 perioperative death occurred in the 20 patients with NCS more than 3 weeks following stenting. ***Catheter Cardiovasc Interv 2004;63:141–145.*** © 2004 Wiley-Liss, Inc.

Key words: coronary stents; percutaneous coronary intervention; noncardiac surgery

INTRODUCTION

Percutaneous coronary intervention (PCI) before high-risk noncardiac surgery (NCS) is frequently undertaken in hopes of reducing the risk of perioperative ischemic cardiac events (2002 American College of Cardiology/American Heart Association guideline update for perioperative cardiovascular evaluation for noncardiac surgery). While never subjected to a formal clinical trial, the use of balloon angioplasty for this purpose appears to be associated with low perioperative morbidity and mortality [1–5].

In planning PCI before NCS, coronary stenting must now be taken into account since stents are used in 85% of all PCIs [6]. To prevent stent thrombosis, combined antiplatelet therapy with aspirin and a thienopyridine is usually undertaken for 2–4 weeks poststent placement [7–15]. With such therapy, this complication is encountered in only about 1% of coronary stenting procedures. Its occurrence, however, is associated with myocardial infarction (MI) and death [14–19].

Thus, stent use creates a dilemma for the clinician. Because the perioperative milieu increases the risk of stent thrombosis, surgery performed soon after the coronary stenting may be followed by stent thrombosis in patients who are not on antiplatelet agents. On the other hand, it may be associated with perioperative bleeding complications when a thienopyridine is continued. Limited data suggest that postoperative catastrophes do occur when NCS is performed soon after coronary stenting, probably as a result of stent thrombosis [20]. This study was undertaken to assess the clinical outcomes of patients who underwent NCS within 90 days of coronary stenting and to determine the optimal timing for surgery after that revascularization procedure.

MATERIALS AND METHODS

Patients

Under a protocol approved by the institutional review board of the Medstar Research Institute, we identified all patients from the hospital administrative database who underwent major NCS within 90 days of PCI between January 1995 and December 2000.

Data Collection

The hospital charts of all patients so identified were reviewed. The following data were collected: baseline clinical characteristics, PCI procedural information, date of PCI and surgery, type and details of surgery, use of antiplatelet therapy during the perioperative period, and the occurrence of in-hospital death, Q- and non-Q-wave MIs, stent thrombosis, surgical bleeding complications,

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and repeat revascularization procedures. Special attention was given to the time of initiation as well as the withdrawal or continuation of antiplatelet therapy during the peri- and postoperative period.

Revascularization and Stent Placement

Coronary stent placement was performed using conventional catheter-based systems and standard percutaneous techniques. The choice of stent and deployment pressure was at the discretion of the operator.

Antiplatelet Therapy

All patients received preprocedural oral aspirin (325 mg) and intravenous heparin targeted to achieve an activated clotting time of 300 sec, or 250 sec when a platelet glycoprotein IIb/IIIa inhibitor was used. Ticlopidine was administered before or after the procedure with an initial loading dose of 500 mg, and followed by 250 mg twice a day for 2–4 weeks, in addition to aspirin 81–325 mg daily. Since 1998, clopidogrel was substituted for ticlopidine and was given as a loading dose of 300 mg either immediately before or during the procedure followed by 75 mg daily for 2–4 weeks.

Terms and Definitions

The following definitions were established a priori. Successful stent placement was defined as a final residual stenosis within the stent of $< 30\%$ by visual estimation and without complications. Death was defined as all-cause mortality. Postoperative MI was defined by the presence of at least two of the three following criteria: chest pain > 30 min, electrocardiographic changes of acute myocardial infarction, and elevations in creatine kinase MB (> 3 times normal). Q-wave myocardial infarction and non-Q-wave myocardial infarction were defined as presence or absence of pathological Q-waves on electrocardiogram. Excessive bleeding was defined as need for perioperative transfusion or need for reoperation to stop bleeding. Patients were considered to be off antiplatelet therapy when neither ticlopidine nor clopidegrel was administered during the 5 days prior to surgery.

Endpoints

The occurrence of death, Q-wave MI, non-Q-wave MI, and surgical bleeding complications were recorded.

Statistical Analysis

Discrete variables are presented as percentages and compared by means of contingency tables; if appropriate, Fisher's exact test was employed. Continuous variables are described by their mean and standard deviation. A P value of < 0.05 was considered statistically significant.

RESULTS

Sixty-two patients were identified by the study criteria; 15 were excluded based on coding errors (n = 5), unsuccessful PCI (n = 3), or CABG within 90 days of PCI but before surgery (n = 7). The remaining 47 were included in the analysis. After an appraisal of the raw data, we grouped patients into those in whom NCS was undertaken within 3 weeks of the PCI (n = 27) or later (n = 20). We chose this cut point since no adverse postoperative events occurred in patients after NCS undertaken between 17 and 67 days post-PCI.

Baseline demographics are shown (Table I). All patients had successful PCI and stent placement. Among them, only current cigarette smoking was significantly different for patients operated within 3 weeks and those operated later. No operation was emergent, and there were no differences between the two groups in the type of NCS performed (Table II).

Clinical Outcomes

Thienopyridine was stopped at least five preoperative days in 7 (25.9%) of the 27 patients operated within 3 weeks of the stent procedure. Of the seven, six (85.7%) died 1 to 17 days after their NCS (Table III). In two, death was sudden and unexpected while in three a Q-wave MI and in one cardiogenic shock preceded death. Stent thrombosis was demonstrated by angiography in one. In contrast, only 1 (5%) of 20 patients in whom thienopyridine was continued through surgery succumbed in the perioperative period ($P < 0.001$). That death was sudden.

Perioperative bleeding requiring blood transfusion occurred with equal frequency regardless of the use of antiplatelet agents. Five (25%) of the 20 patients in whom thienopyridine treatment was continued and 3 (43.8%) of 7 in whom it was stopped ($P = 0.63$) had significant hemorrhage.

Very few adverse perioperative events were encountered in the 20 patients operated more than 3 weeks after PCI. One died and two had non-Q-wave MI. These events occurred 2–5 days post-NCS and 67–72 days poststent placement. In-stent restenosis was demonstrated in one of the two with non-Q-wave MI. The only death was a sudden event after repair of an abdominal aortic aneurysm in an 82-year-old man. It is possible this reflected late stent thrombosis. None of these three patients was on thienopyridine. Despite the fact that 14 (70.0%) of these patients were on thienopyridine, none required perioperative transfusion.

DISCUSSION

This study demonstrates that the risk of cardiac complications and death after NCS is high in the first

TABLE I. Baseline Clinical Features

	NCS < 3 weeks	NCS > 3 weeks	*P*
Number	27	20	
Age (years)	70.4 ± 11.5	68.8 ± 10.9	0.62
Male	15 (55.6%)	9 (45%)	0.67
Diabetes mellitus	13 (48.1%)	6 (30%)	0.34
Hypertension	19 (70.4%)	13 (65%)	0.94
Hypercholesterolemia	9 (33.0%)	9 (45%)	0.61
Smoking	8 (29.6%)	13 (65%)	0.03
Previous MI	7 (25.9%)	8 (40%)	0.98
Previous PCI	2 (7.4%)	3 (15%)	0.65
Previous CABG	5 (18.5%)	2 (10%)	0.44

TABLE II. Type of Surgery Performed

	NCS < 3 weeks	NCS > 3 weeks	*P*
Number	27	20	
Vascular	7	7	0.73
Gastrointestinal	13	5	0.19
Urological	3	2	1.0
Cancer	2	4	0.38
Orthopedic	1	2	0.58
Other	1	0	1.0

TABLE III. Adverse Events in Patients Undergoing Noncardiac Surgery Within 3 Weeks of Stent Placement

	On thienopyridine	Off thienopyridine	*P*
Death	1/20 (5%)	6/7 (85.7%)	< 0.001
Hemorrhage	5/20 (25%)	3/7 (43.8%)	0.63

3 weeks following stent placement. It is in that period that the patient is most susceptible to stent thrombosis. Six of the seven deaths occurred in patients not on antiplatelet therapy. Moreover, although somewhat counterintuitive, our data indicate that significant perioperative bleeding is no more common in patients on thienopyridine than in those who were not. This experience supports a view that noncardiac surgery should be delayed if possible for at least 3 weeks after stent placement, but that when it must be undertaken, antiplatelet therapy should be continued (Fig. 1).

Stent thrombosis is a rare event in the contemporary practice of PCI; however, its association with a high morbidity and mortality has important implications [14–19]. The risk is highest within the first few days after stent placement and negligible after 4 weeks [13,14,19]. While all MIs and cardiac deaths during the first 3 postoperative weeks in this analysis are presumed to have been due to stent thrombosis, this assumption was angiographically confirmed in only one. In a previous report, only two of the eight deaths had angiographic documentation of stent thrombosis [19]. In this and the previous report [20], most deaths were rapid and involved unsuccessful efforts to resuscitate sudden hemodynamic collapse. Without autopsy, the proximate cause of these events is uncertain.

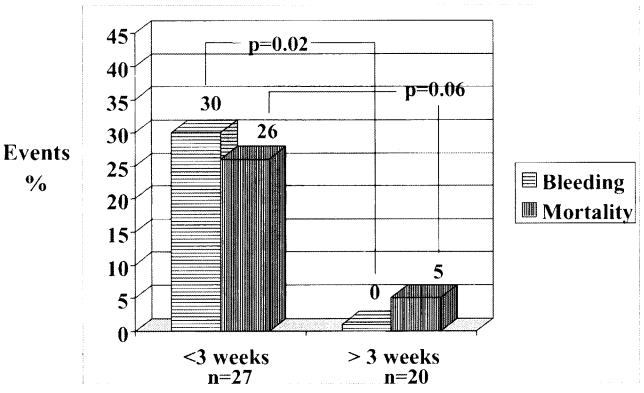

Fig. 1. Timing of surgery after PCI.

This is in contrast to stent thrombosis outside of the surgical period in which 86–100% of cases are angiographically confirmed [13].

Major noncardiac surgery is a special clinical setting that imposes two important issues that are directly relevant to stent thrombosis. First, surgery creates a prothrombotic milieu with increased procoagulant clotting factors and impaired fibrinolysis [21–23]. Moreover, the physiologic stress associated with the operative procedure activates the sympathetic nervous system causing the release of epinephrine and norepinephrine that may further promote platelet activation. Second, antiplatelet therapy is often stopped preoperatively to minimize bleeding complications. Stent thrombosis is likely to occur in this situation, especially if the stent reendothelialization process is not complete. Stent deployment leads to a complete disruption of the endothelial surface. Complete reendothelialization takes up to 8 weeks [24,25], while the return of endothelial function may take up to 6 months [26]. Despite this, clinical studies have shown that 2 weeks of antiplatelet therapy allows at least partial endothelialization, thereby significantly reducing the risk of stent thrombosis [27,28].

The sequence of pathophysiological events after stent deployment can be conceptualized as follows. First, as shown in this and a previous study [7], NCS during the first 3 weeks of PCI carries a high rate of cardiac death probably due to stent thrombosis if antiplatelet drugs are withdrawn to avoid perioperative hemorrhage. Second, after 8 weeks, restenosis becomes a significant issue. In-stent restenosis was documented in one patient who had surgery 72 days after PCI. Delaying NCS long enough to allow restenosis may result in a loss of the intended protective effect of the initial PCI. Thus, we agree with the American College of Cardiology/American Heart Association guidelines that surgery should not be delayed for more than 8 weeks. The optimal time for

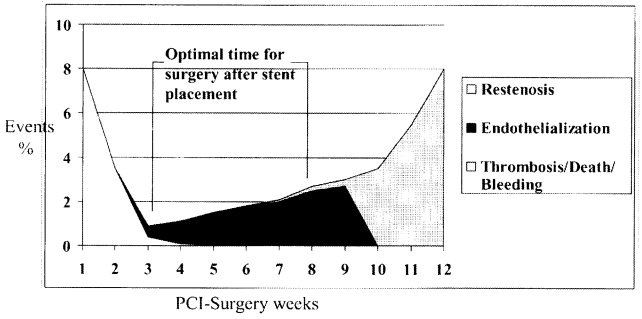

Fig. 2. Time course of pathophysiological events.

NCS appears to lie between 3 and 8 weeks after coronary stenting (Fig. 2). It should be noted that this safe period may not apply to patients who are treated with intracoronary radiation since reendothelialization may be significantly delayed [29].

There are limited data and no randomized clinical trials to show that prophylactic PCI with balloon angioplasty, stents, or any other device reduces perioperative ischemia, MI, or death. Nevertheless, this strategy is often considered. Among the studies of a strategy of balloon angioplasty before NCS, the perioperative mortality and infarction rate has ranged between 0% and 3% and 0% and 6%, respectively. We know of only one prior report that addresses the impact of stent use in the perioperative period [20]. In a study of 40 patients with a mean time of PCI to surgery of 13 days, an alarming 20% mortality rate was reported. Further, mortality was dependent on time lapse between PCI and surgery; 32% among patients operated within 2 weeks vs. 0% after 2 weeks. In the current analysis, mortality was 25.9% among those who had surgery within 3 weeks of PCI and 5% when operation was delayed beyond that mark. Thus, these two small but congruent studies contrast sharply with earlier reports in which balloon angioplasty alone was used.

Despite our small series to the contrary, there is almost certainly an excess risk of bleeding in patients who undergo major NCS while on antiplatelet therapy, particularly major vascular surgery [30–32]. The surgeon and cardiologist are therefore confronted with a therapeutic dilemma. It may seem desirable to mitigate the risk of bleeding by temporarily discontinuing antiplatelet medication before surgery. Such a choice greatly increases the risk of stent thrombosis in the postoperative period. This issue requires an individualized approach with thorough evaluation of potential risks and benefits.

Study Limitations

This is a small retrospective study and the results are subject to all the limitations of such reports. Several are worth consideration. First, the occurrence of a major complication of PCI would have prevented patients from proceeding with elective surgery. Therefore, that group of patients is missing from this analysis. Second, patients undergoing a variety of surgical procedures were included. Each has its inherent procedural mortality and bleeding rates. Finally, while no specific evidence or evaluation was noted for pulmonary embolism, sudden death due to that event cannot be excluded.

It appears advisable to defer elective major noncardiac surgery for at least 3 weeks after coronary stent placement. This will allow completion of antiplatelet therapy, reendothelialization, thereby prevent stent thrombosis and cardiac death.

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