Clinical Studies

Drug-Eluting Stent Thrombosis During Perioperative Period

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SUMMARY

Recently, the number of patients in whom a drug-eluting stent (DES) has recently been implanted and who need to undergo surgery or the most invasive procedure is increasing. However, there are limited data about the risk of perioperative thrombosis of DES. We evaluated the incidence and the risk factors of DES thrombosis during the perioperative period.

Between January 2002 and December 2006, 141 patients who underwent surgery requiring discontinuation of a dual antiplatelet agent within 12 months of DES implantation were enrolled in one of the 3 study hospitals. We reviewed the clinical and procedural characteristics of the patients who developed stent thrombosis during the perioperative period.

Stent thrombosis occurred in 7 cases (5.0%). The clinical outcomes of the patients with stent thrombosis were death in 5 cases and nonfatal MI in 2 cases. The patients with stent thrombosis were found to be older (64.2 ± 9.7 versus 71.7 ± 6.0 years, $P = 0.045$), to use a Taxus stent more frequently (36.6 versus 85.7%, $P = 0.014$), and to have a more prolonged period of discontinuation of clopidogrel (12.7 ± 10.0 versus 51.3 ± 33.2 days, $P = 0.022$) than the patients without stent thrombosis. Multivariate analysis revealed that 7 days or longer discontinuation of clopidogrel (OR 12.8, 95% CI 1.3-121.6, $P = 0.021$) and the use of a Taxus stent (OR 10.2, 95% CI 1.1-95.7, $P = 0.043$) were significant independent predictors of stent thrombosis during the perioperative period.

A prolonged period of discontinuation of clopidogrel was associated with higher risk of stent thrombosis during the perioperative period. An earnest effort to continue antiplatelet therapy throughout the perioperative period can minimize the risk of stent thrombosis. (Int Heart J 2008; 49: 135-142)

Key words: Stent thrombosis, Drug-eluting stents, Perioperative care

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DRUG-eluting stents (DES) are the most recent breakthrough in the field of interventional cardiology. Their main benefit is the reduction of restenosis. However, there is a potential downside of this stent, which is stent thrombosis. It is a rare but severe complication after DES implantation, and almost always causes acute myocardial infarction (MI) or sudden cardiac death.[1-3] Stent thrombosis is associated with a suboptimal angiographic result, specific high risk lesion characteristics, high risk patients and, importantly, early cessation of dual antiplatelet therapy.[4-9] Obtaining a good angiographic result and administering dual antiplatelet therapy with aspirin and clopidogrel are the cornerstones of stent thrombosis prevention.

Recently, the number of patients in whom a DES has recently been implanted and who need to undergo surgery or the most invasive procedure is increasing. Most available data about the risk of stent thrombosis in the perioperative period are derived from studies of bare metal stents.[10-12] Most authors and guidelines recommend that the surgery be avoided during the 12-month period of dual antiplatelet therapy after DES implantation,[13,14] however, there are limited data about the risk of perioperative thrombosis of DES.

Therefore, we evaluated the incidence and the risk factors of DES thrombosis during the perioperative period.

METHODS

Subjects: We identified all patients who underwent surgery requiring discontinuation of dual antiplatelet agents within 12 months of DES implantation between January 2002 and December 2006. Three tertiary heart centers participated in this retrospective review. Exclusion criteria included (1) noncardiac death during the in-hospital period; and (2) incomplete data for review. The protocol was approved by the Institutional Review Boards of the participating hospitals.

Data collection: The hospital charts of all identified patients were reviewed. The following data were collected: baseline clinical characteristics, percutaneous coronary intervention (PCI) 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, MI, stent thrombosis, and repeated revascularization procedures. Special attention was given to the time of initiation as well as the withdrawal or continuation of antiplatelet therapy during the pre- and postoperative period.

Definitions: Stent thrombosis was defined as (1) angiographically proven thrombosis or occlusion (proven stent thrombosis); and (2) unexplained death or target vessel MI (possible stent thrombosis). Postoperative MI was defined as the presence of at least two of the 3 following criteria: chest pain > 30 minutes, electro-

cardiographic change of acute myocardial infarction, and elevations in cardiac troponin. The endpoint was defined as the occurrence of any type of stent thrombosis.

Statistical analysis: All measurements are presented as the mean ± standard deviation. Intergroup analysis was performed using the independent *t*-test, χ^2 test, and Fisher's exact test using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL). A multivariable logistic regression model was constructed for the prediction of stent thrombosis during the perioperative period. For continuous variables, the median value was used as a cut-off point to define the two subgroups in logistic regression analysis. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 141 patients were identified by the study criteria. Six patients had undergone cardiac surgery, 78 intraperitoneal surgery, 25 brain or spinal surgery, 10 retroperitoneal surgery, 18 orthopedic surgery, and 4 transurethral resection of prostate (TURP). Approximately 60 percent of the patients received emergency surgery. All of the patients were prescribed dual antiplatelet therapy (aspirin and clopidogrel) before surgery.

The baseline demographics are shown in Table I. The mean timing of surgery was 7.6 ± 3.3 months after PCI. Only 5 patients underwent surgery within 4 weeks of PCI. Thirteen patients (9.2%) were administered a parenteral antiplatelet agent after the withdrawal of oral antiplatelet therapy during the perioperative period. Aspirin administration was stopped in all but 7 patients during the period of clopidogrel discontinuation.

Table I. Baseline Clinical Characteristics

Age	64.6 ± 9.7
Reason for stenting (%)	
ST segment elevation myocardial infarction	32 (22.7)
Non-ST segment elevation myocardial infarction	22 (15.6)
Unstable angina	53 (37.6)
Stable angina	34 (24.1)
Planned operation type (%)	
Cardiac surgery	6 (4.3)
Noncardiac surgery	135 (95.7)
Parenteral agent during the surgery (%)	13 (9.2)
Timing of surgery after stenting (months)	7.6 ± 3.3
Duration of clopidogrel discontinuance (days)	14.7 ± 14.6
Stent thrombosis (%)	7 (5.0)
Proven / Possible	2 (1.4)/5 (3.5)

Table II. Clinical and Procedural Characteristics

	ST (-)	ST (+)	*P*
Age (years)	64.2 ± 9.7	71.7 ± 6.0	0.045
Male (%)	87 (84.9)	6 (85.7)	0.423
Hypertension (%)	75 (56.0)	6 (85.7)	0.239
Diabetes (%)	45 (33.6)	3 (42.9)	0.690
Smoker (%)	57 (42.5)	2 (28.6)	0.699
Emergency surgery (%)	88 (65.7)	4 (57.1)	0.694
Procedural characteristics			
MI presentation (%)	52 (38.8)	2 (28.6)	0.708
Multivessel disease (%)	63 (47.0)	3 (42.9)	1.000
Stent number	1.6 ± 0.8	2.1 ± 1.3	0.292
Stent length (mm)	42.3 ± 22.8	55.6 ± 30.6	0.299
Cypher/Taxus (%)	93 (69.4)/49 (36.6)	2 (28.6)/6 (85.7)	0.014
Maximal size (mm)	3.3 ± 0.3	3.3 ± 0.5	0.735
Minimal size (mm)	3.1 ± 0.3	3.0 ± 0.3	0.393
Stent overlapping (%)	32 (23.9)	4 (57.1)	0.070
Time after stenting (months)	7.7 ± 3.0	5.7 ± 2.9	0.334
Withdrawal of clopidogrel (day)	12.7 ± 10.0	51.3 ± 33.2	0.022
Withdrawal of aspirin (day)	12.1 ± 9.9	38.4 ± 33.1	0.080

ST indicates stent thrombosis and MI, myocardial infarction.

Table III. Multivariate Analysis for Prediction of Stent Thrombosis During the Perioperative Period

Variable	OR	95% CI	*P*
> 7 days of clopidogrel discontinuation	12.8	1.3-121.6	0.027
Use of Taxus stent	10.2	1.1-95.7	0.043
Stent overlapping	4.3	0.7-25.2	0.109
Age > 65 years	4.4	0.5-42.1	0.202

Stent thrombosis occurred in 7 cases (5.0%). The clinical outcome of the patients with stent thrombosis was death in 5 cases and nonfatal MI in 2 cases. The patients with stent thrombosis were found to be older (64.2 ± 9.7 versus 71.7 ± 6.0 years, $P = 0.045$), to use a Taxus stent more frequently (36.6 versus 85.7%, $P = 0.014$), and to have a more prolonged period of discontinuation of clopidogrel (12.7 ± 10.0 versus 51.3 ± 33.2 days, $P = 0.022$) than the patients without stent thrombosis. The mean stent length, number, and size were similar between the two groups (Table II).

Multivariate analysis revealed that clopidogrel discontinuation of 7 days or longer (OR 12.8, 95% CI 1.3-121.6, $P = 0.021$) and the use of a Taxus stent (OR 10.2, 95% CI 1.1-95.7, $P = 0.043$) were significant independent predictors of

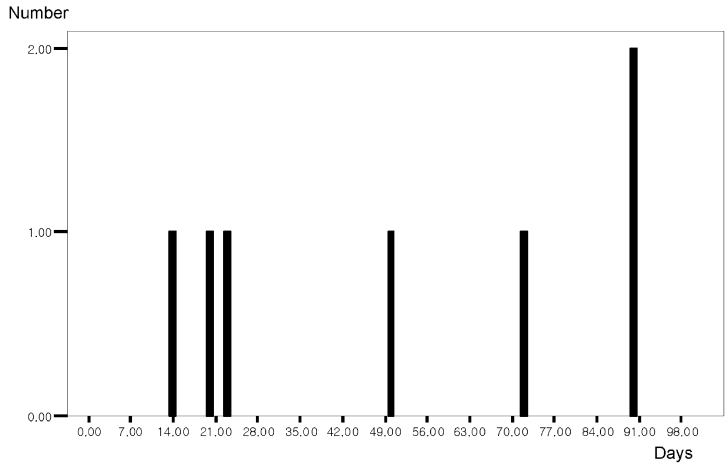

Figure. Incidence of stent thrombosis after discontinuation of clopidogrel. There was no stent thrombosis in patients in whom clopidogrel was discontinued for less than 14 days.

stent thrombosis during the perioperative period (Table III). None of the patients with clopidogrel discontinuation of less than 14 days had stent thrombosis (Figure).

DISCUSSION

This study demonstrates that a prolonged period of discontinuation of clopidogrel is associated with a higher risk of stent thrombosis during the perioperative period. This experience supports the view that the withdrawal of antiplatelet therapy should be short, or more specifically no longer than 1 to 2 weeks.

Several studies of patients with bare metal stents have demonstrated that the risk of stent thrombosis is highest in the first 4 to 6 weeks after implantation.[10-12] From Mayo Clinic data, the cardiac risk was 3.8 to 7.1% during the first 6 weeks after stenting, but no event was seen in the patients who had surgery 6 to 8 weeks after stenting.[10] Schouten, *et al* reported that bare metal stent thrombosis occurred in 2.2% of patients who had noncardiac surgery 1 and 28 days after implantation; aspirin and clopidogrel had been withheld during surgery in patients with stent thrombosis.[15] As a result of these observational studies, the 2002 American College of Cardiology/American Heart Association guidelines on perioperative cardiovascular care recommended that if a bare metal stent is placed prior to noncardiac surgery, the surgical procedure should be delayed for

at least 2 weeks, and ideally 4 to 6 weeks, to allow for at least partial endothelization of the stent.[16] However, data for patients with DES is not well established.

DES contain an antiproliferative agent that reduces neointimal proliferation and the incidence of in-stent restenosis. There is delayed healing and incomplete endothelization of stent struts up to 4 years after DES implantation.[17] Delayed endothelization prolongs the period of thrombogenic risk and raises the susceptibility of DES to late thrombosis.[18] Therefore, surgical timing after stenting may not be as important as it is in cases of bare metal stents. Rather, continuous antiplatelet therapy despite the surgery is more important.

The risk of stent thrombosis persists long after the cessation of antiplatelet therapy. In large series, stent thrombosis occurred in 8 cases between 2 to 26 months after DES implantation whilst on aspirin monotherapy or when antiplatelet agents were discontinued.[7] No events occurred while the patients were on dual therapy. Our observational study also revealed a very high incidence (5%) of stent thrombosis during premature discontinuation of dual antiplatelet therapy for surgery. Thus, the guideline recommended that the surgery be avoided during the 12-month dual antiplatelet therapy after DES implantation.[13] Surgery was in most cases the main reason for premature discontinuation of antiplatelet therapy. In some procedures, such as neurosurgery and spine operations, any increase in bleeding may have catastrophic consequences, and therefore all antiplatelet therapies need to be discontinued for at least 5 and often 10 days prior to surgery. In these cases, early reinitiation is likely to reduce the frequency of DES thrombosis, because thrombosis may not occur until several days after surgery.[19] Some authors suggest that a 600 mg loading dose of clopidogrel should be given as soon after surgery as the surgeon will allow.[20] Our results support a clopidogrel reinitiation strategy, with which no DES thrombosis occurred until 14 days after surgery.

It has not yet been determined whether any specific type of DES is more likely to develop stent thrombosis. A direct comparison of the stent thrombosis rate between sirolimus- and paclitaxel-eluting stents in clinical trials may not reflect the true thrombogenicity, because of the differences in patient and lesion characteristics. Several meta-analyses revealed similar incidences of stent thrombosis between the two types of stents.[9,21-22] The present study showed that implantation of a paclitaxel-eluting stent was a predictor of stent thrombosis. However, this result was not generalized because the number of patients was small and this study was not randomized.

The present study was limited to patients who underwent surgery, and the patient population was small. Furthermore, the timing of discontinuation of clopidogrel and the stent thrombosis rate were not directly compared. Accordingly,

prospective multicenter studies with large numbers of patients in various settings are required.

In conclusion, more than 2 weeks of discontinuation of clopidogrel was associated with a higher risk of stent thrombosis during the perioperative period. An earnest attempt to continue antiplatelet therapy throughout the perioperative period can minimize the risk of stent thrombosis.

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