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Comparison of Initial Efficacy and Long-term Follow-up of Heparin-coated Jostent With Conventional NIR Stent

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SUMMARY

The implantation of heparin-coated stents was reported to be well tolerated, but there are conflicting results about acute in-hospital complications, (sub)acute thrombosis rates, and long-term follow-up compared to uncoated stents. We compared the angiographic and clinical results after coronary placement of two stent models: the heparin-coated premounted Jostent and the uncoated premounted NIR stent. Of 710 patients revascularized, a total of 426 patients received Jostent (n = 230) or NIR stent (n = 196) implantation. The primary end points were acute or subacute thrombosis, urgent CABG, AMI or death, while the secondary end points were the comparison of the restenosis rates of the stents at the 6th month and of the functional angina classification of the stent groups at the 1st, 6th and 12th months. There were no significant differences between the Jostent and NIR stent groups regarding angiographic and procedural success. Acute thrombosis rates in the Jostent and NIR stent groups were similar while no subacute thrombosis was observed in either group. The major adverse cardiac event rates of the groups also did not differ. Angiographic restenosis occurred in 17% of the Jostent group and 16% of the NIR stent group (NS). The combined clinical and angiographic restenosis rate was also similar between the Jo and NIR groups (19% and 18%, respectively). Comparison of functional angina classes at the 1st, 6th and 12th months revealed no significant difference between the study groups.

In conclusion, when compared with implantation of an uncoated premounted NIR stent, implantation of a heparin-coated premounted Jostent does not provide any more benefit with respect to initial efficacy, sub(acute) thrombosis and 6-month restenosis rates and 12-month clinical outcomes. (Jpn Heart J 2003; 44: 889-898)

Key words: Coronary stents, Coating, Heparin, Coronary disease, Restenosis

In an animal model it has been suggested that stent surface material and geometric configuration may be more important than operator-dependent variables in determining the degree of neointimal hyperplasia and thrombosis.[1)] Data from

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animal studies indicate that heparin-coated stents were shown to be effective in reducing thrombosis in porcine coronary arteries.[2] Heparin coating of metallic coronary stents decreases their thrombogenicity but does not improve late vessel patency and neointimal hyperplasia at follow-up in a porcine coronary model.[3] Animal studies using high-activity heparin-coated stents have shown that up to 80% of the antithrombin III binding activity is lost 4 weeks after stent implantation.[2] Nevertheless, reductions in the rates of stent thrombosis in animal studies led to the evaluation of high-activity end-point-attached heparin-coated stents in the Benestent II pilot study[4] and the Benestent II randomized trial.[5] The purpose of this study was to investigate and compare the acute and subacute thrombosis and restenosis rates of a heparin-coated Jostent and a conventional NIR stent, a novel second generation tubular stent that was designed to overcome some of the limitations of the earlier Palmaz-Schatz (PC) stent design.

MATERIALS AND METHODS

We performed an analysis of the cardiac catheterization database from January 1998 through May 1999 and found data on all patients who underwent coronary revascularization in which a premounted Jostent or NIR stent was attempted in all treated segments. Of the 710 patients who were revascularized during this period, a total of 426 patients received Jostent or NIR stent implantation. At the beginning of the study, the patients in both groups were evaluated in terms of clinical and demographic properties. The patients were informed about the procedure and gave their written informed consent. Coronary angiography was performed according to conventional techniques through the femoral route. All of the subjects revascularized had a > 70% diameter stenosis in their native vessels. Percent diameter stenosis was assessed during diastole using the most severe stenosis in at least two angiographic views. The proximal and distal reference vessel diameters were averaged to obtain a mean reference vessel diameter. The same measurements were used in the same views during follow-up angiograms. A 7-Fr. guiding catheter and a 0.014 inch coronary guidewire were used as the delivery system. During the procedure, a total of 10,000 to 15,000 units of heparin were given as a bolus injection. Choice of predilatation with balloon catheters or of stent type was at the discretion of the operator. Stents were sized according to a stent-to-artery ratio of 1.1 to 1.0. Procedural success was defined as successful deployment of the stent in the absence of a major cardiac event [MACE - Death, acute myocardial infarction (AMI), coronary artery bypass grafting (CABG)]. High-pressure inflations (> 12 atm.) were used to optimize stent expansion after initial deployment of the stent. A < 10% residual diameter stenosis following final deployment of the stent was used to define angiographic

success for stent implantation. Patients were given ticlopidine and aspirin for 1 month and indefinitely, respectively, following successful stent implantation. Complete blood count was performed on all patients who received ticlopidine at 2 and 4 weeks.

Control coronary angiography was performed in available patients in both groups following a 6 month follow-up. Repeat percutaneous transluminal coronary angioplasty (PTCA) was attempted in patients with restenosis who accepted reintervention. Other patients in both groups were assessed by clinical information obtained through an interview during outpatient clinic visits or from the patient or family by telephone.

The primary clinical end points of the study were acute (occurring in the interventional site while the guiding catheter was still in place or in the first day following stent implantation) or subacute (occurring after removal of the guiding catheter following stent implantation or outside the interventional site) thrombosis, urgent CABG, AMI or death, while the secondary end points were the comparison of functional angina classes of patients in both groups, according to the Canadian Cardiovascular Society (CCS) classification, at the 1^{st}, 6^{th}, and 12^{th} month and of the restenosis rates of the stents at the 6^{th} month. Clinical restenosis for both stent groups was defined as having symptoms or signs of ischemia at the 6^{th} month follow-up. Angiographic restenosis was defined as a diameter stenosis of > 50% at 6-month reangiography measured at any point within the stented segment.

Continuous variables are expressed as the mean ± SD. Absolute numbers (%) were used for categorical variables. Statistical analysis was performed using Student's *t*-tests for continuous data and chi-square analysis for categorical data. Statistical significance was assumed at the 5% level.

RESULTS

The baseline clinical characteristics are shown in Table I. There were no significant differences in age, sex, diagnosis, risk factors, or other patient characteristics. Angiographic data for both stent groups are outlined in Table II. Lesion characteristics in both groups, according to the American College of Cardiology/ American Heart Association Task Force criteria, were identical. The diameter stenosis before stenting did not differ significantly among the groups. The difference between the number of diseased vessels in the groups was not significant. Table III shows the procedural and postprocedural characteristics of the groups. With respect to indications for revascularization, the differences between the groups were not significant. Angiographic success and procedural success were similar in the 2 groups. The number of MACE in the Jo and NIR groups did not

Table I. Patient Characteristics

	Jo Group (*n*=230)	NIR Group (*n*=196)	*P* Value
Male (%)	184 (80)	165 (84)	NS
Age (years)	57 ± 10	56 ± 9	NS
Stable angina pectoris (%)	81 (35)	43 (22)	NS
Unstable angina pectoris (%)	83 (36)	94 (48)	NS
Acute myocardial infarction (%)	37 (16)	24 (12)	NS
Recent AMI (%)	60 (26)	43 (22)	NS
Prior AMI (%)	30 (13)	35 (18)	NS
Prior streptokinase (%)	0	2 (1)	NS
Prior PTCA (%)	14 (13)	10 (5)	NS
Prior CABG (%)	4 (2)	4 (2)	NS
Coronary risk factors (%)			
Smoking history	104 (45)	76 (39)	NS
Diabetes	25 (11)	27 (14)	NS
Cholesterol ≥ 200 mg/dL	41 (18)	38 (20)	NS
Hypertension	81 (35)	65 (33)	NS
Family history	41 (18)	31 (16)	NS

Data presented are the mean ± SD or number (%) of patients. AMI= acute myocardial infarction; PTCA= percutaneous transluminal coronary angioplasty; CABG= coronary artery bypass grafting; NS= nonsignificant.

Table II. Angiographical Data

	Jo Group (*n*=230)	NIR Group (*n*=196)	*P* Value
Number of lesions (%)	254	224	NS
L AD	129 (51)	114 (51)	NS
CX	53 (21)	34 (15)	NS
RCA	72 (28)	76 (34)	NS
ACC/AHA lesion type (%)			
A	31 (12)	22 (10)	NS
B1	53 (21)	52 (23)	NS
B2	134 (53)	121 (54)	NS
C	36 (14)	29 (13)	NS
% diameter stenosis	88 ± 12	89 ± 12	NS
Reference vessel diameter (%)			
< 3 mm	177 (70)	134 (60)	NS
≥ 3 mm	77 (30)	90 (40)	NS
Number of diseased vessels (%)			
1 vessel disease	119 (52)	82 (42)	NS
2 vessel disease	86 (37)	84 (43)	NS
3 vessel disease	25 (11)	30 (15)	NS

Data presented are the mean ± SD or number (%) of patients or lesions. LAD=left anterior descending artery; CX=circumflex artery; RCA=right coronary artery; ACC/AHA=American College of Cardiology / American Heart Association; NS= nonsignificant.

differ significantly. Subacute thrombosis was not observed in either group. The difference between the number of stents per patient did not reach statistical significance. Bleeding complications requiring blood transfusion or surgical repair were not encountered in either group. The patients in both groups were discharged home after a mean period of 1.5 days.

The clinical end points at the 6th month are outlined in Table IV. The angiographic restenosis rate did not differ significantly between the Jo and NIR groups. The combined clinical and angiographic restenosis rate also did not reach statistical significance between the groups. Repeat PTCA of the restenotic segments was successful without any complications. The differences between the rates of any event at 6th month follow-up were not significant. There were no significant differences between the study groups with respect to the functional angina classes according to the CCS classification of the patients at the 1st, 6th and 12th month. The angina classification of the patients in the two groups is summarized in Table V.

Table III. Procedural and Postprocedural Characteristics

	Jo Group (*n*=230)	NIR Group (*n*=196)	*P* Value
Indication for revascularization (%)			
Planned	158/254 (62)	146/224 (65)	NS
Unplanned			
Suboptimal result	58/254 (23)	42/224 (19)	NS
Acute closure	20/254 (8)	25/224 (11)	NS
Restenosis following prior PTCA	18/254 (7)	11/224 (5)	NS
Angiographic success (%)	100	100	NS
Major cardiac event (%)	2 (1)	7 (4)	NS
Death	1	4	NS
AMI	1	1	NS
Urgent CABG	0	2	NS
Procedural success (%)	252/254 (99)	217/224 (97)	NS
Acute thrombosis (%)	4 (2)	2 (1)	NS
Subacute thrombosis (%)	0	0	NS
Number of stents / patient (%)			
Single stent	205 (89)	151 (77)	NS
2 stents	21 (9)	33 (17)	NS
3 stents and over	4 (2)	12 (6)	NS
Maximum atmosphere	12.8 ± 2	13.0 ± 2	NS
Predilatation (%)	221 / 254 (87)	188 / 224 (84)	NS
Blood transfusion (%)	0	0	NS
Surgical repair (%)	0	0	NS

Data presented are the mean ± SD or number (%) of patients or lesions. PTCA= percutaneous transluminal coronary angioplasty; AMI= acute myocardial infarction; CABG= coronary artery bypass grafting; NS= nonsignificant.

Table IV. Clinical End Points at 6 Months

	Jo Group (*n*=230)	NIR Group (*n*=196)	*P* Value
Control angiography (%)	100 (43)	68 (35)	NS
Combined clinical and angiographic restenosis rate (%)	44 / 230 (19)	36 / 196 (18)	NS
Angiographic restenosis rate (%)	17 / 100 (17)	11 / 68 (16)	NS
TVR (%)	10 / 100 (10)	7 / 68 (10)	NS
AMI (%)	2 (1)	2 (1)	NS
CABG (%)	2 (1)	4 (2)	NS
Death (%)	5 (2)	8 (4)	NS
CVA (%)	0	0	NS
Any event at 6 month follow-up	19 / 230 (8)	21 / 196 (11)	NS

Data presented are number (%) of patients; TVR: target vessel revascularization; AMI=acute myocardial infarction; CABG=coronary artery bypass grafting; CVA=cerebrovascular accident; any event=TVR, AMI, CABG, death or CVA; NS=nonsignificant.

Table V. Angina Classification of Patients in Jo Stent and NIR Groups (*)

	No angina (%)		Class I (%)		Class II (%)		Class III (%)		Class IV (%)	
	Jo	NIR	Jo	NIR	Jo	NIR	Jo	NIR	Jo	NIR
1st month	89	83.5	1.8	7.2	9.2	8.2	0	1	0	0
6th month	89	86	1.8	4.3	4.6	3.2	3.7	3.2	0.9	3.2
12th month	86.3	85.1	2.7	6.4	2.7	2.1	2.7	4.3	5.5	2.1

(*) Comparison of functional angina classes of patients according to Canadian Cardiovascular Society classification revealed no significant difference.

DISCUSSION

Stents have been shown to successfully treat acute or threatened vessel closure after failed PTCA[6] and to significantly reduce restenosis.[7-9] Adjunctive use of potent antiplatelet agents such as ticlopidine or clopidogrel markedly decreased the incidence of stent thrombosis and bleeding complications.[10] To further improve the clinical results of coronary stenting, attention was directed to coating the stent with material that would reduce their inherent thrombogenicity and decrease the incidence of in-stent restenosis.[2,4,5,11-29] Most coatings tested are placed mainly to provide a biologically inert barrier between the stent surface and the circulating blood. In contrast to these, immobilized-heparin surface coatings have been studied as means of providing a biologically active exterior that interacts with the circulating blood.[30] Some of the heparin-coated stents available for clinical use include the heparin-coated PS stent, on which heparin is end-linked

to the stent surface with a patented Carmeda coating technology, the Wiktor heparin-coated stent (Hepamed coating),[29] and the Jostent (Corline heparin coating), on which heparin is randomly attached.[30] The heparin-coated Wiktor stent appeared to be an efficacious device to treat Benestent-like lesions, yielding angiographic and clinical results comparable to a heparin-coated PS stent.[29] A stent coated with releasable heparin has been reported to be beneficial in reducing neointimal formation and subsequent in-stent restenosis in porcine coronary arteries.[31] The implantation of stents coated with polyamine and end-point-attached heparin in stable patients with one significant *de novo* coronary lesion is well tolerated, is associated with no (sub)acute stent thrombosis, and results in a favorable event-free survival after 6 months. Meanwhile, there was no compelling evidence indicating that heparin coating is actively affecting the neointimal hyperplasia within the stent.[4] Over a 12-month follow-up, a strategy of elective stenting with the heparin-coated PS stents has been reported to be more effective but also more costly than balloon angioplasty.[32] A randomized study with blind angioscopic assessment for heparin-coated versus uncoated PS stent in native coronary circulation reported that the implantation of heparin-coated stents in a nonselected population was well tolerated and associated with no clinical or angioscopic evidence of new thrombus formation, resulting in favorable long-term clinical and angiographic outcomes.[33] Some of the limitations of the earlier PS stent design led to the development of a novel second generation tubular NIR stent. The NIR stent showed excellent deliverability with slightly better acute angiographic results and an equivalent or better 9-month target vessel failure rate when compared with the PS stent.[34] Our study shows that the NIR stent is as favorable as the heparin-coated Jostent with regard to early and late clinical and angiographic outcomes. Our findings that both MACE and acute thrombosis rates were similar in the heparin-coated Jostent and the NIR stent groups could be explained by the state that procedural failure is mainly due to dissection or inadequate expansion of the stent and is independent from the stent structure or stent coating. Absence of subacute thrombosis and major bleeding complications in both the Jo and NIR groups in our study is in accordance with the findings that careful and intensive monitorization of heparin administration during the procedures until the removal of femoral sheaths and that use of the potent antiplatelet agent ticlopidine for 1 month have been shown to prevent subacute thrombosis rates and bleeding complications due to anticoagulant medication.

It has been reported that controversy exists about the usefulness of heparin coating.[35] Although the incidence of subacute stent thrombosis was extremely low in the Benestent II trial (0.2% compared with 3.5% in Benestent I using a noncoated stent), the trials may not be comparable concerning this particular complication because the Benestent I trial was conducted in an era of different

stenting protocols. Otherwise, angiographic restenosis rates were similar (22% and 18% for Benestent I and II studies, respectively)[36,37] When compared with the uncoated Jostent, the Corline heparin coating of the Jostent had no impact on the in-hospital complication rate, stent thrombosis, or restenosis.[38] The similar effects for heparin coated Jostent and NIR stent implantation on restenosis rates and CCS angina classification in our study support the knowledge that, in addition to thrombus formation at the site of intervention, smooth muscle cell proliferation, arterial remodeling, and vascular recoil are also responsible for the development of restenosis[39]; however, the relative importance of each remains to be determined. Although the same data confirm the influence of the coronary stent design, especially of the strut thickness of the stents, on restenosis rate and cardiac events,[40-42] the strut thickness of the Jostent and NIR stent is somewhat similar (90 μm and 100 μm, respectively). All of the results above indicate that the role of heparin coating remains an open question.[35]

Heparins are glycosaminoglycans that, in addition to their anticoagulant activity, have interactions with growth factors and other glycoproteins. These interactions may stimulate neointimal hyperplasia when heparin is delivered locally on stents and stent-grafts. Modifying the structure of heparin to retain its anticoagulant activity while minimizing these stimulatory effects on the vascular endothelium is desirable and may be achieved by understanding the relationships between the structure and functions of the various parts of the heparin molecule.[43] The development of the end-point attached heparin-coated stent should be regarded against the early unfavorable results with uncoated stents in the pre-IVUS and pre-ticlopidine era. Considering the quite low incidence of early complications of noncoated second generation stents, it may require very large trials to test the clinical efficacy of the heparin-coating against noncoated devices. However, even if the 'added value' of the heparin-coating will never be clinically proven, it has helped to enhance the penetration of stent therapy in interventional cardiology.[44]

In conclusion, the heparin-coated Jostent and the uncoated conventional NIR stent enable favorable procedural success, (sub)acute thrombosis, and 6-month restenosis rates and have similar 12-month clinical outcomes.

Limitations of the study: Several limitations can be observed in the current study. Because this study had a retrospective design, a prospective, randomized study is mandatory to validate our findings. Another limitation is that computerized quantitative coronary angiography was not available in our laboratory. The fact the study was performed in a single center is the third limitation. Our timing for follow-up coronary angiography at 6 months may be too short to evaluate the restenosis rates of the stents.

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