Paper II

Early Mobilization After Protamine Reversal of Heparin Following Implantation of Phosphorylcholine-Coated Stents in Totally Occluded Coronary Arteries

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Immediate removal of the femoral artery sheath after coronary angioplasty may allow rapid mobilization and reduces the number of in-hospital days. We studied the early and 1-month clinical and angiographic follow-up of patients having heparin reversed with protamine after implantation of phosphorylcholine-coated metal (Divysio) stents, followed by removal of the femoral artery sheath. Fifty patients (37 men, mean age 59 ± 10 years) with stable angina pectoris and a single totally occluded artery (1 unprotected left main stem, 15 left anterior descending, 11 left circumflex, 23 right) underwent coronary angioplasty. Antithrombotic medication was salicylic acid 75 to 160 mg before, heparin bolus 7,500 IU during, and protamine sulfate 25 mg and oral ticlopidine 250 mg after the procedure. Angiography was performed after 30 minutes and at 1 month. The mean number of stents was 1.4 ± 0.6/lesion, with a mean final diameter of 2.69 ± 0.40 mm. One stent thrombus was detected after 30 minutes and was treated with balloon dilatation. One patient underwent emergency bypass surgery for non–stent-related problems. Forty-six patients were mobile after 5 hours, and 2 after >5 hours. At 1 month there had been no major coronary end points, rehospitalizations, groin bleeding, or more thrombi. One episode of transient pulmonary edema occurred after protamine injection. Thirty-eight patients (79%) had no angina at 1 month, maximal bicycle exercise capacity increased from 128 ± 42 to 160 ± 45 W (p <0.05), and left ventricular ejection fraction increased from 63% to 68% (p <0.05). Thus, reversal of heparin with protamine sulfate after implantation of a phosphorylcholine-coated stent enables early mobilization. This approach seems safe in patients with 1-vessel total occlusions and angioplasty could be performed as an outpatient procedure. ©2000 by Excerpta Medica, Inc.

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Early mobilization after coronary angioplasty reduces patient discomfort, may allow outpatient procedures in subgroups of patients, and is desirable because of a limited number of hospital beds with the growing number of angioplasties. Heparin reduces intracoronary thrombosis and complications during invasive procedures.[1,2] However, prolonged treatment does not appear to improve outcome after angioplasty[3,4] and increases puncture site complications, even at low doses.[5,6] Protamine sulfate has been used to reverse heparin after coronary angioplasty procedures to treat bleeding complications.[7,8] Its use as a routine drug to reverse heparin and enable early mobilization after angioplasty has not been studied before. Stents with phosphorylcholine coating have been shown in animal experiments to be well accepted by the arterial wall[9] and to have low thrombogenicity,[10] and could therefore have a potential use in patients undergoing angioplasty with reversal of heparin after a procedure. In this study, protamine sulfate was administered after successful angioplasty to a total occlusion treated with implantation of a phosphorylcholine-coated stent.

METHODS

Patients with stable or medically stabilized unstable angina pectoris undergoing angioplasty on a single totally occluded coronary artery were eligible for the study. The reference artery diameter had to be >2.5 mm and the length of the occlusion <15 mm. Patients were excluded if they had a left ventricular ejection <30%, occlusion of a vein graft, or known adverse effects to protamine sulfate. Among 775 consecutive coronary angioplasty procedures, 113 were performed on single occluded arteries; of these, 84 (74%) were succesfully opened. Fifty-one patients met the inclusion criteria, and 1 patient refused to participate. The study protocol was approved by the local ethics committee and all patients gave written informed consent.

Angioplasty procedure: Coronary angioplasty was performed using 8Fr guiding catheters via an 8Fr sheath in the femoral artery. After predilatation of the occluded artery, a 15-mm phosphorylcholine-coated Divysio stent (BCP Inc., Farnham, Surrey, United Kingdom) was implanted at a pressure of >12 atm. The operator could decide to implant additional iden-

tical stents to the same lesion if clinically indicated. Femoral venous sheaths were not inserted.

Phosphorylcholine-coated Divysio stent: The Divysio stent is a slotted tube laser-cut stent composed of stainless steel with an interlocking arrowhead design.[11,12] The expanded stent covers 15% of the wall surface and is coated with phosphorylcholine, which adheres strongly to stainless steel. The coating is composed of methacrylate polymers, which serve as a backbone to which phosphorylcholine is attached. Phosphorylcholine is a zwitter ion and binds water, and makes the coated surface nonthrombogenic. All stents were hand crimped on a commercially available angioplasty balloon catheter.

Antithrombotic medication: An intraarterial bolus of 7,500 IU of heparin was injected via the femoral sheath at the start of the procedure. Additional doses were not supplied during or after the procedure. Protamine sulfate 25 mg was administered slowly intravenously after successful implantation of the stent. Activated clotting time (Hemochron, Edison, New Jersey) was determined in arterial blood at baseline, within 20 minutes after heparin administration, before protamine sulfate and 10, 20, and 30 minutes afterward. Activated clotting time >800 seconds was assigned a value of 800 to calculate mean values.[13] All patients were receiving treatment with acetylsalicylic acid (75 to 160 mg/day) for at least 24 hours before angioplasty and continued indefinitely. Ticlopidine (250 mg/day or twice daily) was started immediately after stent implantation and continued for 1 month.

Study end points: The study end points were successful mobilization after 5 hours, stent thrombosis, or target vessel reocclusion verified on angiography, fatal or nonfatal acute myocardial infarction, hospital admission for unstable coronary syndromes, femoral artery bleeding, or hematoma.

Coronary angiography: Angiography was performed at baseline, at the end of the procedure, 30 minutes after injection of protamine sulfate, and after 1 month. Standard procedures for perfoming angiography in our laboratory were followed.[14] Intracoronary thrombus was defined as an intraluminal filling defect or new occlusion at follow-up angiography. Reduced contrast and hazy appearance were defined as possible thrombus.[15] In each patient, identical angiographic views were used at baseline and during follow-up. Intracoronary nitroglycerin 0.1 to 0.2 mg was administered before angiography. The Siemens Quantcor system (Siemens AG, Erlangen, Germany) was used to quantitate minimal luminal diameter and reference diameter.

Clinical and laboratory evaluation: A 12-lead electrocardiogram was recorded at baseline, ½ hour after the injection of protamine sulfate, after 24 hours, and at 1 month. Myocardial infarction was defined as the appearance of new Q waves or new ST-T changes with a simultaneous elevation in the serum creatine kinase level to >3 times the upper limit with elevated myocardial band isoenzyme (creatine kinase-MB) values. Blood samples were collected at baseline, and within 24 hours of the procedure. No patient was lost to clinical follow-up.

Sheath removal and mobilization: The arterial sheath was removed immediately after 30-minute control angiography. Bleeding was stopped with a pneumatic groin compression device (Femostop, Radi Medical Systems AB, Uppsala, Sweden).[16] The groin was examined for local puncture complications before mobilization and at discharge the next morning. Major hematoma was defined as a palpable mass with a diameter of >5 cm. Major bleeding was defined as a significant decrease of >3 g/dl in hemoglobin or a bleeding necessitating blood transfusions. All other bleeding was defined as minor.

Statistical analysis: Data are presented as mean ± SD. The paired t test was used to compare blood samples, minimal luminal diameter, left ventricular ejection fraction, and exercise tests at different times. Statistical analysis was performed with the statistical computing program SPSS for Windows version 8.0 (Chicago, Illinois).

RESULTS

Baseline characteristics of the 50 patients are listed in Table I. The coronary occlusion time varied between 0.5 and 19.5 months (mean 7.3). Angiography showed definite hypokinesia or akinesia related to the perfusion area of the occluded artery in 18 patients. In 3 patients (6%) the occlusion was a restenosis. The stented arteries were 1 unprotected left main, 15 left anterior descending, 11 left circumflex, and 23 right coronary arteries.

The mean balloon pressure used for stent implantation was 15.6 ± 1.6 atm, the mean final stent diameter was 2.69 ± 0.40 mm (Table II), and the mean

TABLE I Baseline Patient Characteristics

Mean age (yrs)	59 ± 10 (37–78)
Women/men	13 (26%)/37 (74%)
Mean weight (kg)	80.5 ± 12.1 (57–115)
Mean height (cm)	174 ± 9 (152–190)
Risk factors	
Treated hypertension	20 (40%)
Familiar coronary artery disease	41 (82%)
Current smoker	7 (14%)
Former smoker	28 (56%)
Diabetes mellitus (insulin dependent)	5 (10%)
	2 (4%)
Peripheral vascular disease	2 (4%)
Cholesterol at inclusion (mmol/L)	5.1 ± 1.1
(medically treated)	44 (88%)
Angina (Canadian Cardiovascular Society class)	
IIA	11 (22%)
IIB	18 (36%)
III	18 (36%)
IV	3 (6%)
Previous myocardial infarction (Q wave)	31 (62%)
	13 (36%)
Previous procedure	
Coronary bypass	3 (6%)
Coronary angioplasty	4 (8%)
Both	1 (2%)

Values are expressed as mean ± SD (range) or number (%).

TABLE II Quantitative Angiography at Baseline, After Implantation of Divysio Stent, and at Follow-Up After One Half Hour and at One Month

Baseline		After Stenting		½-Hour Follow-Up		1-Month Follow-Up	
Ref. diameter	MLD	Ref. diameter	MLD	Ref. diameter	MLD	Ref. diameter	MLD
2.55 ± 0.50	—	2.85 ± 0.47*	2.69 ± 0.40	2.80 ± 0.46	2.65 ± 0.44	2.84 ± 0.45	2.55 ± 0.44†

*p <0.05 compared with baseline; †p <0.05 compared with minimal lumen diameter after stenting.
Values are expressed as mean ± SD.
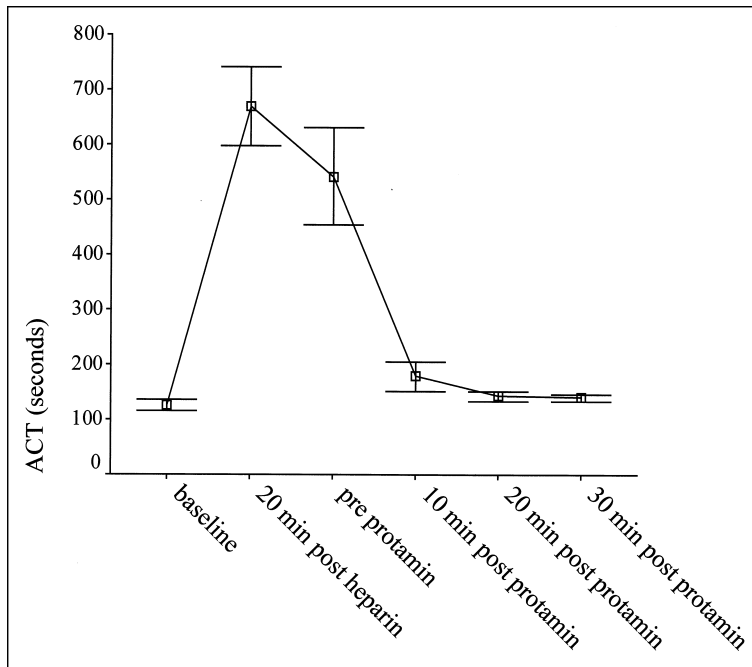MLD = minimal lumen diameter inside the stent; Ref. = reference.

FIGURE 1. Mean levels ± SD of activated clotting time (ACT) at baseline, within 20 minutes after heparin bolus, before the administration of protamine (protamin) sulfate and 10, 20, and 30 minutes after protamine sulfate was given. Patients with stent thrombosis and those referred for emergency coronary bypass surgery did not receive protamine sulfate and are excluded.

number of stents per lesion 1.4 ± 0.6. A single stent was implanted in 32 patients (64%), 2 stents in 17 (34%), and 4 stents in 1. The mean time from insertion of the arterial sheath to administration of protamine sulfate was 76 ± 29 minutes. The mean heparin dose was 99 ± 20 IU/kg body weight. Activated clotting time values are shown in Figure 1.

Clinical end points: No major bleeding or hematomas were observed. Forty-six patients were mobile after 5 hours, and 2 patients had only a few hours' delay of mobilization due to minor hematoma in the groin. Myocardial infarction was not detected.

Angiographic end points: Visible thrombus with chest pain was detected in 1 patient 30 minutes after the injection of protamine. The patient was successfully treated with a second angioplasty and the infusion of abciximab (Reo-Pro, Centocor BV, Leiden, The Netherlands). Three patients did not undergo follow-up angiography at 1 month: 1 refused, 1 had diagnosed esophegeal cancer, and 1 was referred for

emergency coronary bypass surgery for non-stent reasons (guiding catheter-induced left main stem dissection during the initial procedure). No thrombus was detected in the remaining 47 patients at 1 month (Figure 2).

Side effects of protamine sulfate: One patient developed transient pulmonary edema a few minutes after injection of protamine sulfate. Hypotension, tachycardia, or skin rashes were not observed.

One-month follow-up: Left ventricular ejection fraction measured by angiography increased from 63% (range 28% to 77%) at baseline to 68% (range 37% to 82%) at 1 month (p <0.05). Thirty-eight patients (79%) were in funcional class I, and there was significant improvement during the bicycle exercise test in maximal workload, total exercise time, and ST depression (Table III). No patient was admitted to the hospital for unstable angina pectoris.

DISCUSSION

We have shown that antagonizing heparin with protamine sulfate after implantation of ≥1 phosphorylcholine-coated stent enables immediate removal of an 8Fr sheath from the femoral artery. Patients can be mobile the same day without bleeding complications and without the occurrence of coronary adverse effects.

Pan et al[17] recently administered protamine sulfate after angioplasty in patients undergoing stent implantation without detecting adverse coronary effects. However, in that study low molecular weight heparin was administered to prevent stent thrombosis, and early mobilization was therefore not attempted. In our study patients were pretreated with only aspirin; therapy with ticlopidine was begun after the procedure. Yet, stent thrombosis was observed in only 1 patient 30 minutes after injection of protamine. This makes our strategy suitable for performing fast-track ambulant angioplasty. However, our results should be interpreted with some caution because of the relatively small study population.

The low frequency of adverse effects to protamine sulfate in our study may be explained by several factors. The drug was administered slowly, and all
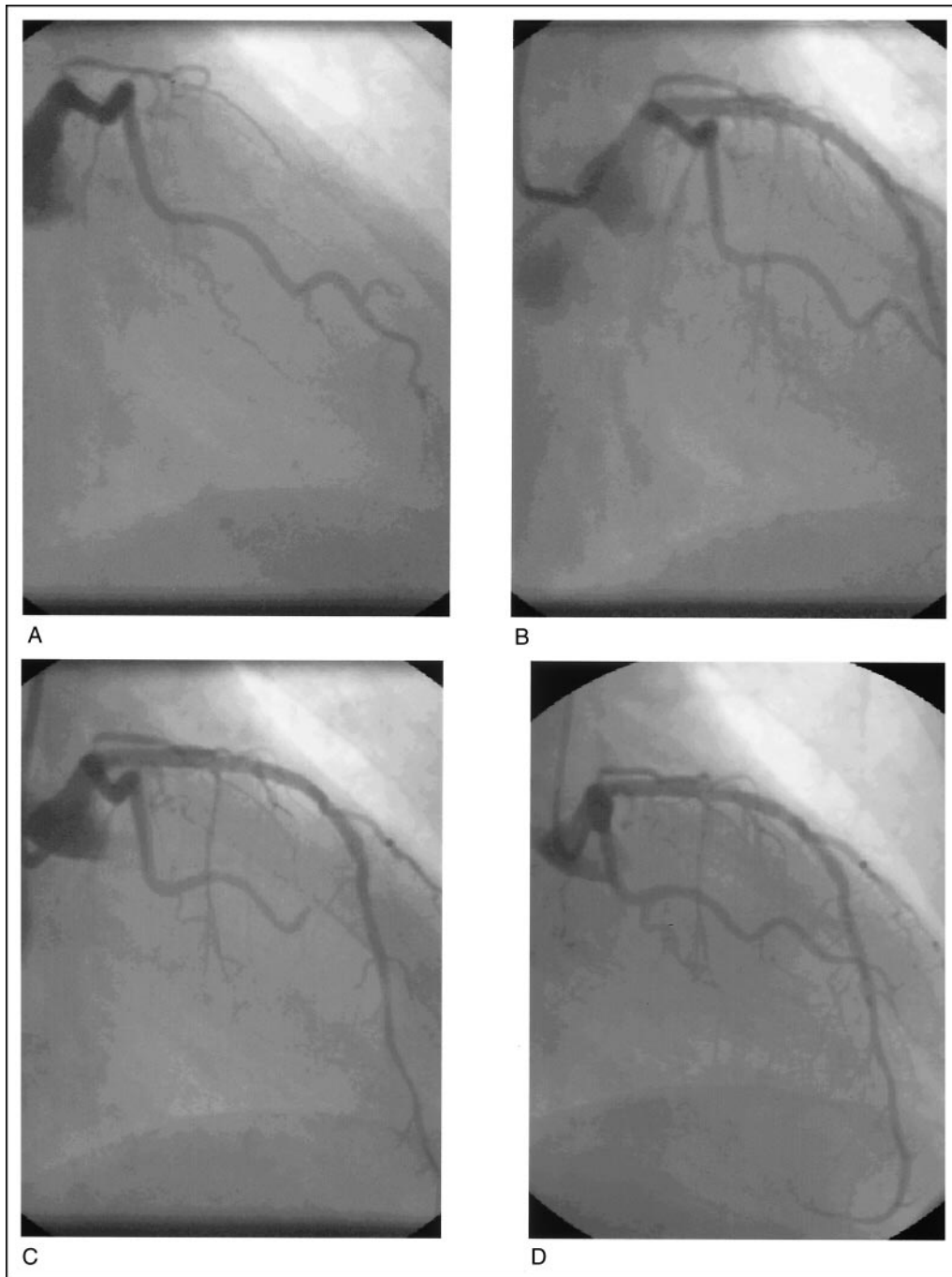
FIGURE 2. *A to D,* totally occluded left anterior descending artery before dilation *(A)* and after stent implantation *(B).* The angiographic appearance is unchanged one half hour after administration of protamine sulfate *(C).* Angiography at 1-month follow-up *(D).*

patients in this study were taking aspirin, which is a known thromboxane A_2 inhibitor, thus avoiding pulmonary vasoconstriction and bronchoconstriction.[18] Furthermore, our patients were treated for 1-vessel disease. Administration of protamine to a patient with multivessel disease has been reported to cause fatal cardiogenic shock[19]; there are no prospective studies to confirm or refute that this is generally an important problem. Avoiding high doses of protamine is impor-

tant because this can provoke bleeding via an antiplatelet effect and interaction with fibrinogen.[20]

An increased risk of protamine reactions in neutral protamine Hagedorn insulin-dependent diabetics has been reported,[21] but in another study[22] these reactions were not observed after administration of protamine in the dose range of <50 mg. In our study only 2 patients with insulin-dependent diabetes were included, and they had no adverse effects from protamine.

TABLE III Exercise Tolerance Test Before the Procedure and at One-Month Follow-Up

	Before PTCA (n = 48)	One-Month Follow-Up (n = 46)
Chest pain ETT	37 (74%)	5 (10%)
Total exercise time (s)	327 ± 118	409 ± 139*
ST-segment depression (mm)	1.6 ± 1.3	0.3 ± 0.7*
Maximal workload (W)	128 ± 42	160 ± 45*

*p <0.05.
Values are expressed as mean ± SD or number (%).
ETT = exercise tolerance test; PTCA = percutaneous transluminal coronary angioplasty.

Several approaches for ambulant angioplasty have been proposed, including low-dose heparin (i.e., 5,000 IU) in combination with 6Fr catheters using the femoral artery.[23] However, 8% of the patients had to continue heparin treatment after the procedure, whereas stents were only implanted in 15% of the patients, and puncture site complications were reported to be >2%. Outpatient coronary angioplasty via radial access can be performed without bleeding complications by experienced operators,[24] but loss of pulse is recorded in 3% of the patients undergoing transradial coronary angioplasty.[25,26] Also, fast-track angioplasty via the radial artery is dependent on routine diagnostic angiographies being performed the same way.

Vascular hemostasis devices like Vasoseal (Datascope Corp., Montvale, New Jersey) have been introduced for immediate sheath removal after interventional procedures, but serious groin complications after Vasoseal vary between 10% and 34%.[27] With use of Vasoseal, only 50% of patients were able to be mobile at 6 hours after percutaneous transluminal coronary angioplasty.[28] The relative high cost is another shortcoming of these devices.

This study was not specifically designed to examine the phosphorylcholine coating. The coated Divysio stent was chosen on the basis of promising experimental data showing low thrombogenicity.[9,10] Because there are no previous data on the use of protamine with stents, we anticipated that the risk could be further reduced by including only patients with total occlusions. The thrombosis risk of protamine with uncoated metal stents may be equally low, but the large number of patients with chronic occlusions needed for comparing stents would require a large multicenter study.

Our patients with total occlusions constituted a very low risk group. The results may therefore not be applicable to the general population of patients undergoing angioplasty. We are currently studying the use of protamine sulfate in patients whose stented vessel is not occluded to begin with.

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