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Effect of Short-Term Prostacyclin Administration on Restenosis After Percutaneous Transluminal Coronary Angioplasty

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The effect of short-term prostacyclin (PGI_2) administration on the incidence of restenosis after coronary angioplasty was studied in a prospective single-blind randomized trial of 286 patients. Of the 270 patients in whom dilation was successful, 134 received prostacyclin and 136 received placebo. Intracoronary prostacyclin was administered before and after dilation and then intravenously for 48 h. The control group received intracoronary placebo infusions before and after dilation. All patients received aspirin and dipyridamole before and after angioplasty, at least until follow-up angiography.

Follow-up angiograms were obtained in 93% of patients in whom angioplasty was successful. Restenosis of one or more lesions was present in 34 patients (27%) who were given prostacyclin compared with 40 patients (32%) in the control group (p = NS). Acute vessel closure and ventricular tachyarrhythmias were more common in the control group than in the patients who received prostacyclin (acute vessel closure occurred in 14 [10.3%] of 136 versus 4 [3.0%] of 134, respectively, $p < 0.01$; ventricular tachyarrhythmias occurred in 5 [3.4%] of 147 versus 0 of 139 respectively, $p < 0.05$).

Short-term administration of prostacyclin did not significantly lower the risk of restenosis after coronary angioplasty.

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Coronary artery restenosis after successful percutaneous transluminal coronary angioplasty occurs in 17% to 45% of patients (1). Attempts to reduce the incidence of restenosis by administration of drugs such as warfarin (2), calcium channel blockers (3,4), aspirin (5) and ticlopidine (6) have been unsuccessful. However, two studies (7,8) reported a lower incidence of restenosis with omega-3 fatty acid administration, and a preliminary report (9) suggested that treatment with the prostacyclin analog Ciprostene (epoprostenol sodium) resulted in a trend to fewer instances of restenosis.

Although the mechanism of restenosis is not completely understood, platelet deposition and degranulation are considered to play a pivotal role in acute reclosure and probably contribute to late restenosis as well (10). Platelets adhere to the endothelium early after it is traumatized by balloon inflation (11–13). This injury might further augment platelet aggregation by interfering with local production of prostacyclin (PGI_2). The thrombosis that results (14,15), as well as the subsequent proliferative and inflammatory responses, may lead to stenosis or obliteration of the lumen. Aspirin, which inhibits the production of thromboxane (16), is commonly used in an attempt to prevent early reclosure and restenosis. However, it also inhibits endothelial production of prostacyclin, which has potent antiplatelet and vasodilating properties (17,18).

We therefore hypothesized that optimal antiplatelet and vascular effects could be achieved by the administration of prostacyclin in addition to aspirin and dipyridamole, a hypothesis consistent with the positive findings of the previously mentioned studies of omega-3 fatty acid and ciprostene (7–9). Accordingly, we conducted a prospective randomized clinical trial to determine if short-term intracoronary and intravenous administration of prostacyclin would reduce the incidence of restenosis after angioplasty.

Methods

Patient selection. Between June 1984 and September 1985, 286 patients who were referred for coronary angioplasty were enrolled in the study. The protocol was approved by the Conjoint Medical Ethics Committee of the

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University of Calgary and the Foothills Hospital and the Research and Development Committee at the Holy Cross Hospital. All patients gave written informed consent.

Exclusion criteria included age <18 or >75 years, menstruating women, uncontrolled hypertension or diabetes, history of stroke or recent (<3 months) gastrointestinal bleeding, previous angioplasty in the artery to be dilated, myocardial infarction within the previous month or prolonged chest pain in the preceding 24 h. Patients were also excluded if they had been treated with a thrombolytic agent within 3 months or had participated in a drug trial within 9 drug half-lives. Coronary artery anatomy and severity of disease did not influence enrollment.

Study protocol. Patients were stratified according to whether single or multivessel dilations were to be performed and were randomized to receive either prostacyclin (Group A) or placebo (Group B). Immediate and noticeable facial flushing in Group A precluded effective double-blinding in this study. Patients did not know the treatment they received. Because the prime study end point was based on a blinded angiographic interpretation, the single-blind study design was believed to carry a low risk of bias. All patients received aspirin (325 mg) and dipyridamole (75 mg) three times daily (19,20), beginning the evening before angioplasty and continuing at least until follow-up angiography.

Immediately before angioplasty, all patients received sublingual nifedipine (10 mg) and nitroglycerin (0.3 mg), intravenous heparin (10,000 IU) and intracoronary nitroglycerin (200 μg). After selective coronary angiography, patients in Group A received an intracoronary infusion of prostacyclin (Upjohn Company of Canada) at a rate of 0.05 ng/kg per min, which was increased to 7.0 ng/kg per min over 5 min and then continued for an additional 10 min (21,22). Patients in Group B were given prostacyclin diluent at an identical infusion rate and for the same period of time. When both the left and right coronary arteries were to be dilated, the total infusion dose and time were divided equally between both vessels.

Angioplasty was subsequently performed using a steerable angioplasty system (U.S.C.I.–C. R. Bard Inc.). When two or more lesions were to be dilated, the "culprit" lesion was prospectively identified and angioplasty of that lesion was attempted first. The procedure was terminated if dilation of the culprit lesion was unsuccessful. In patients in Group A, prostacyclin (PGI_2) was infused immediately after angioplasty into the dilated coronary artery for an additional 15 min at 7 ng/kg per min and, when appropriate, the infusion was divided equally among the arteries that were dilated. Prostacyclin was then infused intravenously for 48 h at 8.0 ng/kg per min. Early in the study, the dose was reduced to 5.0 ng/kg per min because of the high incidence of side effects. If nausea occurred during the intravenous infusion, it was discontinued for 5 min and resumed at progressively lower infusion rates until symptoms abated. Patients in the control group received an intracoronary infusion of an equivalent volume of diluent over 15 min immediately after angioplasty, but did not have diluent administered intravenously. In addition to prostacyclin or placebo, all patients received nifedipine (10 mg) and isosorbide dinitrate (10 mg) orally four times daily for 48 h after the procedure. Repeat angiography was performed 6 months after angioplasty or earlier when dictated by symptoms.

Data analysis. Angiograms performed at the time of initial and follow-up angioplasty were analyzed simultaneously by a single angiographer who did not know which patients had been treated. Luminal diameter stenosis was measured by caliper, comparing the narrowest segment with the proximal adjacent "normal" segment, and the average of the measurements from two or three angiographic views was recorded. A single view was used when it was the only one in which the stenosis was adequately visualized. Lesion length was also measured. Interobserver variability was determined by comparison of measurements made by a second angiographer, who also did not know the treatment group, in 40 randomly selected patients, 20 with restenosis. Correlation between measurements by the two observers was very good ($r = 0.89$, SEE = 12%, $p < 0.001$). All lesions compared were classified identically with regard to presence or absence of restenosis.

Angiographic definitions. Two definitions for restenosis were prospectively defined: 1) luminal diameter reduction <50% in the coronary artery segment previously dilated, and 2) >50% loss of the immediate gain after angioplasty (23). Lesion length was considered to be the length over which the luminal diameter was reduced by ≥50%. Coronary artery dissection was defined as a linear opacification in or adjacent to the dilated segment immediately after angioplasty. Successful angioplasty was defined as one in which the luminal diameter was increased by 20%, with a final diameter stenosis <50%, provided there was no death, myocardial infarction or need for emergency bypass surgery. When dilation of only the culprit lesion was successful, the procedure was considered successful. Analysis of follow-up angiograms was performed only in patients with successfully dilated lesions.

Acute vessel closure was deemed to be present if within 24 h after successful angioplasty, repeat coronary angiography (performed because of recurrent symptoms or electrocardiographic changes) failed to completely opacify the vessel distal to the dilated stenosis.

Statistical analysis. Two hundred sixty-eight patients would be required to demonstrate a 50% reduction in the restenosis rate, assuming a restenosis rate of 30% ($\alpha = 0.05$, $\beta = 0.2$) (24). Comparisons between continuous data were made using unpaired Student's t tests, and discrete data were assessed with the chi-square statistic. The null hypothesis was rejected at $p < 0.05$. All data are presented as mean values ± 1 SD.

Table 1. Clinical Characteristics in 286 Patients

	Prostacyclin Group (Group A, n = 139)	Control Group (Group B, n = 147)
Age (yr)	55 ± 9	57 ± 11
Male (%)	84	83
Hypertension (%)	34	38
Diabetes mellitus (%)	8	15
Cigarette abuse (%)	50	42
Serum cholesterol (mmol/liter)	5.34 ± 0.88	5.51 ± 1.1
Unstable angina (%)	46	56
Previous MI (%)	42	44
Ejection fraction	0.66	0.64

There were no statistically significant differences among these baseline variables. MI = myocardial infarction.

Results

Patient characteristics (Tables 1 to 3). There were no statistically significant differences in baseline characteristics between patients who received prostacyclin (Group A) and those given placebo (Group B) (Table 1). The angiographic findings and data related to the procedures in both groups of patients are listed in Table 2. There were no statistically significant differences between the groups in any of the observed variables. The distribution of vessels dilated in each of the patient groups is shown in Table 3.

Table 2. Angiographic and Procedural Data in 286 Patients

	Prostacyclin Group (Group A, n = 139)	Control Group (Group B, n = 147)
No. of vessels dilated	159	156
Lesion length (mm)	4.6 ± 2.8	4.8 ± 3.1
Calcification	45%	39%
Primary success	96%	92%
Luminal diameter reduction (%)		
Before dilation	80 ± 11	79 ± 11
After dilation	24 ± 11	25 ± 11
Total occlusion (before dilation)	9 (5%)	7 (4%)
Lesion gradient (mm Hg)		
Before dilation	46 ± 14	47 ± 16
After dilation	11 ± 7	11 ± 6
Dissection	36%	34%
Balloon size (mm)	3.1 ± 0.4	3.1 ± 0.4
Maximal balloon pressure (atm)	9.0 ± 1.4	9.2 ± 1.4
No. of inflations		
Range	1–27	1–22
Mean	3.9 ± 3.9	3.9 ± 3.6
Total inflation time (s)	145 ± 109	146 ± 126
Time intervals (min)		
1st ic infusion to balloon inflation	41 ± 35	37 ± 28
1st balloon inflation to 2nd ic infusion	40 ± 32	34 ± 29

There were no statistically significant differences among any of the variables. ic = intracoronary.

Results of angioplasty. Figure 1 illustrates the results in all 286 patients enrolled in the study. Angioplasty was successful in 134 (96%) of 139 patients who received prostacyclin (PGI_2) (Group A) and 136 (92%) of 147 control patients (Group B) (p = NS). Among the five patients in Group A with unsuccessful angioplasty, emergency surgery was performed for acute closure in two, the lesion could not be crossed in two and an inadequate final angiographic result was obtained in one. Among the 11 patients in Group B with unsuccessful angioplasty, emergency surgery was performed for acute closure in 1, Q wave myocardial infarction occurred in 3 (including the 1 patient sent for emergency surgery and 1 who subsequently died of infarction extension), the lesion could not be crossed in 3 and an inadequate final angiographic result occurred in 5.

Follow-up results. Follow-up angiography was performed in 125 (93%) of 134 successfully treated patients in Group A and 125 (92%) of 136 successfully treated patients in Group B. Reasons for not performing follow-up angiography in patients in Group A included late bypass surgery in one patient, patient refusal in three, late death in one and four patients were lost to follow-up study. In Group B, lack of follow-up angiography was due to late bypass surgery performed in one, patient refusal in six, late death in two and two patients were lost to follow-up study.

Incidence of restenosis (Tables 3 and 4). At the time of follow-up angiography, restenosis was present in 34 patients (27%) in Group A and 40 patients (32%) in Group B (p = NS). Similar results were obtained regardless of which definition of restenosis was applied. The incidence rate of restenosis in each of the vessels dilated is shown in Table 3. There was a 9% incidence of restenosis in the left circumflex artery in patients in Group A, which was significantly lower than that in Group B (39%) ($p < 0.05$). Restenosis was present in 35 (22%) of 159 arteries in patients in Group A and in 45 (29%) of 156 arteries in patients in Group B (p = NS).

The time to follow-up angiography (Table 4). Angiography was performed more commonly in the first 3 months after angioplasty (that is, before the end of the scheduled 6 month follow-up period) because of recurrence of symptoms in patients in Group B compared with Group A (12 versus 3, $p < 0.01$). The mean time to follow-up angiography was similar in both groups (170 days in Group A versus 141 days in Group B, p = NS).

Of the 34 patients in Group A with restenosis, 19 (56%) had successful repeat angioplasty, 2 (6%) had bypass surgery and 13 (38%) had symptoms that were controlled by medical therapy alone. Of the 40 patients in Group B with restenosis, 25 (63%) had repeat angioplasty, 3 (8%) had bypass surgery and 12 (30%) received medical therapy.

Complications (Table 5). Acute vessel closure was seen in 4 patients in Group A and 14 patients in Group B (p <

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Table 3. Incidence of Coronary Restenosis

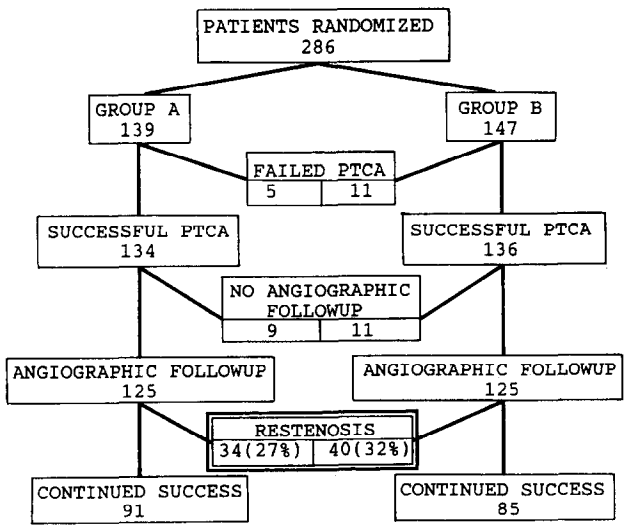
	All Patients		Prostacyclin Group (Group A)		Control Group (Group B)		p
	No.	Restenosis	No.	Restenosis	No.	Restenosis	Value
LAD (total)	160	44 (28%)	82	22 (27%)	78	22 (28%)	NS
Proximal	102	29 (28%)	58	15 (25%)	44	14 (32%)	NS
Diagonal	5	2 (40%)	2	1 (50%)	3	1 (33%)	NS
RI	4	0	1	0	3	0	NS
RCA	77	19 (24%)	41	9 (22%)	36	10 (28%)	NS
LCx (total)	69	17 (25%)	33	3 (9%)	36	14 (39%)	<0.05
Marginal	12	3 (25%)	6	1 (17%)	6	2 (33%)	NS
Total	315	70 (22%)	159	35 (22%)	156	45 (29%)	NS

LAD (total) = native left anterior descending coronary artery (LAD), diagonal branches and ramus intermedius (RI); LCx (total) = native left circumflex coronary artery (LCx) and marginal branches; RCA = right coronary artery.

0.01). Angiographic films obtained immediately after angioplasty and after acute closure were reviewed to determine the mechanism of acute closure. The predominant mechanism was deemed to be thrombosis if an abrupt cutoff was seen on the initial angiogram after closure and the lesion could be recrossed. Although a contributing role of thrombosis could not be excluded in any case, dissection appeared to be the main mechanism in all 4 acute vessel closures in Group A and 9 (64%) of the 14 acute closures in Group B. Successful reopening was accomplished in 1 of 4 and 12 of 14 patients in Group A and Group B, respectively. (The specific technique used to facilitate successful reopening was not documented in each case, but our standard approach during that period was prolonged inflations followed by use of a larger balloon if stabilization did not result.)

Ventricular tachycardia or fibrillation did not occur in patients who received prostacyclin but occurred in five patients in the control group ($p < 0.05$). Q wave myocardial infarction occurred in one and three patients in Group A and Group B, respectively (p = NS). Emergency bypass surgery was performed in two Group A patients and one Group B patient. The only procedure-related death occurred in the control group. Minor side effects—in particular, nausea and vomiting—were common in patients who received prostacyclin, and were the reason for premature drug termination in two patients. No patient required transfusion for bleeding complications during the course of this study. Hypotension occurred more often in patients in Group A (4.8% versus 0.0% in Group B, $p < 0.01$); affected patients always responded quickly to fluid replacement and did not require discontinuation of the drug.

Figure 1. Results in 286 patients enrolled in this study, 139 (Group A) receiving prostacyclin and 147 (Group B) receiving placebo. PTCA = coronary angioplasty.



Discussion

Does prostacyclin protect against restenosis? The purpose of this prospective randomized single-blind study was to determine whether short-term prostacyclin (PGI_2) administration in addition to aspirin and dipyridamole therapy would reduce the incidence of restenosis after angioplasty. The principal end point was restenosis demonstrated angiographically at 6 months, or earlier when symptoms recurred. There was no significant difference in the occurrence of restenosis in patients treated with prostacyclin compared with those given placebo. The incidence of restenosis in both

Table 4. Time From Coronary Angioplasty to Angiographic Detection of Restenosis

Time Interval	Prostacyclin Group (Group A)	Control Group (Group B)	p Value
0 to 3 months	3	12	<0.01
3 to 6 months	22	17	NS
6 to 9 months	9	10	NS
>9 months	0	1	NS
Mean (days)	170 ± 61	141 ± 88	NS

Table 5. Complications of Coronary Angioplasty

	Prostacyclin Group (Group A)	Control Group (Group B)	
	No. (%)	No. (%)	p Value
Major			
Acute reclosure	4 (2.9)	14 (9.5)	<0.05
Q wave MI	1 (0.8)	3 (2.0)	NS
V tach/fib	0	5 (3.4)	<0.05
Emergency CABG	2 (1.4)	1 (0.7)	NS
Death	0	1 (0.7)	NS
Minor			
Nausea	66 (48)	2 (1.5)	<0.001
Vomiting	28 (20)	1 (0.7)	<0.001
Diarrhea	8 (6)	0	<0.005
Phlebitis	4 (3)	0	<0.05
Hypotension	6 (4.8)	0	<0.01

CABG = coronary artery bypass grafting; MI = myocardial infarction; V tach/fib = ventricular tachycardia/fibrillation.

Group A and Group B (27% and 32%, respectively) was similar to that previously reported (1), and the similarity in restenosis rate was not altered when analyzed for single and multivessel dilation. These findings differ from the preliminary report (9) concerning the use of similarly administered ciprostene.

In this study, prostacyclin was initially administered by the intracoronary route before and after dilation, and then intravenously for 48 h. After endothelial injury, local production of prostacyclin resumes within 48 h and becomes normal after several weeks (25). Although it remains possible that more prolonged therapy with prostacyclin may prevent restenosis, the cost implications of a longer hospital stay might make such an approach impractical.

Although the difference in the incidence of restenosis between groups was not statistically significant, it was slightly lower in patients given prostacyclin. To establish that the observed difference was real would require a study of approximately 2,660 patients. The lower incidence of restenosis in patients who received prostacyclin and had angioplasty in the circumflex coronary artery may be an artifact of multiple comparisons because there is no reason to expect an artery-selective benefit.

Mechanisms of restenosis. Although the mean time to detection of restenosis was similar in both groups of patients, fewer patients who were treated with prostacyclin required angiography because of recurrent symptoms within 3 months of angioplasty. This finding may be explained, at least in part, by our current understanding of the mechanism of restenosis (12). The early "deep" injury that is likely to be responsible for acute vessel closure and early restenosis is characterized by atheroma fracture and intraluminal debris, both being potent stimuli to thrombus formation. The "late" form, seen with even relatively superficial injury, involves smooth muscle cell proliferation, which is a complex process mediated in part by growth factors derived from platelets and neutrophils. Platelet deposition, important in both early and late mechanisms, is also augmented by turbulence and increased local shear forces (10). Mechanisms that prevent endothelial platelet accumulation in normal coronary arteries include endothelial production of heparin sulfate (26), tissue plasminogen activators (27) and prostacyclin (28). Administration of these substances when endothelial production is reduced may limit platelet accumulation during angioplasty (29). Prostacyclin administration may also enhance local production of tissue plasminogen activator (30). Thus, this preliminary observation suggests that the administration of prostacyclin may interfere with early thrombus formation even though there is no apparent difference in long-term outcome, perhaps because it does not interfere with neointimal smooth muscle cell proliferation. Although platelet-endothelial interaction may play a role in late restenosis, long-term aspirin and dipyridamole therapy does not appear to influence the process (5).

Acute vessel closure after angioplasty: role of thrombosis versus dissection. In the present study, patients who received prostacyclin had a lower incidence of acute closure and ventricular arrhythmias. If thrombosis is the common denominator in the pathogenesis of these complications during angioplasty, our findings are consistent with previous reports of a similar benefit observed with antiplatelet agents such as aspirin (5), ticlopidine (31), and prostaglandin E_1 (PGE_1) (32). The incidence of acute closure in our control group was higher than expected from past experience. (Of 3,400 procedures performed in Calgary, 2.8% have been complicated by acute closure.) The reason for this is not clear. Although this unexpectedly high rate precludes the conclusion that prostacyclin exerted a protective effect during coronary angioplasty, there is reason to suspect that varying amounts of thrombosis account for the different acute closure rates. Angiographic analysis suggested that thrombosis was a prominent feature in acute closure in the control group but not in the group treated with prostacyclin. It is possible that the prolonged intracoronary instrumentation needed for placebo infusion without concomitant administration of additional antithrombotic agents contributed to this increased acute closure rate.

Antiarrhythmic effect of prostacyclin. Prevention of acute ischemia by an antithrombotic effect may explain the apparent antiarrhythmic activity of prostacyclin (33–37). This activity is unlikely to be due to the quinidine-like effect of prostacyclin because it only occurs at very high concentrations of the drug (38). It has been proposed that the balance between thromboxane and prostacyclin release during acute ischemia influences electrical stability (39) and that this is favorably altered by infusion of prostacyclin (40). Furthermore, prostacyclin influences noradrenalin release during ischemia, reflecting changes in autonomic nervous system activity (41). Finally, because prostacyclin is a peripheral

vasodilator, it may reduce ventricular wall stress, thereby reducing ventricular irritability (42).

Conclusions. Short-term administration of intracoronary and intravenous prostacyclin (PGI_2) did not lead to a significant reduction in coronary artery restenosis after angioplasty. Should a larger study confirm that the differences noted were real, the extent of this difference and the high incidence of minor side effects would not support the routine use of prostacyclin. Acute vessel closure and ventricular arrhythmias were more common in the control group. Despite the potential role of thrombosis as a cause for these complications, this study does not support routine use of prostacyclin during angioplasty.

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