Catheterization and Cardiovascular Diagnosis 37:382–391 (1996)

Lesion-Directed Administration of Alteplase With Intracoronary Heparin in Patients With Unstable Angina and Coronary Thrombus Undergoing Angioplasty

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Percutaneous coronary revascularization in patients with unstable angina and coronary thrombus carries a high complication rate. A new strategy to reduce thrombus burden before revascularization was tested in a multicenter prospective trial. Patients with unstable angina and coronary thrombus (n = 45) received alteplase through an infusion catheter at the proximal aspect of the target lesion and concomitant intracoronary heparin via a standard guiding catheter. Angiography was performed before and after lesion-directed therapy and post-intervention. Systemic fibrinogen depletion and thrombin activation were not observed, while fibrinolysis was evident for ≥4 hr after treatment. Target lesion stenosis did not change significantly after lesion-directed therapy, but thrombus score was reduced, particularly among patients who had large thrombi (mean 2.2 vs. 1.6, $P = 0.02$). Revascularization was successful in 89% of patients. Median final stenosis was 30% and mean final thrombus score was 0.4. Complications included recurrent ischemia (11%), MI (7%), abrupt closure (7%), severe bleeding (4%), and repeat emergency angioplasty (2%). Patients with overt thrombus appeared to derive the most angiographic benefit from lesion-directed alteplase plus intracoronary heparin. Later revascularization was highly successful. This strategy may be a useful adjunct to percutaneous revascularization for patients with unstable angina and frank intracoronary thrombus.

Key words: PTCA, thrombolysis, anticoagulation, thrombus

INTRODUCTION

The presence of intracoronary thrombus in patients with unstable angina treated with percutaneous intervention is associated with low procedural success rates and high subsequent rates of adverse clinical outcomes [1–5]. Angiographic resolution of intracoronary thrombus has been variable after intracoronary thrombolysis before angioplasty [6–12]. A recent large randomized, placebo-controlled trial showed that intracoronary urokinase given 5–15 min before angioplasty did not lead to thrombus resolution, and higher rates of abrupt closure and periprocedural ischemia were seen in the active-treatment group [13]. This lack of efficacy may be a result of inadequate amounts of fibrinolytic agent reaching the thrombus [14] or excessive thrombin activation from local fibrinolysis, which contributes to rethrombosis and subsequent abrupt closure [12].

Since lesion-directed thrombolysis has been shown to restore patency by a pharmacomechanical effect in the

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Received June 29, 1995; revision accepted August 5, 1995.

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A complete list of investigators and personnel of the Study Group is given in the Appendix.

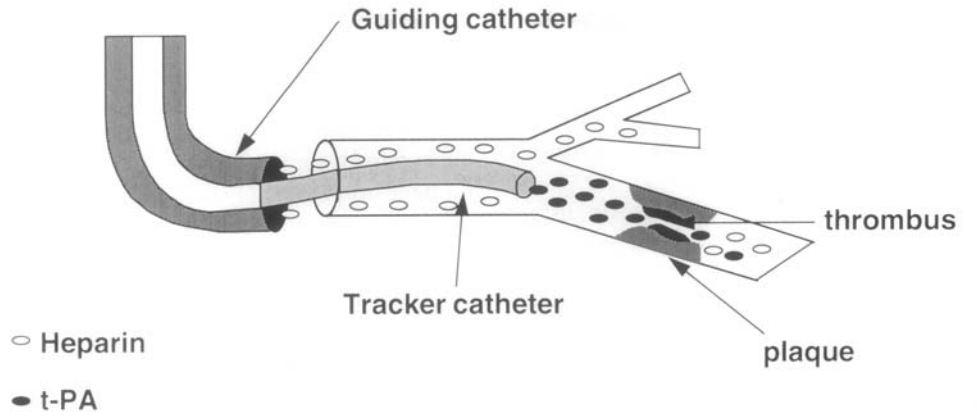

Fig. 1. Method of drug delivery for alteplase (t-PA) and heparin.

setting of acute myocardial infarction [15], we performed a multicenter trial to evaluate whether delivery of recombinant tissue-plasminogen activator (alteplase) to the thrombus could facilitate local fibrinolysis and reduce the thrombus burden before percutaneous coronary intervention. Intracoronary heparin was administered simultaneously to reduce thrombin activation caused by fibrinolysis [16–19] and to potentially enhance thrombolysis [20]. The protocol was designed to test whether lesion-directed alteplase with intracoronary heparin could reduce the angiographic presence of thrombus or severity of the target lesion as assessed by quantitative coronary angiography and to provide a rationale for a clinical efficacy trial.

METHODS

We studied patients with unstable angina and angiographically suspected intracoronary thrombus undergoing elective or urgent percutaneous revascularization at nine hospitals from July 1993 to February 1994. The protocol was approved by the institutional review board at each hospital, and all patients signed informed consent upon enrollment. The clinical sites, investigators, and coordinators are listed in the Appendix. The study was managed from a central coordinating center independent from the sponsors of the trial.

Patient Selection

Patients were eligible if they had unstable angina—defined as new onset of severe angina, accelerated angina, or rest angina occurring on maximum medical therapy—that was also associated with documented electrocardiographic changes (persistent or transient during pain). Patients with early (<14 days) post-infarction angina were also considered to have unstable angina. Angiographic inclusion criteria included the presence of frank thrombus (filling defects) or findings suggestive of thrombus (hazy appearance).

Exclusion criteria included myocardial infarction within 48 hr, normal electrocardiogram (ECG) during angina, history of significant bleeding diathesis, major surgical procedure or trauma within 2 months, recent cerebrovascular accident (<6 months), prior intracranial aneurysm, tumor or arteriovenous malformation, recent (<2 months) intracranial or intraspinal surgery, uncontrolled hypertension (systolic pressure >200 mm Hg or diastolic pressure >110 mm Hg), pregnancy or childbearing potential, heparin or aspirin allergy, and inability to provide informed consent. Patients with restenotic lesions were also excluded.

Study Protocol

Patients who met the entry criteria had baseline angiography, performed in orthogonal views that best defined the target lesion, following administration of intracoronary nitroglycerin. Patients then received intravenous heparin to maintain the activated clotting time at 300–400 sec. All patients received at least 325 mg aspirin daily. Prior vasodilator and additional antiplatelet therapy were not controlled. Intravenous heparin (15 U/kg/hr) was continued for ≥12 hr post-procedure.

The drug delivery method is depicted in Figure 1. Following baseline angiography (see below) and clotting time adjustment, a 0.014-in. coronary guidewire was placed at the proximal aspect of the target lesion. Attention was given not to cross the lesion with the wire. An infusion catheter (Tracker-18 HiFlow, Target Therapeutics, San Jose, CA) was advanced to the tip of the wire, and the guidewire was then retracted.

A total of 20 mg alteplase (Genentech, Inc., S. San Francisco, CA) was then delivered (20 ml of a 1-mg/ml

solution) through the infusion catheter to the lesion in 2-ml boluses via hand injection every 2 min. Concomitantly, 2-ml boluses of heparin (250 U/ml) were delivered through the guide catheter to the ostium of the target artery immediately after each alteplase bolus, for a total dose of 5,000 units.

After completion of the alteplase and heparin administration (alteplase–heparin) the infusion catheter was removed. Repeat angiograms using the same orthogonal projections were performed 20 min later, after administration of intracoronary nitroglycerin. At the discretion of the attending physician, balloon angioplasty or directional atherectomy was then performed in the standard manner. At completion of the procedure, intracoronary nitroglycerin was administered and angiograms were again performed in the same orthogonal projections.

Definitions of Clinical Outcomes

Clinical outcomes were prospectively defined. Myocardial infarction (Q- or non-Q-wave) was determined when two of the following occurred: (1) elevation in serum cardiac enzyme levels to above-normal limits; (2) ECG evidence of infarction: development of new Q waves, new ST-segment elevation, new bundle branch block, or deep T-wave inversions; and (3) typical angina for >15 min. In the absence of chest pain or ECG changes, a myocardial infarction was deemed to have occurred if the total creatine kinase myocardial band isoenzyme (CK-MB) level was ≥ 2 times the normal limit or total CK was ≥ 3 times the upper limit of normal. Recurrent ischemia was determined by the occurrence of anginal symptoms with ECG changes (ST-segment depression or T-wave inversion), new hypotension, pulmonary edema, or a new or worsening holosystolic murmur with ischemic symptoms. Stroke was defined as an acute neurological abnormality persisting for >24 hr, confirmed by a neurologist and by computed tomography (CT), magnetic resonance imaging (MRI), or autopsy. Congestive heart failure was defined as radiographic evidence of pulmonary edema, an S3 gallop, or $>1/3$ basilar rales requiring new or increasing diuretic therapy.

Bleeding complications were graded using standard definitions. Severe or life-threatening bleeding was defined as intracranial hemorrhage or bleeding that caused hemodynamic compromise: drop in systolic pressure from baseline to <90 mm Hg that required blood or fluid replacement, inotropic support, ventricular assist devices, surgical intervention, or cardiopulmonary resuscitation to maintain cardiac output. Moderate bleeding was bleeding that required blood transfusion but that did not cause hemodynamic compromise. Mild bleeding was bleeding that did not require transfusion and did not cause hemodynamic compromise.

Coronary Angiography and Assessment

Coronary angiography was performed in near 90° orthogonal views. Intracoronary nitroglycerin (0.1–0.3 mg) was given before each set of injections. All cineangiograms were interpreted by two experienced reviewers blinded to patient clinical information. The presence of intracoronary thrombus was described using a modification of the TIMI thrombus scale [21]. Grade 0 reflected no angiographic evidence of thrombus. Grade 1 had characteristics suggestive of thrombus, but no frank intraluminal filling defects with characteristics such as reduced contrast density, haziness, irregular or ulcerated lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus. Grade 2 was defined as a definite intraluminal filling defect with the largest dimension not more than one-half the diameter of the target vessel lumen. Grade 3 was a filling defect of more than one-half but <2 target vessel lumen diameters. Grade 4 was a filling defect of ≥ 2 target vessel lumen diameters. Coronary perfusion was graded by the TIMI classifications [22]. Coronary artery luminal diameter was graded visually by an interval scale as previously described [23]. Lesion location and morphology were specified using previously reported descriptors [5]. The TIMI thrombus grade and flow, lesion location and morphology, and presence of distal emboli were determined at baseline, 20 min after alteplase–heparin delivery and at the end of the procedure. Angiographic success was defined as a residual stenosis of $<50\%$ of the target lesion.

Quantitative Coronary Angiography

Percent diameter stenosis and minimum luminal diameter were determined at baseline, 20 min after alteplase-heparin, and at the completion of the procedure by quantitative angiographic techniques using a computerized edge-detection algorithm [24]. Percent diameter stenosis was determined from the projection revealing the greatest degree of obstruction. All 45 cinearteriograms were included for possible analysis. We could perform quantitative analysis in 98% (44/45) of patients at baseline, in 91% (41/45) at 20 min following alteplase–heparin, and in 93% (41/44) at the completion of the procedure.

Hematological Laboratory

Blood samples for measurement of the plasma concentrations of fibrinogen, D-dimer, heparin (Xa inhibition), prothrombin fragment 1.2, and fibrinopeptide A (FPA) were taken from the indwelling groin catheter before systemic heparinization for the procedure, at the end of the procedure, and at 2, 4, and 12–18 hr post-procedure. Blood was drawn into vacutainer tubes containing 3.8% sodium citrate (Becton Dickinson Inc., Rutherford, NJ)

for the fibrinogen and heparin assays and 4.5 mM EDTA, 150 U/ml Aprotinin, and 10 μM D-PheoProArg-Chloromethyl ketone for the prothrombin fragment 1.2 and FPA assays. Samples were centrifuged at 1,000*g* for 15 min; the plasma was then separated and stored at −70°C until assay.

Plasma fibrinogen concentration was measured by the method of Clauss as cited by Bovill et al. [25] with a normal range of 150–400 mg/dl and an interassay coefficient of variation (CV) of 2.8%. D-Dimer was measured as previously described with a normal range of 177 ± 83 ng/ml with an interassay CV of 7% [26]. Heparin Xa plasma concentration was measured with the Asserchrome Xa chromogenic assay (American Bioproducts, Parsippany, NJ) following the manufacturer's instructions with an interassay CV of 8%. Fragment 1.2 [27] was measured using an enzyme-linked immunsorbent assay (ELISA) kit (American Dade, Miami, FL) following the manufacturer's instructions with a normal range of <0.38 nM and an interassay CV of 7.4%. Fibrinopeptide A [28] was measured using a radioimmunoassay (RIA) kit (Byk-Sangtec, Marburg, Germany) according to instructions with a normal range of 1.1–11 ng/mL. The interassay coefficients of variation for the FPA assay were 10.1%, 3.8%, and 4.7%, respectively, for controls with the following mean values: 1.3 nM, 8.65 nM, 35.4 nM. Samples with an FPA level >50 ng/ml were discarded under the assumption that they represented samples drawn from inadequately heparinized vascular access sites.

Enzyme Core Laboratory

Creatine kinase MB fraction (CK-MB) and myoglobin were drawn at baseline, after the procedure, and at 2 and 24 hr and were measured at the enzyme core laboratory. CK-MB "mass" and myoglobin were measured using the Stratus II (Baxter Diagnostics, Miami, FL). The systems and methods for CK-MB and myoglobin measurement were used in accordance with the manufacturer's recommendations. Normal reference intervals were <7 ng/ml for CK-MB and <110 ng/ml for myoglobin.

Statistical Analyses

The primary endpoints were the percent change in diameter stenosis as measured by quantitative coronary angiography and the change in TIMI thrombus score from baseline to post-infusion angiogram. Changes in percent diameter stenosis and TIMI thrombus score within a patient were examined with Wilcoxon's signed-rank test. Differences in FPA levels over time were assessed with repeated measures of analysis of variance. Continuous variables are described as medians (25th, 75th percentiles) or means ±SD, and categorical variables are summarized as the number (percentage) of patients.

RESULTS

Fifty-three patients with unstable angina were enrolled after giving informed consent. Baseline clinical and angiographic characteristics of the population are shown in Table I. Eight patients (15%) could not begin the lesion-directed therapy: the Tracker catheter could not be placed in three patients due to proximal tortuosity, two patients had occlusion of the target artery shortly after guide catheter placement, two did not have thrombus present after repeated angiographic injections, and one developed hematuria after urinary catheter placement in the cardiac catheterization laboratory. The alteplase–heparin infusion was begun in the remaining 45 patients after placement of the Tracker catheter; the 20-min infusion was completed in 42 patients (93%). Worsening angina with ST-segment changes occurred in three patients during infusion, resulting in immediate angioplasty.

Angiographic results are shown in Table II. Lesion-directed therapy sufficiently reduced the thrombus and lesion severity in one patient such that revascularization was not required. Median percent diameter stenosis and median minimum luminal diameter within individual patients improved by 0.5% (−1.7%, 10%) ($P = 0.08$) and 0.04 mm (−0.06, 0.18 mm) ($P = 0.07$), respectively. Lesion-directed therapy significantly reduced the mean TIMI thrombus score from 2.2 to 1.6 ($P = 0.02$). TIMI thrombus score improved in 15 (36%), remained unchanged in 23 (55%), and worsened in four patients (9%) after lesion-directed therapy (Fig. 2). The greatest benefit was observed among patients with overt (TIMI thrombus score >1) thrombus. The no-reflow phenomenon was not observed in any patient.

Percutaneous interventions were used in 44 patients after lesion-directed therapy. A standard balloon was the first device used in 59% and a perfusion balloon was used first in 25%. The median maximum inflation time for angioplasty was 6 (3, 11) min. Directional atherectomy was used in three patients (7%), and a coronary stent was placed in two patients (6%). The angiographic success (<50% residual stenosis) rate was 86%. Percutaneous intervention improved the median diameter stenosis by 37% (28%, 48%) ($P = 0.0001$), median minimum luminal diameter by 0.99 (0.72, 1.35) mm ($P = 0.0001$), and the mean TIMI thrombus score ($P = 0.001$), as shown in Table II and Figure 2.

Lesion-directed therapy caused no changes in serum fibrinogen levels, as shown in Figure 3. Despite the absence of fibrinogenolysis, there was evidence of fibrinolysis: a fivefold increase in the D-dimer levels by 2 hr after the alteplase infusion (Fig. 3). Heparin Xa plasma concentrations were 0.80 U/ml at 2 hr post-infusion and 0.78 U/ml at 4 hr post-infusion. Prothrombin fragment 1.2 levels showed no change from baseline up to 4 hr

TABLE I. Baseline Characteristics

Characteristic	(n = 53)
Age (years)[a]	63 (52,67)
Male sex	38 (72%)
Hypertension	28 (53%)
Diabetes	11 (21%)
History of smoking	40 (76%)
Hypercholesterolemia	24 (45%)
Characteristics of unstable angina	
Rest pain	29 (57%)
Post-infarction angina	15 (29%)
Accelerating pattern	30 (59%)
Pain with ECG changes	25 (48%)
Prior infarction	33 (62%)
Prior angioplasty	3 (6%)
Prior bypass surgery	3 (6%)
No. of vessels with significant disease[b]	
1	14 (26%)
2	27 (51%)
3	12 (23%)
Ejection fraction (%)[a]	59 (50,65)
Target artery	
Left anterior descending	17 (32%)
Left circumflex	11 (21%)
Right coronary	25 (47%)
Lesion characteristics[c]	
Eccentric	37 (93%)
Ulcerated	38 (90%)
Angulation	
Mild–moderate	43 (81%)
Severe	1 (2%)
Calcification	
None–mild	41 (93%)
Moderate	3 (7%)
Discrete	28 (65%)
Diffuse	12 (28%)
Ectatic	3 (7%)
Visual stenosis (%)[a]	75 (75,83)

[a]Median (25th, 75th percentile).
[b]≥50% visual stenosis.
[c]Read by the Angiographic Core Laboratory.

after the alteplase–heparin therapy. FPA was elevated at baseline and demonstrated suppression ($P = 0.002$) over the first 4 hr.

There were minor changes in median CK-MB levels from 0.6 (0, 1.3) ng/ml pre-procedure to 1.0 (0.2, 3.4) ng/mL ($P = 0.003$) 24 hr later, while serum myoglobin levels remained unchanged: baseline 37 (26, 49) mg/ml, post-procedure 36 (28, 50) mg/ml, 2 hr later 36 (24, 65) mg/ml.

The median activated clotting time upon arrival to the laboratory was 168 (139, 210) sec. The median procedural dose of heparin was 18,333 (15,000, 25,000) units, and the peak procedural clotting time was 376 (341, 417) sec. The median procedure duration was 181 (150, 225) min.

In-hospital clinical outcomes in all enrolled patients (n = 53) and in those who received any lesion-directed therapy (n = 45) are shown in Table III. The majority of adverse clinical events were due to recurrent ischemia post-intervention. One patient suffered a small intracranial hemorrhage >24 hr after the procedure. He had no neurological deficits or sequelae and was discharged home after 5 days. Most patients receiving blood transfusion did so because of groin bleeding (70%) or decreased hematocrit (30%). The patients receiving blood transfusions were more likely undergo bypass surgery (30% vs. 0), vascular surgery (10% vs. 2%), or intracoronary stenting (10% vs. 2%) than those who did not receive transfusions. Distal embolization occurred in one patient during lesion-directed therapy and in two patients during percutaneous intervention.

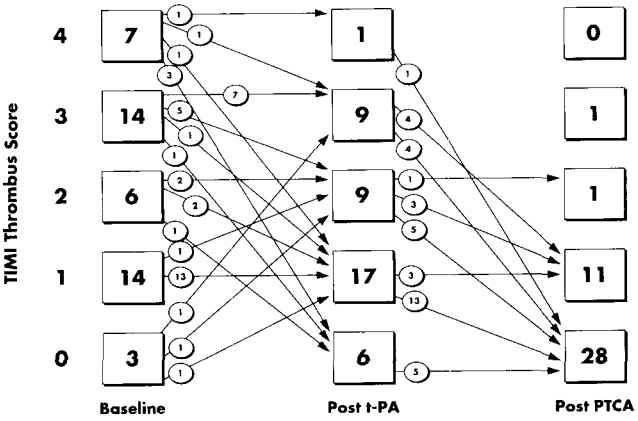

Fig. 2. Results of lesion-directed alteplase (t-PA) and angioplasty on TIMI thrombus scores.

Six-month follow-up was completed in 51 patients, and detailed information was available in 48. Death occurred in two patients (4%), myocardial infarction in none, bypass surgery in three (6%), repeat revascularization in five (10%), and recurrent hospitalization in 11 patients (23%).

DISCUSSION

Our results, from the largest prospective evaluation of lesion-directed thrombolysis in patients with unstable angina and intracoronary thrombus undergoing percutaneous revascularization, suggest that administration of lesion-directed alteplase with intracoronary heparin resulted in local fibrinolysis and thrombus reduction without systemic fibrinogenolysis. This delivery method differs from that of previous studies of intracoronary thrombolysis in several respects. First, the total dose of alteplase was lower, to avoid systemic effects. Second, the thrombolytic agent was directed at the proximal aspect of the target lesion instead of the ostium of the target vessel [7–13], to provide more direct contact between the

TABLE II. Angiographic Results*

Quantitative coronary angiography	Baseline (n = 44)	After lesion-directed alteplase (n = 41)	P	After PTCA (n = 41)	P
Diameter stenosis (%)	72 (61, 82)	69 (59, 80)		30 (20, 41)	
Change (%)	—	0.5 (−1.7, 10)	0.08	37 (28, 48)	0.0001
Minimum luminal diameter (mm)	0.75 (0.56, 1.07)	0.85 (0.58, 1.10)		2.00 (1.43, 2.17)	
Change (mm)	—	0.04 (−0.06, 0.18)	0.07	0.99 (0.72, 1.35)	0.0001
TIMI flow grade[a]					
0	3 (7%)	3 (7%)		0	
1	1 (2%)	2 (5%)		0	
2	7 (16%)	3 (7%)		4 (10%)	
3	33 (75%)	33 (81%)		37 (90%)	
Distal embolization[a]	—	1 (2%)		2 (5%)	
Abrupt closure[a]	—	3 (7%)		1 (2%)	
Dissection[a]					
Minor	—	0		12 (30%)	
Major	—	0		37 (9%)	

*Values are medians (25th, 75th percentiles) or the number (percentage) of patients in each category.
[a]Visual readings performed on 45 patients, of whom 1 did not have PTCA after lesion-directed therapy.

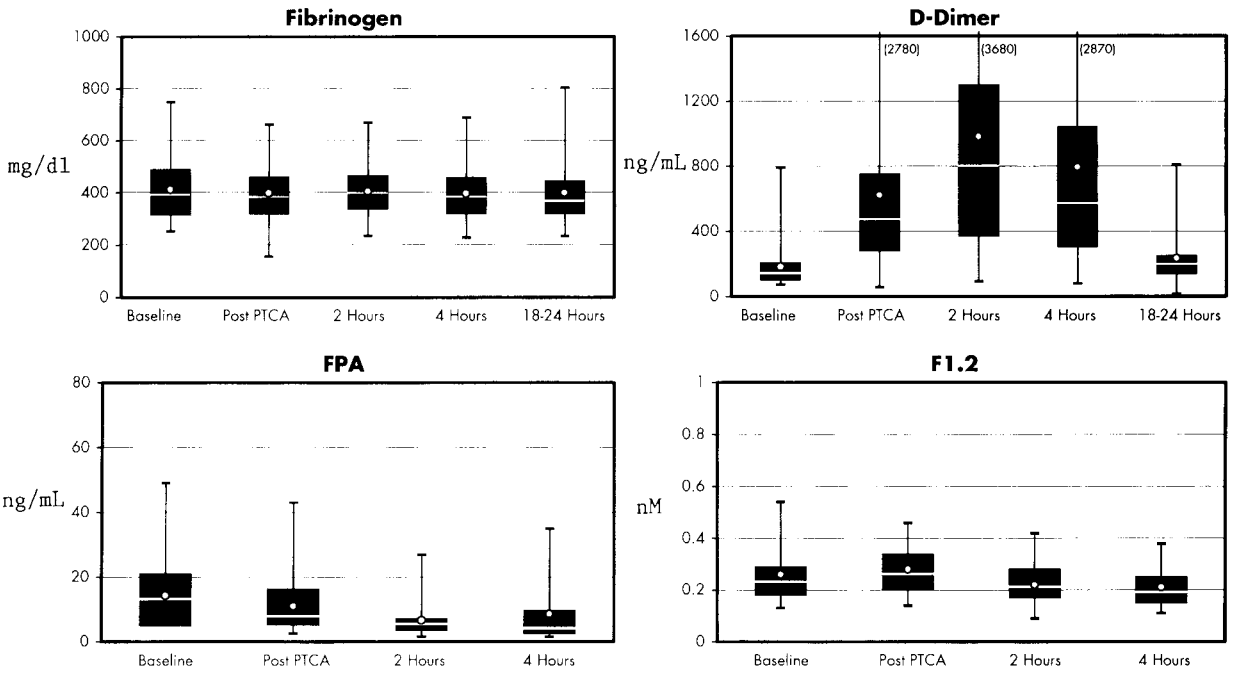

Fig. 3. Changes in serum fibrinogen, D-dimer, fibrinopeptide A (FPA), and Fragment 1.2 (F1.2) levels. The box lengths represent the interquartile ranges (25th, 75th percentiles). Medians are represented by lines within the boxes, and means by circles. The lines extending from the boxes represent the highest to lowest values.

agent and its target. Finally, the alteplase was administered in bolus injections in an attempt to disrupt the thrombus mechanically and increase the surface area of the thrombus for drug binding.

Lesion-directed therapy appeared to be most effective in patients with frank thrombus (TIMI thrombus score >1). This suggests that this method of adjunctive therapy should be reserved for patients with larger thrombi, which may be more friable and thus more pharmacologically responsive to this therapy. On the other hand, angiographic *worsening* of thrombus burden after lesion-directed therapy occurred only in patients with low TIMI thrombus scores (0–1). Since angiography is limited in its ability to detect thrombus in the presence of low

TABLE III. In-Hospital Clinical Outcomes

Outcome	Patients treated (n = 45)
Death	0
Myocardial infarction	3 (7%)
Stroke	
Embolic	0
Intracranial hemorrhage	1 (2%)
Abrupt closure	3 (7%)
Repeat emergency angioplasty	1 (2%)
Bypass surgery	
Emergency	1 (2%)
Urgent	2 (4%)
Recurrent ischemia	5 (11%)
Vascular complications	
Loss of pulse	1 (2%)
Vascular surgery	2 (4%)
Hemorrhagic complications	
Moderate	9 (20%)
Severe	2 (4%)
Transfused	10 (22%)
Non-bypass patients	7 (17%)
No. units transfused*	0.7 ± 1.6

*Mean ± standard deviation.

thrombus scores, it is possible that some of these patients did not have true intravascular thrombus. In the absence of angiographically "overt" thrombus, the potential benefits of lesion-directed treatment may be outweighed by the thrombolytic-mediated procoagulant effects observed in this population, which may have also contributed to the high abrupt closure rates seen in previous studies of intracoronary thrombolysis (see below).

Prior Experience With Intracoronary Thrombolytic Therapy

The effects of adjunctive intracoronary alteplase have been evaluated in nonrandomized studies of small numbers of patients. Ruocco and colleagues treated 12 patients with complete or nearly complete coronary occlusions (TIMI 0 or 1 flow) <3 weeks old with a slow, selective infusion of alteplase (18.5 mg/90 min or 25 mg/hr) and found improvement in TIMI flow and lesion stenoses after treatment [29]. Subsequent angioplasty was successful in 94% of patients. Similarly, successful thrombolysis has been reported by local alteplase infusions in peripheral arterial thrombosis [30]. However, in treating seven patients with unstable angina and complex lesions with a higher dose of intracoronary alteplase (50 mg) over 50 min, DiSciascio et al. [12] found worsening of the lesion in three patients. These investigators speculated that partial thrombus resolution or exposure of denuded endothelium occurring after thrombolysis could have provided the stimulus for rethrombosis. More recently, the efficacy of adjunctive intracoronary urokinase has been evaluated in a prospective randomized pilot study (TAUSA Pilot Trial) by Ambrose and colleagues [6]. In this study, urokinase was delivered in low total doses into the ostium of the target artery in patients with ischemic rest pain. The results suggested that adjunctive urokinase resulted in fewer postprocedural intraluminal filling defects than placebo. In the larger follow-up TAUSA trial, however, more than 500 patients with complex lesions had increased rates of acute closure and recurrent ischemia with urokinase treatment [13]. In these studies, heparin administration was uncontrolled, and the thrombolytic was administered into the ostium of the culprit vessel. With severe occlusive coronary disease, ostial administration could result in lesser amounts of the drug reaching the target lesion because of the preferential blood flow occurring upstream from the stenosed area (Fig. 1).

Lesion-Directed Thrombolytic Therapy

There has been considerable interest in local delivery of thrombolytic therapy using various catheter-based methods [14,31]. These methods have employed thrombolytic agent coatings of hydrogels or angioplasty balloon surfaces and are designed to enhance intramural drug delivery by diffusion down a concentration gradient [31]. Other methods have delivered agents through perforation balloons under pressure to facilitate delivery [32]. The method we describe directs the thrombolytic agent to the thrombus through a simple end-hole catheter placed immediately proximal to the lesion. Fundamental to the effective use of thrombolytic therapy is the presence of circulating plasminogen [33]. By directing the thrombolytic therapy toward the lesion, local plasminogen can be activated and cause fibrinolysis. Lesion-directed delivery of alteplase provides a high local concentration in the immediate area of the thrombotic lesion. This locally high concentration induced a measurable fibrinolysis, as indicated by a fivefold increase in plasma D-dimer concentration, in the absence of systemic fibrinogenolysis. In addition, a small mechanical effect of the delivery method may have aided in breaking down the thrombus, thus increasing the surface area for alteplase binding.

Thrombolysis also causes an increase in thrombin activation, as suggested by changes in fibrinopeptide A levels [18,20]. Prior studies have confirmed that thrombin activation following intravenous thrombolysis can be reduced by systemic heparin administration [20]. In the present study, we administered intracoronary heparin (concomitant with the lesion-directed alteplase) to prevent thrombin activation. Heparin levels were within or above the therapeutic range and appeared to control thrombin proteolytic activity, as reflected by the suppression of plasma FPA concentrations over the 4 hr following the procedure. By contrast, thrombin genera-

TABLE IV. Intracoronary Thrombus and Risk of Abrupt Closure After Angioplasty

Study	Year	Patients	Patients with thrombus	Abrupt closure	
				With thrombus	Without thrombus
Mabin et al. [36]	1985	238	15 (6%)	73%	8%
Sugrue et al. [1]	1986	297	34 (11%)	24%	13%
Ellis et al. [2]	1988	451	48 (11%)	14%	9%
Detre et al. [3]	1990	1,801	205 (11%)	10%	4%
Lincoff et al. [4]	1992	1,309	—	23%	—
Tenaglia et al. [5]	1994	658	79 (12%)	44%	—
Ambrose et al. [13]	1994	469	56 (12%)	14%	—
Total		5,223	437 (11%)	29%	8.5%

tion (as measured by plasma F1.2 concentration) was not entirely suppressed by heparin. Thrombin generation is autoamplified by thrombin activation of coagulation factor Va and autosuppressed by thrombin activation of protein C, which inactivates factor Va. Although these data do not allow for a more detailed dissection of the balance between factor Va activation and inactivation, it is apparent that thrombin generation was not completely inhibited. These findings suggest that more specific targeting of the hemostatic mechanism, such as specific inhibition of factor Xa, might enhance the effectiveness of anticoagulation. Any enhancement in the antithrombotic effect of anticoagulation, however, must be weighed against the increased risk of hemorrhagic complications.

The clinical outcomes in the present study are comparable with those of a recent pooled analysis (3 clinical trials, 238 patients with unstable angina and intracoronary thrombus) [34] and those of a smaller trial of 20 patients receiving alteplase delivered by a porous balloon [35]. The abrupt closure rate of 7% also compares favorably with those of other studies (Table IV) and may have resulted from a reduction in residual thrombus caused by the high local alteplase levels.

Limitations

Since this was a nonrandomized evaluation of a novel treatment approach, comparisons with clinical outcomes of other studies are limited. The dose of alteplase was chosen to avoid systemic effects; however, the optimum local dose to achieve thrombolysis is uncertain. The optimum time to allow for the action of lesion-directed alteplase–heparin before percutaneous intervention also requires more study. Furthermore, the need for large systemic doses of heparin, such as those given during conventional angioplasty, is likewise uncertain when local heparin is used. The high total doses of heparin in the current study could have contributed to the incidence of bleeding. In the present study, the relative contributions of intracoronary and systemic heparin to thrombin inhibition are unknown. Future studies will be necessary to determine if thrombin activation can be inhibited locally by intracoronary or local delivery of antithrombins, thus leading to a less intense and prolonged level of systemic anticoagulation during and after angioplasty. Finally, since technical considerations may preclude the use of local catheters for drug delivery, not all patients can be treated with this technique. However, this method should be easily undertaken by those experienced in cardiovascular interventions.

CONCLUSIONS

Combined thrombus-directed, low-total-dose alteplase and intracoronary heparin caused prolonged local thrombolysis and thrombus reduction in patients with unstable angina undergoing percutaneous coronary revascularization, particularly among patients who had large thrombi, without inducing fibrinogenolysis or thrombin activation. In this study, lesion-directed therapy in combination with percutaneous revascularization had a high success rate with a low incidence of abrupt closure. Further study of this novel technique is warranted to determine whether this approach can reduce the need for large doses of intravenous agents, thus avoiding systemic effects, and improve clinical outcomes in patients with unstable angina and thrombus who need revascularization.

ACKNOWLEDGMENTS

This study was supported by grants from Genentech, South San Francisco, California, and Target Therapeutics, San Jose, California. The authors would like to thank Mrs. Sandy Turner and Ms. Sabrina Knight for their secretarial expertise in preparing this manuscript.

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APPENDIX

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