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Tissue plasminogen activator in refractory unstable angina. A randomized double-blind placebo-controlled trial in patients with refractory unstable angina and subsequent angioplasty

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To evaluate the effect of recombinant tissue plasminogen activator (alteplase) on the clinical course, angiographic changes and the outcome of subsequent coronary angioplasty, 36 patients with angina at rest, despite bedrest and medical treatment including heparin, and with concomitant ECG changes, were studied. After diagnostic angiography, patients were randomized to receive either alteplase 100 mg in 3 h (19 patients), or placebo (17 patients). The mean interval between qualifying anginal episode and initial angiography was 10 and 9 h for the alteplase and placebo group, respectively. Angiography was repeated and angioplasty was performed within 24 hours.

Between the first and the second angiogram, five patients in the alteplase and seven in the placebo group had recurrent ischaemic episodes, while four alteplase and three placebo patients showed signs of myocardial necrosis (creatine kinase (CK) rise ≥ twice the upper limit for normal). Intracoronary clots were recognized in three alteplase patients and one placebo patient at the first angiogram, while two alteplase patients and one placebo patient showed total occlusion of the ischaemic-related vessel. After infusion, thrombi were present in four alteplase patients and one placebo patient, and total occlusion in three alteplase patients and one placebo patient. Quantitative coronary angiography showed no change in the percentage diameter stenosis of the ischaemia-related segment after drug infusion, (alteplase 67 ± 16 to 69 ± 16%; placebo 65 ± 11 to 63 ± 12%). Angioplasty was successful in 14 of 19 alteplase and 14 of 16 placebo patients. Three patients after alteplase and two placebo patients developed myocardial necrosis during percutaneous transluminal coronary angioplasty (PTCA), and one alteplase patient required urgent bypass surgery. Minor bleeding complications were observed in six alteplase patients before the second angiogram and in five alteplase patients and one placebo patient after PTCA. One patient after alteplase developed a fatal retroperitoneal haemorrhage.

In patients with unstable angina refractory to medical treatment, including heparin, alteplase has no beneficial effect on the severity of coronary stenosis, on the clinical course, or on the success of a subsequent angioplasty procedure. Thus thrombolytic therapy with alteplase for unstable angina cannot be recommended on the basis of this investigation.

Introduction

In patients with unstable angina pectoris, intracoronary thrombus has been documented by angiography[1–5] and angioscopy[6], while biochemical studies have suggested the presence of thrombi in the circulation[7]. In some patients intracoronary thrombi can be resolved by intracoronary administration of streptokinase[3,8,9]. Resolution of such thrombi by thrombolytic therapy may be expected to improve coronary blood flow, and to prevent or reduce subsequent ischaemic episodes.

A few studies have reported a reduction in recurrent ischaemic episodes, in the incidence of sudden death and an improvement in the ischaemic threshold during atrial pacing[10–13]. Furthermore, it might be expected that thrombolytic therapy could reduce acute thrombotic occlusion during PTCA of the ischaemia-related segment, which occurs in approximately 10% of patients who undergo PTCA for unstable angina[14,15].

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In order to assess the value of thrombolytic therapy with alteplase in patients with ongoing unstable angina despite medical therapy including heparin, a randomized trial was undertaken. Quantitative analysis of the coronary arteriogram was performed in order to verify whether the culprit lesion was improved by thrombolytic therapy. Furthermore the clinical course and outcome of the subsequent PTCA procedures were compared in patients treated with alteplase or placebo.

Patient selection and methods

Included in the study were patients between 21 and 75 years with: (a) Recurrent episodes of chest pain after hospital admission, despite bedrest and medical treatment, with at least one episode with concomitant reversible ST-T segment changes or persistent negative T waves on the electrocardiogram. (b) A diagnostic coronary arteriogram, within 24 h after the last episode of chest pain. (c) The 'culprit' coronary lesion suitable for PTCA. Total occlusion of an ischaemia-related vessel, which supposedly was of recent date, was considered acceptable for angioplasty. (d) Ability to perform a second coronary

angiogram, followed by PTCA within 24 h after the diagnostic angiogram.

Excluded were patients with known bleeding disorders, recent major trauma, including resuscitation, or a bleeding history in the past 3 months, including cerebrovascular, gastric or genito-urinary tract bleeding. Patients with persistent hypertension and patients unable to give informed consent were also excluded, as were patients with previous angioplasty of the same coronary segment now judged to be related to the ischaemic myocardial zone, the so-called 'culprit' lesion. Informed consent was obtained after completion of the first (diagnostic) angiogram.

Reversible ST-T segment changes were classified in one of four categories: ST segment elevation or depression of at least 0·1 mV, persistent negative T-waves, or minimal ST-T segment changes not fulfilling the criteria for the other categories.

All patients were treated with the following combination of medication: (1) Heparin 1000 IU.h^{-1}, or a dose sufficient to prolong the activated partial thromboplastin time to twice the normal value, after a bolus injection of 5000 IU of heparin. (2) Beta-blockers, metoprolol 50–200 mg, in order to reduce heart rate to 60 beats.min^{-1}. (3) Calcium antagonists, nifedipine, in a dose of 40–120 mg.day^{-1}. (4) Intravenous nitroglycerin in a dose between 50 to 300 μg.min^{-1}.

The patients were randomized to receive either alteplase infusion (Actilyse^{R}) or placebo, supplied by Boehringer Ingelheim International. The study medication was started as soon as possible after the first coronary angiogram, in a double-blind manner. An injection of 10 mg i.v. was followed by an infusion of 50 mg in the first hour and 20 mg.h^{-1} for the subsequent 2 h. Thus, a total dose of 100 mg alteplase or placebo was administered in 3 h.

Coronary angiography was performed using the Judkins technique as soon as possible after the qualifying anginal attack and repeated within 24 h after the start of the study medication. The coronary artery responsible for the ischaemia was identified by means of electrocardiographic location of the reversible ST segment changes during chest pain. In patients with multiple lesions in the ischaemia-related vessel, the most severe lesion was considered the 'culprit' lesion. At least two orthogonal projections were made of the coronary artery segment with the culprit lesion, after intracoronary injection of 1 to 3 mg isosorbide dinitrate. The culprit lesion was filmed in exactly the same projections in the first and second angiogram. Low osmolar contrast medium (iopamidol) was employed. Intracoronary clot was defined as an intraluminal filling defect surrounded by contrast material. A totally occluded vessel was considered as representing intracoronary thrombus, only if the distal margin had a convex, irregular or hazy shape, and contrast retention or staining occurred. All coronary angiograms were scored by at least two observers who were blinded with respect to the treatment.

The angiograms were analysed in a quantitative manner with the Cardiovascular Angiography Analysis System[16]. Minimal lumen diameter (Dm) and interpolated reference diameter (Dr) were calculated in mm[16] using the catheter tip as a calibration measure. Percent diameter stenosis was calculated.

The extent of the obstruction was determined from the diameter function on the basis of curvature analysis and expressed in millimeters. 'Plaque area' is the difference in area in mm^2 between the reference and detected contours over the length of the lesion[17]. Area stenosis was calculated by videodensitometry. The densitometric profile was measured at the site of maximal narrowing of the vessel, and compared with the area of a reference segment.

The second angiogram to be followed by angioplasty was scheduled between 12 and 24 hours after the first angiogram. If patients had recurrent ischaemia, the second angiogram and angioplasty were performed on an emergency basis. Before the start of the PTCA procedure, 250 mg of acetyl salicylic acid and 100 mg of heparin were administered intravenously. An extra dose of 50 mg of heparin was administered every hour after the start of the procedure. Monorail Piccolino (Schneider-Shiley, Zürich) balloons were employed, introduced over high torque floppy 0·014″ guide wires, (Advanced Cardiovascular Systems, Billerica, Ma). In case of abrupt occlusion of a dilated lesion, oversized balloons, longer inflation duration and intracoronary streptokinase infusion were attempted in this order. Primary success was defined as a less than 50% residual diameter stenosis in the culprit lesion, without signs of myocardial infarction or recurrent ischaemia within 24 hours, and without urgent coronary bypass surgery.

The efficacy of treatment was assessed in several ways:

1. Frequency of recurrent ischaemic events between the first and the second angiogram (maximal 24 hours).
2. Incidence of myocardial infarction during this observation period as assessed by serial serum enzyme measurements. For this purpose, serum CK was measured every 12 hours until at least 72 hours after the first angiogram, and 6 hours after each episode of chest pain. Myocardial necrosis was considered to be present when serum CK content was at any time more than twice the local upper limit for normal (i.e. ≥ 200 IU.l^{-1}).
3. Quantitative angiographic differences between the first and the second coronary angiogram.
4. Presence or absence of intracoronary filling defects in both angiograms.
5. Procedural complications during angioplasty, such as death, myocardial infarction, abrupt closure of the dilated vessel and the need for emergency coronary bypass surgery.

STATISTICAL ANALYSIS

Differences between groups were analysed with a two-tailed Student t-test. Changes in quantitatively measured coronary artery stenosis in each group were compared with a two-tailed paired t-test. Differences in incidence of recurrent ischaemic attacks, myocardial infarction, presence of intracoronary clots and the occurrence of abrupt occlusion during angioplasty between groups

Table 1 Clinical, haemodynamic, electrocardiographic and angiographic characteristics of each patient group

Group	Alteplase	Placebo
N	19	17
Male/female	16/3	13/4
Mean age (years)	59	62
Previous infarct	7	10
Previous CABG	0	1
ECG changes during ischaemia		
ST-T elevation $\geq 0{\cdot}1$ mV	5	9
ST-T depression $\geq 0{\cdot}1$ mV	5	4
Persistent negative T waves	5	2
Other ST-T changes	4	2
Ischaemia-related vessel		
Left anterior descending artery	11	6
Right coronary artery	6	7
Left circumflex artery	2	4
Multi vessel disease	5	5
Ejection fraction:		
$<0{\cdot}50$	3	2
$\geq 0{\cdot}50$	16	14
Missing	0	1

CABG, coronary artery bypass graft.

treated with alteplase or placebo were determined with Fisher's exact test.

Results

Between November 1987 and April 1989, 38 patients with refractory unstable angina pectoris were enrolled in the study. Two placebo patients were excluded from the analysis because bleeding disorders, already present at the time of randomization, had been overlooked. One patient had a groin haematoma, and did not receive trial medication. In the other patient haematuria and bleeding from a subclavian vein puncture were disclosed after a bolus injection of 10 mg of trial medication, which was subsequently discontinued.

Clinical characteristics of the remaining 36 patients are summarized in Tables 1 and 2. The 17 preceding infarctions had occurred more than 1 month before admission to the trial. At the time of the qualifying episode 50% of patients were treated with intravenous nitroglycerin, while 92% received oral anticoagulants, heparin or aspirin. At the time of the first angiogram all patients except two were on intravenous nitroglycerin, while 94% were on intravenous heparin or antiplatelet drugs. Antiplatelet therapy before the qualifying attack and at the time of the first angiogram consisted of aspirin 80 to 500 mg per day, except in one placebo patient who received dipyridamol, 300 mg per day, before the qualifying attack.

RECURRENT ISCHAEMIA AND MYOCARDIAL NECROSIS

Between the start of drug infusion and the second angiogram, 11 patients had one or more episodes of chest pain, five in the alteplase group and six in the placebo group (NS). Severe recurrent ischaemia, not subsiding with medical measures, necessitated urgent PTCA in five patients, four in the alteplase and one in the placebo group. In these patients angiography and PTCA were performed between 4·5 and 8·5 h after the first angiogram. Four of these five patients developed myocardial infarction, with peak CK values between 257 and 2019 IU.l^{-1}. Clinical and electrocardiographic evidence, as well as the timing of CK peaks indicate that myocardial infarction occurred prior to the angioplasty procedure. Another eight patients had signs of myocardial necrosis, four in the alteplase and four in the placebo group. In retrospect, two of these had already a CK rise before the first angiogram, one had a CK rise before angioplasty, and five developed myocardial infarction during or directly after angioplasty (Table 3).

QUALITATIVE AND QUANTITATIVE CORONARY ANGIOGRAPHIC DATA AND THE PRESENCE OF INTRACORONARY CLOTS

The sites of the culprit lesions are presented in Table 1. In the first angiogram three patients had an occluded ischaemia-related segment, and thrombi were recognized in four patients. The occlusions were resolved at the time of the second angiogram in all but one patient, but three other new occlusions appeared (Fig. 1). Thrombi resolved in two patients in the alteplase group, while at the same time new clots appeared in two other patients from the same group (Fig. 1).

Data obtained by quantitative angiography are summarized in Table 4. Twenty-nine patients showed non completely obstructed vessels in all three angiograms, 15 in the treatment and 14 in the placebo group. No significant differences were found between the two groups at any time, i.e. during the first angiogram, or before or after angioplasty. A significant reduction in obstruction diameter and percentage diameter obstruction was found in both groups after angioplasty. Changes in diameter stenosis, obstruction length and plaque area between the first and second angiogram were not significant neither within, nor between both groups.

ANGIOPLASTY PROCEDURE

Angioplasty was performed in all 19 alteplase patients and in 16 patients of the placebo group. One placebo patient did not undergo angioplasty because the second angiogram showed extensive clotting in the right coronary artery, without a significant localized stenosis. In this patient streptokinase $1{\cdot}5 \times 10^6$ IU was subsequently administered i.v., without effect on the proximal intracoronary thrombus but with some resolution of a peripheral embolus in the posterolateral branch of the right coronary artery. After elective administration of 100 mg of alteplase i.v., all clots resolved, leaving a virtually normal coronary artery.

Dilatation was angiographically successful in all 16 patients in the placebo group and in 17 out of 19 patients in the alteplase group. One patient with unsuccessful PTCA had a totally occluded right coronary artery at the beginning of an emergency angioplasty procedure, which

Table 2 Medical therapy at the time of occurrence of angina at rest and at the time of the first angiogram

Medical therapy	At the time of the qualifying anginal episode		At the time of the first angiogram	
	Alteplase	Placebo	Alteplase	Placebo
Oral anticoagulants	0	2	0	0
Intravenous heparin	11	10	16	16
Antiplatelet drugs	5	5	1	1
i.v. nitroglycerin	9	9	18	16
Oral nitrates	4	5	1	0
Beta blocker	16	9	17	10
Calcium antagonist	7	11	10	15
No therapy	0	0	0	0

Table 3 Incidence of myocardial necrosis with maximal CK rise in $IU.l^{-1}$ in the alteplase and placebo group

Alteplase group (n = 19)		Placebo group (n = 17)	
Before PTCA (n = 4)	After PTCA (n = 3)	Before PTCA (n = 3)	After PTCA (n = 2)
257*	288	222	636
348	357	275*	656
824*	758	490	
2019*			

*Indicates patients who underwent urgent angioplasty.

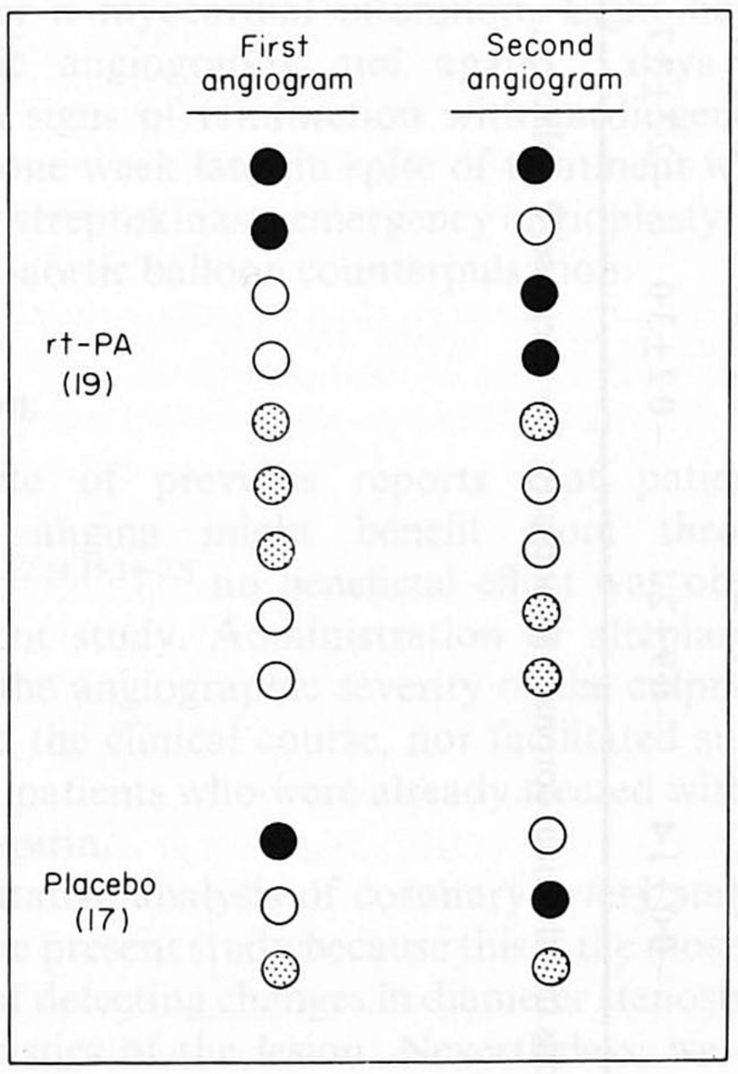

Figure 1 Qualitative coronary angiographic data before and after alteplase or placebo infusion. ○, Non-totally occluded coronary artery without intracoronary filling defect; ●, totally occluded coronary artery; ◎, intracoronary filling defect. Non-totally occluded vessels, without intracoronary clots in both angiograms, are not depicted.

could not be reopened permanently. The other patient had an occlusion of the left anterior descending artery immediately after angioplasty and was operated on as an emergency. Two other patients in the alteplase group and two patients in the placebo group had a CK rise after angioplasty. Thus the primary success rate of dilatation of the ischaemia related vessel was 74% and 88% in the alteplase and placebo groups, respectively. A second stenotic site was successfully dilated in three out of four vessels in the alteplase and in four out of four vessels in the placebo group. A third stenotic vessel was successfully dilated in one patient in the alteplase group.

In the alteplase group transient reocclusion was seen in two patients. Both were treated successfully with oversized balloons, longer inflation duration and intracoronary infusion of streptokinase, 500 000 IU, but nevertheless necrosis developed, documented by elevated serum enzymes. One other patient sustained a side branch occlusion complicated by ventricular fibrillation. In the placebo group three patients had transient reocclusion, all treated successfully with standard procedures, although ventricular fibrillation occurred in one patient. Two of these patients developed elevated enzymes after the angioplasty procedure.

BLEEDING COMPLICATIONS

Bleeding between the first and second angiogram occurred in five alteplase patients, but not in the placebo

Table 4 Quantitative angiographic data. The extent of the obstruction and plaque area could only be measured in non-occluded vessels. Values are given as mean values ± standard deviation. All differences between and within groups were not significant before angioplasty

	Extent obstruction (mm)		Plaque area (mm^2)		Obstruction diameter (mm)		Percentage diameter obstruction		Percentage area stenosis	
	A	P	A	P	A	P	A	P	A (n = 10)	P (n = 9)
First angiogram (1)	7·4 ± 2·1	8·8 ± 3·8	10·2 ± 5·3	11·8 ± 7·0	1·0 ± 0·4	1·1 ± 0·4	67 ± 16	65 ± 11	87 ± 11	84 ± 8
Second angiogram prePTCA (2)	7·4 ± 2·4	7·9 ± 3·5	10·0 ± 6·9	9·6 ± 5·3	0·9 ± 0·4	1·0 ± 0·4	69 ± 16	63 ± 12	90 ± 9	84 ± 14
Post PTCA (3)	6·8 ± 3·1	7·1 ± 2·7	5·7 ± 4·7	6·1 ± 3·6	1·9 ± 0·6	1·9 ± 0·2	37 ± 19	36 ± 8	48 ± 17	49 ± 11
△ 1–2	−0·0 ± 1·4	−0·9 ± 2·1	−0·2 ± 3·0	−2·2 ± 3·7	−0·1 ± 0·6	−0·1 ± 0·5	3 ± 17	−2 ± 17	3 ± 15	0 ± 12

PTCA = percutaneous transluminal coronary angioplasty; A = alteplase; P = placebo.

group. Four had a haematoma at the puncture site in the groin, one at another site.

Bleeding was observed after angioplasty in six other patients after alteplase and in one in the placebo group. One patient in the alteplase group died of the sequelae of intimal dissection, which occurred when the guiding catheter was advanced through the common iliac artery. The other femoral artery was punctured and a proximal LAD lesion was successfully dilated. At the end of the procedure blood pressure dropped, a retroperitoneal haematoma was diagnosed and the patient underwent laparotomy. After drainage of this haematoma the circulation seemed to be restored and the abdomen was closed. He was treated with blood transfusions and measures to restore normal coagulation. The next day the patient was in good haemodynamic condition but showed signs of occlusion of the right femoral artery. Embolectomy and a crossover operation from the left iliac artery were performed. However, bleeding in the retroperitoneum progressed with subsequent ischaemia of the bowel and the right leg. The patient died 48 h after the angioplasty procedure.

The other five patients had local haematoma in the groin, three of them with prolonged bleeding from the puncture site after removal of the sheaths, and one with combined microscopic haematuria. One patient in the placebo group had haematemesis and localized haematoma at a previous puncture site. In two patients with bleeding in the alteplase group, 6 and 7 units of blood were administered while the patient in the placebo group was treated with Haemacel^{R}. One patient who was excluded from the analysis had an uncomplicated course. The other patient was entered in the trial for recurrent ischaemia 3 days after a myocardial infarction. Eight hours after diagnostic angiography and again 2 days later he exhibited signs of reinfarction with cardiogenic shock. He died one week later in spite of treatment with intracoronary streptokinase, emergency angioplasty, alteplase and intra-aortic balloon counterpulsation.

Discussion

In spite of previous reports that patients with unstable angina might benefit from thrombolytic therapy[9,12,14,15,19–22] no beneficial effect was observed in the present study. Administration of alteplase neither reduced the angiographic severity of the culprit lesions, improved the clinical course, nor facilitated subsequent PTCA in patients who were already treated with heparin and/or aspirin.

Quantitative analysis of coronary artery stenosis was used in the present study because this is the most sensitive method of detecting changes in diameter stenosis or other characteristics of the lesion. Nevertheless, we observed no significant decrease in the severity of the underlying coronary artery stenosis, either after alteplase, or in the placebo group. The extent of the obstruction, plaque area, minimal lumen diameter and obstruction area revealed no significant change in either group. Similar findings were reported by others[15,18], while one recent report demonstrated a small improvement in percent diameter stenosis in patients treated with alteplase and/or heparin[22]. In these studies the calculated diameters of 'culprit' stenosis were similar to those in the present study.

Measurement of percent diameter stenosis might not be the optimal indicator of the remaining lumen in cases of intracoronary thrombus or asymmetric lesions[23]. However, densitometric measurements did not disclose a change in severity of stenosis after alteplase infusion in our study population. Similarly, videodensitometric measurements of area stenosis did not improve after intracoronary infusion of 100 000 to 300 000 IU of streptokinase in another study of 37 patients with unstable angina or non Q infarction[19].

The lack of a beneficial effect of thrombolytic therapy raises the question whether intraluminal thrombosis is indeed a major cause of 'instability' of the symptoms in these patients. The presence of intracoronary thrombus has been reported in 1 to 52%[1–5] of patients with unstable angina, using coronary arteriography as a diagnostic criterion. However, the individual criterion in these studies differed widely, ranging from occlusion, supposedly caused by thrombus, intraluminal defects and intraluminal staining, to a reduction of stenosis severity after streptokinase infusion. Intraluminal defects, suggestive of clots, were observed in four patients in this study, while three other patients had a total occlusion suggesting recent clot formation. Two out of three patients treated with alteplase showed resolution of clots in the second angiogram, and in one other patient, initially given placebo, extensive clotting in the right coronary artery resolved when alteplase was administered after the second angiogram. Thus thrombolytic therapy with alteplase may be beneficial in a few selected patients with unstable angina and extensive clots visible on the angiogram[20]. However, systematic therapy with thrombolytic drugs in patients with unstable angina does not seem warranted. In fact new clots appeared in three patients in spite of preceding treatment with alteplase.

The lack of efficacy of thrombolytic therapy in the current study may be related to the fact that 92% of the patients were treated with oral anticoagulants, heparin, or antiplatelet drugs at the time of the qualifying episode of angina. It is likely that factors other than intracoronary thrombosis contribute to the acute coronary syndrome in those patients who remain 'unstable' in spite of anticoagulation and anti-platelet therapy. This also explains the relatively low incidence of visible intracoronary clots in our study.

In three studies which reported higher incidences of intravenous thrombosis, between 41% and 68%, the patients were not pre-treated with heparin[20,21,24].

ANGIOPLASTY PROCEDURAL COMPLICATIONS

Major complications of angioplasty, defined as procedure-related death, myocardial infarction or urgent surgery are infrequent (5%) in patients with stable angina. Complications are more frequent (10%) in patients with unstable angina, and may amount to 20% of patients requiring urgent angioplasty for intractable angina[10,25],

as in the present study. It should be noted that after the first coronary arteriogram all patients were treated with i.v. nitroglycerin and heparin, while the majority were already receiving heparin and/or aspirin at the time of the qualifying episode of angina. Despite this intensive medical treatment, seven patients developed a myocardial infarction before the second angiogram. In four of these and one other patient urgent angioplasty was performed.

Successful angiographic dilatation (diameter stenosis after angioplasty of less than 50%), was achieved in 89 and 100% of patients in the alteplase and placebo groups respectively, although five patients developed a moderate CK rise after intermittent reocclusion during the procedure. Thus the primary success rate was 74 and 88%. It should be noted that no intracoronary clot was observed prior to the angioplasty procedure in the patients with transient reocclusion. All five patients with intracoronary clots pre angioplasty and three patients with a totally occluded ischaemia-related vessel had successful uncomplicated angioplasty procedures.

Conclusion

Intravenous administration of alteplase in this patient group with unstable angina, in spite of extensive medical therapy, did not have any favourable effect, either on the culprit lesion, the clinical course, or the outcome of subsequent angioplasty. On the contrary one fatality occurred, which might be ascribed to a complication of the procedure and the administration of a thrombolytic drug. It is possible that thrombolytic therapy is beneficial in selected patients with angiographically demonstrated intracoronary clots as observed in one patient. However, based on the presently available data, thrombolytic therapy cannot be recommended in patients with unstable angina.

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