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Correlation between clinical course and quantitative analysis of the ischemia related artery in patients with unstable angina pectoris, refractory to medical treatment

Results of two randomized trials

Marcel J.B.M. van den Brand[1], Addy van Miltenburg[1], Menko J. de Boer[2], L. Ron van der Wieken[3], Pim J. de Feyter[1], Maarten L. Simoons[1] & The European Cooperative Study Group

[1] *Thoraxcenter, Erasmus University and University Hospital Dijkzigt, P.O. Box 1738, 3000 DR Rotterdam;* [2] *Department of Cardiology, de Weezenlanden Ziekenhuis, Zwolle;* [3] *Department of Cardiology, Onze Lieve Vrouwen Gasthuis, Amsterdam, The Netherlands*

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Abstract

Patients with unstable angina, refractory to intensive medical therapy, are at high risk for developing thrombotic complications, such as recurrent ischemia, myocardial infarction and coronary occlusion during coronary angioplasty. As both platelet aggregation and/or thrombus formation play an important role in this ongoing ischemic process, a monoclonal platelet GPIIb/IIIa receptor antibody (c7E3) or thrombolytic therapy (alteplase) might be able to modify the clinical course and underlying coronary lesion morphology. To evaluate whether alteplase or c7E3 could influence the incidence of complications, we randomized 36 and 60 patients, respectively to alteplase or placebo, or c7E3 or placebo. All patients exhibited dynamic ECG changes and recurrent pain attacks, despite maximal tolerated medical therapy. Patients were randomized in both studies after initial angiography had demonstrated a culprit lesion amenable for angioplasty. After study drug infusion quantitative angiography was repeated and angioplasty performed. Recurrent ischemia during study drug infusion occured in 5, 6, 9 and 16 patients from the alteplase, placebo, c7E3 and placebo group, respectively. Major events defined as death, myocardial infarction or urgent intervention occurred in 7, 3, 1 and 7 patients, respectively. Two patients died: one in the alteplase group and one in the placebo group from the c7E3 study. The first patient due to retroperitoneal hemorrhage, the second as a result of recurrent infarction. Qualitative angiography showed resolution of clots in the c7E3 group only, while the same group of patients showed in 20% an improvement in TIMI flow grade, without deterioration in any patient from this group. Quantitative angiography showed a significant improvement in percentage diameter stenosis in the c7E3 group, which was not observed in all three other groups, although differences between groups were not significant. Alteplase infusion in patients with refractory unstable angina did not change the clinical course, nor the coronary morphology, c7E3 on the other hand, both improved the clinical course and the coronary lesion morphology and rheology in the same category of patients.

Introduction

In 1989 Braunwald provided a classification for patients with unstable angina, based on the clinical circumstances under which the syndrome occurred and the severity of the symptoms [1]. A further subdivision took the intensity of medical treatment and the presence or absence of reversible electrocardiographic changes during anginal attacks into consideration.

The underlying cause of unstable angina is thought to be rupture and ulceration of a pre existent atherosclerotic plaque, leading to platelet adhesion and aggregation and thrombus formation [2, 3]. In most patients the syndrome can be stabilized with bed rest and anti-ischaemic and anti-thrombotic therapy [4].

However, in a minority of patients ischemic symptoms continue in spite of intensive medical therapy. Such patients with unstable angina refractory to medical treatment are usually referred for urgent angioplasty or bypass operation, which interventions are associated with a higher complication rate compared with stable or stabilized unstable angina patients [5, 6]. Prevention and or resolution of platelet aggregates and thrombi may help to prevent ongoing ischemic attacks and angioplasty complications.

The value of administration of thrombolytic therapy in recent myocardial infarction has clearly been demonstrated. It opens occluded coronary arteries, improves left ventricular function and reduces mortality by limiting infarct size [7, 8]. As unstable angina and myocardial infarction share a common pathogenetic substrate, it seems reasonable that thrombolytic therapy should ameliorate the syndrome of unstable angina pectoris [9]. Several studies have shown that thrombolytic therapy can reduce the incidence of sudden death, the number of ischemic episodes, and improve the threshold for ischemia during atrial pacing [10-18] in patients with unstable angina. More recent randomized trials found an angiographic improvement after thrombolytic therapy in patients with unstable angina by opening occluded coronary arteries and reducing the incidence of intracoronary thrombi, however without decreasing in hospital cardiac events [19, 20].

CentoRx^{R} (c7E3) is a monoclonal antibody that blocks the platelet fibrinogen receptor, glycoprotein IIb/IIIa. By preventing the binding of fibrinogen to the platelet surface, platelet aggregation and platelet thrombus formation are inhibited [21].

We designed two studies in patients with ongoing unstable angina despite medical treatment, who were candidates for coronary angioplasty. In the first study patients were randomized to thrombolytic therapy with alteplase or placebo. In the second study another group of patients with the same syndrome was randomized to CentoRx^{R} (c7E3) or placebo. Quantitative analysis of coronary angiograms was essential in both studies, both before and after trial drug infusion.

Patients and methods

Patients selection

Included in both studies were patients between 21 and 75 years and

- manifesting recurrent episodes of chest pain after hospital admission, occurring at rest and pending medical treatment, with at least one of these episodes with concomitant reversible ST-T segment changes or persistent negative T-waves on the electrocardiogram;
- undergoing a diagnostic coronary arteriogram within 24 hours (alteplase) or 12 hours (c7E3) of the most recent episode of coronary ischemia (chest pain and/or ST-T segment changes);
- exhibiting a 'culprit' coronary lesion in a native vessel suitable for PTCA. A single vessel must be clearly indicated as ischemia related. Total occlusion of this vessel was considered acceptable for angioplasty, if it showed signs of recent occlusion such as the presence of intracoronary thrombi or contrast-staining at the obstruction site;
- ability to perform a second coronary angiogram followed by angioplasty within 24 hours after randomization;
- providing informed consent after completion of the first diagnostic angiogram and prior to the initiation of protocol specific measures.

Excluded for both studies were patients exhibiting features of ongoing ischemia which required immediate intervention, prior PTCA of the same coronary segment within 6 months, recent major trauma including resuscitation, gastro intestinal or urinary tract bleeding within 3 months, persistent hypertension and known bleeding disorders. The c7E3 trial also excluded patients with prior Q-wave myocardial infarction within 7 days, and patients with a platelet count of less than 100,000/mm^3.

Medical treatment

Patients were designated as refractory unstable angina if anginal attacks continued despite bed rest and medical treatment which required minimally i.v. heparin and oral or i.v. nitroglycerin. After randomization all patients were treated with the following combination of medication:

- heparin 1,000 IU/hour, or a dose sufficient to prolong the activated partial thromboplastin time to twice the control value, after a bolus injection of 5,000 IU of heparin;
- intravenous nitroglycerin ranging in dose from 50 to 300 μg/min;
- metoprolol 50-200 mg, in order to reduce heart rate to 60 beats/min;
- nifedipine in a dose of 40-120 mg/day.

After informed consent and randomization by a telephone answering service, study drug infusion was started as soon as possible, but at least within 4 hours after the first angiogram.

For the alteplase trial a bolus injection of 10 mg i.v. was followed by an infusion of 50 mg in the first hour and 20 mg/hour for the subsequent 2 hours. Thus a total amount of 100 mg of alteplase or placebo was administered in 3 hours.

For the c7E3 trial, patients received a bolus dose of 0.25 mg/kg followed by a 10 μg/min continuous infusion for at least 18 hours. Patients to receive placebo were administered a bolus of human serum albumin, likewise followed by continuous infusion. The infusion continued until one hour following the completion of PTCA.

Alteplase (Actilyse^R) was supplied by Boehringer Ingelheim International, and c7E3 (CentoRx^R) by Centocor, Malvern PA.

Coronary arteriography and angioplasty

Coronary arteriography and left ventricular angiography were performed as soon as possible after the qualifying anginal attack using the Judkins technique. Heparin 2,500 to 5,000 IU was administered at the beginning of the procedure. A second angiogram was performed within 24 hours after the start of study medication followed by angioplasty. The coronary artery responsible for the ischemia was identified by means of electrocardiographic location of the reversible ST-T segment changes, and left ventricular wall contraction abnormalities. At least two orthogonal projections were made of the culprit coronary artery, after injection of 1-3 mg of isosorbide dinitrate. During the first and the second angiogram the same projections and X-ray gantry setting were employed to compare lesion severity. Low osmolar contrast medium (iopamidol) was used for all angiograms. All coronary and left ventricular angiograms were scored by at least two observers who were blinded with respect to the treatment assignment. Qualitatively the following items were scored after the first contrast injection:

- TIMI flow grade [22] of the culprit artery;
- presence of intracoronary thrombus, defined as an intraluminal filling defect, visible during at least one complete cine-run, and surrounded on 3 sides by contrast medium [23]. A total occluded coronary artery could contain a filling defect, but was not automatically scored as containing such a defect;
- stenosis severity as visually assessed in multiple projections.

Quantitative analysis of coronary angiograms

Quantitative coronary angiography

All cineangiograms were analyzed with the computer-assisted cardiovascular angiography analysis system by the Core laboratory at Cardialysis, Rotterdam, NL. This system has been discussed in detail previously [24, 25]. The important steps will be briefly described. Any area sized 6.9 × 6.9 mm in a selected cineframe (overall dimensions 18 × 24 mm) encompassing the desired arterial segment can be digitized by a high-resolution CCD-camera with a resolution of 512 × 512 pixels and 8 bits of gray level. Vessel contours are determined automatically based on the weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions of an arterial segment. A computer-derived estimation of the original arterial dimension at the site of the obstruction is used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analyzed region (assuming there was no disease present) according to the diameter function. The absolute diameter of the stenosis as well as the reference diameter are measured by the computer, which used the known guiding catheter diameter as a calibration factor. All contour positions of the catheter and arterial segments are corrected for pincushion distortion.

'Plaque area' is the difference in area in mm^2 between the reference and the detected contours over the length of the lesion [26].

The second angiogram to be followed by angioplasty was performed between 12 and 24 hours in the alteplase trial and between 18 and 24 hours in the c7E3 trial after the start of drug administration. Angiograms of the culprit artery were obtained in the same projec-

Table 1. Baseline clinical, electrocardiographic and angiographic characteristics of patient groups.

Group	Alteplase	Placebo	c7E3Fab	Placebo
N	19	17	30	30
Male/Female	16/3	13/4	20/10	24/6
Mean age (years)	59	62	61	60
Previous infarct	7	10	9	16
Previous CABG	0	1	0	2
Previous PTCA			4	5
Medication prior to qualifying ischemic attack				
Heparin	11	12	26	27
Aspirin	5	5	21	23
Nitrates				
* intravenous	9	9	24	27
* oral	4	5	4	2
β-Blocker	16	9	22	24
Calcium channel blocker	7	11	15	22
Ischemia related vessel				
Left anterior descending artery	11	6	16	14
Left circumflex artery	2	4	8	6
Right coronary artery	6	7	6	10
Multivessel disease	5	5	6*	15*
Ejection fraction				
< 0.50	3	2	n.a.	n.a.
≥ 0.50	16	14		
Unknown	0	1		

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; n.a. = not assessed, * $p = 0.03$.

tions as during the first angiogram, after intracoronary injection of isosorbide dinitrate.

Assessments

The efficacy of treatment was assessed in several ways:

- Frequency of recurrent ischemic events between the first and the second angiogram (maximal 24 hours).
- Incidence of major events, defined as death, myocardial infarction or urgent intervention during this observation period and during and after angioplasty.
- Quantitative and qualitative analysis of all angiograms, before and after study drug infusion.

Statistical analysis

Differences between groups were analyzed with a two-tailed Student t test. Changes in quantitatively measured coronary artery severity stenosis in each group were compared with a two-tailed paired t test. Differences in incidence of recurrent ischemic attacks, myocardial infarction and presence of intracoronary clots were determined between treatment and respective placebo groups with Fisher's exact test.

Results

Baseline characteristics

The alteplase/placebo study was conducted between November 1987 and April 1989 in one hospital. The c7E3 Fab/placebo trial enrolled patients between September 1991 and July 1992 in five different hospitals. Baseline characteristics of the patients enrolled in both studies are summarized in Table 1. More patients in both placebo groups had sustained a previous infarct compared with the treatment groups, but

left ventricular ejection fraction was similar in the alteplase/placebo groups, while this parameter was not assessed in the c7E3 Fab/placebo study. Also significantly more patients in the placebo group from the last trial demonstrated multivessel disease, defined as a more than 50% diameter stenosis in one of the three main epicardial vessels. All other baseline parameters were similar between each treatment and respective placebo group.

Recurrent ischemia

Between the start of drug infusion and the second angiogram 5, 6, 9 and 16 patients from the alteplase, placebo, c7E3 Fab and placebo group respectively, had one or more episodes of recurrent ischemia defined as chest pain, with or without ECG changes. Severe recurrent ischemia, not subsiding with medical measures, necessitated urgent coronary angioplasty in 4, 1, 0 and 3 patients from the alteplase, placebo, c7E3 Fab and placebo groups respectively.

Major events

In the two studies a major event defined as death, myocardial infarction or urgent intervention occurred in 7, 3, 1 and 7 patients from the alteplase, placebo, c7E3 Fab and placebo group respectively. The nature of these major events in all four groups is summarized in Table 2.

Death in the alteplase patient occurred 48 hours after angioplasty, complicated by dissection of the right common iliac artery and retroperitoneal hemorrhage.

One other patient from the placebo group in the c7E3 Fab study died, 26 days after allocation after a complicated clinical course, including two urgent PTCA procedures and myocardial infarction.

Qualitative evaluation of coronary angiograms

TIMI flow grade 3 in culprit arteries, assessed centrally by the Core Laboratory, was present in 57 to 76% of all patients at the first angiogram. Of all 4 groups studied, a substantial improvement in coronary blood flow occurred after treatment in the c7E3 Fab patient group only, while all three other groups showed both improvement and deterioration in TIMI flow score (Table 3).

Extensive filling defects in the coronary arteries were seldom encountered. Most filling defects were single, visible in more than one direction and located

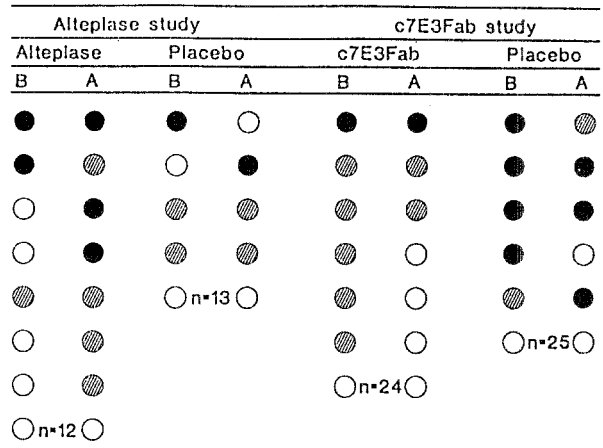

Fig. 1. Qualitative coronary angiographic data of the ischemia related coronary artery before (B) and after (A) study drug infusion.
● Totally occluded coronary artery
▨ Intracoronary filling defect
○ Patent coronary artery, without filling detect
Note: The number of non totally occluded vessels, without filling defects in both angiograms, is depicted in the bottom line.

Table 2. Major events in all 4 study groups.

	Alteplase	Placebo	c7E3Fab	Placebo
N	19	17	30	30
Death	1	0	0	1
Myocardial infarction	7	3	1	4
Before PTCA	4	1	0	1
After PTCA	3	2	1	3
Urgent procedure	5	1	-	7
PTCA	4	1	-	3
CABG	1	-	-	3
Stent	-	-	-	1
Total nr of patients with one or more major events	7	3	1	7

CABG = coronary artery bypass grafting;
PTCA = percutaneous transluminal coronary angioplasty.

distally from the culprit lesion. The number of intracoronary clots, and total occlusions from both studies, in the pre and post treatment angiogram are shown in Fig. 1. In the alteplase study new occlusions of culprit arteries occurred in both groups, while other occluded coronary arteries became patent after study drug infusion. In the c7E3 Fab study a new occlusion was observed in the placebo group only, but also restored patency of a total occluded vessel in two cases with thrombotic remnants in one case. Three out of five

Table 3. Qualitative angiographic data.

Group	Alteplase		Placebo		c7E3Fa		Placebo	
N	19		17		30		30	
TIMI flow	B	A	B	A	B	A	B	A
0	2	3	1	1	1	1	4	3
1	0	0	0	0	2	1	0	1
2	3	3	3	2	10	5	7	6
3	14	13	13	14	17	23	19	20
Improved		3		2		6		4
Worsened		4		2		0		3
Intracoronary filling defect	1	4	2	2	5	2	1	1

B = before study drug infusion; A = after study drug infusion.

Table 4. Quantitative angiographic data from the first angiogram (I) and after study drug infusion (II) and the difference between both measurements (II-I).

Treatment	Alteplase (n = 19)		Placebo (n = 17)		c7E3Fab (n = 30)		Placebo (n = 30)	
Variable	n		n		n		n	
DS (%)								
I	19	66.7 (16.1)	17	63.1 (13.1)	30	65.7 (8.6)	29	67.7 (16.1)
II	19	67.0 (14.8)	17	61.6 (13.5)	30	62.3 (10.5)	29	65.6 (15.8)
II-I	19	0.3 (20.2)	17	- 1.6 (16.2)	30	- 3.4 (6.7)*	29	- 2.1 (12.4)
MLD (mm)								
I	19	1.0 (0.4)	17	1.1 (0.5)	30	0.9 (0.3)	30	0.9 (0.4)
II	19	0.9 (0.4)	17	1.1 (0.5)	30	1.0 (0.3)	30	0.9 (0.4)
II-I	19	- 0.1 (0.6)	17	0.0 (0.4)	30	0.1 (0.2)	30	0.0 (0.3)
Ext Ob (mm)								
I	17	7.1 (2.2)	16	9.2 (4.0)	29	7.3 (2.2)	26	7.2 (3.4)
II	17	7.0 (2.6)	16	7.8 (3.3)	29	6.9 (2.1)	26	7.3 (2.9)
II-I	16	- 0.1 (1.4)	15	- 0.9 (2.0)	29	- 0.5 (1.2)*	26	0.3 (1.8)
Plq Area (mm^2)								
I	17	10.0 (5.3)	16	12.0 (7.6)	29	8.2 (3.4)	29	9.1 (6.8)
II	17	9.5 (6.8)	16	8.9 (5.3)	29	7.1 (2.5)	27	8.6 (4.8)
II-I	15	- 0.2 (3.0)	15	- 2.1 (3.6)*	29	- 1.1 (1.9)*	25	- 0.5 (3.3)
AS (%)								
I	14	87.7 (9.6)	15	84.6 (15.7)	20	89.2 (6.7)	21	90.7 (7.9)
II	16	88.2 (8.4)	14	85.5 (17.4)	23	88.3 (8.4)	22	89.6 (10.2)
II-I	12	- 1.1 (10.4)	14	1.1 (9.6)	19	1.8 (8.1)	19	- 1.3 (6.4)

DS = diameter stenosis; MLD = miminal lumen diameter; AS = area stenosis; Ext Ob = extent of the obstruction; Plq area = plaque area; * p [PI]DW 0.05. Data are given as mean values (standard deviation).

coronary clots resolved in the treatment group of the c7E3 study.

Quantitative coronary angiographic analysis

Quantitative coronary angiographic data are summarized in Table 4. One patient from the c7E3 Fab study

with a very proximal LAD lesion is missing in the calculated percentage diameter stenosis, because the reference diameter could not be ascertained. All videodensitometric area calculations of more than 100% obstruction were left out, while plaque area and extent of obstruction could naturally only be calculated in patent coronary arteries.

In the alteplase study, no significant changes were observed in the quantitative parameters nor within nor between groups.

In the c7E3 Fab study significant decreases in percentage diameter stenosis, extent of obstruction and plaque area were observed in the c7E3 Fab patients.

In the placebo group the same changes were observed to a lesser extent, except for the extent of obstruction, which decreased in the c7E3 Fab patients, but increased in the placebo group patients. Differences between groups were not significant.

Discussion

When thrombolytic therapy revived for the treatment of acute myocardial infarction and showed beneficial effects, a logic next step was to add thrombolytics to the drug regimen of patients with ongoing unstable angina refractory to that regimen. Several studies have been conducted since using different thrombolytic agents in different classes of unstable angina [11-20, 27-31]. Only the study of Gold, including only 23 patients, showed a beneficial reduction in cardiac events from 55% to 9%. And although inclusion criteria varied in the interval between the last anginal attack and study drug infusion, in the classification according to Braunwald, and the presence of angiographically demonstrated significant coronary artery disease, all shared a common outcome of no clinical benefit. Only the study of Ardessino [28] showed a lower mortality in the group treated with alteplase, all other studies manifesting an equal [19] or higher mortality in the group treated with a thrombolytic agent [13, 18-20, 30, 31]. Also the incidence of myocardial infarction during and after treatment with thrombolytic agents was higher in the treated patients than in those receiving placebo (29 of 270 and 15 of 289 patients respectively), while both groups were on intravenous heparin as background therapy [12, 13, 17-20, 29, 31, 32].

Some studies included quantitative analysis of coronary angiograms before and after study drug infusion, the angiography result being part of the inclusion process [12, 13, 17, 19, 20, 28, 31]. These studies all showed a minimal reduction in percentage diameter stenosis, both in the treatment and placebo groups, reaching only statistical significance in the treated group in two studies [17, 20]. Part of the problem of most studies was the small number of patients included, varying from 24 to 159 patients. The two studies with a significant reduction in diameter stenosis in the treated groups included a relatively large number of patients of 70 and 159 respectively.

The thrombolytic study reported here treating patients with refractory unstable angina showed a high incidence of cardiac events in both groups, possibly reflecting the severe nature of the syndrome in these patients, already treated with routine medication, including heparin and aspirin.

Two recent editorials addressed the relative inefficacy of thrombolytic agents in patients with unstable angina [9, 33]. They both explain the apparent discrepancy between the effects of thrombolytic agents in myocardial infarction and unstable angina pectoris by the difference in underlying disease and enhanced thrombosis formation. Opening of an occluded artery as in myocardial infarction, and keeping an artery open as in unstable angina require different approaches. In the Unasem study e.g. a significant reduction in diameter stenosis was only achieved by opening occluded arteries with anisoylated plasminogen streptokinase activator complex [20]. Several studies suggest that thrombolytic therapy might enhance thrombin formation and activate platelets to further coronary thrombosis [34-40]. These effects of tissue plasminogen activator can be countered by the monoclonal antiplatelet GPIIb/IIIa receptor antibody as has been demonstrated in a canine model [41].

It is conceivable that this antibody alone prevents occlusion of coronary arteries in unstable angina and prevents platelet aggregation. In fact we demonstrated that c7E3 Fab ameliorated the clinical course of patients with refractory unstable angina. Also the modest but significant reduction in diameter stenosis of the culprit lesion corroborates these optimistic expectations.

These results look quite promising and might be confirmed in a larger trial which is now underway. Quantitative assessment of coronary arteriograms could make the clinical results more understandable, all the more because the absence of clinical benefit in patients with unstable angina pectoris treated with thrombolytic agents has not been attended by quantitative improvement of coronary artery lesions.

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