Half-dose thrombolysis to begin with, when immediate coronary angioplasty in acute myocardial infarction is not possible

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Background. **Low-dose lytic drugs are sometimes administered to patients with ST-elevation acute myocardial infarction (AMI) as a bridge to coronary angioplasty (facilitated PTCA). Reports are scarce. The characteristics and outcomes of a recent series of consecutive patients treated in our Center are presented.**

Methods. **In August 2000 facilitated PTCA with half-dose reteplase was started in our Center in all cases when the cath lab was not immediately (< 30 min) available, or the patient had to be transferred to us. Since August 2000, 153 patients were admitted to our cath lab to undergo facilitated (n = 80) or primary (n = 73) PTCA. The data of all patients were prospectively collected, and were analyzed on an "intention-to-treat" basis.**

Results. **No significant differences were found between facilitated and primary PTCA patients with regard to: gender, diabetes, hypertension, previous PTCA/bypass surgery, heart rate at admission, systolic blood pressure, anterior AMI, number of leads with ST-segment elevation, total ST-segment deviation, collateral flow to the infarct-related artery, and three-vessel disease. In our series, facilitated vs primary PTCA patients had a better risk profile: they were younger (61 ± 13 vs 66 ± 11 years, p = 0.016), less frequently had a previous AMI (7 vs 24%, p = 0.01), had a shorter time from pain onset to first emergency room admission (122 ± 104 vs 168 ± 162 min, p = 0.045), and a trend to a shorter total time to the cath lab (209 ± 121 vs 255 ± 183 min, p = 0.073) despite a similar emergency room-to-cath lab component (89 ± 50 vs 98 ± 92 min, median 74 vs 65 min, p = NS). Moreover, they presented with a lower Killip class on admission (1.1 ± 0.4 vs 1.5 ± 0.98, p = 0.01), with more patients in Killip class 1 (95 vs 74%, p = 0.001). One vs 8% of patients were in shock. Facilitated vs primary PTCA patients had an initial TIMI 2-3 flow in 42 vs 25% of cases (p = 0.031), a final TIMI 3 flow in 82 vs 71% (p = NS), ≥ 50% ST-segment resolution in 73 vs 58% (p = NS), and both of the latter in 62 vs 45% (p = 0.099); distal coronary embolization occurred in 9 vs 14% of cases (p = NS); intra-aortic balloon counterpulsation was used in 5 vs 12% and glycoprotein IIb/IIIa inhibitors in 10% of the whole population. The overall in-hospital mortality was 3.7 vs 9.6% (p = NS), and 2.5 vs 4.5% (p = NS) when patients in shock at admission were not considered. Reinfarction occurred in 2 patients submitted to facilitated PTCA (who had had no immediate PTCA, due to full reperfusion) and in none of the patients submitted to primary PTCA; no patient presented with stroke or major bleeding.**

Conclusions. **Pre-treatment with thrombolysis often provides a patent vessel before PTCA, appears to be safe, and may improve reperfusion after PTCA. In this setting, the additional use of glycoprotein IIb/IIIa inhibitors before PTCA only in non-reperfused patients may be significantly risk- and cost-effective.**

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Background

There seems to be little doubt that coronary angioplasty (PTCA) is superior to thrombolysis in patients with ST-elevation acute myocardial infarction (AMI) admitted to a hospital where such interventions are performed on a regular basis by experienced operators[1-3]. This may be true even when PTCA is not available on site, and patients must be transported to another hospital, if a delay < 2 hours is added[4,5]. Although the effectiveness of thrombolysis – as compared to PTCA – in achieving reperfusion seems to be particularly blunted by a longer time interval from pain onset[6], the earlier reperfusion is achieved with either treatment, the greater the amount of myocardium salvaged[7]. This translates into better clinical outcomes[8-10] and a lower mortality in patients presenting with TIMI 3 flow before PTCA[11]. The idea of "facilitating" PTCA with early upstream administration of thrombolytic drugs, glycoprotein (GP) IIb/IIIa inhibitors, or both has gained acceptance. Although some studies

on facilitated PTCA (F-PTCA) with either strategy have shown some benefit[12-16], evidence of a substantial improvement in the outcomes of patients is scarce.

Our Center has been running a program (around the clock, 7/7 days) of emergency PTCA in AMI since 1993. In August 2000 we started administering half-dose thrombolysis to these patients whenever the delay of the procedure was expected to exceed 30 min, followed by PTCA as soon as possible. Our experience with F-PTCA, as compared to primary PTCA (P-PTCA) is reviewed in this paper. This brief report is intended as a contribution to the general knowledge of the outcomes of both treatment strategies as used in clinical practice.

Methods

In our Center, emergency PTCA has been the treatment of choice for high-risk patients with AMI since 1993. Patients with large (ST-segment deviation in > 4 leads), anterior, right ventricular, or recurrent AMI, as well as those with acute left ventricular failure (Killip class > 2) are considered high-risk.

Since August 2000, AMI patients who were candidates for PTCA have been treated with reteplase 10 U (F-PTCA) when the angiography room was expected to be unavailable for at least 30 min (because it was busy with another patient, or its crew was at home on call), or when the patient had to be transported from another hospital. Coronary angiography was then performed as soon as possible, followed by PTCA in most cases. On the other hand, when the angiography room was expected to be ready within 30 min, no thrombolytic drug was administered, and the patient was immediately transported from our emergency room to the cath lab (P-PTCA). No other *a priori* criterion was used in the choice between facilitated and primary PTCA by the attending cardiologist in the emergency room, with the very rare exception of an absolute contraindication to even half-dose lysis. It is of note that, during the time interval of this study, nearby hospitals have used emergency transfer to our Center for PTCA in AMI primarily for high-risk patients in whom thrombolysis was contraindicated or had failed.

Aspirin 500 mg i.v. and heparin 5000 IU i.v. were administered to all patients in the emergency room. Additional heparin was administered during the interventional procedure, to obtain activated clotting time values ≥ 300 s. Access through the femoral artery was preferred for cardiac catheterization. A left ventriculogram was not routinely performed. The use of thrombus aspiration systems (Rescue, Boston Scientific, Scimed, Maple Grove, MN, USA) and of GP IIb/IIIa inhibitors was at the operator's discretion. Immediate PTCA was generally withheld when the baseline angiogram showed a TIMI 3 flow in the infarct-related artery (IRA) with a heavy thrombotic component, and when at least 50% ST-segment resolution was apparent on the 12-lead ECG. In these cases elective myocardial revascularization (either elective PTCA after treatment with heparin and ticlopidine ≥ 48 hours or bypass surgery when indicated) was scheduled. Intra-aortic balloon counterpulsation was regularly used in patients with left ventricular failure, when the aorto-iliac anatomy was not unfavorable. Ticlopidine 500 mg/day *per o*s and aspirin 100 to 250 mg/day were started within hours of stent implantation and continued for 1 month, and i.v. heparin was administered for 48 hours after the procedure.

From August 2000 through November 2003, 153 patients were admitted to our cath lab to undergo F-PTCA (n = 80) or P-PTCA (n = 73). Eight patients in the F-PTCA group and 7 patients in the P-PTCA group, in whom a major contraindication to lytic drugs was apparent (recent bleeding in 2, prolonged basic life support maneuvers in 4, severe malignancy in 1) had been transferred from nearby hospitals. The baseline, procedural and outcome data of all patients were prospectively collected as part of a quality assurance program, and were analyzed on an "intention-to-treat" basis (i.e., even when PTCA was not performed immediately or not performed at all). During the same time period, the total number of patients admitted to our coronary care unit with a diagnosis of AMI (ICD-9-CM code 410, first episode of care) was 599.

A 12-lead ECG was recorded before and immediately (< 30 min) after the procedure in all patients; ST-segment elevation and deviation were diagnosed in 69 F-PTCA and 60 P-PTCA patients (in the absence of pacemaker rhythm or left bundle branch block) and were computed as the sum of all elevations and deviations respectively. Cineangiographic data were reviewed by three angiographers who were unaware of the clinical and ECG data.

Statistical analysis. Univariate analysis of the clinical, ECG and angiographic characteristics was performed in both groups. The χ^2 test and the Student's t-test were used for the comparison of proportions and means, respectively. A p value < 0.05 was considered as statistically significant.

Results

The only significant differences in the baseline historical characteristics of F-PTCA and P-PTCA patients (Table I) were a younger age (61 ± 13 vs 66 ± 11 years, p = 0.016) and a lower prevalence (7 vs 24%, p = 0.01) of previous AMI in the former.

The clinical and ECG picture at presentation (Table II) showed a shorter time interval between symptom onset and admission to the first emergency room in the F-PTCA group (122 ± 104 vs 168 ± 162 min, median 90 vs 114 min, p = 0.045), and a consistent trend to a shorter total interval between symptom onset and pro-

Table I. Baseline clinical data.

	P-PTCA (n=73)	F-PTCA (n=80)	p
Age (years)	66 ± 11	61 ± 13	0.016
Female gender	25%	16%	NS
Diabetes mellitus	17%	14%	NS
Hypertension	44%	50%	NS
Previous CABG	3%	4%	NS
Previous PTCA	11%	10%	NS
Previous AMI	24%	7%	0.01
Transfer from other hospitals	10%	10%	NS

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; F = facilitated; P = primary; PTCA = coronary angioplasty.

Table III. Angiographic findings and procedural data.

	P-PTCA (n=73)	F-PTCA (n=80)	p
Multivessel disease	34%	26%	NS
Initial IRA TIMI 3 flow	8%	16%	NS
Initial IRA TIMI 2-3 flow	25%	42%	0.031
Collaterals to the IRA	48%	47%	NS
PTCA performed immediately	99%	91%	0.092
Intra-aortic counterpulsation	12%	5%	NS
Thrombus aspiration devices	8%	5%	NS
GP IIb/IIIa inhibitors	10%	10%	NS

F = facilitated; GP = glycoprotein; IRA = infarct-related artery; P = primary; PTCA = coronary angioplasty.

cedure start (209 ± 121 vs 255 ± 183 min, median 170 vs 198 min, p = 0.073), despite an overall similar delay from the first emergency room admission to the cath lab (89 ± 50 vs 98 ± 92 min, median 74 vs 65 min, p = NS). This delay was longer in both the 8 F-PTCA and 7 P-PTCA patients who had been transferred from nearby hospitals (122 ± 34 vs 254 ± 179 min, median 121 vs 210 min, respectively). A less marked impairment of left ventricular function was also apparent in F-PTCA patients, in terms of both a higher prevalence of Killip class 1 upon admission (95 vs 74%, p = 0.001), and a lower mean Killip class in their group (1.09 ± 0.43 vs 1.46 ± 0.89, p = 0.001). Cardiogenic shock on admission was present in 1 vs 8% of F-PTCA and P-PTCA patients respectively (p = NS).

The angiographic findings and procedural data are listed in table III. A patent IRA (TIMI 2-3 flow) was present in a larger proportion of F-PTCA patients (42 vs 25%, p = 0.031). It is of note that in view of the presence of a patent IRA, PTCA was not performed immediately in 7 out of 80 F-PTCA patients; in 3 of them it was performed later during hospitalization, after treatment with ticlopidine 500 mg/day for at least 3 days. Three patients had severe three-vessel disease and were submitted to bypass surgery before discharge. One patient had only moderate stenosis of the IRA and was discharged on medical treatment. Immediate PTCA was not performed in 1 patient in the P-PTCA group, due to a patent IRA without severe residual stenosis; he was discharged on medical treatment after a negative ischemia test.

The post-procedural angiographic and ECG data are listed in table IV. All indicators of IRA recanalization and of myocardial reperfusion were slightly more favorable in the F-PTCA group, with a definite trend toward a better reperfusion outcome (final TIMI 3 flow and ≥ 50% ST-segment resolution in 62 vs 45% of patients, p = 0.099).

The in-hospital outcomes are detailed in table V. The difference in overall mortality (3.75% in the F-PTCA vs 9.58% in the P-PTCA group) albeit striking, did not reach statistical significance, and appeared to be parallel to the higher incidence of cardiogenic shock on admission in the P-PTCA group. Two patients in the F-PTCA group, in whom immediate PTCA had been withheld due to a patent IRA and ST-segment resolution, had reinfarction before the planned PTCA and under-

Table II. Clinical and ECG picture at presentation.

	P-PTCA (n=73)	F-PTCA (n=80)	p
Heart rate (b/min)	79 ± 21	73 ± 18	NS
Systolic blood pressure (mmHg)	124 ± 27	127 ± 24	NS
Anterior AMI (%)	41	35	NS
No. leads with ↑ ST	4 ± 2	4 ± 2	NS
No. leads with ↑↓ ST	7 ± 3	8 ± 3	NS
Sum of ↑ e ↓ ST (mm)	17 ± 10	18 ± 10	NS
Interval between symptom onset and first emergency room admission (min)	168 ± 162	122 ± 104	0.045
Interval between symptom onset and procedure (min)	255 ± 183	209 ± 121	0.073
Interval between first emergency room admission and procedure (min)	98 ± 92	89 ± 50	NS
Killip class 1 (%)	74	95	0.001
Killip class (mean)	1.46 ± 0.89	1.09 ± 0.43	0.001
Shock (%)	8	1	NS

AMI = acute myocardial infarction; F = facilitated; P = primary; PTCA = coronary angioplasty.

Table IV. Post-procedural angiographic and ECG data.

	P-PTCA (n=73)	F-PTCA (n=80)	p
Final IRA TIMI 3 flow	71%	82%	NS
Final IRA TIMI 2-3 flow	92%	96%	NS
Distal embolization	14%	9%	NS
Resolution ↑ ST < 50%	42%	27%	NS
Resolution ↑ ST ≥ 50% < 70%	16%	17%	NS
Resolution ↑ ST ≥ 70%	42%	56%	NS
Final IRA TIMI 3 flow + resolution ↑ ST ≥ 50%	45%	62%	0.099

F = facilitated; IRA = infarct-related artery; P = primary; PTCA = coronary angioplasty.

Table V. In-hospital outcomes.

	P-PTCA (n=73)	F-PTCA (n=80)	p
MB peak (U/l)	297 ± 227	335 ± 2	NS
LVEF at admission (%)	47 ± 10	50 ± 8	NS
Death (in-hospital) (%)	9.6	3.7	NS
Death (shock excluded) (%)	4.5	2.5	NS
Reinfarction (%)	0	2.5	NS
Stroke (%)	0	0	–

F = facilitated; LVEF = left ventricular ejection fraction; P = primary; PTCA = coronary angioplasty.

went emergency PTCA. In no patient did stroke and major bleeding complications occur. Bleeding at the vascular access site occurred in 4 patients in each group, but in no case was transfusion or surgical repair necessary.

Discussion

Although evidence of substantial benefit from early upstream administration of thrombolytic drugs, GP IIb/IIIa inhibitors, or both before PTCA in AMI is limited[12-16], F-PTCA has gained acceptance in some centers[17-20], including ours, where it is believed to compensate for a longer-than-ideal time interval before emergency PTCA. No data from large observational studies are available, and the results from ongoing randomized trials with combined half-dose lytics and GP IIb/IIIa inhibitors (CARESS, FINESSE) or full-dose thrombolysis (ASSENT-4) before PTCA are eagerly awaited.

Despite the fact that limited number of patients included in our single-center prospective registry precludes meaningful statistical workup with multivariate analysis, some observations from this intention-to-treat-based, consecutive series may be of interest[21], and may accrue to the experience of others.

The overall in-hospital mortality in our patients (6.5%) was the same as observed in patients treated with P-PTCA in a recent nationwide survey[22]. Although the anticipated early availability of the angiographic room was the only deliberate criterion we used in the selection of P-PTCA vs F-PTCA, our patients treated with the former had a worse clinical profile on admission. In fact, despite a similar ECG presentation, they were older, more often had a previous AMI, had a longer time interval from the onset of symptoms to treatment, and had signs of more severe left ventricular impairment. The observed trend toward a higher in-hospital mortality in our P-PTCA patients is likely to be a reflection of their higher baseline risk. The patients who were transferred for P-PTCA from nearby hospitals (due to an existing contraindication to lysis) may partly explain this, since 3 of them had severe left ventricular impairment, and 3 had been resuscitated after an out-of-hospital cardiac arrest; 2 of these patients died in hospital. On the contrary, the 8 patients who were transferred for F-PTCA were all in Killip class 1 and none died.

It is of note that, overall, the (first) door-to-balloon interval did not significantly differ between groups. Both the P-PTCA and the F-PTCA groups included a similar number of transfer patients with a longer-than-average interval between arrival to the first emergency room and the start of the PTCA procedure. The time interval between arrival to our emergency room and the start of the invasive procedure was 9 ± 10 min for transfer patients (indeed, for transfer patients our emergency room is only a run-through, while the cath lab is ready and its crew is waiting), while it was 85 ± 75 and 80 ± 50 min (p = NS) for P-PTCA and F-PTCA patients respectively, who had not been transferred. This should mean, on the one hand, that in a busy center, even when both the angiography room and the interventional crew give a green light, the door-to-balloon time for the center's own patients is often longer than anticipated, and there may be room for starting some "facilitation" pretreatment. On the other hand, the door-to-balloon time itself must be kept under constant monitoring, even in centers with experienced personnel, as part of quality assurance programs.

Infarct-related artery recanalization before coronary angioplasty. Not surprisingly, 42% of our F-PTCA patients showed a patent IRA before PTCA. In fact, an initial TIMI 2-3 flow in the IRA was observed in 61% of patients treated with alteplase 50 mg in the PACT trial[12], and in 40% of 80 patients treated with half-dose lysis in the retrospective series of Politi et al.[17]. Pre-administration of GP IIb/IIIa inhibitors may achieve variable IRA patency rates, depending on the time interval to angiography: abciximab yielded a TIMI 2-3 flow in the IRA at 45 min in 40% of cases in the GRAPE study[23], and in 26% of cases in the ADMIRAL study[14]. Administration of tirofiban before transportation to the cath lab was associated with TIMI 2-3 patency of the IRA in 43% of patients[16], similar to what observed in a previous study[24]. The combined treatment with GP IIb/IIIa inhibitors and reduced-dose lyt-

ic agents may result in a higher rate of IRA patency. In fact, a TIMI 2-3 flow 90 min after reteplase 5+5 U plus abciximab was reported in 73% of patients in the TIMI 14 study[25], and in 96% of patients 60 min after eptifibatide double bolus plus half-dose tenecteplase in the INTEGRITI trial[26]. A TIMI 2-3 patency before PTCA was also observed in 77% of patients in the series of Manari et al.[20], with > 70% ST-segment resolution before PTCA in 35% of cases. A TIMI 3 patency was reported by Zanini et al.[18] in 58% of patients.

Bleeding complications were infrequent in our patients, and were similar to those observed in the reteplase and placebo groups (8.5 vs 8.2%) in the PACT trial[12]. Minor bleeding was more frequent in abciximab than in control patients in ADMIRAL (12.1 vs 3.3%), but major bleeding was not (0.7 vs 0%)[14]. Major and/or minor bleeding complications tend to increase when the combined treatment with GP IIb/IIIa inhibitors and reduced-dose lytic agents is used[13,15,19,20,25,26]. Besides, more or less severe thrombocytopenia is not uncommon when abciximab is administered[14,25,27].

Recanalization and reperfusion after coronary angioplasty. The successful use of PTCA in restoring TIMI 3 flow in the IRA did not significantly differ neither between our F-PTCA and P-PTCA patients (82 vs 71%), nor between the present study and the PACT trial[12]. However, in our F-PTCA patients a definite trend to a better reperfusion result was apparent, as shown by the concomitant TIMI 3 flow and ST-segment resolution (62 vs 45% of patients). A significant improvement in both IRA recanalization and early ST-segment resolution after PTCA has been reported when abciximab is administered at any time before PTCA, either alone[14,28,29] or together with reduced-dose lytic drugs[13,20,25,30].

The impact of PTCA facilitation on the clinical outcomes is controversial. The randomized PACT trial[14] was not powered to study the comparative outcomes of patients treated with half-dose thrombolysis or placebo, whose 30-day mortality, reinfarction and stroke rates were not significantly different. In contrast with previous data gathered before the stent era[31], however, recent studies have shown that immediate stenting after thrombolysis may be performed with good results[32] [and Avilés F. Grupo de Analisis de la Cardiopatia Isquemica Aguda (GRACIA-2) Study. European Society of Cardiology Congress, 2003, unpublished data]. Beneficial clinical effects of treatment with abciximab before emergency PTCA and stenting in AMI have been so far documented in three randomized trials[14,29,33], each showing a significantly lower 30-day incidence of the composite endpoint of death, reinfarction and new target vessel revascularization, as compared to controls. This held true even when abciximab was administered after coronary angiography, immediately before PTCA[29,34]. Evidence of some benefit was also apparent following re-analysis of the data of the CADILLAC trial[35]. This issue has been reviewed in a recent editorial in a major journal[36], where the conclusion is reached that, until there are new data available, catheter-based reperfusion with adjunctive abciximab therapy should be regarded as the preferred reperfusion therapy for AMI.

Conclusions. Data from our limited experience and from the literature show that in AMI, administering half-dose thrombolysis to begin with, when the PTCA room is not immediately available, is safe. Thrombolytic drugs have also been used by non-cardiologists for more than 20 years, are available in every emergency department, and have reasonable costs. This treatment may be easily administered to all AMI patients bound for emergency PTCA, as early as possible on their way to the cath lab. Adjunctive abciximab therapy might be particularly beneficial, and both risk- and cost-effective, in selected patients, in whom vessel recanalization and/or myocardial reperfusion are unsatisfactory at coronary angiography, and immediate PTCA has to be performed. The results of this strategy deserve further evaluation in appropriately designed prospective studies.

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