Original articles

Angioplasty in acute myocardial infarction after low-dose alteplase and abciximab in transferred patients. A comparison with primary angioplasty on site

Antonio Manari, Vincenzo Guiducci, Nicola Muià, Paola Giacometti, Stefano Fioroni, Alessandro Navazio*, Gianpaolo Gambarati*, Stefano Bendinelli*, Gabriele Bruno*

*Division of Invasive Cardiology, S. Maria Nuova Hospital, *Department of Cardiology, AUSL, Reggio Emilia, Italy*

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Coronary angioplasty; Myocardial infarction.

Background. **The most important limitation in primary percutaneous coronary interventions (PCI) for acute myocardial infarction (AMI) is the small number of catheterization laboratories and their non-homogeneous territorial distribution. The aim of this study was to evaluate the safety and efficacy of an organizational model based on a network including tertiary referral centers and community hospitals for the treatment of AMI with alteplase plus abciximab followed by PCI.**

Methods. **From October to November 2002, 232 patients ≤ 75 years with AMI at high risk (84 transferred from four community hospitals and 148 patients admitted directly at the tertiary center) underwent PCI at our Institution. We compared procedural results and clinical outcome in patients with AMI undergoing PCI with or without transfer to tertiary centers.**

Results. **Patient transferal from community hospitals determines a greater door-to-balloon time (120 vs 55 min, p < 0.001), while complications observed during transportation are limited (5.9%). Transferred patients have a greater percentage of infarct-related artery patency (77 vs 22%, p < 0.001) and of ST-segment resolution 90 min post-PCI (77 vs 57%, p < 0.005) in comparison with direct-access patients. The incidence of clinical events (death, reinfarction, angina) was not different between the two groups at 30 days and at 6 months of follow-up.**

Conclusions. **In our experience the integrated model between tertiary centers and community hospitals represents a valid network system offering homogeneous therapeutic (alternatives) options to all patients with AMI regardless of the hospital where they are first admitted.**

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Address:

Dr. Antonio Manari

U.O. di Cardiologia Interventistica Azienda Ospedaliera S. Maria Nuova Viale Risorgimento, 80 42100 Reggio Emilia E-mail: manari.antonio@asmn.re.it

Introduction

Reperfusion therapy in acute myocardial infarction (AMI) can be accomplished medically, with thrombolytic agents, or mechanically with balloon angioplasty. The advantages of balloon angioplasty with regard to mortality, reinfarction and the risk of bleeding at the site of balloon angioplasty have been documented in randomized trials[1] and registries[2]. Furthermore, a primary percutaneous coronary intervention (PCI) allows an immediate coronary anatomical diagnosis and prognostic stratification[3] which, in turn, imply a shorter in-hospital stay in uncomplicated cases[4,5]. The most important limitation of a primary PCI in AMI is represented by the small number of catheterization laboratories (CL) able to offer: a) an all-year, 24-hour availability for emergency PCI, and b) a structured inter-hospital network which ensures the recommended deadline of a door-to-balloon time < 60 min. On the other hand, increasing the number of CL has already been demonstrated as being an impracticable alternative because of its high economic costs and because of the risk of an inadequately low procedural volume in several CL[6]. A more rational alternative system could be represented by a network between tertiary referral centers, where complex diagnostic and therapeutic interventions are routinely performed, and community hospitals without CL facilities. This kind of organization is theoretically able to offer a homogeneous access to highly effective, latest-technology treatment to all residents in a quite large area, at a satisfactory level of competence whilst at the same time fulfilling the requirements of both a rational resource use and a good quality of care. The Danish Trial in Acute Myocardial Infarction-2, a multicenter randomized study on thrombolytic therapy versus acute coronary

angioplasty (Andersen HR. Final results of the DANAMI-2 trial. Presented at the Late Breaking Clinical Trials Session at the Annual Meeting of the American College of Cardiology, Atlanta, GA, USA, March 2002), represents, on a large scale, an example of this kind of organization. It showed the possibility of transferring, by ambulance, patients with AMI who were candidates for coronary angioplasty from 22 community hospitals to 5 Danish tertiary centers.

Studies on primary PCI in transferred patients showed contrasting results. In fact, despite similar midterm outcomes[7,8], transferred patients had a larger necrotic area and a lower left ventricular contractility at hospital discharge[9].

The primary concern with patient transferal is the longer reperfusion time. Some authors suggest immediate pharmacological treatment followed by transfer for PCI[10,11]. By combining the best of the two complementary therapies one would be able to utilize the transport time for reperfusion purposes. Previous studies showed the inefficacy of fibrinolytic therapy followed immediately by PCI during AMI[12,13]. This concept has been overruled by the use of stents[14-16] and drugs[17,18] able to modify the vascular reactivity of the lesion containing a thrombus consequent to PCI-induced barotraumas.

The aim of this study was to evaluate the safety and clinical results of a strategy based on an immediate alteplase plus abciximab therapeutic regimen followed by an early transfer to a tertiary center for PCI in patients admitted to community hospitals with AMI.

Methods

In the province of Reggio Emilia (population 436 000 residents) there are 6 hospitals where patients with AMI may be admitted. One has a CL and cardiac surgery facilities (tertiary center), and the other 5 are community hospitals: three with their own coronary care unit and two with a specific section in the Department of Medicine, where AMI patients are usually admitted. In the latter two hospitals cardiology consultants are not available on a 24-hour basis.

Since 1999 there has been a network between these hospitals based on ambulance transportation from the peripheral to the tertiary center where diagnostic and interventional procedures are performed. This network has allowed for the performance, in 2001, of 645 elective procedures (which represent 39.9% of all coronary interventions performed in the CL) on transferred patients. Since January 2000 high-risk AMI patients admitted to our Institution have been submitted to primary PCI and, since October 2000, an interventional program for patients with high-risk AMI transferred from community hospitals was approved by the local ethics committee. This protocol was activated in 4 out of 5 community hospitals (with nearly 200 000 residents). The distances between these community hospitals and the tertiary center ranges between 13 and 36 km. Due to logistic aspects, the fifth small hospital (located in a mountainous region 50 km from the tertiary center) was not included. The protocol consists of immediate treatment with fibrinolytic therapy plus abciximab at the first hospital where the patient is admitted, and an early transfer to the CL where the patient is submitted to coronary angiography and, if indicated, to PCI. Ambulance services with a medical and paramedical staff equipped to transfer critically ill patients are used for patient transport. Patients are transferred back to the referring centers 24-48 hours later if their clinical situation is stable.

Study population. Our study population included patients ≤ 75 years with symptoms lasting < 12 hours and al least one of the follow criteria: a) extensive AMI, defined as the presence of ST-segment elevation in ≥ 5 leads (anterior wall myocardial infarction) or as the sum ↑ ↓ of an ST-segment deviation ≥ 8 in 15 leads (non-anterior wall myocardial infarction); b) recurrent AMI; and c) shock.

Patients with contraindications for thrombolysis admitted in community hospitals were excluded from the transportation protocol.

Informed consent for transfer and for the procedure was obtained from all patients.

Pharmacological treatment protocol. In the transferred patients (group A) we used the following protocol[19]:
- aspirin 250 mg i.v.;
- alteplase (50 mg total): a 15 mg bolus followed by i.v. infusion of 35 mg in 60 min;
- abciximab: a 0.25 mg/kg bolus followed by infusion of 0.125 μg/kg/min (max 10 μg/min) for 12 hours;
- a bolus of unfractionated heparin (60 IU/kg).

The use of beta-blockers, nitroglycerin and calcium antagonists was left to the discretion of the physician.

Nontransferred patients (group B) undergoing primary PCI were given:
- i.v. heparin 5000 to 10 000 IU;
- aspirin 250 mg i.v.

In this group the intraprocedural administration of Abciximab was left to the discretion of the operator.

Percutaneous coronary interventions. Once a diagnosis of AMI was made, the patients were referred directly to the cardiac CL where two trained nurses and one out of three experienced interventional cardiologists (each of whom performing > 150 procedures per year) were on 24-hour duty. Immediate coronary and left ventricular angiography were performed via the femoral approach. Angioplasty was performed at the site of the culprit lesion only in patients with ≥ 50% diameter stenosis. It was attempted in all cases of TIMI 0-2 flow grade and even if a TIMI 3 flow grade was doc-

umented, unless severe three-vessel disease was present and the anatomical morphology was unsuitable for transcatheter revascularization.

The coronary flow in the infarct-related artery (IRA) was visually assessed by the operator and classified according to the TIMI grading system on a scale of 0 to 3[20]. In all patients who underwent PCI we prospectively evaluated the following time intervals: pain onset-hospital admission; hospital admission-start of pharmacological therapy; hospital admission-beginning of transfer; time of transport; CL arrival-first balloon inflation.

Electrocardiographic analysis. ST-segment resolution data were collected and the ECG at the time of admission to the hospital (first ECG) was compared with that recorded at the CL (second ECG) and with that recorded 90 min after the procedure (third ECG). The magnitude of ST-segment deviation between baseline and the next ECGs was determined as the sum of the ST-segment elevations measured 20 ms after the end of the QRS complex in leads I, aVL and V_1-V_6 for anterior, and in leads II, III, aVF and V_5-V_6 for non-anterior myocardial infarction. An improved ST-segment resolution was defined as the percent resolution from baseline to the second and third ECGs[21].

Clinical follow-up. Follow-up data were collected from all patients during office visits or by telephone interview performed 30 days and 6 months after the procedure. Follow-up catheterization was performed for recurrent ischemic symptoms or after abnormal function testing.

Reinfarction was defined on the basis of the patient's symptoms and on the onset of new ECG changes and of new increases in the creatinine kinase or creatine kinase-MB isoenzyme levels. Re-angioplasty was defined as a repeated angioplasty performed within 24 hours of a new ischemic episode. The choice between performing a new PCI or maintaining the patient on medical therapy or sending him for bypass surgery was left to the judgment of the physicians. Bleeding complications were classified according to the TIMI score index[22].

Due to the lack of a blinded clinical-event adjudication committee, the data were evaluated by the authors in accordance with the above-mentioned definitions.

Statistical analysis. Statistical comparisons were performed using the Fisher's exact test for categorical variables and the Wilcoxon two-sample test for continuous variables. All computations were carried out using SAS version 10.0 software.

Results

From October 2000 to October 2002, 128 patients who met the above inclusion criteria were admitted in four community hospitals in the province of Reggio Emilia. Eighty-four out of the 128 patients were transferred to the CL (group A). The reasons for not having transferred the remaining 44 patients are listed in table I. During the same period, 148 consecutive patients satisfying the same inclusion criteria were directly admitted to the tertiary center and underwent primary PCI (group B). Therefore, a total of 232 patients with AMI underwent PCI at our Institution. The patients' clinical characteristics are shown in table II. Due to a stricter interpretation of the inclusion criteria adopted by community hospital investigators, a higher percentage of acute anterior myocardial infarction was seen in group A. Transferal back to the first hospital was performed within 24 hours in 28% and within 48 hours in 35% of the cases. In no case was it necessary to transfer the patient back to the CL due to further complications.

Table I. Reasons for excluding patients with a myocardial infarction from the transferring protocol.

	No. patients
Ambulance not immediately available	9
Physician's decision	22
Misdiagnosis	4
Lack of informed consent	7
Terminal phase of cardiogenic shock	2
Total	44

Table II. Patient characteristics.

	Group A (n=84)	Group B (n=148)	p
Age (years)	61.2 ± 10.5	58.3 ± 10.7	NS
Male	65 (74%)	111 (75%)	NS
Diabetes	10 (12%)	18 (12%)	NS
Hypertension	30 (37%)	50 (34%)	NS
Prior AMI	7/84 (8.3%)	14 (9.4%)	NS
Anterior AMI	62 (74%)	71 (48%)	< 0.0001
HR at admission (b/min)	79 ± 14.9	74 ± 17	NS
SBP at admission (mmHg)	131 ± 25	134 ± 31	NS
Shock	4 (4.7%)	9 (6.0%)	NS

AMI = acute myocardial infarction; HR = heart rate; SBP = systolic blood pressure.

Complications during transport. Complications occurred in 5 patients (5.9%): 3 patients had life-threatening ventricular arrhythmias (ventricular fibrillation in 2 and ventricular tachycardia in 1) and were successfully defibrillated using an external DC-shock by the ambulance staff; 1 patient had a transient atrioventricular block and was treated with atropine; and 1 patient had cardiac tamponade with hemodynamic compromise. No bleeding complications were observed.

Percutaneous coronary interventions. Of the 84 transferred patients one died of cardiac tamponade secondary to rupture of the left ventricular free wall at the emergency room of Reggio Emilia whereas an acute pericarditis was misdiagnosed in a second patient. Coronary angiography was performed in the remaining 82 patients and 74 were submitted to PCI on the IRA. Eight patients who did not undergo PCI had residual stenosis < 30% (3 patients) and three-vessel disease with IRA patency (5 patients). It was decided to submit these latter 5 patients to pharmacological stabilization and subsequent elective coronary bypass surgery.

The procedural and follow-up data of the patients enrolled in the protocol were analyzed and compared to those of the 148 patients who, during the same period, had been admitted directly to the tertiary center and had undergone primary PCI. Table III reports the treatment delay in the two groups. Transferred patients had door-to-balloon times double those of non-transferred patients, but pharmacological therapy at the community hospitals was started very early after admission with a median delay of 15 min. In view of the short distance between hospitals and the good road system, the transportation time was acceptable.

The baseline angiographic variables are reported in table IV and the procedural data of the patients undergoing PCI are shown in table V.

In spite of a similar rate of post-procedural TIMI 3 flow grade, the IRA patency (TIMI flow grade 2-3) at angiographic control (performed on average 102 min after hospital admission in group A, and 45 min after hospital admission in group B) was significantly higher in the transferred patients (77 vs 22%, p < 0.001). This determined a higher percentage of direct stenting in group A (65 vs 39%, p < 0.0002). Twenty-six out of 74 transferred patients showed an ST-segment resolution > 70% upon arrival to the CL (before PCI) and 90 min after PCI the percentage was significantly higher in group A (77 vs 57%, p < 0.005).

Table III. Median times (in minutes) and the corresponding interquartile ranges (in brackets) of the different interventional steps.

Time	Group A (n=84)	Group B (n=148)	p
Pain-admission	90 (50-148)	100 (60-154)	NS
Admission-therapy	15 (10-30)		
Admission-transfer	50 (35-75)		
Transportation time	35 (25-45)		
Admission-first inflation	120 (93-137)	55 (42-73)	< 0.001
Pain-balloon inflation	210 (170-275)	156 (115-219)	< 0.05

Table IV. Baseline angiographic variables.

	Group A (n=82)	Group B (n=148)	p
Infarct-related artery	–	–	
LAD	66	66	
LCx	4	13	
RCA	12	63	
Saphenous vein graft	0	6	
TIMI 2-3 flow grade pre-PTCA	62 (77%)	33 (22%)	< 0.001

LAD = left anterior descending coronary artery; LCx = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

Table V. Procedural data.

	Group A (n=74)	Group B (n=148)	p
TIMI 3 flow grade post-PTCA	69 (93%)	140 (95%)	NS
ST resolution > 70% pre-PTCA	26 (35%)	0	< 0.001
ST resolution > 70% post-PTCA	57 (77%)	84 (57%)	< 0.005
Stent overall	57 (77%)	129 (87%)	< 0.038
Direct stenting	37 (65%)	51 (39%)	< 0.0002
Abciximab	74 (100%)	111 (75%)	< 0.0001
Emergency bypass surgery	0	0	NS
Intraprocedural death	0	2 (1.3%)	NS

PTCA = percutaneous transluminal coronary angioplasty.

In-hospital outcome. During the period of hospitalization, 3 transferred patients (3.5%) and 2 non-transferred patients (1.3%) died. Two hundred and twenty-seven patients were discharged alive. One transferred patient (1.1%) and one non-transferred (0.6%) had a re-infarction. The latter patient had a subacute stent thrombosis 24 hours after the index procedure and he was successfully retreated with a new PCI.

In group A two major bleeding episodes were observed (1 retroperitoneal hematoma causing severe hypotension associated with reinfarction, and 1 case of gastrointestinal bleeding). Minor bleeding occurred in 8 patients, mainly at the puncture site on the groin (5 patients). In 2 patients a subcutaneous hemorrhage (at the site of venipuncture) was observed, and 1 patient with bronchiectasis presented with hemoptysis.

Follow-up. The 30-day follow-up data are shown in table VI. In group A the overall mortality was 5.9% and included one patient who died before arriving at the emergency room and a second one who was scheduled for bypass surgery 20 days after angiography. This patient had severe three-vessel disease and a depressed left ventricular contractility at the acute angiographic control. The 30-day mortality among the patients who underwent PCI of the IRA was 3.1%. The rate of target vessel revascularization at 30 days (both PCI and coronary bypass) was 2.4% in group A and 0.6% in group B.

At 6 months, the total number of deaths was 5 (7.7%) in the transferred group and 6 (5.4%) in the non-transferred group while a reinfarction occurred in 2 (3.0%) of

Table VI. Thirty-day follow-up.

	Group A (n=84)	Group B (n=148)	p
Death	5 (5.9%)	5 (3.4%)	NS
Reinfarction	1 (1.2%)	2 (1.3%)*	NS
Angina	1 (1.2%)	2 (1.3%)	NS
Re-PTCA	0	1 (0.6%)*	NS
Bypass surgery	2 (2.4%)	0	NS
Hemorrhage			
Intracranial	0	0	NS
Major non-intracranial	2 (2.4%)	0	NS
Minor	8 (9.5%)	2 (1.3%)	0.05
Total	19 (22.6%)	12 (8.1%)	0.02

PTCA = percutaneous transluminal coronary angioplasty. * one patient had a reinfarction and thereafter underwent repeat PTCA.

the transferred patients and in 4 (3.6%) of the non-transferred patients. The rate of target vessel revascularization was 12.2% in group A and 6.3% in group B. There were no statistically significant differences regarding cumulative clinical events between transferred and non-transferred patients at 6 months of follow-up (Table VII).

Discussion

In Italy the distribution of CL is not homogeneous and this determines differences in the number of interventional procedures performed at each CL: in the northern region there are 1294 PCI/million, in the central region 932 PCI/million and in the southern region 576 PCI/million[23]. The BLITZ observational study (Chiarella F, Di Chiara A. BLITZ, preliminary results. Symposium on ANMCO Clinical Trials. XXXIII National Congress of the Italian Association of Hospital Cardiologists, Florence, Italy, May 2002), conducted by ANMCO in 2001 in 296 Italian coronary care units confirmed that 71% of the coronary care units did not have on-site interventional CL. Similar data are reported in the United States where hospitals with CL represent 20% of all hospitals[24]. In view of this, it is possible that the best therapy that a patient may receive depends on the type of hospital he is admitted to and therefore on casual factors and geographic dislocation rather than on real clinical needs.

Table VII. Six-month follow-up.

	Group A (n=65)	Group B (n=111)	p
Death	5 (7.7%)	6 (5.4%)	NS
Reinfarction	2 (3.0%)	4 (3.6%)	NS
Angina	3 (4.6%)	5 (4.5%)	NS
Re-PTCA	4 (6.1%)	4 (3.6%)	NS
Bypass surgery	4 (6.1%)	3 (2.7%)	NS
Total	18 (27.6%)	22 (19.8%)	NS

PTCA = percutaneous transluminal coronary angioplasty.

In our study nearly one third of eligible patients were not transferred from the community hospitals. This happened during the initial phase of our study and was probably due to the concern with moving patients during the acute phase of myocardial infarction and to some limitations in the short-notice availability of the ambulance. This could possibly have determined a selection bias affecting our positive results. However, our purpose was not to demonstrate that all patients with myocardial infarction have to be moved from the community hospital to tertiary centers with CL facilities, but just to assess the feasibility and safety of a well defined transferal model.

Even with these limitations, the results observed in our transferred patients confirm that transferal between the hospitals of our province was safe and did not determine additional risks. This is similar to the results of recent trials based on the inter-hospital transport of patients with an ST-segment elevation AMI[25] (and DANAMI-2). Arrhythmic events were the most significant complications during transportation. Because of the presence of an experienced medical and paramedical staff on the ambulance, all complicated situations were treated without clinical consequences for the patients. Other authors[7,26] showed a similar low incidence of complications and also confirmed the safety of transport of patients with AMI.

In our study, the door-to-balloon time for transferred patients was greater than that for non-transferred patients, and also greater than those reported in the literature. Vermeer et al.[27] compared the results of a rescue and primary PCI in patients with an extensive myocardial infarction admitted to hospitals without PCI facilities. They reported a mean time between randomization and angiography of 85 min for patients undergoing primary PCI without transferal and of 100 min for the transferred group. The distance between the referring centers and the PCI center ranged from 25 to 50 km. Even Liem et al.[9] analyzed a group of transferred patients undergoing primary PCI and found a mean door-to-balloon time of 60 min in non-transferred patients and of 103 min in transferred ones. In our experience the greater door-to-balloon time in transferred patients was due to the organization delays of the transportation system (ambulance availability and on-call physician at the community hospital) and to the pharmacological pre-treatment at the first hospital started before sending the patient at the tertiary center. In spite of this, our data suggest a favorable mid-term clinical outcome for transferred patients, similar to that of non-transferred patients for whom the door-to-balloon time was significantly shorter. The 30-day mortality for the transferred patients was low and similar to that observed for the non-transferred patients submitted to primary PCI. Major recent trials[28,29] evaluating thrombolytic agents still report a 30-day mortality rate of about 6-7%. Despite the high-risk clinical characteristics of patients selected for PCI in our observational se-

ries, the 30-day mortality rate was quite similar to those reported in these trials.

In our registry the number of re-angioplasty at 30 days and at 6 months was not elevated. This was due to the fact that surgical revascularization was chosen (2.4% within 30 days and 8.8% at 6 months) in case of IRA restenosis in patients with multivessel disease and to a more conservative medical approach in case of recurrent angina controlled by pharmacological therapy.

A second point of our strategy regarded the pharmacological pre-treatment administered at the first hospital. Early administration of thrombolytic drugs increases the percentage of patients with an AMI who arrive to the CL with a patent IRA. IRA patency before the intervention influences the results of primary PCI and improves the mid-term outcome[30,31]. In the recent literature there are examples of pre-PCI pharmacological therapy with full[32,33] or low[34] doses of fibrinolytic agents and with abciximab[35] or an association of low-dose fibrinolytic agents and glycoprotein IIb/IIIa inhibitors[19,36]. We selected the combined drug regimen because of the great percentage patency reported for this combination. However, it must be emphasized that the combo therapy is not recommended in the recent European guidelines, and our registry was started after approval of the local ethics committee. Our data showed that fibrinolytic therapy associated with glycoprotein IIb/IIIa inhibitors did not determine episodes of bleeding during transportation. However, the transport time in our province is short and the road system is good. Even late bleeding complications were found to be mild or moderate and their incidence was similar to those reported in studies in which the same combined drug regimens were used[19,36]. Our results showed, at the pre-PCI angiographic control, a greater percentage of TIMI 2-3 flow grade in the group of transferred patients after combination therapy. This finding allowed a wider use of direct stenting and could have determined the better ST-segment resolution we observed.

In conclusion, our prospective feasibility registry suggests that in a logistic scenario of intermediate dimensions and with an adequate transportation system it is possible to organize an immediate inter-hospital transfer for patients with an extensive myocardial infarction. This allows to extend the availability of a PCI in case of AMI to all the population of a given territory, with a good use of resources. Furthermore, this hospital network satisfies the need for a high standard of service in high-volume centers able to perform emergency revascularization 24 hours a day and 7 days a week even in complicated cases.

If the benefits of immediate pharmacological pre-treatment at the first hospital will be confirmed by future studies, it may be that they could be extended to the scenarios that predict a prolonged time to arrival at the CL (> 90 min) offering greater guarantees to the physician who has to decide the patient transferal and giving him more time to organize the transportation.

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