Original Article

A comparison of outcomes of routine early angiography versus delayed ischemia-guided angiography after thrombolytic therapy in ST segment-elevation myocardial infarction

HA Basiri, R Kiani, S Abdi, A Zahedmehr, HR Sanati, F Shakerian, A Firoozi

Department of Interventional Cardiology, Shaheed Rajaie Cardiovascular Center, Tehran University of Medical Sciences, Tehran, Iran

Background: Thrombolytic therapy continues to be the common treatment in acute ST elevation myocardial infarction in the majority of heart centers worldwide. However, thrombolytic therapy is associated with high re-occlusion and re-infarction rates. So, most patients now undergo early diagnostic angiography and possibly angioplasty of the culprit artery but the controversy about the timing of angiography after thrombolysis continues to remain unresolved. In this prospective cohort study, we compared the outcome of early invasive strategy versus delayed invasive approach in ST-elevation MI patients who had received successful thrombolytic therapy. Primary endpoint of the study was Major Adverse Cardiovascular Events or MACE (the combined rate of death, re-infarction, major bleeding and cerebrovasular events. Secondary endpoints were re-infarction and re-hospitalization rate.

Method: The study comprised 142 patients of which 87 had a routine angiography in less than 10 days of acute event and 55 underwent ischemia-guided angiography after 10 days of index event. Stenting of the culprit vessel was done in 60% of the routine angiography group and 63% of the ischemia-guided group. The patients were followed for 8.8 ± 2.8 months after the index event.

Results: The primary endpoint occurred in 6.9% of routine angiography patients and 10.9% of the control group (P= 0.4). The rate of re-infarction was significantly higher in the delayed invasive arm than routine early invasive arm (10.9% vs. 1.1, P:0.01),and mostly occurring before angiography.

Conclusion: routine angiography as soon as possible after thrombolysis can reduce re-infarction and was not associated with any increased risk of adverse events in our study.

Keywords: Coronary Angiography, Myocardial Infarction, Thrombolytic Therapy

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Introduction

In patients with ST-elevation myocardial infarction (STEMI) who receive successful thrombolytic therapy, the referral for angiography and its timing has been a matter of debate over the past 2 decades. Early studies before the stent era showed no benefit from performing routine angiography after thrombolysis.[1,2] but more recent studies demonstrated promising results of early invasive strategy in terms of reducing mortality, re-infarction, cerebrovascular accidents (CVA) and re-hospitalization.[3-6]

In many studies it has been shown that even if thrombolysis is successful, thrombolysis in myocardial infarction [TIMI], flow grade 3 can be achieved in up to 60% of patients[7-9] which implicates higher rates of cardiac events in this group. Suboptimal flow in the culprit vessel after fibrinolysis is partly due to persistence of the significant culprit stenosis which caused the first event. Thus, the chance of re-occlusion and re-infarction in the culprit vessel will remain high (up to 28%) if mechanical relief of stenosis is not attempted after the index event.[10,11]

This study attempted to compare the short and

Correspondence:
R Kiani
Department of interventional cardiology, Rajaie Heart Center, Tehran, Iran.
Tel:+98-2123922547 Fax: +98-2122055594
Email: re.kiani@gmail.com

medium-term results of routine early angiography strategy and ischemia guided angiography in our STEMI patients who underwent successful thrombolytic treatment in the acute phase of myocardial infarction.

Method

From November 2008 to August 2009, we enrolled 142 consecutive patients admitted to our center with the diagnosis of acute STEMI who were eligible for fibrinolytic treatment. All patients had received standard stereptokinase protocol, a 300 mg loading dose of aspirin and a loading dose of 300 mg clopidogrel in the first 12 hours of the event and had an uncomplicated course of hospitalization. Patients with any complications such as hemodynamic instability, recurrent chest pain or secondary ventricular tachyarrhythmias were excluded. The routine-invasive group (87 patients ,61.3%) underwent routine coronary angiography in less than 10 days after the event and the other group (55 patients ,38.7%) had an angiography 10 days or more after the cardiac event, mostly indicated by clinical or non-invasive evidence of myocardial ischemia. The choice of each strategy was completely at the discretion of the responsible physician.

Inclusion criteria

This study comprised patients eligible for fibrinolysis and aged over 18 years who presented with ST elevation MI by diagnostic electrocardiogram in the first 12 hours. [12]

Exclusion criteria

1- Primary percutaneous coronary interventions
2- Contraindication to fibrinolysis
3- A history of coronary artery bypass graft surgery [CABGs]
4- Dialysis-dependent renal insufficiency
5- Pregnancy
6- Cardiogenic shock at presentation [12]
7-Patients with an obvious indication for angiography such as recurrent ischemic pain or dynamic ST segment changes.

The subsequent treatment schedule was dictated by angiographic findings and included culprit lesion or multi-vessel PCI, emergent or elective CABGs, or medical therapy if revascularization was not a viable option. The patients then were followed by regular clinical visits for a possible change in medications or redirection in treatment strategy. The primary endpoint was a composite of death, nonfatal MI, CVA and major bleeding. The secondary endpoints were re-infarction and re-hospitalization rate in the follow-up period.

Statistical analysis

Demographic and clinical information was expressed as percentages in categorical variables and for continuous variables as median or mean ±SD. For a comparison of baseline characteristics, we used chi square, fisher's exact test for categorical variables and student's t test for interval data.

Table 1. Demographic and angiographic data in the whole study group

Age (year)		55±11
female		20(14%)
Diabetes		35(24.6%)
Dyslipidemia		64(45.1%)
Hypertension		53(37.3%)
Smoking		72(50.7%)
Infarct related artery	LAD	73(51.4%)
	LCX	18(12.7%)
	RCA	50(35.2%)
CAD severity	3 vessel disease	35(24.6%)
	2 vessel disease	50(35.2%)
	Single vessel disease	51(35.9)
Previous MI		6(4.2%)
LVEF%		39.6±9.4
Type of revascularization	PCI of culprit artery only	62(43.7%)
	PCI of culprit artery and other vessels	21(14.8%)
	CABGs	19(13.45)

CAD: coronary artery disease; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; MI: myocardial infarction; LVEF: left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABGs: coronary artery bypass graft surgery.

Mann Whitney U test was performed for interval data without normal distribution between study groups.

Pearson' chi square or Fisher's exact test were used for a comparison of clinical events between the two groups. Statistical analysis was performed using SPSS 15 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The demographic and clinical characteristics of

Table 2. Comparison of demographic, angiographic and revascularization characteristics between the two groups.

		Routine invasive group	Control group	P value
Age		56.6±11.4	53.1±11.2	0.070
Female		16(18.4%)	4(7.4%)	0.060
LVEF%		40.5±9	38.3±9.9	0.180
Diabetes		21(24.1%)	14(25.5%)	0.850
Dyslipidemia		44(50.6%)	20(36.4%)	0.090
Hypertension		38(43.7%)	15(27.3%)	0.049
Previous MI		3(3.4%)	3(5.5%)	0.560
Extent of CAD	Single-vessel disease	29(33.7%)	22(40%)	0.740
	2-vessel disease	30(34.9%)	20(36.4%)	
	3-vessel disease	24(27.9%)	11(20%)	
Revascularization strategy	PCI of culprit lesion only	37(44%)	25(48.1%)	0.620
	PCI of culprit and other vessels	11(13.1%)	10(19.2%)	
	CABGs	13(15.5%)	6(11.5%)	

LVEF: left ventricular ejection fraction; MI: myocardial infarction; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABGs: coronary artery bypass graft surgery.

142 patients under study, 121(85.2) males and 21 females (14.8%), are shown in Table 1. The median age of the patients was 54 (range: 27 to 86 years). Coronary risk factors of which smoking was the most common (50.7%) were present in 135 patients. Anterior, inferior and posterolaterral MI were found in 73 (51.4%), 50 (35.2%) and 18 (12.7%) patients respectively. The respective numbers of patients in the routine invasive and delayed ischemia-guided groups were 87 and 55. Table 2 shows a comparison of demographic and angiographic variables between the two groups. Only Hypertension was more common in the routine early angiography group by a marginal significance (P=0.049). Other variables are comparable in the two groups.

Table 3. Comparison of adverse outcomes between routine invasive group and control group

	Routine invasive group	Control group	P value
Death	2(2.3%)	3(5.5%)	0.320
CVA	2(2.3%)	0	0.504
Major bleeding	2(2.3%)	0	0.504
Re-infarction	1(1.1%)	6(10.9%)	0.014
Re-hospitalization	7(8.0%)	9(16.4%)	0.127
Peri-PCI MI	4(4.6%)	1(1.8%)	0.649
MACE	6(6.9%)	6(10.9%)	0.402

CVA: cerebrovascular accident; PCI: percutaneous coronary intervention; MI: myocardial infarction; MACE: major adverse cardiovascular events.

The average time interval from fibrinolytic initiation to angiography was 5 days in the routine invasive group and 23 days in the control group (P< 0.001). If the patient was a candidate for PCI, it was always performed at the time of angiography (time interval from fibrinolysis up to PCI was 4 days and 21 days in the routine invasive and control arms respectively, P<0.001). Stenting of the culprit artery was done in 62 patients (43.7%), multi-vessel stenting in 21 (14.8%), CABGs in 19 patients (13.4%) and medical therapy was recommended in 34 (23.9%). Stenting of the culprit artery was done in 60% of the routine invasive arm and 63% of the delayed invasive arm. The patients were followed for 263± 84 days.

Table 3 shows the outcome of patients during the follow-up period. MACE or composite of death, re-infarct, major bleeding and CVA in the follow up period was not significantly different (P= 0.504) in early invasive group (10.9%) compared to control group (6.9%). Also 30-day MACE was not significantly increased (P= 0.402) in the control group (6.9%) compared to early invasive group (12.7%). Likewise, the result of in-hospital MACE showed no significant difference between the 2 groups. (4.6% in the routine invasive group vs. 1.8% in the controls, P= 0.649)

In the routine invasive group, 2 patients died

in the follow-up due to cardiovascular problems (1 pump failure and 1 sudden death). While in the control group cardiac death occurred in 3 (2 pump failures and 1 re-infarction, P= 0.320).

The incidence of re-infarction in the follow up period was significantly higher in the control group (10.9% vs. 1.1%, P= 0.014) and most of these events occurred before angiography.

In regard to the rates of CVA and bleeding no significant difference was found between the 2 groups.

PCI was done in 60% of the early invasive group and 63% of the control group (P= 0.400). Peri-procedural infarction was defined as rise of creatinin kinase MB > 5 times the normal value during PCI which was not significantly different. (4.6% vs. 1.8% respectively, P= 0.649)

Re-hospitalization due to acute coronary syndrome occurred in 8.0% of the early invasive group while in the control group it was 16.4% (P=0.127).

Study endpoints have also been analyzed in more details in sub-groups of the early invasive arm (Table 4). There were no statistically significant differences between the rates of MACE, cardiac death, bleeding and re-infarction in patients who underwent PCI, surgical revascularization or medical treatment in the early invasive group. However, there was insufficient number of events in subgroups of medical treatment and CABGs which may limit the power of this analysis.

Table 4. comparison of outcomes in different groups in the early-invasive arm

	PCI	CABGs	Medical management
Death	2(3.4%)	0(0%)	0(0%)
CVA	1(1.7%)	1(6.3%)	0(0%)
Major bleeding	2(3.4%)	0(0%)	0(0%)
Minor bleeding	1(1.7%)	0(0%)	0(0%)
TVR	1(1.7%)	0(0%)	0(0%)
Re-infarction	5(8.5%)	0(0%)	0(0%)
MACE	10(16.9%)	1(6.3%)	0(0%)

CVA: cerebrovascular accident; PCI: percutaneous coronary intervention;CABGs: coronary artery bypass graft surgery;TVR: target vessel revascularization; MACE: major adverse cardiovascular events.

Discussion

Despite numerous studies, no consensus on the proper timing of angiography in thrombolysed STEMI patients has been reached so far. Also, it has remained controversial whether all such patients should undergo routine angiography or catheterization should be performed on the basis of clinical or noninvasive evidence of ischemia. Early trials concerning this matter, like TIMI-2 and SWIFT trials in the early 1990s showed no benefit from routine angiography after successful thrombolysis in STEMI patients but did demonstrate increased bleeding complication rates in the invasive arm.[1,2] However these trials were performed before the routine use of stents, clopidogrel and glycoprotein IIb/IIIa receptor antagonists. Subsequent studies in the stent era have shown a different result. Four randomized controlled trials on disputed matter were published between 2003 and 2005; GRACIA-1, SIAM-III, CAPITAL-AMI, and LPLS.[3-6] These studies showed significant reductions in primary endpoint of combined death, MI and recurrent ischemia and also a reduction in infarct size in the LPLS study. The results of the recently published study TRANSFER-AMI [13] was in complete agreement with these studies and showed a reduction in the combined primary end-point of death, repeat MI, heart failure, recurrent ischemia and shock by 41% in the invasive group as compared to the “wait and see group”. On the other hand the results of facilitated PCI (immediate transfer for PCI after successful thrombolysis) were not promising. Regarding this concept, 2 large studies, ASSENT-4 and FINESSE, showed higher incidence of death, re-infarction, CVA and bleeding complications in the invasive arm.[14,15]

In this study we extended the time definition of early invasive strategy to the in-hospital period which practically included all interventions performed in less than 10 days after the index event. This extension of early invasive period renders our study different from the previously mentioned studies,[3-6] where in most cases routine angiography was performed as early as 24-48 hours of the event. This difference may explain to some extent why most of the primary endpoints of the study were statistically equal in the 2 arms. These results may show the importance of referring for angiography as early as possible to achieve the best outcome from the intervention. Lack of randomization was another drawback of this study and certainly had a confounding effect on the results because there was a tendency to refer higher risk patients for angiography earlier than low risk patients and this bias may be responsible for a lack of significant decrease in the rate of adverse events with routine early invasive strategy. Also, another limitation of this study was the low

number of controls compared to routine invasive group which may have a negative impact on data analysis. This was partly due to the changing policy of our center which shifted toward routine referral of thrombolysed patients for angiography which made it difficult for us to enroll equal controls in the study. However, in our statistical analysis we did not find any trend toward the reduction of the primary endpoints of death, CVA, bleeding and MACE in the early invasive group. Only re-infarction showed a significant reduction in the routine invasive arm compared to the control arm. Whether this reduced rate of re-infarction could have an effect on lowering mortality or re-hospitalization, is a matter that needs to be resolved by longer follow-up periods.

Early referral for angiography after successful thrombolytic therapy has been associated with reduced rate of adverse cardiac events in many recent trials and seems to be superior to the classic approach of ischemia-guided invasive strategy. In this study we observed a significantly reduced re-infarction rate if intervention was performed in less than 10 days of index event. It is possible that decreased re-infarction will have a positive impact on survival and may reduce re-hospitalization and other complications in medium term. Larger studies are needed to clarify the benefits and pitfalls of this approach.

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