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The Relationship between Grade of Ischemia, Success of Reperfusion, and Type of Thrombolytic Regimen

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Background: This study was aimed to determine whether the grade of ischemia can predict the success of reperfusion in patients treated with thrombolytic therapy (TT) for ST elevation myocardial infarction (STEMI).

Material/Methods: We enrolled 229 consecutive patients with diagnosis of STEMI and receiving TT. Patients were divided into 2 groups – grade 2 ischemia (GI2) and grade 3 ischemia (GI3) – according to initial electrocardiogram (ECG). As TT, fibrin-specific (tissue plasminogen activator (t-PA)) or non-fibrin-specific (streptokinase (SKZ)) regimens were used. Successful reperfusion was defined as >50% resolution of the maximal ST segment on 90-min ECG. We tried to evaluate whether the grade of ischemia could predict the success of reperfusion and if there were any differences in terms of successful reperfusion between different thrombolytic regimens.

Results: The successful reperfusion rate was significantly higher in GI2 than GI3 (82.4% *vs.* 64.4% respectively, p=0.002). The success rate was lowest at anterior GI3 (55.8%). Although there was no significant difference between thrombolytic regimens in all groups (p=0.77), t-Pa was superior to SKZ in anterior GI3 (63,6% *vs.* 30%, p=0.061). In addition, in multivariate analysis, GI and infarct localization were found as independent predictors for successful reperfusion with TT (p=0.006 and p=0.042, respectively).

Conclusions: In the current study, we found that GI2 is an independent predictor for successful reperfusion in STEMI treated with TT. Fibrin specific regime should be preferred in anterior GI3.

MeSH Keywords: Ischemia • Myocardial Reperfusion • Thrombolytic Therapy

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Background

In the mid-1970s, acute myocardial infarction (AMI) was identified as being the result of a ruptured atherosclerotic plaque, causing thrombosis and occlusion of the coronary artery [1]. Randomized trials have indicated that primary percutaneous coronary intervention (PPCI) during the early hours of AMI offers certain advantages over TT [2–5]. The major limitation of primary angioplasty as "firstline" therapy on a community basis is restricted availability of 24-hour cardiac catheterization laboratories staffed with skilled cardiologists. Most hospitals do not have facilities for 24 hour coronary angioplasty, and the large majority of patients with AMI are admitting to a non-PCI capable hospital. TT is, however, the standard of care for patients with AMI, because of its widespread availability and its efficacy for reduction of mortality [6–9].

The ischemia grade system (GI) is an electrocardiographic classification of STEMI based on ST segment and QRS complex changes on baseline ECG [10]. This classification composes of three grades [10]. Grade1: Tall sharp T waves without ST segment elevation; GI2: ST segment elevation in >2 contiguous leads without terminal QRS deformation; and GI3: ST segment elevation with terminal QRS deformation in >2 contiguous leads. Previous studies have shown that patients with GI3 on the presenting ECG have a worse prognosis [11–14], larger infarct size [11,15–18], less benefit from TT [11,17] and less hibernation in the infarcted myocardium [19] than patients with GI2. The progression of necrosis develops much faster in GI3 than GI2 [20–22]. Thus, fibrin-specific regimens should be used in patients with GI3 if there is no possibility for PPCI. However, there is no study investigating relation between GI and the effect of fibrin-specific regimens.

Our study is unique in the literature that compares fibrin and non-fibrin-specific drugs according to GI. The purpose of the study was to evaluate whether the success of reperfusion can be predicted by GI and to consider the effects of TT according to types of TT, GI, and infarct localization.

Material and Methods

In the current study, we enrolled 229 consecutive patients admitted with the diagnosis of AMI and who received TT. Patients admitted within 12 hours after the onset of symptoms and chest pain lasting at least 20 minutes with ST-segment elevation of at least 0.2 mV in 2 or more adjacent leads on admission ECG were included. The exclusion criteria were isolated posterior AMI, left bundle branch block, Killip Class 2 and 3 at admission, presence of any contraindication for TT, and prior AMI.

All patients received either t-PA as fibrin-specific or SKZ as non-fibrin-specific regimen for treatment of STEMI. t-PA was administered with a loading dose of 15 mg, then a maintenance dose of 50 mg (0.75 mg/kg not exceeding 50 mg) over 30 minutes and 35 mg (0.50 mg/kg not exceeding 35 mg) over the next 60 minutes. SKZ was administered in a dose of 1.5 million IU over 1 hour.

Patients were dived into GI2 or GI3 groups according to the grade of ischemia, and as anterior or non-anterior according to the infarct location on baseline ECG and their combinations as GI2 anterior, GI2 non-anterior, GI3 anterior, and GI3 non-anterior. Rates of successful reperfusion in the groups and their relations with GI and infarct localization were evaluated.

ST segment resolutions were evaluated at 90 minutes of TT administration. If there was 50% or more ST segment resolution at maximally elevated ST segment, it was accepted as successful reperfusion. If there was less than 50% ST segment resolution, it was accepted as failed reperfusion and the patient was taken into the cardiac catheterization laboratory for rescue percutaneous coronary intervention.

ECG analysis

The baseline ECGs were performed before TT were analyzed and classified as GI2 or GI3. In ECGs with GI3, QRS configuration was deformed – either lack of an S wave in >2 leads that have a terminal S wave (usually V1 to V3), or J point amplitude >50% of the R wave amplitude in 2 of all other leads [10]. ECGs not meeting GI3 criteria was defined as GI2 (Figure 1).

Statistical analysis

Baseline characteristics of the patients with GI2 and GI3 were compared by the chi-square test for categorical variables. The t test was used for continuous variables. Backwards stepwise logistic regression analysis was performed to identify the

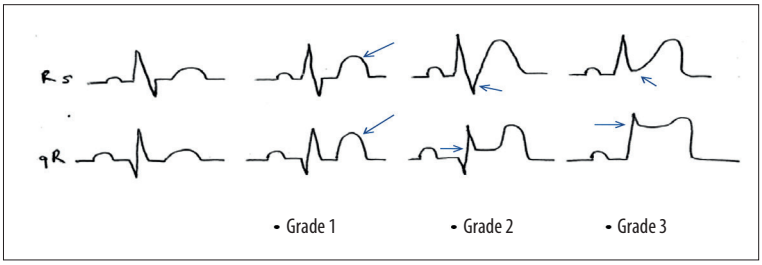

Figure 1. Example of GI1, GI2 and GI3 on electrocardiogram. GI: grade of ischemia.

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Table 1. Baseline characteristics of the patients in terms of GI.

	Grade 2 (n=125)	Grade 3 (n=104)	P value
Male, n (%)	113 (90.4)	89 (85.5)	0.26
HT, n (%)	40 (32.0)	33 (31.7)	0.54
DM, n (%)	22 (17.6)	23 (22.1)	0.36
Hyperlipidemia, n (%)	12 (9.6)	11 (10.5)	0.8
Smoking, n (%)	91 (72.8)	64 (61.5)	0.07
CAD, n (%)	12 (9.6)	15 (14.4)	0.26
Family history, n (%)	48 (38.4)	35 (33.6)	0.54
Preconditioning*, n (%)	69 (69.6)	51 (52.5)	0.27
Onset of symptoms (minutes)	211±45	245±33	0.07

GI – grade of ischemia; HT – hypertension; DM – diabetes mellitus; CAD – coronary artery disease; * having stable or unstable angina pectoris before myocardial infarction.

Table 2. Relationship between GI and the rate of successful reperfusion.

	Grade 2 n=125	Grade 3 n=104	P value
Rate of successful reperfusion (%)	103 (82.4)	67 (64.4)	0.002

GI – grade of ischemia.

Table 3. The relationship between localization grade of ischemia and thrombolytic treatment.

Localization	GI	SKZ n=89	t-PA n=140	P value
Anterior, reperfusion rate * (%)	Grade 2	12/16 (75.0)	36/47 (76.5)	0.89
	Grade 3	3/10 (30.0)	21/33 (63.6)	0.061
Non-anterior reperfusion rate* (%)	Grade2	36/41 (87.8)	19/21 (90.4)	0.75
	Grade3	16/22 (72.7)	27/39 (69.2)	0.77

GI – grade of ischemia; SKZ – streptokinase; t-PA – tissue plasminogen activator; * patients with succesful reperfusion with TT/all patients with TT in each groups.

independent predictors of reperfusion. Variables included in the regression analysis were: GI, localization, age, kind of TT, preconditioning, and time of onset of symptoms.

Results

Nearly 89.1% of 229 patients with STEMI were admitted within the first 4 hours of symptom onset, and 9.2% of patients were admitted at between 4 to 6 hours of symptom onset. The remaining 1.7% of patients were admitted at more than 6 hours of symptom onset. There was no statistically significant relationship between GI and time of onset of symptoms.

Nearly 55% of patients presented with GI2 and 45% with GI3. There was no relationship between the GI and gender, hypertension, hyperlipidemia, diabetes, family history, or previous coronary artery disease. Smokers had more GI3 on ECG at presentation (Table 1). There was no relationship between the GI and infarct localization. Rate of successful reperfusion with TT was found to be significantly higher in patients with GI2 than in patients with GI3 (82.4% *vs.* 64.4%, respectively, p=0.002) (Table 2). Therefore, GI3 was observed as having negative predictive value for reperfusion (p=0.042) (Table 3). According to the infarct localization, higher rates of successful reperfusion with non-anterior than anterior localization were observed (anterior 67.9% & non-anterior 79.8%, p=0.043). Successful reperfusion rate was lowest in patients with anterior GI3 (55.8%).

SKZ was administered to 38.9% of patients and t-PA was the choice of TT in 61.1% of patients. Patients with GI3 who

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Table 4. Multivariate analysis of infarct localization, GI, preconditioning, onset of symptoms, kind of TT and age for successful reperfusion.

	P value	Odd ratio
Localization	0.006	2.737
GI	0.042	0.485
Preconditioning	0.058	1.924
Onset of symptoms	0.06	0.379
Kind of TT	0.812	1.095
Age	0.15	0.976

GI – grade of ischemia; TT – thrombolytic treatment.

received the t-PA regimen significantly more than GI2 patients (p=0.022). However, there was no difference between t-PA and SKZ in successful reperfusion (t-PA 75.2% and SKZ 73.5%, p=0.77).

SKZ achieved successful reperfusion in 84.2% of GI2 patients and t-PA achieved success in 80.8% of GI2 patients (p=0.2). While 56.2% of GI3 patients had successful reperfusion by SKZ, 66.6% of GI3 patients had successful reperfusion by t-PA (p=0.5). There was no significant difference between SKZ and t-PA in terms of infarct localization according to the success of reperfusion (57.6% by SKZ and 71.2% by t-PA in anterior [p=0.19] and 82.5% by SKZ & 76.6% by t-PA in non-anterior [p=0.41]).

Patients with anterior GI3 gained more benefit from t-PA administration. The rates of successful reperfusion were significantly higher for patients treated with t-PA than patients treated with SKZ in the GI3 anterior group (t-PA 63.6% and SKZ 30%, p=0.061) (Table 3).

It was observed that the ejection fraction of patients with GI3 was significantly lower than patients with GI2 (GI2 43±7% and GI3 41±6.2%, p=0.039).

The relationship between successful reperfusion and gender, hypertension, hyperlipidemia, smoking, diabetes, family history, and previous coronary artery disease was not statistically significant. Independent predictors of reperfusion by multivariate analysis were GI (p=0.006), infarct localization (p=0.042), preconditioning (p=0.058), and symptom onset (p=0.06) (Table 4).

Discussion

It is now widely accepted that for patients with STEMI, PPCI is the preferred reperfusion strategy if it can be delivered in a timely fashion. Although, thrombolytic regimens may be perceived as an old-fashioned treatment of AMI, they are still used widely. In fact, most STEMI patients present to hospitals without PPCI capability and require transfer to PCI-capable hospitals. Timely transfer has been shown to occur in a minority of patients [23]. TT is the first choice for treatment of AMI in clinical practice. However, after adding pharmaco-invasive therapy for AMI to current guidelines, TT has begun to be discussed again.

Non-fibrin-specific regimens are cheaper than fibrin-specific regimens and their efficacy has been established. Thus, non-fibrin-specific regimens like SKZ are used more than other regimens. However, non-fibrin-specific regimens might be inadequate for some patients, especially those in high-risk groups. The purpose of our study was to identify patients at high risk for failed reperfusion while non-fibrin-specific regimens were administered for treatment of AMI.

In our study, there was no significant difference in baseline characteristics, except for smoking, between GI3 and GI2. Current smokers presented with more GI3 on admission ECG. The incidence of hypertension, dyslipidemia, diabetes mellitus, positive family history, previous coronary artery disease, and prior angina did not differ between the groups. In contrast to previous studies [11–13,24], more patients with GI3 were current smokers. In addition, the DANAMI2 sub-study confirmed these findings [24]. The sub-study from the GUSTO1 trial indicated that AMI develops in smokers at earlier periods of coronary disease without any significant coronary lesion and thus the impact of TT is better in smokers than non-smokers [25]. These findings may clarify why smokers have more GI3 on admission ECG. Probably, during AMI, smokers do not have collaterals protecting the myocardium.

The current study shows that patients with GI3 and anterior MI localization had less benefit from TT. When we evaluated the rate of successful reperfusion, no significant difference was observed between t-PA and SKZ in GI3 patients. Although t-PA reperfused infarct-related arteries faster than non-fibrin-specific regimens, surprisingly, it was not more successful than SKZ in our study except in anterior GI3 patients. Also, DANAMI2 and GUSTO 2b sub-studies demonstrated that there was no difference in mortality between fibrin-specific regimens and primary PCI in GI3 patients [24,26].

Birnbaum et al. assessed final infarct size (using predischarge Selvester score) by 3 electrocardiographic variables in 267 patients with first anterior wall AMI undergoing TT or not. They found that the presence of distortion of the terminal portion of QRS (GI3) on admission ECG were associated with final infarct size. Moreover, although TT reduced infarct size (by Selvester

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score) in GI2 anterior patients, TT did not reduce infarct size in GI3 anterior patients [16].

In the retrospective analysis of the GUSTO2b angioplasty substudy, it was found that GI3 on admission was associated with higher in-hospital mortality and reinfarction and a trend towards a higher mortality rate within 30 days. The mortality among the GI3 patients was comparable between those treated with pPCI and TT. Similarly, there was no difference in mortality between PPCI and TT among the GI2 patients [26].

The DANAMI2 sub-group study showed that the GI3 on admission ECG in patients with AMI is an independent predictor of mortality, regardless of kind of reperfusion treatment. In addition, patients with GI3 achieved the most benefit from PPCI if they were treated within 3 hours of symptoms onset [24].

In our study, we found that GI3 and anterior localization are the strongest predictors of failed thrombolysis. Therefore, our study supported findings of previous studies showing that GI3 is associated with a worse prognosis, larger infarct size, and less benefit from TT [11–18]. So, PPCI should be the first-choice therapy for patients with GI3 and anterior localization. However, if there is no possibility of PPCI or transfer to a PCI-capable hospital, fibrin-specific thrombolytics would be preferred. The patients with both GI3 and anterior localization have the lowest chance for reperfusion with thrombolytic regimens; 55.8% of these patients were successfully reperfused with TT. Moreover, non-fibrin-specific regimens are the worst choice for treatment of GI3 anterior patients. While SKZ achieved successful reperfusion in only 30% of these patients, t-PA achieved successful reperfusion in 63.6%. Thus, this group had the lowest benefit from TT.

Conclusions

Treatment of AMI should be individualized and prompt identification of high-risk criteria at admission has crucial importance. In the current study, we found that GI2 is an independent predictor for successful reperfusion in STEMI treated with TT. Patients with anterior and GI3 on presenting ECG are accepted as having high risk and fibrin-specific thrombolytics should be preferred for treatment.

References:

1. Davies MJ, Woolf N, Robertson WB: Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. Br Heart J, 1976; 38: 659–64
2. Grines CL,Browne KF,Marco J et al: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction.The Primary Angioplasty in Myocardial Infarction Study Group. N Engl JMed, 1993; 328: 673–79
3. Zijlstra F, deBoer MJ, Hoorntje JC et al: A comparison of immediate coronary angioplasty with intra venous streptokinase in acutemyocardial infarction. N Engl J Med, 1993; 328: 680–84
4. Gibbons RJ, Holmes DR, Reeder GS et al: Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med, 1993; 328: 685–91
5. Keeley EC, Boura J, Grines CL: Primary angioplasty versus intra venous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003; 361: 13–20
6. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med, 1993; 329: 673–82
7. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI): Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Lancet, 1987; 2: 871–74
8. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico: GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet, 1990; 336: 65–71
9. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both,or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. Lancet, 1988; 2: 349–60
10. Billgren T, Birnbaum Y, Sgarbossa EB et al: Refinement and inter observer agreement for the electrocardiographic Sclarovsky-Birnbaum Ischemia Grading System. J Electrocardiol, 2004; 37: 149–56
11. Birnbaum Y, Kloner R, Sclarovsky S et al: Distortion of the terminal portion of The QRS on the admission electrocardiogram in acute myocardial infarction and correlation with infarctsize and long term prognosis (Thrombolysis In Myocardial Infarction 4 Trial). Am J Cardiol, 1996; 78: 396–403
12. Birnbaum Y, Herz I, Sclarovsky S et al: Prognostic significance of the Admission electrocardiogram in acute myocardial infarction. J Am Coll Cardiol, 1996; 27: 1128–32
13. Birnbaum Y, Goodman S, Barr A et al: Comparison of primary coronary angioplasty versus thrombolysis in patients with ST-segment elevation acute myocardial infarction and gradeII and gradeIII myocardial ischemia on the enrollment electrocardiogram. Am J Cardiol, 2001; 88: 842–47
14. Lee CW, Hong M-K, Yang H-S et al: Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. Am J Cardiol, 2001; 88: 210–13
15. Birnbaum Y, Criger DA, Wagner GS et al: Grade III ischemia on presentation with acute myocardial infarction predicts rapid progression of necrosis and less myocardial salvage with thrombolysis [abstract]. J Am Coll Cardiol, 2001; 37(Suppl.A): 115A
16. Birnbaum Y, Criger DA, Strasberg B et al: Prediction of the extent and severity of left ventricular dysfunction in anterior acute myocardial infarction by the admission electrocardiogram. Am Heart J, 2001; 141: 915–24
17. Tamura A, Nagase K, Watanabe T et al: Relationship between terminal QRS distortion on the admission electrocardiogram and the time course of left ventricular wall motion in anterior wall acute myocardial infarction. Jpn Circ J, 2001; 65: 63–66
18. Yang HS, Lee CW, Hong MK et al: Terminal QRS complex distortion on the admission electrocardiogram in anterior acute myocardial infarction and association with residual flow and infarct size after primary angioplasty. Korean J Intern Med, 2005; 20: 21–25
19. Sucu MM, Karadede A, Aydinalp O et al: The relationship between terminal QRS complex distortion and early low dose dobutamine stress echocardiography in acute anterior myocardial infarction. Jpn Heart J, 2004; 45: 373–86
20. Birnbaum Y, Drew BJ: The electrocardiogram in ST elevation acute myocardial infarction: correlation with coronary anatomy and prognosis. Postgrad Med J, 2003; 79: 490–504
21. Birnbaum Y, Mahaffey KW, Criger DA et al: GradeIII ischemia on presentation with acute myocardial infarction predicts rapid progression of necrosis and less myocardial salvage with thrombolysis. Cardiology, 2002; 97: 166–74

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22. Billgren T, Maynard C, Christian TF et al: Grade3 ischemia on the admission electrocardiogram predicts rapid progression of necrosis over time and less myocardial salvage by primary angioplasty. J Electrocardiol, 2005; 38: 187–94
23. Nallamothu BK, Bates ER, Herrin J et al: Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)–3/4 analysis. Circulation, 2005; 111: 761–67
24. Sejersten M, Birnbaum Y, Ripa RS et al: Influences of electrocardiographic ischaemia grades and symptom duration on outcomes in patients with thrombolysis versus primary percutaneous coronary intervention: results from the DANAMI-2 trial. Heart, 2006; 92(11): 1577–82)
25. Barbash GI, Reiner J, White HD et al: Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytictherapy for acute myocardial infarction: mechanism of the"smoker'sparadox"from the GUSTO-Itrial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol, 1995; 26: 1222–29
26. Birnbaum Y, Goodman S, Barr A et al: Comparison of Primary Coronary Angioplasty Versus Thrombolysis in Patients With ST-Segment Elevation Acute Myocardial Infarction and GradeII And GradeIII Myocardial Ischemiaon the Enrollment Electrocardiogram. Am J Cardiol, 2001; 88: 842–47

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