Determinants of improvement in epicardial flow and myocardial perfusion for ST elevation myocardial infarction

Insights from TIMI 14 and InTIME-II

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Background When evaluating new reperfusion regimens for ST elevation MI, it is important to adjust for factors that influence the likelihood of achieving normal epicardial flow and complete ST resolution.

Methods and Results A total of 610 patients from TIMI 14 contributed to the angiographic analyses. The electrocardiographic analyses were based on 544 patients from TIMI 14 and 763 patients from InTIME-II. For each hour from onset of symptoms to initiation of pharmacological reperfusion, the odds of achieving TIMI 3 flow at 90 min or complete ST resolution at 60–90 min decreased significantly (P=0.03). Anterior location of infarction was associated with a reduced in the odds of achieving TIMI 3 flow or complete ST resolution. The use of abciximab as part of the reperfusion regimen significantly increased the odds of TIMI 3 flow (P=0.01) and ST resolution (P<0.001). The fibrinolytic administered (alteplase, reteplase, lanoteplase) did not influence the odds of TIMI 3 flow or ST resolution after adjusting for time to treatment, infarct location, and use of abciximab.

Conclusions The influence of time from symptoms on epicardial flow and STRES reinforces the need for increased efforts to reduce treatment delays in patients with ST elevation MI. The significant benefits of abciximab with respect to facilitation of epicardial and myocardial reperfusion are evident even after adjusting for time to treatment and infarct location. To adjust for determinants of success of reperfusion regimens, phase II trials evaluating new drug combinations should consider using a randomization scheme that stratifies patients based on infarct location and time from symptoms.


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Introduction

A shorter interval from the onset of ischaemic symptoms to the initiation of treatment with a fibrinolytic agent in patients with acute ST-elevation myocardial infarction results in a higher rate of infarct-related artery patency, smaller infarct size, and lower mortality[1–3]. Therefore,
the major goal of pharmacological reperfusion has been the rapid restoration of normal (Thrombolysis in Myocardial Infarction (TIMI) Grade 3) flow in the infarct-related artery. However, even among patients with TIMI 3 flow, those with inadequate reperfusion at the myocardial level have a poor prognosis. ST-segment resolution, as measured using the standard 12-lead electrocardiogram (ECG) is a simple method of assessing myocardial reperfusion, and as such is a powerful and independent predictor of mortality following ST-elevation myocardial infarction.

Since contemporary clinical investigations involve manipulation of various components of pharmacological reperfusion regimens it is useful to show the importance of factors influencing the likelihood of establishing normal epicardial flow and complete ST resolution. Some of these factors are distinct from the pharmacological reperfusion administered, such as the time from onset of symptoms to initiation of treatment and infarct artery location, while other factors include features of the pharmacological reperfusion regimen itself, such as the fibrinolytic agent administered and whether an intravenous glycoprotein IIb/IIIa inhibitor was administered. To evaluate the relative influence of the factors noted above when assessing the success of reperfusion regimens we interrogated the databases from the TIMI 14 and InTIME-II trials.

Methods

The enrollment criteria for TIMI 14 were as described previously. All patients received aspirin and adjunctive heparin and one of several different reperfusion regimens. For the purposes of the present analysis, the information from patients receiving either full dose alteplase or reteplase alone, alteplase 50 mg + abciximab, reteplase 5+5 U+abciximab, or reteplase 10+5 U+abciximab were pooled into a common database. InTIME-II, patients with ST-elevation myocardial infarction presenting within 6 h of symptom onset were randomly assigned to treatment with full-dose lanoteplase or alteplase. Institutional committees on human research approved both trials, and all patients provided written, informed consent.

Angiographic analyses

Angiographic analyses were performed exclusively on data from TIMI 14, since the InTIME-II protocol did not include a mandated angiogram. The primary angiographic efficacy end-point was the achievement of TIMI grade 3 flow at 90 min in the infarct artery. All angiograms were evaluated at the Angiographic Core Laboratory, which was blinded to treatment assignment, using previously established procedures for determination of TIMI flow grade. Patients were considered angiographically evaluable if they received the specified reperfusion regimen and had an evaluable 90 minute angiogram.

Electrocardiographic analyses

Data from both TIMI 14 and InTIME-II were used for the electrocardiographic analyses. For TIMI 14, all patients with evaluable ECGs from baseline and 90 min were included. For InTIME-II, ST resolution data were collected at either 60 or 90 min from selected sites as part of a pre-specified substudy. Patients in InTIME-II who received a glycoprotein IIb/IIIa antagonist in conjunction with rescue angioplasty were excluded from the analysis. Time to treatment was defined as the interval from symptom onset to the initiation of fibrinolytic therapy. The magnitude of ST deviation on the baseline and 60–90 min ECGs was determined using previously described methods, and the percent ST resolution from baseline to 60–90 min was calculated. ST resolution was categorized for each patient as complete (≥70%), partial (30–<70%), or none (<30%).

Statistical considerations

Logistic regression analyses assessing the likelihood of achieving TIMI 3 flow at 90 min were performed with the following variables forced into the model: time from the onset of symptoms to treatment, location of the infarct artery, whether the reperfusion regimen contained abciximab, and a term indicating whether alteplase or reteplase was used. The same logistic regression models were used to assess the likelihood of achieving complete (≥70%) ST resolution at 60–90 min with the exception that the term for fibrinolytic agent was expanded to include alteplase, reteplase, or lanoteplase.

Results

Angiographic analyses

A total of 610 patients from TIMI 14 contributed to the angiographic analyses. The likelihood of developing TIMI 3 flow at 90 min was significantly reduced as each hour elapsed from the onset of symptoms until administration of the reperfusion regimen (OR 0·93 per hour; 95% CI 0·88, 0·99; P=0·03) and also tended to be lower if the LAD was the infarct related artery (OR 0·73; 95% CI 0·51, 1·04; P=0·08) (Fig. 1). There was no significant difference in the likelihood of achieving TIMI 3 flow based on whether the thrombolytic was alteplase or reteplase (OR 1·24; 95% CI 0·86, 1·80; P=0·25). Use of abciximab in the reperfusion regimen was associated with a statistically significant 57% increase in the likelihood of achieving TIMI 3 flow (OR 1·57; 95% CI 1·09,
A term testing for the interaction between the use of abciximab and the specific thrombolytic used with respect to achieving TIMI 3 flow was not significant. The regression coefficients for the significant independent predictors were used to expand the logit function from the multivariate analysis for estimating the predicted probability of achieving TIMI 3 flow at 90 min over time. These estimates were stratified by infarct-related artery and whether abciximab was used in the reperfusion regimen as depicted in Fig. 2. While the probability of TIMI 3 flow decreased over time for all groups, regimens containing abciximab had higher predicted rates of TIMI 3 flow at all time points.

**Electrocardiographic analyses**

The electrocardiographic analyses were based on 544 patients from TIMI 14 and 763 patients from InTIME-II. For each additional hour from symptom onset to initiation of pharmacological reperfusion, the odds of achieving early, complete ST resolution decreased by 6% (OR 0.94; 95% CI 0.89–0.99; P=0.03) (Fig. 1). An anterior infarction location was associated with a significantly lower probability of achieving complete ST resolution than anterior infarction (OR 0.36; 95% CI 0.28–0.45; P<0.001) (Fig. 1). The use of abciximab as part of the reperfusion therapy significantly increased the odds of achieving complete ST resolution compared with fibrinolytic therapy alone (OR 2.05; 95% CI 1.51–2.77; P<0.001) (Fig. 1). There were no differences observed between the three fibrinolytic agents with respect to the odds of achieving complete ST resolution (reteplase vs alteplase: OR 1.06; 95% CI 0.74–1.53; P=0.7; lanoteplase vs alteplase: OR 0.97; 95% CI 0.74–1.28; P=0.8).

The regression coefficients from the logistic regression model were used to expand the multivariate model statements for estimating the predicted probability of achieving complete ST resolution over time. Figure 3 presents these estimates stratified by the use of abciximab as a component of the reperfusion regimen as well as by infarct location. The estimated probability of achieving complete ST resolution decreased over time for all groups. However, regimens containing abciximab had higher predicted rates of complete ST resolution at all time points among both anterior and non-anterior infarcts.

**Discussion**

It is of particular interest that use of abciximab significantly increased the probability of achieving TIMI 3 flow at 90 min even after adjusting for time to treatment and infarct location. As shown in Fig. 2, the benefit of abciximab was evident at all time points after the onset of symptoms both for LAD and non-LAD infarct locations. Thus, our model suggests not only that abciximab facilitated thrombolysis in the epicardial infarct artery in situations where reperfusion may be more
readily achieved (e.g. early treatment of non-LAD infarct arteries), but it also facilitated thrombolysis in more difficult situations such as an occluded LAD treated relatively late after the onset of symptoms.

Studies using myocardial contrast echocardiography revealed that myocardial perfusion may be impaired even following restoration of TIMI 3 flow (microvascular ‘no reflow’ phenomenon)\(^{18–20}\). The achievement of complete ST resolution generally indicates the presence of adequate flow within both the epicardial artery and the microvasculature\(^{[5]}\). Thus, ST resolution provides an integrated measure of these biological processes, and therefore adds to the information provided by the TIMI flow grade.

Our finding that earlier treatment with pharmacological reperfusion is associated with a higher rate of complete ST resolution suggests that the benefit of earlier treatment is probably due to improvement in both epicardial and myocardial reperfusion. Our analysis also serves to clarify other factors that influence the likelihood of achieving early, complete ST resolution. Fewer patients with anterior infarction achieved complete ST
resolution compared with patients with non-anterior infarction. This may relate to the larger size of anterior infarcts, with a correspondingly larger degree of microvascular injury. Alternatively, ST resolution may be a less sensitive marker of myocardial reperfusion in anterior infarction because of a greater degree of normal J-point elevation in the anterior leads[5]. The beneficial effects of abciximab on myocardial perfusion, as reflected in ST resolution, persisted after adjusting for infarct location and time to treatment. It is likely that by inhibiting platelet activation and aggregation, abciximab reduces the occurrence of platelet microembolization and subsequent microvascular plugging and dysfunction[10,21]. Use of abciximab doubled the odds of achieving early complete ST resolution, a finding likely to favorably impact on mortality after ST elevation myocardial infarction[7,17].

Although the confidence intervals are wide, in part due to the greater representation of alteplase-treated vs reteplase-treated patients in the combined database, the multivariate analysis of the angiographic data from TIMI 14 suggests there was no significant difference in the probability of TIMI 3 flow at 90 min with alteplase or reteplase after adjusting for time to treatment and infarct location. Also the likelihood of achieving complete ST resolution in the TIMI 14/InTIME-II analyses was similar for alteplase, reteplase, and lanoteplase. This finding suggests that the mode of administration of the fibrinolytic agent (bolus plus infusion, double bolus, single bolus) is of lesser importance in achieving complete ST resolution than factors such as time to treatment, infarct location, and the use of abciximab.

Clinical implications

Since phase 2 dose ranging trials of reperfusion regimens are by nature exploratory and individual dose panels may have a relatively small number of patients, an imbalance in critical determinants of factors that influence the success of fibrinolysis and the extent of ST resolution may lead to inaccurate estimates of the relative benefits of various reperfusion regimens. To circumvent such difficulties a randomization scheme that stratifies patients based on infarct location and time should be considered.

Earlier treatment with pharmacological reperfusion in patients with ST-elevation myocardial infarction results in a higher rate of complete ST resolution, an indicator of reperfusion at the myocardial level. Given the known relation between the achievement of complete ST resolution and improved cardiovascular outcomes, more complete microvascular reperfusion probably explains part of the benefit of early reperfusion therapy. This finding reinforces the need for increased efforts to reduce treatment delays in patients with ST elevation MI.

The findings reported herein also extend our prior observations regarding abciximab in several ways. The benefit of abciximab in facilitating fibrinolysis appears to be similar with alteplase and reteplase, supporting the notion that there is an independent effect of abciximab on the thrombus in the infarct artery. The significant benefits of abciximab with respect to facilitation of fibrinolysis in the epicardial infarct artery and improvement in myocardial perfusion are evident even after adjusting for time to treatment and infarct location. The clinical impact of these findings with respect to death and cardiac ischemic events requires further investigation in large scale randomized trials.

References


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