Intracoronary Administration of Abciximab in ST-Elevation Myocardial Infarction

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Primary percutaneous coronary intervention (PCI) is now the preferred method of treating patients with ST-elevation myocardial infarction (STEMI). Despite restoration of epicardial flow, microvascular obstruction may persist after primary PCI as a result of both atheromatous and thrombotic embolization, neutrophil plugging, edema, and vasospasm.\(^1\)\(^-\)\(^3\) Therefore, studies such as the one by Thiele et al\(^4\) in this issue of Circulation that focus on the prevention and treatment of microvascular dysfunction are informative with respect to the means to improve the primary PCI strategy.

There have been efforts to identify mechanical and pharmacological strategies to improve myocardial perfusion after primary PCI. Compared with the systemic administration of intravenous pharmacotherapies, highly localized administration of intracoronary pharmacotherapy may be associated with a several-hundred-fold increase in the local concentration of an agent in the epicardial artery and microcirculation. A number of pharmacotherapies, including adenosine,\(^5,6\) calcium channel blockers,\(^7\) \(\alpha\)-blockers,\(^8\) \(\beta\)-receptor activators,\(^9\) other vasodilators, antithrombotics,\(^10,11\) and antiplatelet agents,\(^12\)\(^-\)\(^14\) have been used to treat microvascular dysfunction.

There are tens of thousands of glycoprotein IIb/IIIa (GPIIb/IIIa) receptors on the platelet surface.\(^15\) Platelet receptor occupancy studies have demonstrated that if there are fewer GPIIb/IIIa receptors free and available for cross-linking with fibrinogen, then myocardial perfusion is improved.\(^16\) To estimate the number of GPIIb/IIIa receptors available for cross-linking, the absolute platelet count has been multiplied by the percent of receptors available to cross link to calculate an index of the absolute number of GPIIb/IIIa receptors available. The absolute number of GPIIb/IIIa receptors available for cross-linking is reduced among patients with successfull restoration of myocardial perfusion and ST-segment resolution in an STEMI population.\(^16\) Thus, the hypothesized mechanistic basis for intracoronary administration of GPIIb/IIIa inhibitors is that high local concentrations of the drug would lead to fewer GPIIb/IIIa receptors being available for cross-linking with fibrinogen in the coronary microcirculation. This greater blockade of GPIIb/IIIa receptors would in turn reduce the incidence of microcirculatory thrombosis, improve myocardial perfusion, and ultimately improve clinical outcomes.

In a nonrandomized study, Wohrle et al\(^12\) evaluated the efficacy of intracoronary abciximab among 403 patients who received intracoronary \((n=294)\) and intravenous \((n=109)\) abciximab (20-mg bolus followed by 10-mg infusion for 12 hours). Thirty-day death, MI, and urgent revascularization were significantly reduced in the intracoronary group compared with the intravenous group \((10.2\% \text{ versus } 20.2\%; P<0.008)\). The benefit was more evident among patients with Thrombolysis in Myocardial Infarction flow grade 0/1 before PCI \((11.8\% \text{ versus } 27.5\%; P<0.02)\). Likewise, intracoronary administration of small-molecule platelet GPIIb/IIIa inhibitors such as a double bolus of intracoronary eptifibatide\(^14\) and intracoronary tirofiban\(^17,18\) has been associated with improved outcomes in mechanistic studies.

In addition to the antitherapeutic agents, the efficacy of intracoronary fibrinolytic therapy after PCI also been evaluated. Sezer et al\(^19\) randomized 41 patients to undergo primary PCI with \((250\text{ kU over 3 minutes})\) or without the administration intracoronary streptokinase at the completion of PCI. Two days after the procedure, the intracoronary streptokinase group had significantly better coronary flow reserve, microvascular resistance, collateral flow index, mean coronary wedge pressure, systolic wedge pressure, and diastolic deceleration time compared with the control group. Intracoronary tenecteplase has likewise been used to improve no-reflow after high-risk PCI in acute coronary syndromes.\(^11\)

In this edition of Circulation, Thiele et al\(^4\) report that intracoronary abciximab is associated with greater improvements in early measures of infarct size in the setting of STEMI compared with intravenous pharmacotherapy. These findings add to a growing body of moderate-sized, single-center, mechanistic studies supporting the superiority of intracoronary GPIIb/IIIa inhibition over the intravenous dosing of these agents in the STEMI setting.

In the present study, the investigators randomized 154 STEMI patients to either an intracoronary or an intravenous bolus of abciximab \((0.25 \text{ mg/kg body weight})\), which was then followed by a 12-hour intravenous maintenance infusion. Only 83% and 77% of patients in the intracoronary and intravenous groups, respectively, received the study medication before PCI. All patients received a 600-mg loading dose of clopidogrel during PCI \((<10\% \text{ received the drug }>1 \text{ hour before the procedure})\).

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The primary end point, the median infarct size at +2 days, was significantly reduced among patients treated with intracoronary abciximab (15.1% versus 23.4%; \( P=0.01 \)), as was the extent of microvascular obstruction (\( P=0.01 \)), early ST-segment resolution (77.8% versus 70.0%; \( P=0.006 \)), and creatine kinase area under the curve (\( P=0.007 \)). Intracoronary therapy was associated with a trend toward improved myocardial perfusion grades (\( P=0.12 \)) and fewer major adverse cardiac events (death, MI, urgent revascularization, and heart failure; 5.2% versus 15.6%; \( P=0.06 \); relative risk, 0.33; 95% CI, 0.09 to 1.05). It is interesting to note that these improvements in infarct size and myocardial perfusion occurred despite there being no difference in the epicardial TIMI-flow grade after PCI. The greatest benefits in infarct size were noted among patients with an anterior MI, those with impaired myocardial perfusion after the procedure, and those whose symptom-to-balloon time was >4 hours when the clot may have been more organized and resistant to systemic therapy.

Intracoronary abciximab administration appeared safe in that there were no adverse events during its administration and no increased risk of bleeding. The intracoronary strategy was not associated with any significant delay in revascularization compared with the intravenous route.

Future Studies

Certain issues have not been addressed in the study by Thiele et al, and future studies should address the following issues. Limitations of the study include the fact that the drug was administered in an open-label fashion by the investigators, although the core laboratory analyses were blinded. Despite the fact that intracoronary therapy was associated with an improvement in magnetic resonance imaging infarct size, there was no difference in ejection fraction at the 2-day time point. Whether these improvements in microvascular obstruction and infarct size would have persisted at a later time point, nor is the impact on late left ventricular function known. The article does not explicitly state whether any significant benefit was observed among patients with a nonanterior MI.

It is not reported how often patients underwent primary stent placement without predilatation. If intracoronary pharmacotherapy reduced the pre-PCI thrombus burden significantly, it may have facilitated a direct stenting approach. Direct stenting has been associated with improved perfusion and a reduced risk of death and heart failure,\(^1^9\) and it could be hypothesized that a greater use of primary stenting accounted in part for the positive mechanistic and clinical findings. The association of pre-PCI thrombus burden in patent arteries and outcomes is not reported.

Study drug was administered after the wire had crossed the occlusion; therefore, some thrombotic embolization may have occurred before study drug administration. Whether administration of intracoronary pharmacotherapy before thrombotic embolization by the wire would further improve outcomes is not known. Recently, the Thrombus Aspiration in Percutaneous Coronary Intervention Following Acute Myocardial Infarction Study (TAPAS) demonstrated that mechanical clot aspiration was associated with improved myocardial perfusion and mortality at 1 year,\(^2^0\) and use of this mechanical modality is not reported in the present study. The benefits of intracoronary abciximab in conjunction with clot aspiration are unknown. Drug was administered via the guiding catheter, which may allow reflux of drug into the aorta; whether even more selective administration via the balloon catheter or selective infusion devices would further improve outcomes is unknown. The bolus was administered over 1 minute, and the residence time of abciximab after the bolus is likely to be on the order of 30 seconds. Whether a slower intracoronary infusion throughout the course of the intervention would further improve outcomes is unknown.

In the recent Ongoing Tirofiban in Myocardial Infarction Evaluation study (On-TIME 2), high-dose tirofiban was administered at the referring hospital or in the prehospital phase, and this very early administration was associated with improved clinical outcomes.\(^2^1\) Whether delayed but localized intracoronary pharmacotherapy would be superior to early systemic administration of GPIIb/IIIa inhibitors is not yet known. It also is not known whether intracoronary therapy over and above the early systemic therapy would result in improved clinical outcomes without increased adverse events, including major bleeds.

Conclusions

Impaired myocardial perfusion after PCI is associated with adverse clinical outcomes. The present trial adds to a growing body of literature that demonstrates the ability of intracoronary pharmacotherapies to improve myocardial perfusion and other surrogate outcomes. Larger randomized multicenter trials using rigorous clinical end points such as death and MI are required to further substantiate the clinical benefits of this mode of drug delivery.

Disclosures

The authors have received research grant support and consulting fees in the past from all 3 manufacturers of glycoprotein IIb/IIIa inhibitors (Eli Lilly, Schering Plough, and Mediciare).

References


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