Cardiovascular Topics

Intracoronary or intravenous abciximab after aspiration thrombectomy in patients with STEMI undergoing primary percutaneous coronary intervention

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Abstract

Objectives: To test whether aspiration thrombectomy with intracoronary (IC) instead of intravenous (IV) administration of abciximab could reduce the no-reflow phenomenon in patients undergoing primary percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Background: Despite recanalisation with PCI, failure to restore microvascular flow may affect the prognosis of patients with STEMI. A combination of aspiration thrombectomy with IC abciximab may improve distal perfusion.

Methods: After aspiration thrombectomy during primary PCI for STEMI, 160 patients were randomly assigned to either an IV or IC abciximab bolus delivered through the aspiration catheter, both followed by a 12-hour IV abciximab infusion.

Results: ST-segment resolution ≥ 70% was achieved in 36 of 78 patients with IC versus 30 of 82 patients with IV abciximab (46.1 vs 36.6%, p = 0.368), and partial resolution in 28 of 78 versus 31 of 82 patients (35.9 vs 37.8%, p = 0.368). Post-procedural myocardial blush grade (MBG) 3 was obtained in 62.8 vs 63.4% (p = 0.235) and MBG ≥ 2 in 89.7 vs 81.7% (p = 0.148) of patients given IC and IV abciximab, respectively.

There were three deaths in each group (3.8%). Major adverse cardiac events occurred in six of 78 patients given the IC and seven of 82 patients given the IV abciximab bolus (7.6 vs 8.5%, p = 0.410). One stroke occurred in each group, and two patients in the IC and nine in the IV group developed renal failure (2.5 vs 10.9 %, p = 0.414).

Conclusion: IC versus IV abciximab did not enhance myocardial reperfusion in non-selected patients with STEMI undergoing primary PCI after aspiration thrombectomy had successfully been performed.

Keywords: myocardial infarction, primary percutaneous intervention, aspiration thrombectomy, abciximab

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Rapid and sustained restoration of a thrombolysis in myocardial infarction (TIMI) 3 anterograde flow through the epicardial coronary artery, associated with a resolution of ST-segment elevation > 70% within 90 minutes are the primary goals of the current treatment of ST-segment elevation myocardial infarction (STEMI).13 Despite mechanical recanalisation of the occluded artery with primary percutaneous coronary intervention (PCI) and aggressive antithrombotic therapy directed at preventing thrombus growth and mitigating distal embolisation, these goals are not reached in many instances.

A major limitation of primary PCI is the possibility of distal embolisation of thrombus and failure to restore flow at the microvascular level. ST-segment elevation persists in more than 40% of cases of patients in whom a TIMI 3 flow has been achieved by primary PCI, a drawback associated with subsequent impairment of left ventricular (LV) function and a worse prognosis.44

Over the past decade, several approaches have been directed to prevent or reverse the no-reflow phenomenon, including aspiration thrombectomy56 and intracoronary glycoprotein IIb/IIIa inhibitor administration, such as abciximab.57 Abciximab, the Fab fragment of the chimeric human–murine monoclonal antibody 7E3, binds to the glycoprotein IIb/IIIa receptor of
human platelets and inhibits platelet aggregation. However, randomised trials of both thrombus aspiration and intracoronary (IC) versus intravenous (IV) abciximab administration have shown inconsistent results of these adjunctive methods with regard to clinical outcomes as well as to surrogate reperfusion parameters.

In addition, these two approaches have been compared to each other in the INFUSE-AMI study, in which intralesional abciximab was delivered through a dedicated infusion catheter consisting of a microporous balloon (ClearWay RX). IC abciximab delivery resulted in a modest but statistically significant reduction in infarct size compared with aspiration thrombectomy. However, in this trial, there was no control group of patients receiving IV abciximab. Therefore, whether IC or IV abciximab delivery would be more effective after removal of IC thrombotic and atherosclerotic materials has not been tested.

This study was intended to compare the effects of IC versus IV administration of abciximab in patients with STEMI undergoing primary PCI with aspiration thrombectomy. Intracoronary abciximab was administered through the distal part of the same catheter (Export catheter) after aspiration thrombectomy was completed.

**Methods**

This was a two-centre, open-label, controlled, single-blind, randomised study. The study was performed at the Department of Cardiology of the Military Hospital (Hôpital Central de l’Armée) and at the Department of Cardiology A2 of the Mustapha Pacha University Hospital, in collaboration with the Cardiology Oncology Collaborative Research Group (COCRG).

Patients were recruited in this prospective, randomised, blind study from 1 October 2013 to 31 October 2015.

Inclusion criteria were a chest pain suggestive of acute myocardial infarction (AMI) evolving for ≥30 minutes and less than 12 hours, resistant to nitroglycerin administration, and ST-segment elevation recorded ≥1 mm from standard and ≥2 mm from precordial leads.

Exclusion criteria were cardiogenic shock, high blood pressure, not controlled by treatment, after measuring twice (systolic BP ≥240 mmHg, diastolic BP ≥120 mmHg, or both), left bundle branch block, pregnancy, thrombocytopenia, severe kidney or liver failure, major surgery lasting for less than one month, gastrointestinal haemorrhage in the past year, severe ischaemic stroke lasting for less than one month, current staging or treatment of cancer, oral anticoagulant disorders, ischaemic stroke lasting for less than one month, resistant to nitroglycerin administration, after measuring twice (systolic BP ≥70% of the sum of ST-elevation present on the baseline ECG had resolved ≥50% but <70% of the sum of ST-segment elevation). ST-segment resolution was defined if ≥70% of the sum of ST-elevation present on the baseline ECG had resolved by 60 minutes after primary PCI (complete ST-segment resolution). Partial ST-segment resolution was defined if ≥50% but <70% of the sum of ST-segment elevation present on the baseline ECG had resolved by 60 minutes after primary PCI.

Secondary efficacy endpoints consisted of (1) major adverse cardiovascular events (MACE), including cardiovascular death, stent thrombosis, target-vessel revascularisation, and recurrent myocardial infarction at 30 days and six months; and (2) achievement of MBG 2 to 3 after completion of primary PCI.

Recurrence AMI was defined as recurrent symptoms or ST-elevation increase in troponin levels. Target vessel revascularisation was defined as any repeat revascularisation procedure on the infarct-related coronary artery.

Safety endpoints consisted of major and minor bleeding during hospital stay. Major haemorrhage was defined as retroperitoneal or intracranial bleeding, bleeding resulting in a ≥15% absolute decrease in haematocrit or a decrease in haemoglobin level >5 g/dl. Minor haemorrhage consisted of...
clinical or echo/CT scan-documented bleeding associated with a decrease in blood haemoglobin level > 3 g/dl and < 5 g/dl or a decrease in haematocrit > 9% and < 15%.

Statistical analysis

This study was powered for a ST-segment resolution rate of 56% at 60 minutes. Evaluating two groups of 72 patients would provide 90% power to demonstrate a relative 25% difference in ST-segment resolution rate between the IC and IV groups. Assuming approximately 10% lost to follow up, 160 patients were randomised.

All statistical analyses were performed using the SPSS statistical software (graduate pack for Windows, version 20). For categorical variables, the frequencies and percentages were presented as proportions and were compared with the χ² test or the Fisher’s exact test. A p-value < 0.05 was considered significant.

Results

The study flow chart is described in Fig. 1. Baseline characteristics of patients are summarised in Table 1. Patients randomised to IC administration were younger (58.8 ± 14.8 vs 60.6 ± 12.2 years) and less frequently hypertensive (36 vs 53%). An increased waist circumference was less frequently observed (6.4 vs 22.2%, p < 0.05).

There was no significant difference with regard to the patients’ past history between the groups, including prior coronary artery bypass graft (CABG), PCI, stroke and peripheral artery disease. Previous AMI was less frequent among patients with IC versus IV abciximab (5.1 vs 19.5%, p = 0.05). There was no significant difference between the two groups with regard to delay from symptom onset to balloon, heart rate, systolic and diastolic blood pressure, heart failure signs and left ventricular ejection fraction (LVEF) at admission.

Pre-procedural features of the target vessel lesions and coronary angiography findings are summarised in Table 2. The infarct-related coronary artery was the left anterior descending coronary artery (LAD) in 62% of patients with IC and 61% with IV administration (p = 0.470). Single-vessel disease was observed in 70.5 vs 57% in patients with IC vs IV administration (p = 0.127). There was no difference with regard to pre-PCI TIMI flow between the two groups. A TIMI flow of 0 (occlusion) was...
observed in 67% with IC compared to 72% of those with IV administration (p = 0.799).

Procedural characteristics of the two groups are shown in Table 3. There was no difference between the two groups with regard to radial catheterisation, aspiration thrombectomy and stenting rates. Manual aspiration thrombectomy was systematically performed before angioplasty or stenting.

No serious complications, such as flow-limiting dissection or air embolisation occurred after angiography. Direct stenting (stenting after thrombus aspiration without balloon pre-dilatation) was performed in 51.9% of the patients with IC administration and in 53.7% of those treated with IV administration (p = 0.851).

Angiographic outcome is presented in Table 4. Post-procedural TIMI flow grade was similar in both groups, with achievement of a TIMI 3 flow grade in 89.7% of patients with IC and in 89% of those with IV administration (p = 0.747). Post-procedural MBG 3 was obtained in 62.8% of patients with IC and in 63.4% of those with IV administration (p = 0.747). An MBG ≥ 2 was more frequently obtained with IC versus IV administration (89.7 vs 81.7%), but this did not reach statistical significance (p = 0.148).

There was no difference between patients randomised to IC and IV abciximab with regard to ST-segment resolution rate. ST-segment resolution ≥ 70% was achieved in 36 of 78 patients with IC versus 30 of 82 patients with IV abciximab bolus (46.1 vs 36.6%, p = 0.368). Partial ST-segment resolution was achieved in 28 of 78 versus 31 of 82 patients (35.9 vs 37.8%, p = 0.368). No resolution was observed in 14 of 78 versus 21 of 82 patients (17.9 vs 25.6%, p = 0.368) with IC and IV abciximab bolus, respectively.

In-hospital outcome: major cardiac events are listed in Table 5. Occurrence of death, recurrent myocardial infarction and target revascularisation rates within 30 days were similar in the two groups. There were three deaths in each group (mortality rate: 3.8%). MACE occurred in six of 78 patients given the IC, and seven of 82 patients given the IV abciximab bolus (7.6 vs 8.5%, p = 0.410). One stroke occurred in each group, and two patients in the IC and nine in the IV group developed renal failure (2.5 vs 10.9%, p = 0.414).

Major bleeding complications occurred in one patient in the IC group and none in the IV group. Minor bleeding complications occurred in seven of 78 patients given IC versus eight of 82 patients given the IV abciximab bolus (9.3 vs 9.9%, p = 0.578). Thrombocytopenia occurred in five of 78 patients with IC versus three of 82 patients with IV abciximab (6.4 vs 3.7%, p = 0.414).

Short-term clinical outcome: after the one-month follow up, there was only one cardiac death in each group, one stent thrombosis in the IC group, and similar rates of MACE in both groups (2.66 vs 2.53%, p = 0.588). Also, there was no difference in mortality rate (one death in the IV group), stent thrombosis (one in the IC group) and MACE (5.9 vs 8.8%, p = 0.714) after six months of follow up.

Discussion

This study was intended to assess the potential benefit of IC over IV abciximab administration after manual thrombus aspiration in patients undergoing primary PCI for STEMI. It showed that distal, intralesional IC administration of abciximab through the aspiration catheter following aspiration thrombectomy did not provide additional benefit over IV administration of the drug.

Among 160 patients randomised to either IC or IV abciximab bolus, no significant difference between the two groups was observed. Baseline clinical characteristics of patients, symptom-to-balloon time, which impacts on MBG, coronary angiography findings, infarct-related coronary artery, target vessel and procedural characteristics were similar in the two groups. Reperfusion parameters including the primary outcome endpoint, ST-segment resolution, and the secondary endpoint, achievement of MBG grade ≥ 2, did not differ between the groups. Also, no difference was observed with regard to the rate of MACE and major bleeding.

Over the past decade, several approaches have been used to prevent or reverse the no-reflow phenomenon. This included aspiration thrombectomy and intralesional administration of glycoprotein IIb/IIIa inhibitors via dedicated perfusion catheters to achieve higher concentration of the drug at the coronary vascular bed in order to improve myocardial reperfusion and to reduce infarct size.
Initial results from the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) trial suggested that aspiration thrombectomy could be effective in improving revascularisation at the microvascular level. Also, a meta-analysis of randomised trials, including 3,996 patients, showed improved myocardial perfusion, as assessed by ST-segment resolution and MBG. However, aspiration thrombectomy was subsequently challenged by the results of two trials, Thrombus Aspiration in ST-elevation Myocardial Infarction in Scandinavia (TASTE) and Trial of Routine Aspiration Thrombectomy with PCI versus PCI alone in Patients with STEMI (TOTAL), which both failed to show substantial clinical and perfusion benefit in patients despite successful aspiration of clotting material.

Coronary thrombus material triggers thrombotic, inflammatory, vasconstrictor and other pathways, and evacuating a portion of the thrombus and plaque material addresses only a part of the pathophysiological problem. Pharmacologically disrupting thrombus formation may be more effective. Abciximab, a potent inhibitor of platelet aggregation, disrupts fresh thrombus at high local drug concentrations, such as those delivered by IC administration, and also exhibits anti-inflammatory effects by inhibiting smooth muscle cell migration and proliferation, thereby suppressing platelets, white blood cells and endothelial-mediated mechanisms.

Adjunctive abciximab administration has been demonstrated to reduce the rate of mortality and re-infarction in patients with STEMI referred for invasive management. The standard abciximab regimen consists of an IV bolus followed by a 12-hour IV infusion. Intracoronary administration has been suggested to optimise myocardial perfusion beyond recanalisation, since anti-glycoprotein IIb/IIIa concentration has been reported as much as 280-fold higher with local compared with IV delivery.

Initial studies, in which abciximab bolus was delivered through the guiding catheter after wiring the infarct-related artery, were followed by the use of new application systems such as infusion catheters. These systems consist of a perfusion balloon that occludes anterograde blood flow while drugs are infused through a microporous surface, thereby allowing achievement of high drug concentrations and prolonged focal dwelling times at the site of coronary thrombus. Delivery of abciximab through such dedicated catheters (ClearWay Rx, Atrium Medical Hudson, New Hampshire) was associated with a significant reduction in thrombotic burden, improved microcirculatory flow, and lower rates of one-year adverse events, compared with conventional intracoronary drug administration through the guiding catheter in the small, randomised COCTAIL-II trial.

Also, a meta-analysis of eight randomised trials to assess the clinical efficacy and safety of intracoronary versus IV abciximab in STEMI patients undergoing primary PCI showed that intracoronary administration was associated with significant benefits in myocardial perfusion, but not in clinical outcome at short-term follow up.

Another meta-analysis of 14 randomised trials of IC versus IV glycoprotein IIb/IIIa inhibitors with a total of 3,740 patients undergoing primary PCI showed no statistically significant difference between the IC and the IV groups for the primary outcome of MACE. Subgroup analysis showed however that the IC group was superior to the IV group in short-term MACE rate, TIMI 3 flow, MBG 2 to 3 rates, improvement of LVEF, and ST-segment resolution, compared to the IV group, with a trend towards less stent thrombosis.

Among diabetic patients, IC versus IV abciximab bolus was associated with a significantly reduced risk of death and stent thrombosis and increased myocardial salvage. In addition, in the INFUSE-AMI study, randomisation to intraleisional abciximab through a ClearWay Rx catheter resulted in a modest but statistically significant reduction in infarct size compared with aspiration thrombectomy, but not with IV abciximab administration. However, in this trial, there was no control group of patients receiving IV abciximab.

Uncertainties regarding the use of IC abciximab are due, in part, to mixed results observed across studies. Indeed, although initial, small-sized investigations found an improvement in surrogate endpoints with IC abciximab, the AIDA STEMI trial, which was powered to assess clinical outcomes, failed to demonstrate a reduction in the primary endpoint of all-cause mortality, recurrent infarction, or new incidence of congestive heart failure among patients randomised to IC compared to IV abciximab bolus.

In the study by Piccolo et al. in diabetic patients, aspiration thrombectomy was performed in fewer than 20% of patients, while IC abciximab resulted in significant improvement of the effectiveness of PCI, including an increased myocardial salvage index and a reduced risk of death (5.8 vs 11.2%, p = 0.043).

The effectiveness of IC abciximab administration is also supported by the Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-segment Elevation Myocardial Infarction (INFUSE-AMI) trial, in which an IC bolus of the glycoprotein IIb/IIIa inhibitor abciximab was effective in reducing the infarct size, whereas thrombectomy by means of manual aspiration was not. In the INFUSE-AMI trial, which did not include an IV abciximab administration control group, the beneficial effects of intraleisional abciximab and thrombus aspiration were not additional. Nonetheless, although debated, the question of potential benefits of IC abciximab has recently been re-opened.

A recent meta-analysis of 14 trials of IC versus IV glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI also showed improved ST-segment resolution rates and superior angiographic results with IC glycoprotein IIb/IIIa inhibitors, evidenced by improved achievement of post-procedural TIMI 3 flow and MBG 2 to 3, compared with the IV group.

Overall, these observations suggest that adjunctive therapy with aspiration thrombectomy or IC abciximab administration, even in combination, are not required in all patients undergoing PCI. They should rather be considered for selected patients only, including those at increased risk of microvascular obstruction, such as diabetics and patients with a large thrombotic burden or severe distal coronary embolisation. Trials to evaluate the effectiveness of such approaches in these selected patients remain to be undertaken.

**Study limitation**

A major limitation pertains to the selection of patients. Patients with STEMI were included for primary PCI after a rather long delay from symptom onset to catheterisation laboratory of about 300 minutes. This was due to the specific area where the study was
carried out, namely northern Africa. However, similar symptom-to-door and symptom-to-balloon times have been reported in registries from Egypt, Tunisia, and Morocco. Despite this delay, primary PCI was performed instead of thrombolysis in our study, as it was done in about 35% of patients included in northern African registries. We acknowledge that this delay before primary PCI.

Conclusion
These data further compliment the overall INFUSE-AMI trial results. Because the patients who received IC and IV abciximab combined with aspiration thrombectomy had similar rates of ST-segment resolution and MBG, we concluded that IC instead of IV abciximab did not enhance myocardial reperfusion in non-selected patients with STEMI undergoing primary PCI, even after aspiration thrombectomy had successfully been performed.

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References


