Combined Intracoronary Glycoprotein Inhibitors and Manual Thrombus Extraction in Patients with Acute ST-segment Elevation Myocardial Infarction – Does Incorporation of Both Have a Legitimate Role?

Deepak Natarajan

Director, Interventional Cardiology, Moolchand MedCity, New Delhi

Abstract

In a substantial number of patients with acute ST-segment elevation myocardial infarction (STEMI), myocardial perfusion at the myocardial cellular level continues to be impaired despite achieving brisk antegrade flow in the infarct-related coronary artery by primary percutaneous intervention. This is attributable to embolisation of the coronary thrombus into the distal vasculature, producing microvascular plugging, vasospasm, interstitial oedema and cellular injury. There is consequently less salvage of infarct size, reduced left ventricular function and poorer clinical outcomes. Glycoprotein inhibitors are the most potent inhibitors of platelet aggregation and have been repeatedly shown to improve clinical outcomes in acute STEMI when administered intravenously. In recent years, randomised trials have demonstrated that glycoprotein inhibitors administered by the intracoronary route are safe and effective in reducing infarct size and providing better clinical outcomes than when given intravenously. Simultaneously, numerous randomised studies using adjunct manual thrombus extraction during primary percutaneous intervention in patients with acute STEMI have shown significantly better ST-segment resolution and myocardial blush grade, suggesting improved myocardial reperfusion, and, more importantly, significant one-year reductions in mortality. However, manual thrombus extraction cannot be used in all patients because there are occasions when the thrombus burden is too large to be aspirated completely or it is impossible to negotiate the thrombus extraction catheter beyond the occlusion. Similarly, glycoprotein inhibitors albeit delivered by the intracoronary route are unable to produce disaggregation of thrombus in all STEMI patients. A small pilot study involving 40 patients with acute STEMI demonstrated that the combination of intracoronary tirofiban and manual thrombus extraction is both safe and effective. However, there are no randomised data on the combined usage of intracoronary tirofiban and manual thrombus extraction in acute ST-elevation and, therefore, it is imperative that large, adequately powered, randomised studies are undertaken to study the synergistic effects of these two modalities. This article describes the various studies that have compared intracoronary glycoprotein inhibitors with the intravenous route and the rationale behind the advantages of manual thrombus extraction in the setting of acute STEMI.

Keywords

ST-segment elevation myocardial infarction (STEMI), intracoronary tirofiban, manual thrombus suction, glycoprotein inhibitors, primary percutaneous intervention

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Correspondence: Moolchand MedCity, Lajpat Nagar III, New Delhi,110024, India. E mail: deepaknatarajan19@gmail.com

Primary percutaneous coronary intervention (PCI) is the treatment of choice in the management of acute ST-segment elevation myocardial infarction (STEMI). It has been constantly observed that, despite restoring good epicardial flow with PCI, myocardial perfusion at the cellular level remains impaired in nearly 50 % of STEMI patients. This led to the development of a new class of antiplatelet drugs, termed glycoprotein IIb/IIIa inhibitors (GPIs), which were hypothesised to be exquisitely effective in disaggregating the acute coronary thrombus responsible for STEMI. A recent meta-analysis including a little over 10,000 patients confirmed the concept that platelet inhibition beyond that provided by aspirin and thienopyridine with GPIs during elective percutaneous intervention resulted in reduced MI size without a significant increase in major bleeding.[1] The effect of GPIs was studied in 22 randomised studies in the more contemporary setting of coronary stents and thienopyridines.[1] The reduction in target vessel revascularisation at 30 days was not significant, but there was a significant increase in the rate of minor bleeding (from 1.7 to 3 %) and thrombocytopenia, but no increase in stroke. There was no difference in mortality, but that was expected as elective PCI usually involves low-risk patients.

In the setting of STEMI, abciximab is recommended with a high level of evidence in both the American and European guidelines as adjunctive treatment during PCI.[2–4] An excellent meta-analysis of six randomised studies comparing abciximab (n=1,082) with small-molecule GPIs (eptifibatide [n=226] or tirofiban [n=889]) revealed no significant difference in the primary endpoint of 30-day mortality or reinfarction. The take-home message was that, in the setting of STEMI, any GPI could be used as each was equally effective by the intravenous (IV) route.[5] The Swedish coronary angiography and angioplasty registry reported that in 11,479 STEMI patients, eptifibatide was non-inferior to abciximab with respect to death or MI

at one-year follow-up. The registry concluded that either drug could be used in clinical practice. The combined endpoint of death and MI occurred in 353 of 2,355 patients (15 %) treated with eptifibatide and in 1,432 of 9,124 patients (15.7 %) treated with abciximab.[6]

Primary angioplasty has repeatedly been shown in randomised studies to be superior to fibrinolysis in reducing mortality, reinfarction and stroke in patients with STEMI.[7] This is readily explained by the fact that in almost 50 % of patients with acute STEMI, coronary thrombi when examined histologically were found to be not a few hours old but actually a few days to weeks old. Sudden coronary occlusion in STEMI is often preceded by plaque instability and thrombus formation days or weeks before symptom onset. Percutaneous intracoronary (IC) manual thrombectomy was performed in 211 consecutive STEMI patients within six hours of onset of chest pain. The aspirated material was examined histopathologically to confirm that in 51 % of cases, older thrombi were present, suggesting a discrepancy between symptom onset and the actual pathogenesis of the clot.[8]

It has come to be recognised that STEMI is caused by rupture or erosion of an atherosclerotic plaque that results in complete or partial occlusion of the coronary artery, but also that while performing mechanical PCI there is distal release of thromboembolic material leading to microvascular plugging. The microvascular obstruction reduces myocardial perfusion and consequently leads to increased infarct size, reduced recovery of ventricular function and increased mortality. One is confronted with the paradox that, despite a fully patent infarct-related coronary artery achieved by PCI, there is no commensurate improvement in clinical results.

The next step in the evolution of the management of STEMI patients was the introduction of mechanical thrombus extraction. A large randomised study including 1,071 STEMI patients concluded not only that mechanical thrombus aspiration is feasible but also that this technique results in better reperfusion and clinical outcomes in the majority of patients presenting within 12 hours of symptom onset.[9–12] The TAPAS study was able to retrieve atherothrombotic material in 73 % of patients who underwent thrombus aspiration; platelets were the main constituent of the thrombi. The study also made the important observation that angiographic variables such as Thrombolysis in myocardial infarction (TIMI) flow or visible thrombus are not predictors of thrombus extraction efficacy. Other, albeit smaller, trials have also documented the advantages of thrombus aspiration in patients with STEMI.[13–15] A meta-analysis of prospective randomised studies suggested that thrombectomy but not distal protection devices significantly reduced distal embolisation and no reflow, as evaluated by myocardial blush grade (MBG) and ST-segment resolution (STR).[16] More importantly, the Thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction (TAPAS) trial reported a reduction in reinfarction and mortality at one-year follow-up in STEMI patients subjected to manual thrombectomy.[17] Thrombectomy employing manual but not mechanical thrombus-aspirating catheters significantly improved one-year survival in 2,686 STEMI patients undergoing PCI in a pooled analysis of individual patients from 11 randomised trials. The positive effect of thrombectomy was amplified by GPIs. The study found that thrombectomy resulted in significantly lower all-cause mortality (p=0.049) and significantly reduced major adverse cardiac events (MACE) (p=0.011) and death or MI (p=0.015). The survival benefit was confined to patients treated with manual thrombectomy (p=0.011) and not mechanical devices for thrombectomy. The administration of GPIs with thrombectomy led to a mortality rate of 3.3 %, whereas when neither thrombectomy nor GPIs were used there was a mortality rate of 7.4 % (p=0.045).[18]

With the establishment of PCI in patients with acute STEMI, it also became apparent that, despite achieving TIMI 3 flow in almost 40 % of patients, there was no or incomplete resolution of the ST segments on the electrocardiogram.[19,20] The reasons for the no reflow phenomenon were, as mentioned earlier, distal embolisation of thrombus, interstitiitial oedema, spasm in the microvascuature and inflammation owing to acute cell injury. The next objective in the management of STEMI therefore became the prevention of no reflow and current STEMI guidelines strongly recommend manual thrombus aspiration and the administration of abciximab, with a Class IIA, Level of Evidence B indication. The simple practical message for the management of patients with STEMI is that manual thrombus aspiration with IV administration of GPIs produces excellent clinical outcomes.

Surprisingly, there are very limited data on the combined application of IC GPIs and manual thrombectomy in STEMI patients. The randomised Comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. is one of the very few trials comparing the effects of IC versus IV administration of abciximab in STEMI patients undergoing primary PCI with manual thrombosuction. This study, conducted in 534 STEMI patients, showed that the primary endpoint of complete STR (suggesting restored myocardial reperfusion) was similar in both the IC and IV groups given an abciximab bolus (64 versus 62 %; p=0.562). Patients were randomised to either an IC or IV bolus of abciximab (0.25 mg/kg) and all were pre-treated with aspirin, clopidogrel and heparin. The incidence of MBG 2/3 was greater in the IC group than in the IV group (76 versus 67 %; p=0.022). Enzymatic infarct size was smaller in the IC group (p=0.008). MACE rates were similar in both groups (5.5 versus 6.1 %; p=0.786). The conclusions drawn by the study were that, in patients with STEMI who undergo primary PCI with manual thrombus aspiration, there is no difference in improved myocardial reperfusion when assessed by STR. However, IC abciximab resulted in smaller enzymatic infarct size and better myocardial reperfusion when measured by MBG. The apparent discrepancy in myocardial reperfusion as assessed by STR and MBG is explained by the fact that STR and MBG indicate different pathophysiological phenomena. STR may represent the functional state of the cardiac cell while MBG reflects the mechanical patency of the microvasculature. Another explanation provided for the discrepancy is that MBG is assessed directly after primary PCI whereas STR is measured 30–60 minutes post-PCI. This study was underpowered to detect clinical ramifications of IC versus IV abciximab.[21] There are few ongoing trials assessing improvement in clinical outcomes with IC abciximab or other GPIs.[22]

Even though case reports on IC GPIs were published more than a decade ago, routine use of these agents remains to be established.[23,24] A randomised study of 137 STEMI patients demonstrated a smaller troponin rise in the IC abciximab group, but one-year MACE was similar in both IC and IV groups.[25] IC eptifibatide has also been found to be safe in STEMI patients;[26,27] an IC eptifibatide bolus alone without a subsequent infusion has also been shown to be effective.[28]

The reasons for the apparent superiority of IC GPIs was explained by significantly greater GPI receptor occupancy on platelets sampled from the coronary sinus than from IV administration. It is plausible that the higher local concentration achieved with the IC route may be more effective in dissolution of platelet-rich thrombus.[29]

There are sparse data on IC tirofiban in the setting of STEMI. A randomised study of 118 acute coronary syndrome patients showed lower MACE at 14 days with IC tirofiban compared with the IV group (3.5 versus 17.5 %; p=0.030), but the benefit was not sustained at 30 days.[30] Immediately post-PCI, the study group demonstrated better TIMI flow rates (p=0.016). The left ventricular ejection fraction was higher in the IC group at 30 days (67.4 versus 60.7 %; p=0.033). The study concluded that, in patients with acute coronary syndrome, an IC bolus of tirofiban is superior to an IV bolus injection for improving coronary flow, myocardial perfusion and short-term clinical outcomes.

A total of 60 consecutive STEMI patients were randomly divided to receive IC tirofiban bolus (10 µg/kg) prior to first balloon inflation and a similar IV bolus prior to coronary angiography followed by 36-hour IV tirofiban (0.015 µ/kg/minute) for all patients. IC tirofiban produced better TIMI flow grades, myocardial perfusion STR and ejection fraction at five to seven days after PCI. In-hospital MACE and bleeding rates were similar during hospital stay, but the MACE rate was signicantly less on follow-up in the IC tirofiban group (7.1 versus 30.8 %).[31]

An interesting case report described the management of no reflow accompanied by marked hypotension and ST-segment elevation in a patient undergoing PCI for a left circumflex lesion. The catastrophe was promptly corrected with IC tirofiban given at a dose of 10µg/kg.[32] Another case report suggested that IC administration of tirofiban can be safely employed to treat acute stent thrombosis occurring in a left anterior descending artery stent deployment. A bare-metal stent measuring 3.5x18mm was deployed in a 46-year-old male patient presenting with STEMI and there was immediate stent thrombosis leading to severe chest pain and shock. An IC bolus of tirofiban (10µg/kg) was able to quickly achieve good antegrade flow with resolution of symptoms and haemodynamic compromise when repeated attempts with balloon inflation did not succeed.[33]

The possible synergistic effects of a high bolus dose of IC tirofiban and manual thrombectomy in a 50-year-old male patient presenting with acute anterior STEMI has been described in a recent case report. The totally occluded proximal left anterior descending artery was successfully treated with an IC bolus of trofiban (25µg/kg) and multiple manual thrombus suction runs. The report concluded that a high-dose bolus injection of IC tirofiban accompanied by manual thrombectomy was safe, effective and simple to perform in patients with STEMI undergoing primary PCI.[34]

A further case report describes a 50-year-old male who had undergone primary PCI for acute anterior STEMI being readmitted with subacute stent thrombosis owing to inadvertently missing his aspirin dose for almost a week. His angiogram revealed tight subtotal stenosis and large thrombus burden within the sirolimus-eluting stent that had been deployed previously in his proximal left anterior descending coronary artery. Brisk antegrade flow was achieved with a 25µg/kg bolus of IC tirofiban and subsequent plain balloon inflations.[35]

An elegant Japanese study in the meantime used cardiac magnetic resonance imaging to evaluate the effect of manual thrombus aspiration in 62 patients presenting with STEMI. Successful thrombus aspiration was associated with a significant reduction in infarct size (12.2±7.1 versus 17.4±7.1 ml; p=0.01) and preserved myocardial viability.[36]

However, there are no data on the combined use of manual thrombus extraction and IC tirofiban in the world literature. A small, non-randomised pilot study compared the probable synergistic effects of the combination of IC high-dose tirofiban and manual thrombus extraction versus IV tirofiban alone during primary PCI in patients with acute STEMI. Forty patients were divided into two groups; the 20 patients in group A were treated with an IC tirofiban bolus of 25 µg/kg plus manual thrombus extraction, while the 20 group B patients underwent PCI with IV bolus of tirofiban alone without thrombus extraction. Both groups of patients received IV tirofiban for the next 16 hours (0.15 µg/kg/minute). All patients were pre-treated with 325 mg aspirin, 600 mg clopidogrel and heparin. The primary endpoint was STR at 60 minutes, signifying myocardial perfusion. Both groups had similar baseline clinical characteristics and door-to-balloon time. Significantly superior results with STR were seen in group A patients (80 versus 50 %; p<0.05) and a better trend in MBG 2/3 (65 versus 50 %; p=0.06). The incidence of in-hospital MACE was similar in both groups but at 30 days was significantly lower in the patients treated with IC tirofiban and manual thrombus extraction (5 versus 15 %; p<0.05). It is imperative that larger adequately powered controlled studies are conducted to confirm or refute the findings of this small pilot study.[37]

The messages in this review are simple and few. Primary PCI, although the preferred modality of treatment for patients presenting acutely with STEMI, remains inadequate in a substantial number of patients despite opening up the infarct-related epicardial artery and achieving brisk TIMI 3 flow. The reasons for this are that, in mechanically clearing the total/subtotal coronary occlusion, there is antegrade embolisation of coronary thrombus debris that causes microvascular plugging, vasoospasm, interstitial edema and cellular damage. This in turn results in reduced myocardial perfusion, larger infarct size, diminished left ventricular function and poorer clinical outcomes. It is quite probable that these adverse processes can be best reversed by synergistic effects achieved by the combination of IC GPIs and manual thrombus extraction. ■

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